Table 6: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Abbott, D. E., Cantor, S. B., Hu, C. Y., Aloia, T. A., You, Y. N., Nguyen, S., Chang, G. J., Optimizing clinical and economic outcomes of surgical therapy for patients with colorectal cancer and synchronous liver metastases, Journal of the American College of Surgeons, 215, 262-270, 2012 **Ref Id** 845486 **Country/ies where the study was carried out** US **Study type** Retrospective cohort study **Aim of the study** To "… evaluate outcomes and economic implications of	**Sample size** N=60 simultaneous resection; n=84 staged resection **Characteristics** Age in years, median (IQR) Simultaneous 58 (46-64) Staged 53 (46-61) Male sex, n (%) Simultaneous 40 (67) Staged 49 (58) Primary tumour locations, n (%) Colon Simultaneous 26 (43) Staged 31 (37) Rectum Simultaneous 34 (57) Staged 53 (63) Type of liver resection, n (%) Minor (<3 segments) Simultaneous 40 (67) Staged 21 (25) Major (≥3 segments) Simultaneous 20 (33) Staged 63 (75) ≤5 liver metastases, n (%) Simultaneous 55 (92) Staged 57 (68)	**Interventions** Simultaneous or staged resections were all done at the same centre, with curative intent. RFA was sometimes used if resection was not feasible (the resulting liver remnant would be too low in volume).	**Details** Patient data was accessed from an institutional database. "Overall survival was calculated from the date of operation to the date of death. Recurrence-free survival was calculated from the date of operation to the date of cancer recurrence, either locoregional or systemic, or the date of death from another cause. Statistical analysis Survival was analysed using the Kaplan-Meier method. "Multivariable Cox regression analysis with backward stepwise selection was performed to evaluate the association of variables on overall and recurrence-free survival. Final model variables were surgical strategy, body mass index, type of liver resection, and number of liver metastases. These variables were chosen based on their significance on univariate analysis and/or their importance in surgical decision making and their potential influence on	**Results** Overall survival, median 36 months of follow-up Simultaneous n=60 Staged n=84 Adjusted HR 1.4 95% CI 0.74 to 2.65, p=0.3 Recurrence-free survival, median 36 months of follow-up Simultaneous n=60 Staged n=84 Adjusted HR 1.3 95% CI 0.62 to 1.75, p=0.88	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

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

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

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

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	recurrence of colorectal (“liver only” first metastasization from colorectal) from February 2006 to February 2018 at a single unit. Patients undergoing intraoperative radiofrequency ablation (RFA) with a curative intent were also included. **Exclusion criteria:** Patients with a primary rectal squamocellular carcinoma were excluded.	pancolonoscopy. Liver volume assessment was performed when indicated. Magnetic resonance and positron emission tomography (PET) scan were used to rule out doubtful cases. Intraoperative ultrasound sonography (IOUS) was routinely used during liver surgery. Follow-up was done according to a standardized scheduled program including CT scan or abdominal ultrasound, colonoscopy, and blood test examination. It could be modified according to oncologist’s indications."			
Full citation De Haas, R. J., Adam, R., Wicherts, D. A., Azoulay, D., Bismuth, H., Vibert, E., Salloum, C., Perdigao, F., Benkabbou, A., Castaing, D., Comparison of simultaneous or delayed liver surgery for limited synchronous colorectal metastases, British Journal of Surgery, 97, 1279-1289, 2010 **Ref Id** 846441	**Sample size** Case-matched groups n=26 simultaneous; n=26 staged **Characteristics** Case-matched groups: Age in years, mean (SD) Simultaneous 60 (8) Staged 60 (8) Male sex, n/n Simultaneous 17/26 Staged 17/26 Number of liver metastases, n (%) 1 Simultaneous 15 (58) Staged 15 (58) 2-3	**Interventions** Simultaneous resection of colorectal tumour and liver metastases versus delayed hepatectomy (staged resection), both with curative intent "Simultaneous colorectal and liver resection was considered when both the primary tumour and all metastatic disease could be resected curatively, generally in patients with limited liver disease necessitating a limited hepatectomy (fewer than	**Details** Patient data was accessed from a prospectively collected database. Postoperative follow-up consisted of history, physical examination, serum tumour markers, liver function parameters, abdominal ultrasound 1 month after surgery and every 4 months thereafter. Abdominal and thoracic CT was performed every 8 months. Statistical analysis "To obtain highly comparable groups, a one-to-one case match was performed within the total study population, whereby each patient who had undergone a simultaneous colorectal and hepatic resection was matched with a patient in	**Results** Overall survival at 3 years Simultaneous 67% (n=26) Staged 76% (n=26) p=0.78 Progression-free survival at 1 and 2 years Simultaneous 29% and 13% (n=26) Staged 73% and 52% (n=26) p=0.007 60-day mortality Simultaneous 0/26 Staged 0/26 Postoperative morbidity*	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention

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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Mimeault, R., Shabanafady, W., Balaa, F. K., Jonker, D. J., Asmis, T. R., Martel, G., Patterns of recurrence following selective intraoperative radiofrequency ablation as an adjunct to hepatic resection for colorectal liver metastases, Journal of Surgical Oncology, 110, 734-738, 2014 **Ref Id** 846678 **Country/ies where the study was carried out** Canada **Study type** Retrospective cohort **Aim of the study** To "… analyze the patterns of recurrence following intraoperative radiofrequency ablation (RFA) combined with hepatic resection for patients with colorectal liver metastases" **Study dates** January 2003 to December 2009 **Source of funding** "The Liver and	n=150 treated with resection without RFA **Characteristics** "The median age was significantly lower in the RFA/resection group compared to the resection only group. Chemotherapy was used in a majority of cases, although a greater proportion of RFA/ resection patients had neoadjuvant therapy (79% vs. 43%, P=0.18). Patients who underwent RFA /resection had a greater number of total liver lesions (median of 2 vs. 1 resected lesions, P=0.01; plus median of 1 ablated lesion in RFA/resection)." **Inclusion criteria** "(1) patients who underwent liver resection for CLM with curative intent; (2) histologically proven colorectal carcinoma; (3) the absence of disseminated metastatic disease on preoperative imaging (except lung and/or primary tumor site recurrence where there was also an anticipation to curatively address these lesions); and (4) age >18 years." **Exclusion criteria** None reported.	"Typically, the use of RFA in combination with resection was confined to (1) patients in whom complete resection of disease leaving sufficient hepatic parenchyma to support post-resection liver function was judged borderline or not possible, and (2) patients with tumors localized in the liver in such a way that complete resection was judged overly morbid. The decision to utilize RFA for otherwise resectable lesions was individualized, and took into account various patient-level (age, comorbidities, BMI, underlying liver parenchyma, number of cycles, and type of chemotherapy) and tumor-level factors (size, response to chemotherapy, proximity to major vessels, and/or bile ducts). The decision was based on the surgeon's judgment regarding the perceived morbidity of resection for a given patient in the context of his/her comorbidities, and residual liver size and quality."	Patient data was accessed from the institutional database. Primary endpoint was disease recurrence in the liver. Secondary endpoint was overall survival and recurrence-free survival. Statistical analysis Survival was analysed using the Kaplan-Meier method with log-rank test. Multivariate Cox regression models were constructed, variables were included in the model if they reached a p<0.2 in the univariate regression. Variables with p<0.2 in the univariate analysis: age, pre-operative CEA, primary site, neoadjuvant chemotherapy, median size of metastases, no of resected metastases.	Overall survival, median 35 months of follow-up Resection with RFA n=24 Resection alone n=150 Adjusted HR 1.02 95% CI 0.55 to 1.88, p=0.95 Recurrence-free survival, median 35 months of follow-up Resection with RFA n=24 Resection alone n=150 Adjusted HR 1.51 95% CI 0.94 to 4.42, p=0.08	ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

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Pancreas Unit, Ottawa Hospital, receives unrestricted funding for clinical and administrative support from Sanofi."					
Full citation Gleisner, A. L., Choti, M. A., Assumpcao, L., Nathan, H., Schulick, R. D., Pawlik, T. M., Colorectal liver metastases: Recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation, Archives of Surgery, 143, 1204-1212, 2008 **Ref Id** 847034 **Country/ies where the study was carried out** US **Study type** Retrospective cohort **Aim of the study** "To evaluate outcome following resection alone, combined resection-RFA, and RFA alone."	**Sample size** N=55 resection with RFA; n=192 resection alone **Characteristics** Median age 61 years (IQR 53-69.5) Male sex 169/258 Synchronous disease 71/258 "Patients who underwent resection alone were more likely to have larger tumors (median size, 3.5 cm; IQR, 2.0-5.0 cm) vs patients who underwent resection-RFA (median size, 2.5 cm; IQR, 1.9-4.0 cm) (P=.02). In contrast, patients who underwent resection alone had fewer hepatic metastases (median, 1 metastasis; IQR, 1-2 metastases) than patients who underwent resection-RFA (median, 5 metastases; IQR, 3-6 metastases) (P<.001). Among patients who underwent resection alone, 58.3% had solitary tumors (P<.001). Preoperative systemic chemotherapy was less commonly administered to patients before resection alone (38.0%) vs before resection-RFA (65.5%) (P<.001)." **Inclusion criteria** Patients "… with colorectal liver metastases who were operated on with curative intent were	**Interventions** "Radiofrequency ablation of hepatic lesions was performed at the time of laparotomy according to a standardized treatment algorithm. Intraoperative ultrasonography was used to insert needles into the lesions to be treated by RFA. Radiofrequency ablation was administered using an RFA generator (RITA Model 1500X; Rita Medical Systems, Inc, Fremont, California) with an enhanced device (Starburst XL or XLi, Rita Medical Systems, Inc) wherever applicable." Patients were treated with RFA in combination with resection when "at least 1 hepatic tumor was considered unresectable because of location of the disease, inadequate liver remnant, proximity of tumor to major vascular structures, or the presence of medical	**Details** Patient data accessed from a prospective institutional database. Endpoints of interest were systemic and hepatic recurrence, overall survival and disease-free survival. Statistical analysis - Kaplan-Meier method and log-rank test were used for survival outcomes. "To adjust for relative intergroup differences in known risk factors for disease-free and overall survival, a matched control analysis was performed. Patients who underwent RFA with or without resection (ie, cases) were matched 1:1 with patients who underwent resection alone (ie, controls). Matching was moderately successful in identifying cohorts of patients with comparable age, sex, primary tumor characteristics, and metastatic levels of hepatic disease burden (ie, similar number and size of liver lesions)." Because not all factors that were different among the treatment groups were able to be matched a multivariate Cox regression model was used. "Variables that were significant on	**Results** Overall survival Resection with RFA n=55 Resection alone n=192 Adjusted HR 2.82 95% CI 1.64 to 4.85 Disease-free survival Resection with RFA n=55 Resection alone n=192 Adjusted HR 2.09 95% CI 1.28 to 3.42	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

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

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

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

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

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

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

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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Preoperative chemotherapy: Yes - hepatic resection 66 (81.5%); hepatic resection + RFA 61 (89.7%); No - hepatic resection 15 (18.5%); hepatic resection + RFA 7 (10.3%), p = 0.17 Tumor size (cm): hepatic resection 3.1±2.4; hepatic resection + RFA 2.8±1.6, p = 0.45 Tumor number, median (IQR): hepatic resection 5 (4-7); hepatic resection + RFA 5 (4-10), p = 0.10 **Inclusion criteria:** Not reported specifically. **Exclusion criteria:** Not reported specifically.				
Full citation Mayo, S. C., Pulitano, C., Marques, H., Lamelas, J., Wolfgang, C. L., De Saussure, W., Choti, M. A., Gindrat, I., Aldrighetti, L., Barrosso, E., Mentha, G., Pawlik, T. M., Surgical management of patients with synchronous colorectal liver metastasis: A multicenter international analysis, Journal of the American College of Surgeons, 216, 707-718, 2013	**Sample size** N=329 simultaneous resection; n=675 staged resection (n=647 colorectal first; n=28 liver first) **Characteristics** Age in years, median (SD) Simultaneous 60 (30) Colorectal first 61 (18) Liver first 58 (12) Male sex, n (%) Simultaneous 185 (56) Colorectal first 396 (61) Liver first 17 (61) Primary cancer in rectum, n (%) Simultaneous 91 (28) Colorectal first 170 (26) Liver first 15 (54) Bilateral hepatic disease, n (%)	**Interventions** Simultaneous resection of colorectal cancer and liver metastases versus staged resection (mainly colorectal first)	**Details** Patient data was accessed from a multi-institutional database. No details are provided about follow-up. Statistical analysis: Survival was analysed using the Kaplan-Meier method and log-rank test and multivariate Cox regression analysis.	**Results** Overall survival, median 34 months of follow-up Simultaneous n=329 Staged n=675 Adjusted HR 1.08 95% CI 0.88 to 1.31, p=0.472	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended

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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Labianca, R., Portier, G., Tu, D., Nitti, D., Torri, V., Elias, D., O'Callaghan, C., Langer, B., Martignoni, G., Bouche, O., Lazorthes, F., Van Cutsem, E., Bedenne, L., Moore, M. J., Rougier, P., Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: A pooled analysis of two randomized trials, Journal of Clinical Oncology, 26, 4906-4911, 2008 **Ref Id** 844662 **Country/ies where the study was carried out** Belgium, Canada, France, Italy, Switzerland **Study type** Two phase III RCTs (Federation Francophone de Cancerologie Digestive Trial 9002/Association de Chirugie Hepato-Biliare et de Transplantation Hepatique/Association Universitaire de	n=148 allocated to adjuvant chemotherapy; n=154 allocated to surgery alone **Characteristics** Age in years, median (range) Adjuvant chemotherapy 63 (35-77) Surgery alone 62 (20-82) Male sex, n (%) Adjuvant chemotherapy 80 (58) Surgery alone 89 (64) Age ≥70 years, n (%) Adjuvant chemotherapy 28 (20) Surgery alone 29 (21) Primary tumour in rectum, n (%) Adjuvant chemotherapy 49 (36) Surgery alone 51 (36) Prior chemotherapy, n (%) Adjuvant chemotherapy 39 (28) Surgery alone 38 (28) Site of metastases, n (%) Liver Adjuvant chemotherapy 130 (94) Surgery alone 131 (94) Lung Adjuvant chemotherapy 7 (5) Surgery alone 6 (4) Unknown Adjuvant chemotherapy 1 (1) Surgery alone 3 (2) Number of metastases, median (range) Adjuvant chemotherapy 1 (1-7) Surgery alone 1 (1-4) ≥2 metastases, n (%) Adjuvant chemotherapy 46 (33)	intravenously once daily for 5 days plus DL-leucovorin 200 mg/m² administered intravenously for 5 days (FFCD) or FU 370 mg/m² plus L-leucovorin 100 mg/m² for 5 days (ENG), both given for six cycles at 28-day intervals. Adjuvant chemotherapy started between 10 and 35 days after surgery in the FFCD trial, whereas randomization had to occur within 49 days from surgery and treatment had to begin within 7 days from randomization in the ENG trial."	FFCD trial: randomisation was stratified by the number of metastases (1 or ≥2), maximum size of metastases (≤5 or >5 cm), disease-free interval between primary tumour resection and liver progression (≤1 or >1 year), and prior adjuvant chemotherapy (yes or no). ENG trial: randomisation was stratified by treatment centre, number of metastases (1 or ≥2), disease-free interval between primary tumour resection and liver progression (><6 or ≥6 months), site of resected metastatic disease (liver or lung), and prior adjuvant chemotherapy (yes or no). No other details provided. Follow-up/outcomes Monthly follow-up during the adjuvant chemotherapy treatment. Follow-up visits included taking history, physical examination, assessment of performance status, full blood count, serum biochemistry (and CEA level in the FFCD trial). In the FFCD trial: thereafter evaluation every 3 months until 2 years after randomisation, thereafter yearly including history, physical examination, chest X-ray (chest CT as indicated), abdominal ultrasound, and CEA level. In the ENG trial: thereafter an assessment at 9 months and 12 months from randomisation, then every 6 months until 5 years from randomisation, then yearly,	HR 1.32 95% CI 0.95 to 1.82, p=0.095 (chemotherapy as reference, when calculated* as surgery alone as reference HR 0.76 95% CI 0.55 to 1.05) Median overall survival time Adjuvant chemotherapy 62 months 95% CI 45.2 months to not reached Surgery alone 47.3 months 95% CI 40.6 to 57.2 months Progression-free survival HR 1.32 95% CI 1.00 to 1.76, p=0.058 (chemotherapy as reference, when calculated* as surgery alone as reference HR 0.76 95% CI 0.56 to 1.00) Median progression-free survival time Adjuvant chemotherapy 27.9 months 95% CI 21.0 to 41.9 months Surgery alone 18.8 months 95% CI 14.7 to 23.8 months Grade 3 or 4 adverse events (in FFCD trial)** Adjuvant chemotherapy 20/86 Surgery alone N/A *Calculated by the NGA technical team.	Selection bias Random sequence generation: unclear risk (Details not reported.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: unclear/high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear/high risk (No blinding. Risk of bias depends on the outcomes.) Attrition bias Incomplete outcome data: low risk Reporting bias Selective reporting: low risk Other bias Other sources of bias: - **Other information**

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

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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported. **Source of funding** "No funding was received for this study."					
Full citation Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G. J., Schlag, P. M., Rougier, P., Bechstein, W. O., Primrose, J. N., Walpole, E. T., Finch-Jones, M., Jaeck, D., Mirza, D., Parks, R. W., Collette, L., Praet, M., Bethe, U., Van Cutsem, E., Scheithauer, W., Gruenberger, T., Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial, The Lancet, 371, 1007-1016, 2008 **Ref Id** 848901	**Sample size** See Nordlinger 2013 **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G. J., Schlag, P. M., Rougier, P., Bechstein, W. O., Primrose, J. N., Walpole, E. T., Finch-Jones, M., Jaeck, D., Mirza, D., Parks, R. W., Mauer, M., Tanis, E., Van Cutsem, E., Scheithauer, W., Gruenberger, T., Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial, The Lancet	**Sample size** N=364 randomised; n=182 allocated to perioperative chemotherapy; n=182 allocated to surgery alone. **Characteristics** Age in years, median (range) Perioperative chemotherapy 62 (29-79) Surgery alone 64 (25-78) Male sex, n (%) Perioperative chemotherapy 127 (70) Surgery alone 114 (63) Metachronous liver metastases, n (%) Perioperative chemotherapy 121 (66) Surgery alone 115 (63) Time from diagnosis of primary cancer to diagnosis of liver metastases 2 or more years, n (%) Perioperative chemotherapy 49 (27) Surgery alone 43 (24) Previous adjuvant chemotherapy for primary cancer (without oxaliplatin), n (%) Perioperative chemotherapy 78 (43)	**Interventions** Perioperative chemotherapy. Six cycles of FOLFOX4 (each cycle lasted for 14 days, subsequent cycle starting on day 15): oxaliplatin 85 mg/m², folinic acid 200 mg/m² DL form or 100 mg/m² L form on days 1-2 plus bolus, and fluorouracil 400 mg/m² bolus and 600 mg/m² continuous 22h infusion before and after surgery.	**Details** Randomisation and allocation concealment. Randomisation was done with a minimisation method via a web-based randomisation system at the EORTC coordinating data centre, accessed by authorised investigators. Randomisation was stratified according to centre, previous adjuvant chemotherapy to primary surgery for colorectal cancer, and a risk score developed previously by Nordlinger and colleagues. Follow-up/outcomes Follow-up was done every 3 months for 2 years after the end of the treatment and every 6 months thereafter, including chest radiography, abdominal ultrasound or CT scan, and CEA level. Primary endpoint was progression-free survival (time from randomisation to either progressive or recurrent disease, surgery if metastases were	**Results** Overall survival, median 8.5 years of follow-up (event is death from any cause) Perioperative chemotherapy 107 events, n=182 Surgery alone 114 events, n=182 HR 0.88 95% CI 0.68 to 1.14, p=0.34 Median overall survival Perioperative chemotherapy 61.3 months 95% CI 51.0 to 83.4 months Surgery alone 54.3 months 95% CI 41.9 to 79.4 months Progression-free survival, median 8.5 years of follow-up Perioperative chemotherapy 136 events, n=182 Surgery alone 139 events, n=182	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: low risk. Performance bias Blinding of participants and personnel: unclear/high risk (No blinding.) Detection bias Blinding of outcome assessment: low/high risk (No blinding. Risk of bias depends on the outcome.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat analysis done.) Reporting bias Selective reporting: low risk Other bias Other sources of bias: -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Oncology, 14, 1208-1215, 2013 **Ref Id** 848902 **Country/ies where the study was carried out** Australia, Austria, Belgium, France, Germany, Hong Kong, Italy, Norway, Sweden, the Netherlands, UK **Study type** Phase III RCT (EORTC 40983, NCT00006479) **Aim of the study** To study "… the combination of perioperative chemotherapy and surgery compared with surgery alone for patients with initially resectable liver metastases from colorectal cancer". **Study dates** October 10 2000 to July 5 2004 **Source of funding** European Organisation for Research and Treatment of Cancer, Norwegian and Swedish Cancer Societies, Cancer Research UK, Ligue	Surgery alone 76 (42) **Inclusion criteria** 18-80 years old; WHO performance status ≤2; histologically proven colorectal cancer; 1-4 liver metastases that were resectable; no detectable extrahepatic tumours; primary tumour had to be either previously resected (R0 resection) or judged to be resectable (in case of synchronous metastases). **Exclusion criteria** Previous chemotherapy with oxaliplatin; any history with cancer in the past 10 years (except non-melanoma skin cancer or in-situ cervix cancer); major hepatic insufficiency; an absolute neutrophil count <1.5x10^9/l; serum creatinine more than twice the upper limit of normal; grade >1 of common toxicity criteria for peripheral neuropathy; uncontrolled congestive heart failure; angina pectoris; hypertension; arrhythmia; history of significant neurological or psychiatric disorders, active infection; pregnant or breastfeeding.		deemed not resectable, or death from any cause). Secondary endpoints were overall survival (time from randomisation to death from any cause), tumour resectability and tumour response. Statistical analysis Survival was estimated with the Kaplan-Meier method and log-rank test. Intention-to-treat analysis was done.	HR 0.81 95% CI 0.64 to 1.02, p=0.068 Median progression-free survival Perioperative chemotherapy 20.0 months 95% CI 15.0 to 27.6 months Surgery alone 12.5 months 95% CI 9.7 to 17.7 months Treatment-related mortality Perioperative chemotherapy 3/182 Surgery alone 3/182	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Nationale Contre Cancer, US National Cancer Institute, Sanofi-Aventis (pharmaceutical company which also offered free oxaliplatin supplies).					
Full citation Patrono, D., Paraluppi, G., Perino, M., Palisi, M., Migliaretti, G., Berchialla, P., Romagnoli, R., Salizzoni, M., Posthepatectomy liver failure after simultaneous versus staged resection of colorectal cancer and synchronous hepatic metastases, Il Giornale di chirurgia, 35, 86-93, 2014 **Ref Id** 849099 **Country/ies where the study was carried out** Italy **Study type** Retrospective cohort study **Aim of the study** To "… assess the incidence and risk factros of PHLF (posthepatectomy liver failure) after	**Sample size** N=46 simultaneous resection; n=60 staged resection. **Characteristics** Age in years, mean (SD) Simultaneous 64 (12) Staged 61 (9) Male sex, n/n Simultaneous 24/46 Staged 37/60 Primary cancer in rectum, n (%) Simultaneous 8 (17) Staged 13 (22) Extrahepatic metastases, n (%) Simultaneous 7 (15) Staged 6 (10) ≥3 hepatic metastases, n (%) Simultaneous 13 (28) Staged 28 (47) Metastasis diameter >5 cm, n (%) Simultaneous 17 (37) Staged 19 (32) Preoperative chemotherapy (before liver resection), n (%) Simultaneous 13 (28) Staged 51 (85)	**Interventions** Simultaneous resection of colorectal cancer and liver metastases versus staged resection (colorectal first). Simultaneous resection was proposed to all patients regardless of the location of the primary tumour, except in 5 patients who were considered unfit for simultaneous surgery because of age and comorbidities and underwent staged resection. Apart from these 5, all other patients in the staged resection group were patients who underwent colorectal resection in another hospital before being referred to the study hospital for liver resection. During simultaneous resection, the primary colorectal cancer was resected first, colonic	**Details** Patient data was accessed from an institutional database. Overall survival and disease-free survival were calculated from the rate of liver resection. Statistical analysis Survival was analysed using a multivariate Cox regression model, "propensity score was entered as a covariate to adjust for the differences in patients' characteristics between the treatment groups".	**Results** Overall survival at 3 years Simultaneous 55%; Staged 56%, p=0.802	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate ri sk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
simultaneous vs staged resection of colorectal cancer and hepatic metastases" **Study dates** February 1997 to June 2012 **Source of funding** None reported.	Major hepatectomy, n (%) Simultaneous 22 (48) Staged 42 (70) **Inclusion criteria** Consecutive patients with colorectal cancer and synchronous liver metastases who underwent liver resection **Exclusion criteria** None reported.	anastomosis was done after hepatic resection was completed.			
Full citation Portier, G., Elias, D., Bouche, O., Rougier, P., Bosset, J. F., Saric, J., Belghiti, J., Piedbois, P., Guimbaud, R., Nordlinger, B., Bugat, R., Lazorthes, F., Bedenne, L., Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial, Journal of Clinical Oncology, 24, 4976-4982, 2006 **Ref Id** 849222 **Country/ies where the study was carried out** **Study type**	**Sample size** See Mitry 2008 **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Vallance, A. E., van der Meulen, J., Kuryba, A., Charman, S. C., Botterill, I. D., Prasad, K. R., Hill, J., Jayne, D. G., Walker, K., The timing of liver resection in patients with colorectal cancer and synchronous liver metastases: a population-based study of current practice and survival, Colorectal Disease, 16, 16, 2018 **Ref Id** 850356 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort study **Aim of the study** To "… describe temporal trends and inter-hospital variation in surgical strategy, and to compare longterm survival in a	**Sample size** N=198 simultaneous resection; n=198 staged resection (colorectal resection first). (In the study, n=259 simultaneous resection; n=1301 colorectal resection first in total, however, relevant analysis was conducted between groups that were matched according to baseline characteristics, n shown above) **Characteristics** Characteristic in the whole cohort (characteristics of the matched cohort not reported) Age <60 years, n %) Simultaneous 73 (28) Colorectal first 397 (31) Age >70 years, n (%) Simultaneous 105 (41) Colorectal first 432 (33) Male sex, n (%) Simultaneous 141 (54) Colorectal first 814 (63) Primary site rectum, n (%) Simultaneous 54 (21) Colorectal first 315 (24) Charlson comorbidity score ≥2, n (%) Simultaneous 28 (11) Colorectal first 100 (8)	**Interventions** Simultaneous resection versus colorectal resection first (the study also included a group who underwent liver resection first, however, no relevant results are presented comparing liver first to simultaneous, therefore, data from this group has not been included here)	**Details** Patient data was accessed from National Bowel Cancer Audit (NBOCA). This data was linked to the Hospital Episodes Statistics database. "The NBOCA collects data on all patients with newly diagnosed colorectal cancer in England." Statistical analysis "The potential biases to the survival analysis associated with differences in patient characteristics were accounted for by propensity score matching. Propensity score matching can reduce biases associated with multivariable regression modelling because it restricts the comparison to only those patients eligible for either approach" Survival was compared using the Kaplan-Meier method with log-rank test. Cox regression analysis was performed on the matched cohort.	**Results** Overall survival: Simultaneous n=198; Colorectal first n=198, HR 0.92 (95% CI 0.801 to 1.06).	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Serious risk of bias (Limited reporting on the matched cohort, for example, no sample sizes are reported.)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
propensity score-matched analysis" **Study dates** 1 January 2010 to 31 December 2015 **Source of funding** Healthcare Quality Improvement Partnership	ASA grade 3/4, n (%) Simultaneous 71 (30) Colorectal first 234 (19) Major liver resection, n (%) Simultaneous 40 (15) Colorectal first 535 (41) **Inclusion criteria** Patients with colorectal cancer and synchronous liver-limited metastases undergoing elective colorectal cancer and liver resection **Exclusion criteria** Emergency colorectal cancer surgery; extrahepatic disease at diagnosis				
Full citation Van Amerongen, M. J., Van Der Stok, E. P., Futterer, J. J., Jenniskens, S. F. M., Moelker, A., Grunhagen, D. J., Verhoef, C., De Wilt, J. H. W., Short term and long term results of patients with colorectal liver metastases undergoing surgery with or without radiofrequency ablation, European Journal of Surgical Oncology, 42, 523-530, 2016 **Ref Id** 850362	**Sample size** N=98 resection + RFA; n=534 resection alone **Characteristics** Age in years, median (range) Resection + RFA 64 (37-82) Resection alone 65 (31-89) Male sex, n (%) Resection + RFA 63 (64) Resection alone 343 (64) Neoadjuvant chemotherapy, n (%) Resection + RFA 71 (72) Resection alone 170 (32) "Patients were more frequently categorized as ASA class II in combination group as compared to ROG (resection only group), making the average ASA classification of these patients lower (P=0.04). However, there was no further difference in the total presence of	**Interventions** "The main reason to perform RFA was a limited future liver remnant, e.g., excessive loss of parenchyma due to resection because of multifocal disease or ill located lesions which would provide a disproportionate parenchyma loss compared to the tumor size." "With the use of ultrasound, a Cool-Tip(Covidien, Boulder, CO, USA) was placed in the target lesion to achieve complete ablation with a 1 cm margin. Depending on the size of the lesion, a single probe (lesions	**Details** Data collection - Patient data was accessed from a prospective institutional database. Follow-up - Clinical examination and CEA level measurement were done every 4 months. Imaging (ultrasound, CE-CT of chest and abdomen) was performed in different schedule in the two study centres. In one centre: normally every 4 months in the first year, every 6 months for the second year and annually thereafter. In the second centre: every 3 months in the first 3 years, and every 6 months for the next 2 years (up to 5 years). Disease-free survival was defined as the time between hepatic treatment and first disease recurrence. Overall survival was defined as the time between treatment and death.	**Results** Overall survival Resection + RFA n=98 Resection alone n=534 Adjusted HR 1.55 95% CI 1.07 to 2.25, p=0.02 Disease-free survival Resection + RFA n=98 Resection alone n=534 Adjusted HR 1.01 95% CI 0.73 to 1.39, p=0.95	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Serious risk of bias (Confounding expected and controlled for but certain important potential confounders were not included in the multivariate model) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended

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

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

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

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

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

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

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

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

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

residual tumour in the resection margin; R2: macroscopic residual tumour in the resection margin; RCT: randomised controlled trial; RFA: radiofrequency ablation; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions; ROG: resection only group; SD: standard deviation; WHO: World Health Organization