Q6: WHEN TO USE LOCAL THERAPY FOR LUNG OR UNRESECTABLE LIVER METASTASES OF COLORECTAL CANCER?

TABLE OF CONTENTS

LIST OF FIGURES

No table of figures entries found.

LIST OF TABLES

SYNTHESIS

1. INTRODUCTION

1.1. PICO

What is the current standard first line treatment for metastatic inoperable colorectal cancer?	
P (patient)	colorectal cancer with unresectable liver or lung metastases
I (Intervention)	Radio frequency Ablations, Hepatic arterial infusion, Chemo-embolization Radio-embolization, resection of lung metastases
C (comparison)	Systemic chemotherapy
O (outcome)	PFS, OS

2. SEARCH FOR EVIDENCE

2.1. Search strategy

First, guideline databases and websites of international oncology guideline developers were searched for evidence-based guidelines relevant to the subject. Only NICE treated the subject but could not identify any relevant evidence.

Evidence of the retrieved guidelines was updated with literature search from 2009 onwards. Initially, only systematic reviews and meta-analyses were searched. They were searched in the following databases: OVID Medline and PreMedline, EMBASE and Cochrane Database of Systematic Reviews. These searches were performed in January 2013. The search strategy can be found in Appendix 1.

Additional searches for randomized controlled trials (RCTs), observational studies (case series, cohort studies and case-controlled studies) were performed to update the selected reviews. The additional information was searched in OVID Medline and PreMedline, EMBASE and CENTRAL in January 2013. The search strategy is also presented in Appendix 1.

2.2. Study selection

All citations retrieved were screened based on title and abstract. Possible citations of interest were further selected based on the full text article.

The search for systematic reviews and meta-analyses published between 2009 and 2012 retrieved 335 citations, after removal of duplicates. After removal of studies that (based on title and abstract) did not fulfil the selection criteria, 52 citations were left for full text evaluation, 16 were assessed with Amstar (see Appendix 2), data from 5 systematic reviews were extracted (see Appendix 3).

The update with randomized controlled trials and observational studies published departing from 2009 yielded 2789 publications, after removal of duplicates. After removal of studies that (based on title and abstract) did not fulfil the selection criteria, 56 citations were left for full text evaluation, Data from 16 studies were extracted (see Appendix 3).

Comparative cohort studies were included when at least the known risk factors were taken into account and when statistical adjustment was performed for known confounders to measure survival or recurrence. Case series were considered eligible when uniform interventions were performed amongst well defined groups.

Studies were only included when there was a full text available.

3. SUMMARY OF THE EVIDENCE

3.1. Treatment (isolated) liver/lung metastases

3.1.1. Radio-frequency ablation (RFA)

Cirocchi et al.[1] identified in a Cochrane review 18 studies comparing radio-frequency ablation (RFA) with other treatment modalities among patients with resectable and unresectable liver metastases. Seventeen studies were not randomised with an increased risk for selection bias and an imbalance in the baseline characteristics of the participants included in all studies. All studies were classified as having an elevated risk of bias. Survival and local recurrence vary widely between studies; main results are reported in Table 5. The heterogeneity regarding interventions, comparisons and outcomes rendered the data not suitable for pooling, and the general conclusion of the review was that there is insufficient evidence regarding the use of RFA. Weng et al.[2] attempted to pool the same studies but considered this pooling as inappropriate.

A single RCT was included (Ruers 2010) from an abstract of 2010 ASCO Annual Meeting. The final results of the study were published in 2012.[3] It compared 60 patients receiving RFA plus CT versus 59 patients receiving CT alone, it showed that PFS at 3 years was significantly higher in the group that received RFA (HR 0.63; 95%CI 0.42-0.95), but no effect on overall mortality could be demonstrated. 30-month OS was high in both groups, 61.7% (95%CI 48.2-73.9%) in the RFA group and 57.6% (95%CI 44.1-70.4%) in the systemic therapy only group.

We updated the systematic review of Cirocchi et al using the same strategy from the search date of the review. No additional RCT's were found, 3 observational studies case series were excluded as only the abstracts were available and insufficient information was available to assess quality and method.

Table 1 – Systemic chemotherapy with or without radiofrequency ablation of liver metastases: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
PFS at 3 years HR 0.63; 95%CI 0.42-0.95	1 RCT	0	-1	0	-2	0	2: single study 4: CI includes clinical decision threshold, sample size < 400	Very low
OS 61.7% (95%CI 48.2-73.9%) in the RFA group versus 57.6% (95%CI 44.1-70.4%) in the CT only group	1 RCT	0	-1	0	-2	0	2: single study 4: sample size < 400, wide overlapping CI for OS estimations	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Conclusion

- There is limited evidence that radiofrequency ablation added to systemic chemotherapy improves PFS at 3 years in CRC patients with unresectable liver metastases (Ruers 2012, very low level of evidence).
- In CRC patients with unresectable liver metastases, an effect on overall survival when adding radiofrequency ablation to systemic chemotherapy could neither be demonstrated nor refuted (Ruers 2012, very low level of evidence).

3.1.2. Hepatic artery (HAI) chemotherapy in unresectable CRC liver metastases.

Mocellin et al 2011[4] included 10 RCTs that compared hepatic artery infusion (HAI) with systemic chemotherapy in CRC patients with unresectable liver metastases. HAI regimens were based on fluoxuridine (FUDR), 5-fluorouracil or either one of these two fluoropyrimidines in eight and one RCT, respectively. Systemic chemotherapy (SCT) consisted of FUDR or 5-fluorouracil in three and seven RCT, respectively. Only 2 out of ten studies were considered to be of high quality. Crossover to HAI was reported in 4/10 trials and the proportion of patients who received allocated treatment was often low. By pooling the summary data, tumour response rate resulted in 42.9% and 18.4% for HAI and SCT, respectively (RR = 2.26; 95% CI, 1.80 to 2.84; P < 0.0001). Mean weighted median OS times were 15.9 and 12.4 months for HAI and SCT, respectively: the meta-risk of death was not statistically different between the two treatment groups (HR = 0.90; 95% CI, 0.76 to 1.07; P = 0.24). Subgroup analysis taking into account quality of the studies confirmed this result.

No additional RCT's were identified, starting from the search date (January 2011).

Table 2 – hepatic artery infusion (HAI) in unresectable CRCliver metastases: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Risk of death HR 0.90; 95%CI 0.76 to 1.07 (P = 0.24)	10	-1	-1	0	-1	0	1: only 2/10 high quality trials, 4/10 crossover trials 2: unexplained heterogeneity 4: CI includes effect and no effect	Very low

Conclusion

- In CRC patients with unresectable liver metastases, an effect of HAI compared to systemic chemotherapy on overall survival could neither be demonstrated nor refuted (Mocellin 2011, very low level of evidence).

3.1.3. Chemo-embolization

Carter et al 2009 [5] did a systematic review on chemo-embolization and identified two abstracts on two small case series. An update starting from the search date (2008) was done (Table 9).

4 case series and 1 phase 3 trial for which at least a full text report existed were identified published since the Carter review (Table 10).

Fiorentini et al. 2012[6], in an RCT with unclear risk of bias (unclear randomization, no or unclear allocation concealment, no blinding of outcome assessment, albeit only important for progression free survival), randomised 75 patients to either chemo-embolisation with irinotecan eluting beads (DEBIRI) or FOLFIRI. The primary end-point was survival; secondary end points were response, recurrence, toxicity, quality of life, cost and influence of molecular markers. At 50 months, overall survival was significantly longer for patients treated with DEBIRI than for those treated with FOLFIRI (p=0.031, log-rank) Hazard ratio: 0.60 (95%CI 0.37-0.97). Median survival was 22 months (95%CI 21-23 months), for DEBIRI and 15 months (95%CI 12-18 months) for FOLFIRI. Progression-free survival was 7 months (95%CI 3-11 months) in the DEBIRI group compared to 4 months (95%CI 3-5 months) in the FOLFIRI group and the difference between groups was statistically significant (p=0.006, log-rank). Extra-hepatic progression had occurred in all patients by the end of the study, at a median time of 13 (95%CI 10-16) months in the DEBIRI group compared to 9 (95% CI 5-13) months in the FOLFIRI group. A statistically significant difference between groups was not observed (p=0.064, log-rank).The median time for duration of improvement to quality of life was 8 (95%CI 3-13) months in the DEBIRI group and 3 (95%CI 2-4) months in the FOLFIRI group. The difference in duration of improvement was statistically significant (p=0.00002, log-rank).

Martin et al., 2009[7] reported on 55 cases of unresectable colorectal hepatic metastasis patients who had failed standard therapy who received repeat embolisations with irinotecan loaded beads (max 100 mg per embolization) per treating physician's discretion. The median disease free and overall survival from the time of first treatment was 247 days and 343 days.

Vogl et al 2009[8] treated 463 patients (mean age, 62.5 years; range, 34.7-88.1 years) with unresectable liver metastases of colorectal cancer that did not respond to systemic chemotherapy repeatedly treated chemo-embolization in 4-week intervals. In total, 2441 chemo-embolization procedures were performed (mean, 5.3 sessions per patient). The local chemotherapy protocol consisted of mitomycin C alone (n = 243), mitomycin C with gemcitabine (n = 153), or mitomycin C with irinotecan (n = 67). Embolization was performed with lipiodol and starch microspheres for vessel occlusion. Tumour response was evaluated with magnetic resonance imaging. Evaluation of local tumour control resulted in partial response (68 patients [14.7%]), stable disease (223 patients [48.2%]), and progressive disease (172 patients [37.1%]). The 1-year survival rate after chemo-embolization was 62%, and the 2-year survival rate was 28%. Median survival from date of diagnosis of liver metastases was 38 months and from the start of chemo-embolization treatment was 14 months. There was no statistically significant difference between the three treatment protocols.

Albert et al. 2011[9] reported on 121 patients undergoing chemo-embolization with cisplatin, doxorubicin, mitomycin C, ethiodized oil, and polyvinyl alcohol particles, performed at monthly intervals for 1 to 4 sessions. 2 (2%) had partial response, 39 (41%) stable disease, and 54 (57%) progression. Median time to

disease progression (TTP) in the treated liver was 5 months, and median TTP anywhere was 3 months. Median survival was 33 months from diagnosis of the primary colon cancer, 27 months from development of liver metastases, and 9 months from chemo-embolization.

Aliberti et al. 2011[10] reported on 82 patients presenting with metastatic colorectal carcinoma to the liver after failing chemotherapy undergoing chemo-embolisations with drug eluding beads with irinotecan. The primary endpoints were tumour shrinkage, safety, feasibility, compliance, and overall survival. RECIST was used to assess response. Observed adverse effects were: right upper quadrant pain (40%), fever (80%), nausea (27%) and increased transaminases (70%). The median follow-up was 29 months. After the first treatment, 75 out 82 patients declared an improvement of their well being lasting more than 18 weeks. The median duration of response was 6 (range 3-10) months; the median follow up time was 29 (range 7-48) months. The median survival was 25 (range 6-34) months, with progression free survival at 8 (range 4-16) months.

Table 3 – Chemo-embolization for unresectable colorectal liver metastases: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Chemo-embolisation versus chemotherapy								
Overall survival HR 0.60; 95%CI 0.08-0.97	1	0	-1	-1	-1	0	2: Only one study 3. Control chemotherapy was less performing 4: OIS not met and CI compatible with clinically unimportant effect	Very Low
Progression-free survival HR 0.51; 95%CI 0.32, 0.82	1	-1	-1	-1	-1	0	1. outcome assessment not blinded 2: Only one study 3. Control chemotherapy was less performing 4: OIS not met	Very Low

Conclusion

- There are indications that chemo-embolization for the treatment of liver metastases from colorectal cancer may improve progression-free and overall survival (Very low level of evidence).

3.1.4. Radio-embolization, Selective Internal Radiation Therapy (SIRT) for patients with unresectable tumours

Rizell et al. 2010[11] identified eight studies on patients with unresectable liver metastases from CRC. Three studies were controlled studies, two of which being randomised (RCT). The two RCT's were also reported by the Cochrane review of Townsend et al, 2009[12] which only focussed on RCT's. Main results of those RCT's are reported in the evidence profile (Table 4). The other five studies were case series. One of the RCTs was of moderate and the other of low scientific quality. The nonrandomised, controlled study was also of low scientific quality. There was no difference in survival between radio-embolization with 90Yttrium and the control therapy in the RCT of moderate scientific quality or in the non-randomised, controlled study of low scientific quality. The frequency of patients with a complete or partial tumour response varied between 34 – 75 %. Most patients experienced nausea, abdominal pain and extreme fatigue. A serious adverse effect occurred in 2 – 4 % with regard to liver toxicity, in 12 % with regard to bilirubin-toxicity and in 5 – 8 % with regard to gastrointestinal toxicity.

The review was updated from the search date on (January 2010).

Hendlisz et al. 2010[13] reported on a prospective, multicenter, randomized phase III trial in patients with unresectable, chemotherapy-refractory liver-limited metastatic CRC (mCRC) comparing arm A (fluorouracil [FU] protracted intravenous infusion 300 mg/m 2 days 1 through 14 every 3 weeks) and arm B (radio-embolization plus intravenous FU 225 mg/m2 days 1 through 14 then 300 mg/m2 days 1 through 14 every 3 weeks) until hepatic progression. The primary end point was time to liver progression (TTLP). Cross-over to radio-embolization was permitted after progression in arm A. Forty-six patients were randomly assigned and 44 were eligible for analysis (arm A, n = 23; arm B, n = 21). Median follow-up was 24.8 months. Median TTLP was 2.1 and 5.5 months in arms A and B, respectively (hazard ratio [HR] = 0.38; 95% CI, 0.20 to 0.72; P = .003). Median time to tumour progression (TTP) was 2.1 and 4.5 months, respectively (HR = 0.51; 95% CI, 0.28 to 0.94; P = .03). Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after radio-embolization plus FU treatment (P = .10). Twenty-five of 44 patients received further treatment after progression, including 10 patients in arm A who received radio-embolization. Median overall survival was 7.3 and 10.0 months in arms A and B, respectively (HR = 0.92; 95% CI, 0.47 to 1.78; P = .80). The study had following limitations: trial was prematurely closed (with the number of enrolled patients lower than required (based on power analysis); open- label design; liver progression not documented in 3 pts of arm B; in 4 pts from arm B there was an unjustified change in the treatment allocated by randomization.

Chua et al. 2011[14] reported on a prospective database of a major yttrium-90 microsphere radio-embolization treatment centre in Sydney, Australia, that included 140 patients with unresectable colorectal liver metastases. One hundred and thirty-three patients (95%) had a single treatment, and seven patients (5%) had repeated treatments. Response following treatment was complete in two patients (1%), partial in 43 patients (31%), stable in 44 patients (31%), and 51 patients (37%) developed progressive disease. Combining chemotherapy with radio-embolization was associated with a favourable treatment response (P = 0.007). The median overall survival was 9 (95%CI 6.4-11.3) months with a 1-, 2-, and 3-year survival rate of 42, 22, and 20%, respectively. Primary tumour site (P = 0.019), presence of extra-hepatic disease (P = 0.033), and a favourable treatment response (P < 0.001) were identified as independent predictors for survival.

Kosmider et al 2011[15] reported on 19 patients who underwent radio-embolization (RE) plus systemic chemotherapy as a first-line treatment for unresectable liver metastases from colorectal cancer (CRC). Overall response rate according to RECIST was 84% (two complete responses and 14 partial responses). Median progression-free survival (PFS) time was 10.4 months and median overall survival (OS) time was 29.4 months. For patients with disease confined to the liver, PFS improved (10.7 mo versus 3.6 mo; P = .09), with significant prolongation of OS (median, 37.8 mo versus 13.4 mo; P = .03) compared with those who had extra-hepatic disease. Serious treatment-related toxicities included febrile neutropenia with concurrent FOLFOX treatment, a perforated duodenal ulcer, and one death from hepatic toxicity.

Bester et al 2012[16] reported on a retrospective study including 224 patients with chemotherapy-refractory liver metastases treated with yttrium-90 (90Y) resin microspheres, The median OS embolization group was 11.9 months (95% CI: 10.1-14.9 months**).** A comparison was made to a control group of 29 patients who underwent standard care but we did not consider this comparison as valid.

Martin et al 2012[17] reported on twenty-four patients with unresectable mCRC with liver metastases treated with yttrium-90 microsphere radio-embolization. 54% had extra-hepatic disease; 67% had bilobar involvement. The patients had received a median of 3 prior therapies. No objective responses were observed. Five patients had a CEA response. Median PFS and OS were 3.9 months (95% CI, 2.4-4.8 months) and 8.9 months (95% CI, 4.2-16.7 months), respectively. Patients older than 65 years had improved PFS (4.6 vs. 2.4 months) and OS (14 vs. 5.5 months) vs. younger patients, likely due to receipt of 90Y treatment earlier in their disease course. The presence of extrahepatic disease and the absence of CEA response appeared negatively predictive of efficacy.

Seidensticker et al. 2012[18] reported on a matched-pair comparison of patients who received radio-embolization plus best supportive care (BSC) or BSC alone for extensive liver disease. The study included 29 patients who received radio-embolization, retrospectively matched with patients for prior treatments and tumour burden and then 29 patients were consecutively identified with two or more of four matching criteria: synchronous/metachronous metastases, tumour burden, increased ALP, and/or CEA >200 U/ml. Of 29 patients in each study arm, 16 pairs (55.2%) matched for all four criteria, and 11 pairs (37.9%) matched three criteria. Compared with BSC alone, radio-embolization prolonged survival (median, 8.3 vs. 3.5 months; P < 0.001) with a hazard ratio of 0.3 (95% confidence interval, 0.16-0.55; P < 0.001) in a multivariate Cox proportional hazard model. Treatment-related adverse events following radio-embolization included: grade 1-2 fatigue (n = 20, 69%), grade 1 abdominal pain/nausea (n = 14, 48.3%), and grade 2 gastrointestinal ulceration (n = 3, 10.3%). Three cases of grade 3 radiation-induced liver disease were symptomatically managed. This small observational study attempted to control for confounding by matching on a number of criteria but nevertheless there remains a high risk of residual confounding

Table 4 – Radio-embolization for unresectable colorectal liver metastases: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
SIRT + chemotherapy versus chemotherapy								
Progression-free survival HR 0.23; 95%CI 0.08-0.68	1	0	-1	-1	-1	0	2: Only one study 3. Control chemotherapy was less performing 10 years ago. 4: OIS not met	Very Low
Overall survival HR 0.22; 95%CI 0.07-0.74	1	0	-1	-1	-1	0	2: Only one study 3. Control chemotherapy was less performing 10 years ago 4: OIS not met	Very Low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
SIRT + HAI vs. HAI								
Progression-free survival HR: 0.72; 95%CI 0. 43-1.21	1	0	-1	0	-2	0	2: Only one study 4: OIS not met+ confidence interval compatible with considerable harm or considerable benefit	Very Low
Overall survival HR 0.62; 95%CI 0.37-1.05	1	0	-1	0	-2	0	2: Only one study 4: OIS not met+ CI includes effect and no effect	Very Low

SIRT after failed chemotherapy

We attribute a very low level of evidence based on the study of Hendlisz et al. 2010[13], that showed an effect of progression free survival but not on overall survival, and was stopped early and the matched analysis of Seidensticker et al. 2012[18] that showed an effect but where residual confounding cannot be excluded.

Conclusion

- There is limited evidence that SIRT may improve PFS and OS if added to systemic chemotherapy in CRC patient with unresectable liver metastases (Townsend 2009, very low level of evidence).
- In patients with unresectable liver metastases, an effect of SIRT on PFS or OS when added to hepatic artery infusion could neither be demonstrated nor refuted (Townsend 2009, very low level of evidence).

3.1.5. Stereotactic Body Radiation Therapy (SBRT) for liver metastases.

One systematic review of Tipton et al.[19] was excluded because no primary results were reported, however the same systematic review was reported in a more detailed way in a HTA report by Agency for Healthcare Research and Quality (AHRQ).[20]

Two HTA reports were identified. The National Radiotherapy Implementation Group Report from the NHS identified 9 case series on liver metastases, with overall survival ranging from 16 to 92 months and local control ranging from 71 to 92 %.[21] In some of those studies colorectal and other metastases are mixed however.

The AHRQ, in the report mentioned above, identified the same studies and added two small cases series with results within the same range. Neither comparative studies nor RCT's were found after the search date of the AHRQ review (December 2010).

One large case series of Chang et al.[22] was identified, reporting 12-month, 18-month, and 24-month OS rates of 72%, 55%, and 38%, respectively and 12-month, 18-month, and 24-month local control rates of 67%, 65%, and 55%, respectively.

Conclusion

- In CRC patients with unresectable liver metastases, an effect of stereotactic body radiotherapy on overall survival could neither be demonstrated nor refuted.

3.1.6. Stereotactic Body Radiation Therapy (SBRT) for lung metastases

The NHS National Radiotherapy Implementation Group Report summarized eight case series of patients treated with SBRT for lung metastases from different tumours.[21] The number of patients with a colorectal tumour included is unclear. A review of the literature reported grade 3 to 5 toxicity in up to 15% of patients, with a mortality rate of 0.3%. Stated 2 year survival ranged from approximately 40% to 73% and 90%. Survival appears to depend on prognostic factors such as the number of lung metastases, extra-thoracic disease and length of prior disease-free interval.

The HTA report by Agency for Healthcare Research and Quality (AHRQ)[20] identified 68 studies, none of them with a comparison group, on lung tumours and lung metastases reporting similar results. Reported side effects were the following grade 1–4 toxicities, rash, pneumonitis, cough, rib fracture, pneumothorax,(fiducial placements), chest wall pain, fatigue, nausea, interstitial lung tissue changes, shortness of breath, dermatitis, pleural effusion, fibrosis.

Search for recent publications could not identify any reports on treatment of lung metastases from colorectal cancer with stereotactic radiotherapy. Update for lung metastases in general is considered out of the scope of this guideline.

Conclusion

- In CRC patients with limited lung metastases, an effect of stereotactic body radiotherapy on overall survival could neither be demonstrated nor refuted.

3.1.7. Resection of lung metastases

Gonzalez et al. 2012[23] did a meta-analysis of 25 series that included more than 40 patients each, with a total number of 2925 patients. Overall 5-year survival after complete resection of lung metastases ranged from 27 to 68 %, median survival ranged from 18 to 72 months. Associated with poor survival were:

(1) a short disease-free interval between primary tumour resection and development of lung metastases (HR 1.59, 95 % confidence interval [CI] 1.27–1.98);

(2) multiple lung metastases (HR 2.04, 95 % CI 1.72–2.41);

(3) positive hilar and/or mediastinal lymph nodes (HR 1.65, 95 % CI 1.35–2.02);

(4) elevated pre-thoracotomy carcinoembryonic antigen (HR 1.91, 95 % CI 1.57–2.32).

Schule et al. 2012[24] reported on 65 patients who underwent surgery for liver and lung metastases. Five- and 10-year survival rates for all patients are 57% and 15 % from diagnosis of the primary tumour, 37% and 14 % from resection of the first metastasis and 20% and 15 % from resection of the second metastasis. After complete resection, 5- and 10-year survival rates increased to 61% and 18 %, 43% and 17 % as well as 25% and 19 %, respectively. Long-term survivors (≥ 10 years) were seen only after complete resection of both metastases. Complete resection was achieved in 51 patients (79 %) and was less likely in patients with synchronous disease (p = 0.017). Negative margins (p = 0.002), the absence of pulmonary involvement in synchronous metastases (p = 0.0003) and single metastases in both organs (p = 0.036) were associated with a better prognosis.

Hirosawa et al. 2012[25] reported on 266 CRC patients undergoing complete pulmonary resection collected from 19 institutions. The cumulative 2- and 5-year survival rates of the patients who underwent pulmonary resection were 76.6 and 46.7 %, respectively. The independent unfavourable prognostic factors after pulmonary resection included stage T4 (p = 0.0004) and N2 (p = 0.0082) as primary cancer-related factors, and more than three metastases (p = 0.0342), bilateral distribution (p = 0.0450), metastatic disease-free interval (DFI) of less than 2 years (p = 0.0257), and a preoperative carcinoembryonic antigen (CEA) level greater than 5.0 ng/mL (p = 0.0209) as pulmonary metastases-related factors.

Gonzalez et al. 2012[26] reported on a retrospective analysis of 27 consecutive patients (median age 62 years; range: 33-75 years) who underwent resection of pulmonary metastases after previous hepatic metastasectomy from CRC in two institutions from 1996 to 2009. All patients underwent complete resection (R0) for both colorectal and hepatic metastases. Median follow-up was 32 months (range: 3-69 months) after resection of lung metastases and 65 months (range: 19-146 months) after resection of primary CRC. Three- and 5-year overall survival rates after lung surgery were 56 and 39%, respectively, and median survival was 46 months (95% CI 35-57). Median disease-free survival after pulmonary metastasectomy was 13 months (95% CI 5-21). At the time of last follow-up, seven patients (26%) had no evidence of recurrent disease and 6 of these 7 patients presented initially with a single lung metastasis.

Tampellini et al. 2012[27] reported on a retrospective cohort comprising of 155 patients with pulmonary and extra-pulmonary metastases; 104 patients with LM only and no surgery and 50 patients with LM only and submitted to surgery. Median progression-free survival (PFS) times were: 10.3 months, 10.5 months, and 26.2 months for the 3 respective groups. Median overall survival times were 24.2 months, 31.5 months, and 72.4 months, respectively. Survival times were longer in resected patients: 17 survived >5 years and three survived >10 years. In patients with LM only and no surgery, four survived for 5 years and none survived >10 years. In a Cox regression model, adjusting for some confounders, lung surgery was associated with longer progression free survival HR (0.46, 95% CI.0.31 - 0.57) and overall survival HR (0.26, 95% CI.0.06 0.47). Although the authors attempted an adjustment for confounders, characteristics of patients undergoing lung surgery and not undergoing lung surgery is very different and it is unclear how much residual confounding persists.

Marin et al. 2013[28] reported on 44 patients who were strictly selected for pulmonary resection. There was no postoperative mortality and the morbidity rate after pulmonary resection was 1.8%. No patient was lost to follow-up. Overall survival was 93% at 1 year, 81% at 3 years, and 64% at 5 years. Factors related to poor prognosis in the univariate analysis were presence of more than 1 pulmonary metastasis (p = 0.04), invasion of the surgical margin (p = 0.006), and administration of neoadjuvant chemotherapy (p = 0.01 for hepatic metastases and p = 0.02 for pulmonary metastases).

Lida et al. 2012[29] retrospectively analyzed 1030 patients who underwent pulmonary metastasectomy for colorectal cancer from 1990 to 2008. Overall 5-year survival was 53.5%. Median survival time was 69.5 months. Univariate analysis showed tumour number (P < 0.0001), tumour size (P < 0.0001), pre-

thoracotomy serum CEA level (P < 0.0001), lymph node involvement (P < 0.0001), and completeness of resection (P < 0.0001) to significantly influence survival. In multivariate analysis, all remained independent predictors of outcome.

A randomised controlled trial funded by Cancer Research UK.PulMiCC (Pulmonary Metastasectomy in Colorectal Cancer), were patients will be randomly allocated to 'active monitoring' or 'active monitoring with pulmonary metastasectomy' is ongoing, no results are published until now however[30].

Conclusion

- There is insufficient evidence in favour or against the resection of lung metastases from colorectal cancer.

APPENDICES

APPENDIX 1. SEARCH FOR EVIDENCE

Appendix 1.1. Search strategy

– Date	22-10-2012
Database	Medline via OVID (systematic review)
Search Strategy	exp Colorectal Neoplasms/ (136077) 2 (colo$ adj5 cancer$).tw. (79884) 3 (colo$ adj5 neoplas$).tw. (5382) 4 (colo$ adj5 carcin$).tw. (32925) 5 (colo$ adj5 tumo$).tw. (22677) 6 (colo$ adj5 metasta$).tw. (15658) 7 (colo$ adj5 malig$).tw. (4641) 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (169211) 9 exp Neoplasm Metastasis/ (145489) 10 (Metasta$ adj5 hepa$).mp. (11558) 11 (Metasta$ adj5 liver$).mp. (21611) 12 hepa$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (617480) 13 9 and 12 (7392) 14 liver$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (808269) 15 9 and 14 (14292)

16	*liver neoplasm/sc (9050)
17	(Metasta$ adj5 lung$).mp. (20793)
18	(Metasta$ adj5 pulm$).mp. (9646)
19	lung$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (576258)
20	9 and 19 (23306)
21	pulm$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (486379)
22	9 and 21 (5727)
23	*lung neoplasm/sc (6848)
24	10 or 11 or 13 or 15 or 16 (39963)
25	17 or 18 or 20 or 22 or 24 (77389)
26	24 or 25 (77389)
27	8 and 26 (14658)
28	liver/su (5471)
29	lung/su (3849)
30	exp neoplasm metastasis/th (1147)
31	resect$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (206282)
32	surg$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1359109)
33	excis$.mp. (134552)
34	remov$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (402602)
35	metastatect$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (69)
36	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (1820940)
37	exp Ablation Techniques/ (82879)
38	RFA.mp. (2628)
39	(radiofreq$ adj5 ablat$).mp. (9809)

40 37 or 38 or 39 (84801)

41 exp Radiotherapy/ (126945)

42 radiothera$.mp. (159648)

43 *radiosurgery/ (6103)

44 *stereotaxic techniques/ (5159)

45 (intervention$ adj5 radiol$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (6869)

46 41 or 42 or 43 or 44 or 45 (196212)

47 exp radioisotopes/ (226765)

48 chemoembolization, therapeutic/ (3039)

49 (vena adj3 porta adj3 emboli$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (0)

50 (port$ adj3 vein$ adj3 occlus$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (445)

51 radioembol$.mp. (321)

52 microspheres.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (28275)

53 (drug adj3 eluting adj3 beads).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (108)

54 (radio$ adj5 isot$).mp. (10250)

55 yttrium$.mp. (5535)

56 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 (264056)

57 36 or 40 or 46 or 56 (2237149)

58 27 and 57 (7498)

59 exp animals/ not humans.sh. (3799729)

60 58 not 59 (7154)

61 limit 60 to yr="2009 -Current" (1634)

	62 meta-analysis/ (37222) 63 meta analy$.tw. (43058) 64 metaanaly$.tw. (1118) 65 meta analysis.pt. (37222) 66 (systematic adj (review$ or overview$)).tw. (34831) 67 exp review literature/ (1752591) 68 62 or 63 or 64 or 65 or 66 or 67 (1786210) 69 61 and 68 (278)
Note	

date	**January Week 2 2013**
Database	Medline via OVID update systematic reviews
Search Strategy	1 exp Colorectal Neoplasms/ (134723) 2 (colo$ adj5 cancer$).tw. (78550) 3 (colo$ adj5 neoplas$).tw. (5309) 4 (colo$ adj5 carcin$).tw. (32423) 5 (colo$ adj5 tumo$).tw. (22267) 6 (colo$ adj5 metasta$).tw. (15497) 7 (colo$ adj5 malig$).tw. (4601) 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (167265) 9 exp Neoplasm Metastasis/ (144532) 10 (Metasta$ adj5 hepa$).mp. (11520) 11 (Metasta$ adj5 liver$).mp. (21555) 12 hepa$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (611630)

13 9 and 12 (7331)

14 liver$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (799654)

15 9 and 14 (14220)

16 *liver neoplasm/sc (9056)

17 (Metasta$ adj5 lung$).mp. (20531)

18 (Metasta$ adj5 pulm$).mp. (9561)

19 lung$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (569363)

20 9 and 19 (23046)

21 pulm$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (482098)

22 9 and 21 (5664)

23 *lung neoplasm/sc (6775)

24 10 or 11 or 13 or 15 or 16 (39814)

25 17 or 18 or 20 or 22 or 24 (76818)

26 24 or 25 (76818)

27 8 and 26 (14567)

28 liver/su (5439)

29 lung/su (3880)

30 exp neoplasm metastasis/th (1143)

31 resect$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (205802)

32 surg$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1392332)

33 excis$.mp. (134555)

34 remov$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (399156)

35 metastatect$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (69)

36 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (1846480)

37 exp Ablation Techniques/ (82343)

38 RFA.mp. (2637)

39 (radiofreq$ adj5 ablat$).mp. (9807)

40 37 or 38 or 39 (84272)

41 exp Radiotherapy/ (126892)

42 radiothera$.mp. (162898)

43 *radiosurgery/ (6173)

44 *stereotaxic techniques/ (5127)

45 (intervention$ adj5 radiol$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (6864)

46 41 or 42 or 43 or 44 or 45 (199214)

47 exp radioisotopes/ (224871)

48 chemoembolization, therapeutic/ (3023)

49 (vena adj3 porta adj3 emboli$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (0)

50 (port$ adj3 vein$ adj3 occlus$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (444)

51 radioembol$.mp. (318)

52 microspheres.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (28119)

	53 (drug adj3 eluting adj3 beads).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (101) 54 (radio$ adj5 isot$).mp. (10412) 55 yttrium$.mp. (5516) 56 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 (261970) 57 36 or 40 or 46 or 56 (2261430) 58 27 and 57 (7496) 59 exp animals/ not humans.sh. (3747051) 60 58 not 59 (7157) 61 limit 60 to yr="2009 -Current" (1657)
Note	

Date	**05-12-2012**
Database	Premedline via Ovid
Search Strategy	1 (colo$ adj5 cancer$).tw. (4316) 2 (colo$ adj5 neoplas$).tw. (222) 3 (colo$ adj5 carcin$).tw. (1132) 4 (colo$ adj5 tumo$).tw. (899) 5 (colo$ adj5 metasta$).tw. (885) 6 (colo$ adj5 malig$).tw. (240) 7 1 or 2 or 3 or 4 or 5 or 6 (5628) 8 (neoplasm$ adj5 metasta$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (119) 9 (Metasta$ adj5 hepa$).mp. (529)

10 (Metasta$ adj5 liver$).mp. (931)

11 hepa$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (19466)

12 8 and 11 (8)

13 liver$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (19743)

14 8 and 13 (13)

15 (Metasta$ adj5 lung$).mp. (1124)

16 (Metasta$ adj5 pulm$).mp. (355)

17 lung$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (16406)

18 8 and 17 (25)

19 pulm$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (12978)

20 8 and 19 (7)

21 9 or 10 or 12 or 14 (1271)

22 15 or 16 or 18 or 20 (1383)

23 21 or 22 (2493)

24 7 and 23 (488)

25 ((colo$ or rect$) adj5 surg$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (914)

26 ((colo$ or rect$) adj5 resect$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (737)

27 ((colo$ or rect$) adj5 excis$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (158)

28 ((colo$ or rect$) adj5 remov$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (238)

29 metastatect$.mp. [mp=title, abstract, original title, name of substance word, subject heading word,

	protocol supplementary concept, rare disease supplementary concept, unique identifier] (6) 30 25 or 26 or 27 or 28 or 29 (1749) 31 (ablat$ adj5 techn$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (266) 32 RFA.mp. (264) 33 (radiofreq$ adj5 ablat$).mp. (683) 34 31 or 32 or 33 (920) 35 (rad$ adj5 therap$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (3033) 36 radiothera$.mp. (4232) 37 35 or 36 (6439) 38 radioisotop$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (362) 39 radioembol$.mp. (45) 40 (radio$ adj5 isot$).mp. (237) 41 yttrium$.mp. (714) 42 38 or 39 or 40 or 41 (1314) 43 30 or 34 or 37 or 42 (10194) 44 24 and 43 (174)
Note	

Date	**7 Nov 2012**
Database	EMBASE via Embase.com for systematic reviews
Search Strategy	#44. 'large intestine cancer'/exp OR colo* NEAR/5 (neoplasm* OR cancer* OR tumo* OR malig* OR metasta OR carcin*) AND (metasta* NEAR/5 (hepa*

	OR liver*) OR ('metastasis'/exp AND (hepa* OR liver*)) OR metasta* NEAR/5 (lung* OR pulm*) OR ('metastasis'/exp AND (lung* OR pulm*))) AND ('liver resection'/exp OR 'lung surgery'/exp OR resect* OR surg* OR excis* OR remov* OR metastatec* OR 'ablation therapy'/exp OR rfa OR radiofreq* NEAR/5 ablat* OR ('radiofrequency'/exp AND ablation) OR ('tumor'/exp AND ablation) OR 'radiotherapy'/exp OR radiothera* OR 'radiosurgery'/exp OR 'stereotactic procedure'/exp OR intervention* NEAR/5 radiol* OR 'radioisotope'/exp OR 'chemoembolization'/exp OR ('vena'/exp AND porta AND 'embolization'/exp) OR (portal AND 'vein'/exp AND 'occlusion'/exp) OR radioembol* OR 'microspheres'/exp OR ('drug'/exp AND eluting AND beads) OR radio* NEAR/5 isot* OR 'yttrium'/exp) AND 'meta analysis'/exp AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND [humans]/lim AND [2009-2013]/py
Note	
Date	21 Jan 2013 Search for local therapy
Database	EMBASE via Embase.com
Search Strategy	#1. 'large intestine cancer'/exp OR colo* NEAR/5 (neoplasm* OR cancer* OR tumo* OR malig* OR metasta OR carcin*) AND (metasta* NEAR/5 (hepa* OR liver*) OR ('metastasis'/exp AND (hepa* OR liver*)) OR metasta* NEAR/5 (lung* OR pulm*) OR

	('metastasis'/exp AND (lung* OR pulm*))) AND 'ablation therapy'/exp OR rfa OR radiofreq* NEAR/5 ablat* OR ('radiofrequency'/exp AND ablation) OR ('tumor'/exp AND ablation) OR 'radiotherapy'/exp OR radiothera* OR 'radiosurgery'/exp OR 'stereotactic procedure'/exp OR intervention* NEAR/5 radiol* OR 'radioisotope'/exp OR 'chemoembolization'/exp OR ('vena'/exp AND porta AND 'embolization'/exp) OR (portal AND 'vein'/exp AND 'occlusion'/exp) OR radioembol* OR 'microspheres'/exp OR ('drug'/exp AND eluting AND beads) OR radio* NEAR/5 isot* OR 'yttrium'/exp) AND 'human'/de
Note	
Date	21 Jan 2013 Search for treatment lung metastases
Database	EMBASE via Embase.com
Search Strategy	#large intestine cancer'/exp OR colo* NEAR/5 (neoplasm* OR cancer* OR tumo* OR malig* OR metasta OR carcin*) AND metasta* NEAR/5 (lung* OR pulm*) OR ('metastasis'/exp AND (lung* OR pulm*))) AND ('liver resection'/exp OR 'lung surgery'/exp OR resect* OR surg* OR excis* OR remov* OR metastatec* OR 'ablation therapy'/exp OR rfa OR radiofreq* NEAR/5 ablat* OR ('radiofrequency'/exp AND ablation) OR ('tumor'/exp AND ablation) OR 'radiotherapy'/exp OR radiothera* OR 'radiosurgery'/exp OR 'stereotactic

	procedure'/exp OR intervention* NEAR/5 radiol* OR 'radioisotope'/exp OR 'chemoembolization'/exp OR ('vena'/exp AND porta AND 'embolization'/exp) OR (portal AND 'vein'/exp AND 'occlusion'/exp) OR radioembol* OR 'microspheres'/exp OR ('drug'/exp AND eluting AND beads) OR radio* NEAR/5 isot* OR 'yttrium'/exp) AND 'human'/de

Date	**25-10-2012**	
Database	Cochrane Library	
Search Strategy	ID	Search
	#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees
	#2	MeSH descriptor: [Neoplasm Metastasis] explode all trees
	#3	hepa* or liver*
	#4	#2 and #3
	#5	metasta* adj5 hepa*
	#6	metasta* adj5 liver*
	#7	MeSH descriptor: [Liver Neoplasms] explode all trees and with qualifiers: [Secondary - SC]
	#8	#4 or #5 or #6 or #7
	#9	lung* or pulm*
	#10	#2 and #9
	#11	metasta* adj5 lung*
	#12	MeSH descriptor: [Lung Neoplasms] explode all trees and with qualifiers: [Secondary - SC]
	#13	#10 or #11 or #12
	#14	#8 or #13
	#15	#1 and #14
	#16	MeSH descriptor: [Specialties, Surgical] explode all trees
	#17	MeSH descriptor: [Liver] explode all trees and with qualifiers: [Surgery - SU]

#18	MeSH descriptor: [Lung] explode all trees and with qualifiers: [Surgery - SU]
#19	MeSH descriptor: [Neoplasm Metastasis] explode all trees and with qualifiers: [Therapy - TH]
#20	resect* or surg* or excis* or remov* or metastatect*
#21	#16 or #17 or #18 or #19 or #20
#22	MeSH descriptor: [Ablation Techniques] this term only
#23	MeSH descriptor: [Laser Therapy] this term only
#24	MeSH descriptor: [High-Intensity Focused Ultrasound Ablation] this term only
#25	RFA*
#26	radiofreq* adj5 ablat*
#27	#22 or #23 or #24 or #25 or #26
#28	MeSH descriptor: [Radiotherapy] explode all trees
#29	radiothera*
#30	MeSH descriptor: [Radiosurgery] explode all trees
#31	MeSH descriptor: [Stereotaxic Techniques] explode all trees
#32	radiol* adj5 intervention*
#33	#28 or #29 or #30 or #31 or #32
#34	MeSH descriptor: [Radioisotopes] explode all trees
#35	MeSH descriptor: [Chemoembolization, Therapeutic] explode all trees
#36	vena adj3 porta adj3 emboli*
#37	port* adj3 vein* adj3 occlus*
#38	radio* adj5 isot*
#39	radioembol*
#40	MeSH descriptor: [Microspheres] explode all trees
#41	drug adj3 eluting adj3 beads
#42	yttrium*
#43	#34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42
#44	#21 or #27 or #33 or #43
#45	#15 and #44

Note

APPENDIX 2. QUALITY APPRAISAL SYSTEMATIC REVIEWS

	1	2	3	4	5	6	7	8	9	10	11	Selected	Excluded	Type of exclusion	Reason for exclusion
Abdel-Misih SR, et al. 2009			No										x	Design	Narrative review
Baumgaertner I, et al. 2010	No	Can't	Can't	Can't	No	No	No	**No**	NA	No	No		x	Design	Narrative review
Bhardwaj N, et al. 2010													x	Design	Narrative review
Boutros C, et al. 2010													x	Design	Narrative review
Cao C, et al. 2009													x	Population	
Carter, et al. 2010	Can't	Yes	Yes	Yes	Yes	No	Yes	**Yes**	Yes	Yes	Can't	x			
Carpizo DR, et al. 2009	No	No	No										x	Design	Narrative review
Chen J, et al. 2011	No	Yes	Yes	No	No	Yes	Can't	**Can't**	Yes	Yes	No		x	Intervention	
Chua TC, et al. 2010	Can't	Yes	No	Yes	No	Yes	No	**No**	Can't	No	No		x	Design	No systematic search (1 database); no assessment scient quality
Cirocchi R, et al. 2012	Can't	Yes	Yes	Yes	Yes	No	Yes	**Yes**	Yes	Yes	Can't	x			
Deleporte A, et al. 2010													x	Design	Narrative review
Ercolani G, et al. 2011	Yes	Yes	Yes										x	Design	Cost-effectiveness study
Fiorentino F, et al. 2010	Can't	Can't	Yes	Yes	No	No	No	**No**	Can't	No	No		x		No quality appraisal of included studies
Gravante G, et al. 2011	Can't	No	Yes	No	No	Yes	No	**No**	Can't	No	No		?		No quality appraisal of included studies
Gregoire E, et al. 2010	No	No	Yes	No	No	No	No	**No**	NA	No	No		x	Design	No quality appraisal of included studies
Gurusamy KS, et al. 2010	Can't	Yes	Yes	No	NA	NA	NA	**NA**	NA	NA	Yes		x	Intervention	
He J, et al. 2010													x	Other 1	No full text available
Hoffmann RT, et al. 2011	No	No	No										x	Design	Narrative review
Hompes D, et al. 2011															full text niet beschikbaar
Jones C, et al. 2011	No	No	Can't	Yes									x	Design	Narrative review
Jones RP, et al. 2012	Can't	Yes	Yes	Yes	No	No	No	**No**	NA	No	No		x	Design	No quality appraisal of included studies

	1	2	3	4	5	6	7	8	9	10	11	Selected	Excluded	Type of exclusion	Reason for exclusion
Khan AZ, et al. 2009	Can't	No	No	No									x	Design	Narrative review
Lam VW, et al. 2012	Can't	Yes	No	Yes	No	No	No	**No**	No	Can't	No		x	Design	No systematic search (1 database); no assessment scientific quality
Lehmann K, et al. 2012	Can't	Yes	No	Yes	No	No	No	**No**	No	Yes	Yes		x	Design	No systematic search (1 database); no assessment scientific quality
Li YJ, et al. 2012													x	Other 1	No full text available
Maithel SK, et al. 2010													x	Design	Narrative review
Mirnezami R, et al. 2011	Can't	Yes	Yes	Can't	No	No	No	**No**	NA	No	No		x	Design	No quality appraisal of included studies
Mocellin S, et al. 2009	Can't	Yes	Yes	Yes	No	No	Yes	**Yes**	Yes	Yes	No	x			
Nelson RL, et al. 2009	Can't	Can't	Yes		Yes	No	Yes	**Yes**	Yes	Yes	No		x		
Neumann UP, et al. 2010	Can't	Can't	Can't	Can't	No	No	No	**No**	NA	No	No		x	Design	Narrative review
Nguyen KT, et al. 2010													x	Design	Narrative review
Ni TG, et al. 2010													x	Other 1	No full text available
Pathak S, et al. 2011	Can't	Yes	Yes	Yes	No	No	No	**No**	NA	No	No		x	Design	No quality appraisal of included studies
Pfannschmidt J, et al. 2010	Can't	No	No	No	No	Yes	No	**No**	Can't	No	No		x		No systematic review; no quality appraisal of included studies
Poulou LS, et al. 2009	Can't	Yes	No	Can't	No	Yes	No	**No**	Yes	No	No		x		No quality appraisal of included studies
Quan D, et al. 2012	Can't	No	Yes	Yes	No	No	No	**No**	NA	No	No		x	Design	Narrative review
Rizell M, et al. 2010	Yes	Yes	Yes	Can't	Yes	No	Yes	**Can't**	NA	No	No	x			
Robinson S, et al. 2011	Yes	No	Yes	Yes	No	No							x	Design	Narrative review

	1	2	3	4	5	6	7	8	9	10	11	Selected	Excluded	Type of exclusion	Reason for exclusion
Smith MD, et al. 2009	No	No	Yes	No	No	Yes	Yes	**Yes**	Yes	Yes	No		x	Intervention	
Spelt L, et al. 2012	No	No	Yes	No	No	No	No	**No**	NA	No	No		x	Design	No quality appraisal of included studies
Stang A, et al. 2009	Can't	No	No	No	No	No	No	**No**	NA	No	No		x	Design	No systematic review; no quality appraisal of included studies
Stillwell AP, et al. 2010	Can't	Yes	Yes	No	No	No	No	**No**	Yes	No	No		?	Design	No quality appraisal of included studies
Stillwell AP, et al. 2011													x	Design	Narrative review
Tan EK, et al. 2010		Can't	No										x	Design	No comprehensive literature search
Tang JT, et al. 2010	Can't	Yes	Yes	Yes	No	No	No	**No**	Yes	No	No		?	Design	No quality appraisal of included studies
Townsend A, et al. 2009	Can't	Yes	Yes	Yes	No	No	Yes	**Yes**	NA	Yes	No	x			
Vente MA, et al. 2009	Can't	No	Yes	Yes	No	No	No	**No**	NA	No	No		x	Design	No quality appraisal of included studies
Weng M, et al. 2012	Can't	Yes	Yes	Yes	No	Yes	Yes		Yes	Yes			x	Intervention	
Wieser M, et al. 2010	Can't	Yes	Yes	Yes	No	Yes	Yes	**Can't**	Can't	Yes					
Wong SL, et al. 2010	Yes	No	Yes	Yes	No	No	No	**No**	NA	No	No		?	Design	No systematic review (but clinical evidence review); no quality appraisal of included studies
Wu YZ, et al. 2011	Can't	Yes	Yes	No	No	Yes	No	**No**	Yes				?	Design	No quality appraisal of included studies
Fedorowicz Z, et al. 2011	Can't	Yes	Yes	Can't	Yes	Yes	Yes	**Yes**	NA	Yes	No		x	intervention	

APPENDIX 3. EVIDENCE TABLES

Table 5 – Radiofrequency ablation (RFA): systematic review

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Cirrochi 2012[1]	• Design: SR and MA • Sources of funding: Not mentioned • Search date: January 2012 • Searched databases: Medline, Embase, Lilacs, Cochrane, Cochrane register of trials, the Clinical-Trials.gov site • Included study designs: Randomized clinical trials (RCTs), quasi-randomised or controlled clinical trials (CCTs) Observational study designs including comparative	• Patients with colorectal lung metastases (CRLMs) who have no contraindications for RFA. Patients with unresectable extra-hepatic disease • Median FU: not stated	• Intervention: RFA • Comparator: hepatic resection (HR)	• Overall survival: - Aloia 2006 27% in RFA group (30 patients) vs 71% HR group (150 patients) (P < 0.001).. - Berber 2008 30% in RFA group (27 patients) vs 40% in HR group (30 patients) (P = 0.35). - Hur 2009 89.7% in RFA group (25 patients) vs 50.1% in HR group (42 patients) (P = 0.0263). - Kim 2011 31.2% in RFA group (177 patients) vs 45.3% in HR group (278 patients) (P < 0.001). - Lee 2008 38.5% in RFA group (37 patients) vs 65.7% in HR group (116 patients) (P = 0.227). - Otto 2010 48% in RFA group (28	• Marginal recurrence The marginal recurrence was higher in the RFA group vs HR group, respectively: 11/30 vs 8/150 (P = 0.001) Aloia 2006, 8/25 vs 6/42 (P = 0.85) Hur 2009, 3/28 vs 2/82 (P < 0.001) Otto 2010, 7/30 vs 1/59 (P < 0.01) Park 2008, 5/46 vs 2/95 Schiffman 2010, 8/22 vs 0/30 White 2007. • Intrahepatic recurrence The intrahepatic recurrence was higher in the RFA group vs HR group, respectively: 5/30 vs 27/150 Aloia 2006, 8/25 vs 6/42 Hur 2009, 13/30 vs 10/59 Park 2008, 11/46 vs	• Results critical appraisal: High quality review, no pooling attempted due to heterogeneity in population and interventions and the fact that most studies are observational and of relatively poor quality

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	cohort studies comparing RFA to another intervention, single arm cohort studies or case control studies have been included if they have: prospectively collected data, ten or more patients; and have a mean or median follow-up time of 24 months • Number of included studies: 18			patients) vs 51% in HR group (82 patients) (P = 0.930). - Reuter 2009 49% in RFA group (66 patients) vs 45% in HR group (126 patients) (P = 0.31).	10/95 (P=0.026) Schiffman 2010, 1/22 vs 8/30 White 2007.	
			RFA systemic plus CT versus systemic CT alone	In the Ruers study 119 patients were randomised to RFA plus systemic CT or CT alone as first line therapy for metastatic colorectal cancer (Ruers 2010). The median progression free survival was 16.8 months in the RFA + CT group (95% CI, 11.7-22.1) and 9.9 months (9.3- 13.7) in the CT group (P = 0.025). Overall survival (30-months) was 61.7% (95% CI, 48.21-73.93) in the RFA + CT group and 57.6% (44.07-70.39) in the CT group. In eligible patients (RFA + CT; 57 pts, CT; 58 pts) these rates were 64.9% (95% CI, 51.13-77.09) and		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				56.9% (43.23-69.84), respectively.		
			RFA plus HAI versus RFA plus adjuvant HAI and HR	One study compared RFA with HAI or RFA, adjuvant HAI, and surgical resection alone as first line therapy for metastatic colorectal cancer in 50 patients (Scaife 2003). There was no evidence of disease In 26% (5/19) of patients underwent RFA with HAI and in 35% (11/31) of patients underwent RFA with surgical resection and HAI. Overall survival was 73% (14/19) in RFA with HAI group and 61% (19/31) in patients underwent RFA with surgical resection and HAI.		
			RFA plus HR vs HR vs RFA alone vs chemiotherapy	In 190 patients underwent HR there are the best survival (3-year survival 73%, 4-year 65%, 5-year 58%, P 0.0001). RFA (57 pts.) showed a higher incidence of local		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				recurrence: 84% in RFA only, 63% in RHA + HR, 52% in HR. The survival rate was similar in RFA + hepatic resection (101 pts.) and RFA groups (3 years survival 43% vs. 37%, 4-years 36% vs. 22%, P not significant). The poor results in patients underwent RFA was a consequence of the more advanced stage ("unresectable" CR LM). In RFA resection or RFA the survival was better than after chemotherapy alone (70 pts.) (P 0.0017) (Abdalla 2004)		
			RFA with HR vs CSA plus HR	The use of intraoperative RFA was associated with a lower blood loss (median 500 ml vs 200 ml). The incidence of postoperative complications ablation technique related was higher in patients underwent CSA. In CSA group 3 patients developed a hepatic		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				abscess resolved after percutaneous drainage; in RFA group there was not present complications ablation technique related. The local recurrence was similar in both groups: 14% in the RFA arm and 12% in the CSA arm (Kornprat 2007) .		
			RFA vs HR plus RFA	Four studies (Gleisner 2008, Vyslouzil 2009, McKay 2009; Kim 2011) comparing RFA with HR evaluated the overall survival (OS). In McKay's trial the median survival for RFA and resection in combination with RFA was 2.6 years (95% CI = 1.8 to 3.3 years) vs 2.3 (95% CI = 1.6 to 3.2 years), respectively (McKay 2009).		

Table 6 – Hepatic Arterial Infusion (HAI) for CRC patients with unresectable liver metastases

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Mocellin et al, 2012[4]	• Design: SR and MA • Sources of funding: not mentioned • Search date: Jan 2012 • Searched databases: medline embase Cochrane clinical trials, • Included study designs: RCT • Number of included studies: 10	• Eligibility criteria: Patients with colorectal cancer and unresectable liver metastases • Median FU: not given	• Intervention: HAI • Comparator: systemic chemotherapy	**Overall survival** • All studies Hazard Ratio (Random, 95%CI) 0.90 [0.76, 1.07] • subgroup 99 pts 7 studies Hazard Ratio (Random, 95% CI) 0.81 [0.64, 1.03] • subgroup 65% treated 8 studies Hazard Ratio (Random, 95% CI) 1.02 [0.90, 1.15] • subgroup no crossover 6 studies Hazard Ratio (Random, 95% CI) 0.86 [0.67, 1.10] • subgroup high quality 2 dtudies Hazard Ratio (Random, 95% CI) 0.88 [0.54, 1.44]	**Tumour response** 9 studies 901 patients Risk Ratio (M-H, Fixed, 95%CI) 2.26 [1.80, 2.84]	• Level of evidence: Low level of evidence • Results critical appraisal Good systematic review, large heterogeneity amongst studies together with evolution in control systemic chemotherapy, which has considerably improved

Table 7 – Selective Internal Radiation Therapy (SIRT) for patients with unresectable tumours: systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Townsend,	• Design: SR	• Eligibility criteria:	SIRT & Systemic	Van Hazel 2004 (n=21):	Van Hazel 2004 (n=21):	• Level of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
2009[12]	and MA • Sources of funding: not mentioned • Search date: • Searched databases: • medline embase Cochrane clinical trials, ASCO • Included study designs: RCT • Number of included studies: 2	• Patients with colon cancer & hepatic metastases • • Patient characteristics	chemotherapy OR versus Systemic chemotherapy alone	**Progression Free Survival** Chemo + SIRT: 11.5 months vs. Chemo: 4.6 months. HR: 0.23 (CI 0.08-0.68) **Median Survival** Chemo + SIRT: 29.4 months vs. Chemo: 11.8 months. HR: 0.22 (CI 0.07-0.74) **1-year survival** Chemo + SIRT:82% vs. hemo: 50% **2-year survival** Chemo + SIRT: 64% vs. Chemo: 20% **5-year survival** Chemo + SIRT: 0% vs. Chemo: 0% **Response Rate** Chemo + SIRT: 73% vs. Chemo:0%	increased toxicity with the addition of SIRT to systemic chemotherapy with fluorouracil (with 13 grade 3 or 4 events in the combination group compared with 5 grade 3 or 4 events in the chemotherapy alone group. No effect on quality of life	evidence: very low • High quality review that included 2 small studies with different comparisons of moderate quality, both studies were industry sponsored.
			SIRT & HAI Versus HAI alone	Gray 2001 (n=63) **Progression Free Survival** Chemo + SIRT:7.3 months vs. Chemo: 5.9 months. HR: 0.72 (CI 0. 43-1.21) **Median Survival** Chemo + SIRT:17.6 months vs. Chemo: 15.6 months. HR: 0.62 (CI 0.37-1.05) **1-year survival** Chemo + SIRT:71% vs. Chemo:61% **2-year survival**	Gray 2001 (n=63) no significant increase in toxicity with the addition of SIRT to regional chemotherapy with 23 grade 3 or 4 events reported in both groups, although slightly more patients in the SIRT and regional chemotherapy group experienced grade 1 or 2 nausea or diarrhoea (16 compared with 11 in	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				Chemo + SIRT: 37% vs. Chemo: 29% **5-year survival** Chemo + SIRT: 6% vs. Chemo:0% **Response Rate** Chemo + SIRT: 37% vs. Chemo:14%	the regional chemotherapy alone group). No effect on quality of life	
Rizell, 2010[11]	• Design: SR and MA • Sources of funding: Swedisch government • Search date: jan 2010 • Searched databases: medline, embase, Cochrane, CRD • Included study designs: • RCT & observational • Number of included studies: 24	• Eligibility criteria: • Patients with colon cancer & hepatic metastases	SIRT & Systemic chemotherapy OR SIRT & HAI • Reference standard: Systemic chemotherapy OR SIRT	• 2 RCT's: see Townsend et al, above • Controlled trial: Hong 2009 (n=36) **Median Survival** TACE 7,7 months 90Y-RE 6,9 months **1-year survival** TACE 43% 90Y-RE 34% **2-year survival** TACE 10% 90Y-RE 18% **5-year survival** TACE 10% 90Y-RE 18% • **Case series** Cianni 2009 **Median Survival** 12 months **Complete response Rate** 5 % Gray 2000 **Median Survival**	The dominating adverse effects of radioembolization were nausea, mild abdominal pain and fatigue. Grade 3 - 4 liver toxicity was reported in 2 - 4 % of patients, grade 3 - 4 gastrointestinal toxicity in 5 - 8 %, and grade 3 - 4 bilirubin toxicity in 12 % of patients	• Level of evidence: • Very low • Results critical appraisal HTA report based on a good quality review

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				9.9 months **Complete response Rate** 0 % Kennedy 2006 **Complete response Rate** 0 % Mulcahy 2009 **Median Survival** 14.5 months **Complete response Rate** 0 % Stubbs 2006 **Median Survival** 11 months **1-year survival** 48% **2-year survival** 18% **Complete response Rate** 1 %		

Table 8 – radio-embolization: primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Seidensticker, 2012[18]	• Design: retrospectively matched cohort • Sources of funding: not mentioned • Setting: 3 centres in Germany • • Sample size:29 matched pairs	Patients with chemotherapy-refractory liver dominant metastatic colorectal cancer	• Intervention(s): radioembolization plus best supportive care (BSC) • Comparator(s): *BSC*	• Overall survival: prolonged survival (median, 8.3 vs. 3.5 months; P\0.001) with a hazard ratio of 0.3 (95% confidence interval, 0.16–0.55; P\0.001) in a multivariate Cox proportional hazard model	Treatment-related adverse events: included: grade 1–2 fatigue (n = 20,69%), grade 1 abdominal pain/nausea (n = 14, 48.3%), and grade 2 gastrointestinal ulceration (n=3, 0.3%). Three cases of grade 3 radiation-induced liver disease	• Level of evidence: Low • Results critical appraisal matching criteria: retrospectively matched synchronous/metachronous metastases, tumor burden, increased ALP, and/or CEA [200 U/ml]]
Martin, 2012[17]	• Design: case serie • Sources of funding: Not mentioned • Setting: The Ohio State University (US) • Sample size:24	• Eligibility criteria: Patients with metastatic colorectal cancer	Yttrium-90 (90Y) radioembolization	• Effect size primary outcome Median PFS : 3.9 months (95% CI, 2.4-4.8 months) OS :8.9 months (95% CI, 4.2-16.7 months),	•	Very low level of evidence Case series
Hendlisz, 2010[13]	• Design: open-label RCT • Sources of funding: last author received honoraria from	• Eligibility criteria: • Patients with unresectable chemotherapy-refractory liver-limited metastatic	• Intervention(s): Yttrium-90 (^{90}Y) radioembolizatio n (once) + 5FU protracted IV infusion	• Effect size primary outcome: Median OS: 7.3 months (arm A) vs. 10.0 months (arm B), with a hazard ratio	• Effect size secondary outcome: grade 3 or 4 toxicities observed in 6/22 (27%) pts (arm A;	• Level of evidence: very low • Dropouts/ cross-over: cross-over of 16 pts from arm A to arm B (to receive ^{90}Y

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Sirtex Medical • Setting: Multicenter (n=3), Belgium • Sample size: 44 (after exclusion of 1 pt with bone metastases and 1 pt in whom ^{90}Y was technically not possible • Duration: inclusion of pts between December 2004 and November 2007	CRC, not amenable to curative surgery or local ablation and resistant or intolerant to standard chemotherapy; pst had and ECOG performance status of min 2 and had adequate bone marrow, renal and liver function • Patients characteristics: male: 28/44 (64%); median age 66 y.o.(range: 45-91); 41/44 (93%) had more than 1 hepatic lesion • Median FU: 24.8 months (range: 2-41 months)	(225mg/m² D1-14, cycle 1 and 300mg thereafter (arm B); n=21 • Comparator(s): 5FU protracted IV infusion (300mg/m² D1-14) (arm A); n=23 • Chemotherapy endpoint: disease progression, unacceptable toxicity or withdrawal of consent • cave: pts in arm A with documented progression were permitted to cross-over to receive ^{90}Y radioembolizatio n	of 0.92, 95% CI: 0.47-1.78; median time to liver progression (TTLP): 2.1 months (arm A; with 23 events, all situated in the liver) vs. 5.5 months (arm B; with 18 events), with a hazard ratio of 0.38, 95% CI: 0.20-0.72; median time to tumor progression at any site (TTP): 2.1 months (arm A) vs. 4.5 months (arm B), with a hazard ratio of 0.51, 95% CI: 0.28-0.94; best overall hepatic response: 0/23 (0%) pts vs. 2/21 (9.5%) and disaese control rates (i.e. partial response and stable disease): 8/23 (35%) vs. 18/21 (86%).	2 pts who did not receive therapy were not included) vs. 1/21 (5%) pts (arm B); 16 pts from arm A received further therapies (n=10 ^{90}Y radioembolization monotherapy, n=5 cetuximab + chemo and n=1 chemo) vs. 9 pts from arm B (n=3 cetuximab + chemo, n=4 chemo, n=1 palliative brain radiotherapy and n=1 unspicified therapy)	radioembolization); local progression in 4 pts from arm B after unjustified change in the treatment allocated by randomization. • Results critical appraisal: trial was prematurely closed (with the number of enrolled patients lower than required (based on power analysis)); open-label design; liver progression not documented in 3 pts of arm B; in 4 pts from arm B there was an unjustified change in the treatment allocated by randomization;

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Bester, 2012[16]	• Design: comparative retrospective cohort study • Sources of funding: first author is a paid consultant of Sirtex Medical • Setting: referral centre for radioembolization, Australia • Sample size: n= 224 with metastatic CRC who underwent radioembolization and n= 29 with metastatic CRC who underwent standard care (also data on non-CRC pts reported in manuscript) • Duration: inclusion of pts bw February 2006 and	• Eligibility criteria: "salvage" patients with CRC with inoperable liver metastasis, with sufficient hepatic reserve and adequate renal function • Patients characteristics: radioembolization group: male: 142/224 (63%); median age 67 y.o. (range: 27-89) • Median FU: immediate, 1 month and 3 months FU data presented (for all patients, i.e. also for those pts who had a non-CRC primary tumor)	• Intervention(s): radioembolization (n= 224) • Comparator(s): standard care (i.e. conservative treatment or continued supportive care)(n= 29)	• median OS: embolization group 11.9 months (95% CI: 10.1-14.9 months) vs. standard care group: 6.6 months (no 95% CI mentioned), log-rank test: P=0.001.	• outcome: adverse effects only reported for CRC and non-CRC pts together	• Level of evidence: Very low • Dropouts: not mentioned • Results critical appraisal: retrospective design; some (exact number not reported) pts received more than one radioembolization session and only the first treatment was considered in the analysis; no data on drop-out; data on adverse effects not reported for CRC pts only; short FU (i.e. 3 months); comparison group is very small (and good comparator?)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	February 2011					
Kosmider, 2012[15]	• Design: retrospective case series • Sources of funding: 2 co-authors are paid members of the advisory board of Sirtex Medical • Setting: 2 hospitals in Australia • Sample size: n= 19 • Duration: treatment bw Jan 2002 and Oct 2008	• Eligibility criteria: Pts with unresectable liver metastases from CRC, with good performance status, with adequate renal, hemopoietic and liver function • Patients characteristics: male: 16/19 (84%); median age: 62 (range: 44-75); 18 pts had stage IV disease and 1 pat had had FOLFOX chemo for node-positive colon cancer and after 16 months he had a liver meta; median metastatic liver envolvement: 40%; n= 5 with lung meta • FU at 1, 3 and 6 months	• Intervention(s): ^{90}Y radioembolizatio n (on day 3 or 4 of cycle 1) in combination with chemotherapy (oxaliplatin-based (n= 12) or 5-fluorouracil (n=7), at clinician's discretion and according to local protocols); chemo was continued for a maximum of 6 months. • Comparator(s): /	• Effect size primary outcome: median OS: 29.4 months (in liver-only disease: 37.8 months vs. 13.4 months in pts with extra-hepatic disease, p=0.03); median PFS: 10.4 months (in liver-only disease: 10.7 months vs. 3.6 months in pts with extra-hepatic disease, p=0.09); overall tumor response: complete response in 2 pts (11%), partial in 14 (74%), stable disease in 1 (5%) and progressive disease in 1 (5%).	• Effect size secondary outcome: median time to best response: 4.4 months; adverse effects after 0-4 weeks: fever as part of the post-RE syndrome febrile (n=7), neutropenia (n=1, gr 3), abdominal pain (n=4, gr 2 and n=3 gr 3), fatigue (n=6, gr 2 and n=4, gr 3); after 4-12 weeks: bilirubin (n=4, gr 2 and n=1, gr 3), aspartate aminotransferase (n=4, gr 2, n=1, gr 3), alkaline phophatase (n=4, gr 2 and n=1, gr 3), gastritis (n=2, gr 2 and n=4, gr 3), gastric ulceration (n=1, gr 4), liver	• Results critical appraisal: retrospective design; small sample size; no control arm; short term follow-up;

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					dysfunction (n=4, gr 2 and n=1, gr 5 (=death)), anorexia (n=6, gr 2, n=3, gr 3 and n=1, gr 4), ascites (n=4, gr 2 and n=1, gr 3); after 12-24 weeks (mainly related to chemotherapy): neuropathy (n=2, gr 2 and n=1, gr 3), hand-foot disease (n=1, gr 3)	
Chua, 2011[14]	• Design: prospective cohort study • Sources of funding: none reported • Setting: tertiary radioembolization treatment center in Sydney • Sample size: 140 consecutive pts • Period of recruitment:	• Eligibility criteria: Pts with unresectable (i.e. insufficient estimated future liver remnant, vascular invasion, progression under chemotherapy or an unresectable extrahepatic lesion) CRC liver metastases, ECOG performance status of 0-2, adequate	• Intervention(s): ^{90}Y radioembolization (n=133: single treatment and n=7: repeated treatments) with (n= 48/140, 34%) or without (n=92/140, 66%) concomitant or post-radioembolization chemotherapy • Comparator(s): /	median overall survival: 9 months (95% CI: 6.4-11.3); 1-year survival: 42%, 2-year survival: 22% and 3-year survival: 20%; at last follow-up: 103 (74%) pt had died; complete response in 2 (1%) pts, partial response in 43 (31%) pts, stable disease in 44 (31%) and progressive disease in 51 (37%) pts; based on	• no treatment related mortality; early complications (i.e. days 1-30) in 36 (26%) pts: nausea in 7 (5%) pts, vomiting in 1 pt (1%), gastritis in 3 pts (2%), intestinal ulceration in 1 pt (1%) and abdominal pain in 20 (14%) pts; delayed complications in 7	• Results critical appraisal: not explained based on what rationale some pts received chemotherapy; no control arm; short term follow-up;

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	March 2006-May 2009	hematology, renal and hepatic function • Patients characteristics: male: 88/140 (63%); median age: 64 (range: 37-85); colon n=112/140 (80%); extent of liver metastases: 0-25%: 78 (55%), 26-50%: 50 (36%) and 51-75%: 12 (9%) • Median FU: 9 months (range: 1-43)		multivariable analysis sign more favorable treatment response (i.e. complete or partial response) in case of concomitant or post-radioembolization chemotherapy (p= 0.007); based on multivariable analysis sign better overall survival in case of location of primary site in colon (vs. rectum, HR: 1.7, 95%CI: 1.1-2.7, absence of extrahepatic disease (HR: 0.6, 95% CI: 0.4-1.0) and favorable treatment response (HR: 4.6, 95%CI: 2.7-7.8)	(5%) pts: radiation induced liver dysfunction in 3 (2%) pts, intestinal ulceration in 4 (3%) pts and gall bladder and biliary related complication in 1 (1%) pt	

Table 9 – Chemo-embolisaton: systematic reveiws

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Carter, 2010[5]	• Design: SR Sources of funding: • Search date: 2009 • Searched databases: MEDLINE, EMBASE, Science Citation Index, Current Contents and PubMed • Included study designs: RCT & case series • Number of included studies: 2	• Eligibility criteria: Patients with liver metastases from colorectal cancer	• Intervention: *TACE* • Comparator: Any comparator	• Effect size primary outcome Only overall response and side effect reported for two case series: (Aliberti 2006 & Fiorentini 2007)	• Effect size secondary outcome	• Level of evidence: Very low • Results critical appraisal Adequate search strategy but only response rates reported, review only used for reference tracking

Table 10 – Chemo-embolisaton: primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Fiorentini, 2012[6]	• Design: RCT • Sources of funding: not mentioned • Setting: Italy • Sample	• liver metastases in patients with colorectal cancer. • • characteristics: •	• Intervention(s): chemoembolization with Irinotecan eluding beads	• Overall survival Median survival was 22 (95% Confidence Interval CI=21-23) months, for DEBIRI and 15 (95% CI=12-18)	Progression-free survival 7 (95% CI=3-11) months in the DEBIRI group compared to 4 (95% CI=3-5) months in the	• Level of evidence: low Unclear randomisation, no or unclear allocation

	size:74			months for FOLFIRI Log rank test: 0.031, HR 0.60 (95 CI 0.37, 0.97)	FOLFIRI group (p=0.006, log-rank). The median time for duration of improvement to quality of life was 8 (95% CI=3-13) months in the DEBIRI group and 3 (95% CI=2-4) months in the FOLFIRI group. (p=0.00002, log-rank). •	concealment, no outcome blinding Effect on overall survival borderline significant, OIS not fulfilled
Vogl, 2009[8]	• Design: case serie • Sources of funding: not mentioned • Setting: Germany • Sample size:463	• Eligibility criteria: • palliative treatment of liver metastases in patients with colorectal cancer. • • characteristics: • Median FU:29 months	• Intervention(s): 3 different chemo-embolization protocols	• Effect size primary outcome The 1-year survival rate after chemo-embolization was 62%, and the 2-year survival rate was 28%. Median survival from date of diagnosis of liver metastases was 38 months and from the start of chemo-embolization treatment was 14 months. There was no statistically significant difference between the three treatment protocols.	• Effect size secondary outcome partial response (68 patients [14.7%]), stable disease (223 patients [48.2%]), and progressive disease (172 patients [37.1%]).	• Level of evidence: very low • followed untill death • Results critical appraisal Case series consisting of patients treated with different protocols with different patients characteristics,
Martin, 2009[7]	• Design: case serie • Sources of funding: not mentioned	• Eligibility criteria: palliative treatment of unresectable liver metastases in patients	• Intervention(s): Transarterial chemoembolization (TACE) using irinotecan-loaded	• Effect size primary outcome Median disease free survival from the time of first treatment: 247 days	• Effect size secondary outcome Treatment response, judged by the RECIST criteria, 71%	• Very low level of evidence • Results critical appraisal

	• Setting: multi-site (US, Chechia Serbia • Sample size:55 • Duration:	with colorectal cancer. • Patients characteristics: • Median FU:	beads	Overall survival from the time of first treatment : 343 days	responded at 3 months, 56% at 6 months, and 40% at 12 months	Case serie with adequate follow up
Albert, 2011[9]	• Design: case serie • Sources of funding: not mentioned • Setting: US • Sample size: 121	palliative treatment of unresectable liver metastases in patients with colorectal cancer.	Intervention(s): Chemoembolization with cisplatin, doxorubicin, mitomycin C, ethiodized oil, and polyvinyl alcohol particles,performed at monthly intervals for 1 to 4 sessions	Median time to disease progression (TTP) in the treated liver was 5 months, and median TTP anywhere was 3 months. Median survival was 33 months from diagnosis of the primary colon cancer, 27 months from development of liver metastases, and 9 months from chemoembolization	2 (2%) partial esponse, 39 (41%) stable disease, and 54 (57%) progression	• Very low level of evidence • Results critical appraisal Case series with adequate follow up
Aliberti 2012[10]	• Design: case serie • Sources of funding: not mentioned • Setting: US • Sample size: 82 •	metastatic colorectal carcinoma to the liver after failing chemotherapy • Median FU:29 months	DC Bead, drug-eluting bead, loaded with irinotecan	• median survival was 25 (range 6-34) months, with progression free survival at 8 (range 4-16) months	• Adverse observed effects were: right upper quadrant pain (40%), fever (80%), nausea (27%) and increased transaminases (70%)	• Very low level of evidence, case series with reported adequate follow up

Table 11 – Resection lung metastases: systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Gonzalez, 2012[23]	• Design: SR Sources of funding: • Search date: nov 2011 • Searched databases: MEDLINE, Included study designs: & case series • Number of included studies: 25	• Eligibility criteria: • Patients with lung metastases and colorectal cancer	• Intervention: *Metastatectomy*	Overall 5-year survival after complete resection of LM ranged from 27 to 68 % Median survival from 18 to 72 months	Associated with poor survival: (1) a short disease-free interval between primary tumor resection and development of LM (HR 1.59, 95 % confidence interval [CI] 1.27–1.98); (2) multiple LM (HR 2.04, 95 % CI 1.72–2.41); (3) positive hilar and/or mediastinal lymph nodes (HR 1.65, 95 % CI 1.35–2.02); (4) elevated prethoracotomy carcinoembryonic antigen (HR 1.91, 95 % CI 1.57–2.32).	• Level of evidence: very low • Results critical appraisal Only case series identified

Table 12 – Resection lung metastases: primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Schule, 2012[24]	• Design: case serie • Sources of	• Patients with liver and lung metastases in	Patients who underwent liver and lung resection	Five- and 10-year survival rates for all patients are 57 and 15 % from	Negative margins (p00.002), the absence	• Level of evidence: very low

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	funding: not mentioned • Setting: Germany • Sample size:65	patients with colorectal cancer.	for colorectal metastases	diagnosis of the primary tumour, 37 and 14 % from resection of the first metastasis and 20 and 15 % from resection of the second metastasis. After complete resection, 5- and 10-year survival rates increased to 61 and 18 %, 43 and 17 % as well as 25 and 19 %, respectively. Long-term survivors ((greater-than or equal to)10 years) were seen only after complete resection of both metastases.	of pulmonary involvement in synchronous metastases (p00.0003) and single metastases in both organs (p00.036) were associated with a better prognosis	Patients with lung and liver metastases
Hirosawa, 2012[25]	• Design: case serie • Sources of funding: not mentioned • Setting: Japan • Sample size:266	Patients with lung metastases and colorectal cancer	Complete resection of the lung metastases	The cumulative 2- and 5-year survival rates of the patients who underwent pulmonary resection were 76.6 and 46.7 %, respectively	T4 tumor stage and N2 tumor stage as primary cancer-related risk factors, and the number of metastases greater than three, bilateral distribution of pulmonary metastases, DFI less than 2 years, CEA level higher than 5.0 ng/mL prior to pulmonary resection as primary cancer-related risk	• Very low level of evidence • Case series

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					factors, were significant predictors of worse survival	
Gonzalez 2012[26]	• Design: case serie • Sources of funding: not mentioned • Setting: Lausanne/Geneva (Switzerland) • Sample size: 23	• patients who underwent prior resection of hepatic CRC metastases • Median follow-up was 32 months (range:3–69 months)	Metastatectomy in the lung	Three- and 5-year overall survival rates after lung surgery were 56 and 39%, respectively, Median survival: 46 months (95% CI 35–57). Median diseasefree survival after metastasectomy : 13 months (95% CI 5–21)	Factors associated with mortality (None statistically significant) : (1) age [60 years; (2) primary tumor stage III/IV; (3) presence of multiple lung metastases, .	Low level of evidence, case series with reported adequate follow up
Tampellini 2012[27]	• Design: Retrospective cohort • Sources of funding: not mentioned • Setting: University of Torine, Italy) • Sample size: 309	• G1, comprised of 155 patients with pulmonary and extrapulmonary metastases; G2, comprised of 104 patients with LM only and no surgery; G3, comprised of 50 patients with LM only and submitted to surgery	Metastatectomy in the lung	No difference in response rates emerged between G1 and G2. Median progression-free survival (PFS) times were: 10.3 months, 10.5 months, and 26.2 months for G1, G2, and G3, respectively. No difference in PFS times was observed between G1 and G2, whereas there was a statistically significant difference between G2 and G3. Median overall survival times were 24.2 months, 31.5 months, and 72.4	. Survival times were longer in resected patients: 17 survived >5 years and three survived >10 years. In patients with LM only and no surgery, four survived for 5 years and none survived >10 years	Low level of evidence, Retrospective cohort with adjustment for confounders, characteristics of patients undergoing lung surgery and not undergoin lung surgery is very different and it is unclear how much residual confounding

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				months, respectively. Survival times were longer in resected patients: 17 survived >5 years and three survived >10 years. In patients with LM only and no surgery, four survived for 5 years and none survived >10 years In a Cox regression model, adjusting for some confounders lung surgery was associated with longer progression free survival HR (0.46, CI.0.31 - 0.57) and overall survival HR (0.26, CI.0.06 0.47)		persists.
Marin 2013[28]	• Design: case serie • Sources of funding: not mentioned • Setting: Lausanne/Geneva (Switzerland) • Sample size: 44	• Patients with lung metastases from colorectal cancer, strict selection criteria established by a panel of liver surgeons, chest surgeons, oncologists, and radiologists	Lung metastatectomy	Overall survival was 93% at 1 year, 81% at 3 years, and 64% at 5 years.	Factors related to poor prognosis in the univariate analysis were presence of more than 1 pulmonary metastasis (p = 0.04), invasion of the surgical margin (p = 0.006), and administration of neoadjuvant chemotherapy (p = 0.01 for hepatic metastases and p = 0.02 for pulmonary metastases).	Low level of evidence, case series with reported adequate follow up

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Lida 2012[29]	• Design: case serie • Sources of funding: not mentioned • Setting: Japan • Sample size: 1013	• patients with CRC lung metastases •	Metastatectomy in the lung	Overall 5-year survival was 53.5%. Median survival time was 69.5 months.	Univariate analysis showed tumor number (P < 0.0001), tumor size (P < 0.0001), prethoracotomy serum carcinoembryonic antigen (CEA) level (P < 0.0001), lymph node involvement (P < 0.0001), and completeness of resection (P < 0.0001) to significantly influence survival. In multivariate analysis, all remained independent predictors of outcome..	Low level of evidence, case series with reported adequate follow up

Table 13 – Stereotactic body radiotherapy (SBRT)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Chang 2011	Case series	Patients with colorectal cancer and liver metastases	*SBRT*	12-month, 18-month, and 24-month OS rates of 72%, 55%, and 38%, respectively	and12-month, 18-month, and 24-month local control rates of 67%, 65%, and 55%, respectively	• Very low level of evidence • Case series

4. REFERENCES

Reference List

1. Cirocchi R, Trastulli S, Boselli C, Montedori A, Cavaliere D, Parisi A, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. Cochrane Database of Systematic Reviews. 2012(6).
2. Weng M, Zhang Y, Zhou D, Yang Y, Tang Z, Zhao M, et al. Radiofrequency Ablation versus Resection for Colorectal Cancer Liver Metastases: A Meta-Analysis. PLoS ONE. 2012;7(9).
3. Ruers T, Punt C, Van Coevorden F, Pierie JP, Borel-Rinkes I, Ledermann JA, et al. 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). Ann Oncol. 2012;23(10):2619-26.
4. Mocellin S, Pasquali S, Nitti D. Fluoropyrimidine-HAI (hepatic arterial infusion) versus systemic chemotherapy (SCT) for unresectable liver metastases from colorectal cancer. Cochrane Database of Systematic Reviews. 2011(3).
5. Carter S, Martin Ii RCG. Drug-eluting bead therapy in primary and metastatic disease of the liver. HPB. 2009;11(7):541-50.
6. Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, et al. 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 Res. 2012;32(4):1387-95.
7. Martin RCG, Robbins K, Tomalty D, O'Hara R, Bosnjakovic P, Padr R, et al. Transarterial chemoembolisation (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: An interim report. World J. Surg. Oncol. 2009;7:80.
8. Vogl TJ, Gruber T, Balzer JO, Eichler K, Hammerstingl R, Zangos S. Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: Prospective study. Radiology. 2009;250(1):281-9.
9. Albert M, Kiefer MV, Sun W, Haller D, Fraker DL, Tuite CM, et al. Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol. Cancer. 2011;117(2):343-52.
10. Aliberti C, Fiorentini G, Muzzio PC, Pomerri F, Tilli M, Dallara S, et al. Trans-arterial chemoembolization of metastatic colorectal carcinoma to the liver adopting DC Bead(registered trademark), drug-eluting bead loaded with irinotecan: Results of a phase II clinical study. Anticancer Res. 2011;31(12):4581-7.
11. Rizell M, Hultborn R, Bernhardt P, Svensson J, Sternby EM, Samuelsson O, et al. 90Yttrium radioembolisation for hepatocellular carcinoma and colorectal liver metastases (Structured abstract). Health Technology Assessment Database. 2010(3).
12. Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer. Cochrane Database of Systematic Reviews. 2009(4).

13. Hendlisz A, Van Den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, et al. 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. J. Clin. Oncol. 2010;28(23):3687-94.
14. Chua TC, Bester L, Saxena A, Morris DL. Radioembolization and systemic chemotherapy improves response and survival for unresectable colorectal liver metastases. J. Cancer Res. Clin. Oncol. 2011;137(5):865-73.
15. Kosmider S, Tan TH, Yip D, Dowling R, Lichtenstein M, Gibbs P. Radioembolization in combination with systemic chemotherapy as first-line therapy for liver metastases from colorectal cancer. J Vasc Interv Radiol. 2011;22(6):780-6.
16. Bester L, Meteling B, Pocock N, Pavlakis N, Chua TC, Saxena A, et al. Radioembolization versus standard care of hepatic metastases: Comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. J. Vasc. Intervent. Radiol. 2012;23(1):96-105.
17. Martin LK, Cucci A, Wei L, Rose J, Blazer M, Schmidt C, et al. Yttrium-90 radioembolization as salvage therapy for colorectal cancer with liver metastases. Clin. Colorectal Cancer. 2012;11(3):195-9.
18. Seidensticker R, Denecke T, Kraus P, Seidensticker M, Mohnike K, Fahlke J, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc. Intervent. Radiol. 2012;35(5):1066-73.
19. Tipton K, Launders JH, Inamdar R, Miyamoto C, Schoelles K. Stereotactic body radiation therapy: scope of the literature. Ann Intern Med. 2011;154(11):737-45.
20. Tipton KN SN, Bruening W, Inamdar R, Launders J, Uhl S, Schoelles K. Stereotactic Body Radiation Therapy: Technical Brief Number 6. 2011.
21. NHS NCAT. National Radiotherapy Implementation Group Report Stereotactic Body Radiotherapy - Clinical Review of the Evidence for SBRT. In. 1 ed; 2010.
22. Chang DT, Swaminath A, Kozak M, Weintraub J, Koong AC, Kim J, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. Cancer. 2011;117(17):4060-9.
23. Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. Risk Factors for Survival after Lung Metastasectomy in Colorectal Cancer Patients: A Systematic Review and Meta-Analysis. Ann Surg Oncol. 2012.
24. Schule S, Dittmar Y, Knosel T, Krieg P, Albrecht R, Settmacher U, et al. Long-term results and prognostic factors after resection of hepatic and pulmonary metastases of colorectal cancer. Int. J. Colorectal Dis. 2012:1-9.
25. Hirosawa T, Itabashi M, Ohnuki T, Yamaguchi N, Sugihara K, Kameoka S. Prognostic factors in patients undergoing complete resection of pulmonary metastases of colorectal cancer: a multi-institutional cumulative follow-up study. Surg. Today. 2012:1-6.
26. Gonzalez M, Robert JH, Halkic N, Mentha G, Roth A, Perneger T, et al. Survival after lung metastasectomy in colorectal cancer patients with previously resected liver metastases. World J Surg. 2012;36(2):386-91.
27. Tampellini M, Ottone A, Bellini E, Alabiso I, Baratelli C, Bitossi R, et al. The role of lung metastasis resection in improving outcome of colorectal cancer patients: Results from a large retrospective study. Oncologist. 2012;17(11):1430-8.
28. Marin C, Robles R, Conesa AL, Torres J, Flores DP, Parrilla P. Outcome of strict patient selection for surgical treatment of hepatic and pulmonary metastases from colorectal cancer. Dis. Colon Rectum. 2013;56(1):43-50.

29. Iida T, Nomori H, Shiba M, Nakajima J, Okumura S, Horio H, et al. Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: A retrospective analysis. Ann. Surg. 2012.

30. Treasure T, Fallowfield L, Lees B, Farewell V. Pulmonary metastasectomy in colorectal cancer: The PulMiCC trial. Thorax. 2012;67(2):185-7.