National Institute for Health and Care Excellence

Final

Colorectal cancer (update)

[D1] Surgery for asymptomatic primary tumour

NICE guideline NG151

Evidence reviews

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Final

Developed by the National Guideline Alliance part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

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Surgery for the asymptomatic primary tumour in people with metastatic colorectal cancer which cannot be treated with curative intent

This evidence review supports recommendation 1.5.1.

Review question

Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?

Introduction

Current clinical practice varies regarding whether or not the asymptomatic primary tumour is resected in patients with metastatic colorectal cancer that cannot be treated with curative intent. If not resected an asymptomatic primary tumour might later cause symptoms such as bleeding, obstruction or perforation. At the same time resection of the asymptomatic primary tumour might cause operative and postoperative morbidity and mortality. The aim of this review is to examine the effect of resecting the primary tumour compared to not resecting the primary tumour on survival, quality of life and rate of complications.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	Adults with an asymptomatic primary tumour with metastatic colorectal cancer which cannot be treated with curative intent
Intervention	Surgical resection of asymptomatic primary tumour
Comparison	• No resection for primary tumour • Chemotherapy • Radiotherapy
Outcomes	**Critical** • Overall survival • Overall quality of life measured using validated scales • Grade 3 or 4 treatment complications • Time to tumour-related complications (obstruction, perforation, bleeding) **Important** • Median survival time • 90-day mortality

For further details see the review protocol in appendix A.

Methods and process

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

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

Clinical evidence

Included studies

Thirteen retrospective cohort studies were included in this evidence review (Ahmed 2015; Alawadi 2017; Benoist 2005; Galizia 2008; He 2016; Matsumoto 2014; Michel 2004; Miyamoto 2014; Ruo 2003; Samalavicius 2018; Seo 2010; Yun 2014; Zhang 2017).

The included studies are summarised in Table 2.

The studies compared surgery of the asymptomatic primary tumour to no resection. Most patients, if not all, in both arms received chemotherapy in all of the studies included in this review.

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

Excluded studies

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

Summary of clinical studies included in the evidence review

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

Table 2: Summary of included studies

Study	Population	Intervention/Comparison	Outcomes
Ahmed 2015 Retrospective cohort study Canada	N=834 people with stage IV adenocarcinoma of colon and rectum with asymptomatic or minimally symptomatic primary tumour	Intervention: primary tumour resection (43% received chemotherapy, 15% received radiotherapy) Comparison: no primary tumour resection (28% received chemotherapy, 15% received radiotherapy)	• Overall survival
Alawadi 2017 Retrospective cohort study USA	N=6735 people with stage IV colon adenocarcinoma People who underwent tumour-directed surgery within 24 hours of diagnosis and those who underwent metastectomy or surgery on other cancer sites were excluded	Intervention: primary tumour resection (77% received chemotherapy of which 6% neoadjuvant) Comparison: no resection (75% received chemotherapy)	• Overall survival

Study	Population	Intervention/Comparison	Outcomes
Benoist 2005 Retrospective cohort study France	N=59 people with colorectal cancer and unresectable synchronous liver metastases and an asymptomatic primary tumour; performance status that allowed treatment by systemic chemotherapy	Intervention: primary tumour resection (100% received chemotherapy) Comparison: no primary tumour resection (100% received chemotherapy)	• Overall survival • Postoperative complications • Tumour-related complications • Median survival time • 30-day mortality
Galizia 2008 Retrospective cohort study Italy	N=65 people with stage IV colorectal cancer, asymptomatic primary tumour and unresectable liver-only metastases	Intervention: primary tumour resection (100% received chemotherapy) Comparison: no primary tumour resection (100% received chemotherapy)	• Overall survival • Postoperative complications • Tumour-related complications • 30-day mortality
He 2016 Retrospective cohort study China	N=210 people with metastatic colorectal cancer at first diagnosis, ECOG performance status ≤2 Patients with intestinal obstruction, enterobiasis or bleeding at first presentation were excluded	Intervention: primary tumour resection (100% received chemotherapy) Comparison: no primary tumour resection (100% received chemotherapy)	• Median survival time
Matsumoto 2014 Retrospective cohort study Japan	N=88 people with synchronous stage IV colon or rectal adenocarcinoma clinically unresectable for cure and asymptomatic primary tumour	Intervention: primary tumour resection (85% received chemotherapy) Comparison: no primary tumour resection (100% received chemotherapy)	• Overall survival • Postoperative complications • Tumour-related complications • Median survival time
Michel 2004 Retrospective cohort study France	N=54 people with stage IV colon or rectal cancer with unresectable liver metastases	Intervention: primary tumour resection (97% received chemotherapy) Comparison: no primary tumour resection (100% received chemotherapy)	• Tumour-related complications • Median survival time • 30-day mortality
Miyamoto 2014 Retrospective cohort study Japan	N=131 people with unresectable stage IV colorectal cancer; no or moderate primary tumour-related symptoms at diagnosis	Intervention: primary tumour resection (100% received chemotherapy) Comparison: no primary tumour resection (100% received chemotherapy)	• Postoperative complications • Tumour-related complications • Median survival time • 30-day mortality
Ruo 2003 Retrospective cohort study	N=127 people with asymptomatic stage IV metastatic colorectal cancer	Intervention: primary tumour resection (chemotherapy not reported) Comparison: no primary tumour resection (83% received	• Postoperative complications • Tumour-related complications • Median survival time

Study	Population	Intervention/Comparison	Outcomes
USA		chemotherapy, 22% received radiotherapy)	• 30-day mortality
Samalavicius 2016 Retrospective cohort study Lithuania	N=183 people with stage IV colorectal cancer with asymptomatic primary tumour and at least one cycle of palliative chemotherapy	Intervention: primary tumour resection (100% received chemotherapy) Comparison: no primary tumour resection (100% received chemotherapy)	• Overall survival
Seo 2010 Retrospective cohort study South Korea	N=227 people with unresectable stage IV colorectal cancer and asymptomatic primary tumour	Intervention: primary tumour resection (100% received chemotherapy) Comparison: no primary tumour resection (100% received chemotherapy)	• Postoperative complications • Tumour-related complications • Median survival time • 30-day mortality
Yun 2014 Retrospective cohort study South Korea	N=226 people with unresectable stage IV colorectal cancer with asymptomatic primary tumour (defined as the absence of obstruction, perforation, or bleeding)	Intervention: primary tumour resection (66% received chemotherapy) Comparison: no primary tumour resection (100% received chemotherapy)	• Tumour-related complications • Median survival time • 30-day mortality
Zhang 2017 Retrospective cohort study China	N=194 people aged 18–75 years; pathologically confirmed colorectal cancer; unresectable synchronous metastases; resectable primary tumour; ECOG performance status of ≤2; no signs and symptoms of intestinal obstruction, perforation, or bleeding; having received a full colonoscopy	Intervention: primary tumour resection (most patients received chemotherapy) Comparison: no primary tumour resection (most patients received chemotherapy)	• Median survival time

ECOG: Eastern Cooperative Oncology Group; N: number

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

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

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

Excluded studies

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

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Critical outcomes

Overall survival

- Low quality evidence from 6 retrospective cohort studies (N=7848; median follow-up 1.3 to 6.4 years) showed that resecting the asymptomatic primary tumour produces a clinically important benefit in overall survival compared to not resecting the asymptomatic primary tumour in people with metastatic colorectal cancer not treatable with curative intent.
- Very low quality evidence from 1 retrospective cohort study (N=230) showed that resecting the asymptomatic primary tumour produces a clinically important benefit in 2 year overall survival compared to not resecting the asymptomatic primary tumour in people with metastatic colorectal cancer not treatable with curative intent.
- Very low quality evidence from 1 retrospective cohort study (N=226) showed no clinically important difference in overall survival at 5 years between people with metastatic colorectal cancer not treatable with curative intent who underwent resection of the asymptomatic primary tumour and those who did not.
- Very low quality evidence from 1 retrospective cohort study (N=194; median 12 follow-up 12 months) showed no clinically important difference in all-cause mortality between people with metastatic colorectal cancer not treatable with curative intent who underwent resection of the asymptomatic primary tumour and those who did not.

Overall quality of life

No evidence was identified to inform this outcome.

Grade 3 or 4 treatment complications

- Low quality evidence from 5 retrospective cohort studies (N=712) showed a clinically important increase in risk of postoperative complications (not all grade 3 or 4 complications) in people with metastatic colorectal cancer not treatable with curative intent who underwent resection of the asymptomatic primary tumour compared to those who did not). The rate of postoperative complications ranged from 18% to 35% in the resection group.
- Very low quality evidence from 2 retrospective cohort studies (N=315) showed a clinically important difference in risk of grade 3 or 4 postoperative complications with metastatic colorectal cancer not treatable with curative intent who underwent resection of the asymptomatic primary tumour compared to those who did not. The rate of grade 3 or 4 postoperative complications was 5% in the resection group and 1.5% in the no resection group (some people in the no resection group later underwent resection of the primary tumour).

Tumour-related complications

- Low quality evidence from 8 retrospective cohort studies (N=1080) showed a clinically important decrease in risk of tumour-related complications requiring surgical treatment in people with metastatic colorectal cancer not treatable with curative intent who underwent

resection of the asymptomatic primary tumour (compared to those who did not). The rate of tumour-related complications requiring surgical treatment ranged from 6% to 29% in the no resection group.

- Very low quality evidence from 1 retrospective cohort study (N=227) showed no clinically important difference in risk of tumour-related complications not requiring surgical treatment between people with metastatic colorectal cancer not treatable with curative intent who underwent resection of the asymptomatic primary tumour and those who did not.

Important outcomes

Median survival time

- Very low quality evidence from 9 retrospective cohort studies (N=1419) showed that the median survival time was 1 to 8 months longer in people with metastatic colorectal cancer not treatable with curative intent who underwent resection of the asymptomatic primary tumour compared to those who did not but the differences were mostly not statistically significant. One of the studies (N=194) looked at subgroups according to site of the tumour and reported that for people with left-sided colon cancer who underwent resection of the primary tumour median survival time was significantly longer than for those who did not undergo resection (difference of 8 months) whereas for those with right-sided colon cancer there was no significant difference between the groups (difference of 2 months).

30-day mortality

- Very low quality evidence from 7 retrospective cohort studies (N=992) showed no difference in 30-day mortality between people with metastatic colorectal cancer not treatable with curative intent who underwent resection of the asymptomatic primary tumour and those who did not.

Economic evidence statements

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

The committee's discussion of the evidence

Interpreting the evidence

Outcomes that matter the most

Overall survival was a critical outcome for decision making because an increase in survival would be a key motivation for resecting an asymptomatic primary tumour when there is also metastatic disease. Treatment and tumour-related complications were also critical outcomes, as the decision about resection should consider the balance between complications due to surgery and future complications caused by the tumour if not resected. Overall quality of life was also a critical outcome because of the impact that treatment decisions might have on patients in general, considering the potential adverse effects that primary tumour resection or no resection might have on the patient.

Median survival time and 90-day mortality were important outcomes for decision making.

The quality of the evidence

Evidence was available for all of the outcomes except quality of life. The quality of the evidence was assessed using GRADE and varied from low to very low quality.

The most common reasons for downgrading the quality of the evidence were methodological limitations affecting the risk of bias, mainly insufficient controlling for potential confounders in

the analysis, and imprecision due to small sample sizes and low event rates causing uncertainty in the effect estimate.

As only observational evidence was available, it is important to consider the comparability of the intervention and comparison groups and whether the findings are attributable to the intervention of interest (resection of primary tumour) or to the differences in the populations compared. The baseline characteristics (for example age or performance status, tumour location, number of metastases, tumour differentiation grade, CEA level) differed in many of the studies. Although not consistent across all studies, in some studies the resection group were perhaps “lower risk” as they were younger, had better performance status, their tumour was more often well differentiated, or they had fewer metastases. However, all of the included studies used multivariable analysis to control for differences in baseline characteristics between treatment groups. However, the committee was aware that the adjusted analyses might not sufficiently control for the differences between the groups and this reduced their confidence in the findings.

One study in particular was discussed. A retrospective cohort study from the US using data from the National Cancer Data Base was by far the largest study included in the review and provided the most evidence on overall survival, the primary outcome of interest. Their analysis on overall survival, which controlled for baseline differences between the groups, showed a clear benefit for the resection group. However, the study also performed analysis that took into account the proportion of patients undergoing resection in different hospitals. This analysis, which appeared to not have been planned a priori, showed no difference in the relative mortality rate at 3 years. The committee took into account these contradictory results but concluded that regardless of this study the pooled result from the other studies still showed a survival benefit for the resection group. In addition, the committee discussed the relevance of the population in this cohort study. Due to the information available in the National Cancer Data Base it was not possible to ensure that only patients with asymptomatic primary tumours and incurable metastases were included. They did, however, exclude patients who had undergone surgery on the primary tumour within 24 hours of diagnosis (in order to minimise inclusion of patients with symptomatic primary tumours) or surgical treatment on other cancers, including metastectomy (in order to minimise inclusion of patients with curable metastatic disease).

Benefits and harms

Taking into account the quality of the evidence, the committee concluded that resection of the primary tumour should be considered as it may be beneficial, provided that the benefits, harms and options are carefully discussed with the patient. Patients with metastatic disease that cannot be treated with curative intent may receive chemotherapy regardless of the resection of the primary tumour. Resection of the asymptomatic primary tumour could be considered in order to prevent tumour-related symptoms, such as obstruction, perforation, bleeding and pain developing later on. The clinical evidence showed that overall survival was better among people who underwent resection of the asymptomatic primary tumour compared to those who did not. However, there is uncertainty how much longer the patients who have had a resection would survive, with the evidence showing up to median of 8 months longer survival time and other studies showing shorter or no difference.

The evidence also showed that around one fifth of the patients who did not undergo resection of the asymptomatic primary tumour ended up developing symptoms related to the primary tumour that were severe enough to require subsequent surgical treatment. The committee discussed that this could often mean an emergency operation that can have higher risks of complications and stoma. Around one quarter of patients undergoing a resection had some postoperative complications, and around 5% had grade 3 or 4 postoperative complications. There was no difference in 30-day mortality between the groups.

The committee emphasised that the benefits, harms, implications and different treatment options and pathways should be discussed with the patient in order to enable an informed decision when considering the resection of an asymptomatic primary tumour. The committee discussed that it would be beneficial to identify those patients who are at a higher risk of developing symptoms, however, this aspect was not covered by this evidence review.

No evidence was identified on quality of life. This is particularly relevant considering the factors which patients and clinicians will need to consider including the risk of developing cancer related bowel symptoms; risks of surgical intervention including morbidity and mortality; and possible differences in other on-going treatments such as chemotherapy.

Despite the lack of RCT data and the lack of data on quality of life, the committee did not make a research recommendation. The committee was aware of several trials in this context which had failed to recruit and that there are several ongoing trials on the topic that in the future may provide randomised evidence. Most of these trials will also collect evidence on quality of life.

Cost effectiveness and resource use

No economic evidence was identified that addressed this topic.

Resection of the asymptomatic primary tumour may increase costs (in comparison to no resection) but this may be offset, at least partially, by the avoidance of primary tumour related symptoms. The evidence suggests that resection of the primary tumour may improve overall survival and so even if the strategy is more costly it could still be cost-effective in cost per QALY terms.

The recommendation would not be anticipated to have a substantial resource impact as it largely reflects current practice.

References

Ahmed 2015

Ahmed S, Fields A, Pahwa P, et al. (2015) Surgical Resection of Primary Tumour in Asymptomatic or Minimally Symptomatic Patients with Stage IV Colorectal Cancer: A Canadian Province Experience. Clinical Colorectal Cancer 14(4): e41-e47

Alawadi 2017

Alawadi Z, Phatak, U, Hu C, et al. (2017) Comparative effectiveness of primary tumour resection in patients with stage IV colon cancer. Cancer 123(7): 1124-1133

Benoist 2005

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Galizia G, Lieto E, Orditura M, et al. (2008) First-line chemotherapy vs bowel tumour resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases. Archives of Surgery 143(4): 352-358

He 2016

He W, Rong Y, Jiang C et al. (2016) Palliative primary tumour resection provides survival benefits for the patients with metastatic colorectal cancer and low circulating levels of dehydrogenase and carcinoembryonic antigen. Chinese Journal of Cancer 35(1): 58

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Matsumoto T, Hasegawa S, Matsumoto S, et al. (2014) Overcoming the challenges of primary tumour management in patients with metastatic colorectal cancer unresectable for cure and an asymptomatic primary tumour. Diseases of the Colon and Rectum 57(6): 679-686

Michel 2004

Michel P, Roque I, Di Fiore F, et al. (2004) Colorectal cancer with non-resectable synchronous metastases: Should the primary tumour be resected? Gastroenterologie Clinique et Biologique 28(5): 434-437

Miyamoto 2014

Miyamoto Y, Watanabe M, Sakamoto Y, et al. (2014) Evaluation of the necessity of primary tumour resection for synchronous metastatic colorectal cancer. Surgery Today 1-6

Ruo 2003

Ruo L, Gougoutas C, Paty P, et al. (2003) Elective bowel resection for incurable stage IV colorectal cancer: Prognostic variables for asymptomatic patients. Journal of the American College of Surgeons 196(5): 722-728

Samalavicius 2016

Samalavicius N, Dulskas A, Baltruskeviciene E, et al. (2016) Asymptomatic primary tumour in incurable metastatic colorectal cancer: Is there a role for surgical resection prior to systematic therapy or not? Wideochirurgia I Inne Techniki Maloinwazyjne 11(4): 274-282

Seo 2010

Seo G, Park J, Yoo S, et al. (2010) Intestinal complications after palliative treatment for asymptomatic patients with unresectable stage IV colorectal cancer. Journal of Surgical Oncology 102(1): 94-99

Yun 2014

Yun J, Huh J, Park Y, et al. (2014) The role of palliative resection for asymptomatic primary tumour in patients with unresectable stage IV colorectal cancer. Diseases of the Colon and Rectum 57(9): 1049-1058

Zhang 2017

Zhang R, Ma W, Gu Y, et al. (2017) Primary tumour location as a predictor of the benefit of palliative resection for colorectal cancer with unresectable metastasis. World Journal of Surgical Oncology 15(1): 138

1 Appendices

2 Appendix A – Review protocol

3 Review protocol for review question: Does surgery for the asymptomatic 4 primary tumour improve outcomes for people with metastatic colorectal 5 cancer, which cannot be treated with curative intent?

6 **Table 3: Review protocol for surgery of asymptomatic primary tumour in** 7 **people with metastatic colorectal cancer, which cannot be treated** 8 **with curative**

Field (based on PRISMA-P)	Content
Review question	Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?
Type of review question	Intervention
Objective of the review	To determine if surgery for the asymptomatic primary tumour improves outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent
Eligibility criteria – population/disease/condition/issue/domain	Adults with an asymptomatic primary tumour with metastatic colorectal cancer which cannot be treated with curative intent
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Surgical resection of asymptomatic primary tumour
Eligibility criteria – comparator(s)/control or reference (gold) standard	• No resection for primary tumour • Chemotherapy • Radiotherapy
Outcomes and prioritisation	Critical outcomes: • Overall survival (minimally important difference [MID]: statistical significance) • Overall quality of life measured using validated scales (MID: published MIDs from literature, see below) • Grade 3 or 4 treatment complications (MID: statistical significance) • Time to tumour-related complications (i.e. obstruction, perforation, bleeding) (MID: statistical significance) Important outcomes: • Median survival time (MID: statistical significance) • 90-day mortality (MID: statistical significance) Quality of Life MIDs from the literature: • EORTC QLQ-C30: 5 points • EORTC QLQ-CR29: 5 points • EORTC QLQ-CR38: 5 points • EQ-5D: 0.09 using FACT-G quintiles • FACT-C: 5 points

	• FACT-G: 5 points • SF-12: > 3.77 for the mental component summary and > 3.29 for the physical component summary • SF-36: > 7.1 for the physical functioning scale, > 4.9 for the bodily pain scale, and > 7.2 for the physical component summary
Eligibility criteria – study design	• Systematic reviews of RCTs • RCTs • Comparative observational studies will only be considered if eligible RCTs are not available

Other inclusion exclusion criteria	Inclusion:
	• English-language
	• All settings will be considered that consider medications and treatments available in the UK
	• Studies published post 1998
	• Observational studies should include multivariate analysis controlling for the following confounding factors:
	  ○ Age
	  ○ Tumour site (rectal or colon)
	  ○ Comorbidity (for example, ASA grade)
	  ○ Performance status
	  ○ Lymph node vs other metastases
	
	Studies conducted post 1998 will be considered for this review question because the guideline committee considered that treatment techniques have evolved and evidence prior to 1998 would no longer be relevant.

Proposed sensitivity/sub-group analysis, or meta-regression	In case of heterogeneity, the following subgroup analyses will be conducted: • Performance status • Site of primary tumour • Lymph node vs other metastases
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.

	NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Potential sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance, but download all results Dates: from 1998
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual **Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs • ROBINS-I for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual

Methods for analysis – combining studies and exploring (in)consistency	**Synthesis of data:** Pairwise meta-analysis of randomised trials will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled if baselines are comparable. If any studies report both, the method used in the majority of studies will be analysed. **Minimally important differences**: The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except quality of life for which published MIDs from literature will be used (see outcomes section for more information).
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan 5 software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Peter Hoskin in line with section 3 of Developing NICE guidelines: the manual Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 1: methods.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

ASA: American Society of Anesthesiologists; CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; EQ-5D: EuroQol five dimensions questionnaire; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items; EORTC QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (29 items); EORTC QLQ-CR38: European Organisation for Research and Treatment of

Cancer Quality of Life Questionnaire colorectal cancer module (38 items); FACT-C: Functional Assessment of Cancer Therapy questionnaire (colorectal cancer); FACT-G: Functional Assessment of Cancer Therapy questionnaire (general); GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; M0: distant metastasis stage; MID: minimal important difference; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis in Protocols; PROSPERO: International prospective register of systematic reviews; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions; ROBIS: a tool for assessing risk of bias in systematic reviews; SF-12: 12-Item Short Form Survey; SF-36: 36-Item Short Form Survey

Appendix B – Literature search strategies

Literature search strategies for review question: Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?

Databases: Embase/Medline

Last searched on: 12/02/2019

#	Search
1	(exp colorectal cancer/ or exp colon tumour/ or exp rectum tumour/) use emez
2	exp colorectal neoplasms/ use ppez
3	((colorect* or colo rect* or colon or colonic or rectal or rectum) adj3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)).tw.
4	or/1-3
5	metastasis/ use emez
6	neoplasm metastasis/ use ppez
7	(stage IV or stage 4 or advanc*).tw.
8	((unresect* or inopera* or untreat* or incurable*) adj3 (cancer* or tumo?r or metasta*)).tw.
9	or/5-8
10	4 and 9
11	(exp Surgery, Computer-Assisted/ or exp Dissection/ or Endoscopic Mucosal Resection/ or exp Laparoscopy/ or exp Minimally Invasive Surgical Procedures/ or exp Surgical Procedures, Operative/ or exp Transanal Endoscopic Surgery/) use ppez
12	(exp computer assisted surgery/ or dissection/ or endoscopic polypectomy/ or exp endoscopic surgery/ or exp excision/ or laparoscopic surgery/ or exp minimally invasive surgery/ or exp rectum resection/ or exp surgery/ or exp transanal endoscopic surgery/) use emez
13	(dissect* or endoscop* or EMR or ESD or excis* or laparoscop* or operat* or resect* or surger* or surgic* or TAE or TAMIS or TART or TaTME or TEM or TEMS or TME).tw.
14	or/11-13
15	primary tumour/ use emez
16	(primary adj2 tumo?r).tw.
17	or/15-16
18	14 and 17
19	10 and 18
20	limit 19 to (yr="1998 - current" and english language)
21	Letter/ use ppez
22	letter.pt. or letter/ use emez
23	note.pt.
24	editorial.pt.
25	Editorial/ use ppez
26	News/ use ppez
27	exp Historical Article/ use ppez
28	Anecdotes as Topic/ use ppez
29	Comment/ use ppez
30	Case Report/ use ppez
31	case report/ or case study/ use emez
32	(letter or comment*).ti.

#	Search
33	or/21-32
34	randomized controlled trial/ use ppez
35	randomized controlled trial/ use emez
36	random*.ti,ab.
37	or/34-36
38	33 not 37
39	animals/ not humans/ use ppez
40	animal/ not human/ use emez
41	nonhuman/ use emez
42	exp Animals, Laboratory/ use ppez
43	exp Animal Experimentation/ use ppez
44	exp Animal Experiment/ use emez
45	exp Experimental Animal/ use emez
46	exp Models, Animal/ use ppez
47	animal model/ use emez
48	exp Rodentia/ use ppez
49	exp Rodent/ use emez
50	(rat or rats or mouse or mice).ti.
51	or/38-50
52	20 not 51
53	remove duplicates from 52

1 **Databases: Cochrane Library**

2 Last searched on: 12/02/2019

#	Search
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees
2	((colorect* or colo rect* or colon or colonic or rectal or rectum) near/3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)):ti,ab,kw
3	#1 or #2
4	MeSH descriptor: [Neoplasm Metastasis] this term only
5	(stage IV or stage 4 or advanc*):ti,ab,kw
6	((unresect* or inopera* or untreat* or incurable*) near/3 (cancer* or tumo?r or metasta*)):ti,ab,kw
7	{or #4-#6}
8	MeSH descriptor: [Surgery, Computer-Assisted] explode all trees
9	MeSH descriptor: [Dissection] explode all trees
10	MeSH descriptor: [Endoscopic Mucosal Resection] this term only
11	MeSH descriptor: [Laparoscopy] explode all trees
12	MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees
13	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
14	MeSH descriptor: [Transanal Endoscopic Surgery] explode all trees
15	(dissect* or endoscop* or EMR or ESD or excis* or laparoscop* or operat* or resect* or surger* or surgic* or TAE or TAMIS or TART or TaTME or TEM or TEMS or TME):ti,ab,kw
16	{or #8-#15}
17	MeSH descriptor: [Neoplasms, Unknown Primary] explode all trees
18	(primary near/2 tumo?r):ti,ab,kw

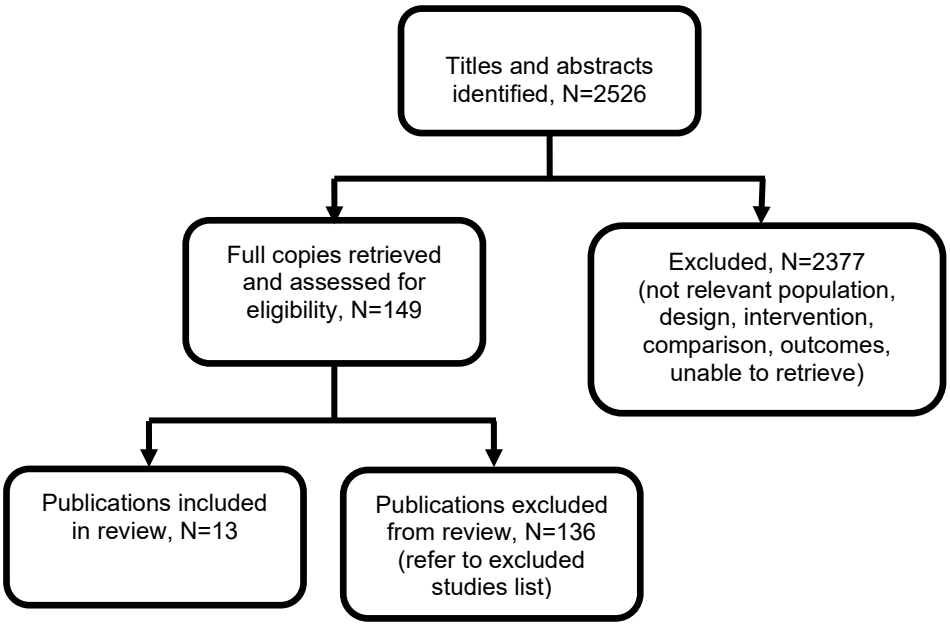
#	Search
19	{or #17-#18}
20	#3 and #7
21	#16 and #19
22	#20 and #21 Publication Year from 1998 to 2018

1
2

Appendix C – Clinical evidence study selection

Clinical study selection for: Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?

Table 4: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ahmed, S., Fields, A., Pahwa, P., Chandra-Kanthan, S., Zaidi, A., Le, D., Haider, K., Reeder, B., Leis, A., Surgical Resection of Primary Tumour in Asymptomatic or Minimally Symptomatic Patients with Stage IV Colorectal Cancer: A Canadian Province Experience, Clinical Colorectal Cancer, 14, e41-e47, 2015 **Ref Id** 871090 **Country/ies where the study was carried out** Canada **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess the prognostic role of surgery in patients with stage IV colorectal cancer with an	**Sample size** N=718 total (excluding 116 patients from the total cohort that underwent metastactomy); n=414 resection; n=304 no resection (chemotherapy) **Characteristics** Surgery, n= 521 Age, years, median (IQR)= 69 (22-93) Male sex, n= 297 Comorbid illness, n= 312 ECOG performance status ≥ 2, n=102 Rectal tumour, n= 156 Treatment, n Chemotherapy=274 Second line treatment= 107 Radiation=80 Second generation chemotherapy=111 Metastasectomy= 107 Control, n=313 Age, years, median (IQR)= 71 (35-92) Male sex, n= 186 Comorbid illness, n= 207 ECOG performance status ≥ 2, n= 113 Rectal tumour, n= 117	**Interventions** Intervention: resection of the primary tumour Control: Did not undergo surgery for the primary tumour and received chemotherapy	**Details** Definition of asymptomatic: absence of obstruction, perforation, and major bleeding (decrease in haemoglobin level of 20 g/L or required blood transfusion) Data collection: Individual medical records were extracted from the Saskatchewan Cancer Registry-Canada using a validated extraction sheet by a trained research assistant. Prognostic factors controlled for: Resection of primary tumour, old age, male sex, major comorbid illness, ECOG performance status, smoking, hypernatremia, renal insufficiency, increased blood urea nitrogen level, hypoalbuminemia, hyperbilirubinemia, increased alkaline phosphatase level, increased CEA level, anaemia, leucocytosis, thrombocytosis, disease	**Results** Overall survival (after excluding 116 patients who underwent metastasectomy) HR 0.52 95% CI 0.43 to 0.65 (no resection as reference) Adjusted for age, sex, major comorbidity, ECOG performance status, smoking, hyponatremia, renal insufficiency, increased blood urea nitrogen level, hypoalbuminemia, hyperbilirubinemia, alkaline phosphatase level, anemia, leukocytosis, thromobocytosis, CEA level, disease site (colon versus rectal), tumour grade, extrahepatic metastases, number of metastatic sites, use of any fluoropyrimidine chemotherapy, second-line chemotherapy, and second-generation chemotherapy	**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: Moderate risk of bias (9/313 patients in control arm underwent metastasectomy) Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias (Outcomes were objective and measured by health care professionals, not participant recall) Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
asymptomatic or minimally symptomatic primary tumour. **Study dates** January 1992 to December 2005 **Source of funding** Saskatchewan Cancer Agency research grant RGSCA2012	Treatment, n Chemotherapy= 87 Second line treatment= 28 Radiation= 48 Second generation chemotherapy= 47 Metastasectomy=9 **Inclusion criteria** Patients with histologically documented stage IV adenocarcinoma of colon and rectum, diagnosed over a period of 14 years (January 1992 to December 2005), in the province of Saskatchewan, Canada **Exclusion criteria** Patients with other histological diagnoses including neuroendocrine tumour or with other active secondary malignancy at the time of diagnosis, a previous diagnosis of early stage colorectal cancer who were treated with curative resection and subsequently developed metastatic disease		site, high-grade tumour, extrahepatic metastases, number of metastatic sites, metastasectomy, use of any fluoropyrimidine chemotherapy, second-line chemotherapy, and second-generation chemotherapy Outcomes: Overall survival (time from the diagnosis of stage IV colorectal cancer to death from any cause or the date at which patient was last confirmed to be alive. Follow up: Until death or until 2005 Data analysis: "Survival was estimated using the Kaplan-Meier method. Survival distribution of different groups was compared using the log-rank test. The overall significance level was set at 0.05. A multivariate Cox proportional hazard regression analysis was performed to determine the relationship between survival and resection of the primary tumour and HR and its 95% CI were estimated. A univariate analysis was performed to assess the relationship between survival and individual clinicopathological variables. All variables that were significantly correlated with survival were fitted into a multivariate model. The		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			proportional hazards assumption was assessed using log-log survival curves for all variables examined in the model."		
Full citation Alawadi, Z., Phatak, U. R., Hu, C. Y., Bailey, C. E., You, Y. N., Kao, L. S., Massarweh, N. N., Feig, B. W., Rodriguez-Bigas, M. A., Skibber, J. M., Chang, G. J., Comparative effectiveness of primary tumour resection in patients with stage IV colon cancer, Cancer, 123, 1124-1133, 2017 **Ref Id** 871107 **Country/ies where the study was carried out** US **Study type** Retrospective cohort study **Aim of the study** To compare mortality rates in patients who had colon cancer with unresectable metastases who did and did not undergo primary tumour resection. **Study dates** 2003-2005 **Source of funding**	**Sample size** N=6735 total "landmark" cohort; n=4972 primary tumour resection; n=1763 no resection The whole cohort was N=15154 with n=8641 in the resection group and n=6513 in the no resection group, however, because of survivor treatment bias, a landmark method was used to overcome this bias. The landmark cohort consisted of all patients who survived for 1 year after diagnosis. "The 1-year landmark was selected because PTR would be expected to have little clinical impact for a patient who was unlikely to survive beyond 12 months. In general, patients who are expected to survive less than 1 year are considered poor operative candidates who would derive limited benefit from elective surgery. To ensure that our choice of landmark did not lead to additional bias, a priori-determined sensitivity analyses were perform using 3-month, 6-month, 9-month, and 15-month landmarks." **Characteristics** The "landmark" cohort: Primary tumour resection n=4972	**Interventions** Surgery: Primary tumour resection Control: No resection 75% of the patients in the no resection group received chemotherapy. 77% of the patients in the resection group received chemotherapy of which 6% was neoadjuvant.	**Details** Definition of asymptomatic: Not defined as not part of the inclusion criteria because that type of data was not available in the database used. However, the study did try to eliminate including patients with symptoms in the following way: "...resections performed to palliate symptoms could not be distinguished from those that were performed in asymptomatic patients. To address this issue, patients who underwent tumour-directed surgery within 24 hours of diagnosis were excluded from the analysis (because their resections were considered non-elective). To ensure that our choice of a 24-hour cut-off did not bias the results, additional sensitivity analyses were perform using 48 and 72 hours, and the results were similar (data not shown)." Data collection: National Cancer Data Base ("a joint program between the Commission on Cancer (CoC) of the American College of Surgeons and	**Results** Overall survival (event is death, median 6.4 years of follow-up) Resection n=4972 (number of events not reported) No resection n=1763 (number of events not reported) HR 0.60 95% CI 0.55 to 0.64 (no resection as reference), adjusted for age, sex, race, year of diagnosis, tumour histology, tumour grade, tumour location, receipt of chemotherapy, insurance status, median income quartile, proportion without a high school degree by residence zip code, population density of residence, facility location, facility type, and co-morbidity However, the study also calculated an instrumental variable-adjusted relative mortality rate which took into account the unmeasured factors that contribute to treatment selection bias: Relative mortality rate 0.97 95% CI 0.87 to 1.06, adjusted for age,	**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 **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
National Institutes of Health/National Cancer Institute, American Society of Colon and Rectal Surgeons Research Foundation	Age at diagnosis, n (%) 18-49 years 810 (16) 50-64 years 1898 (38) 65-74 years 12569 (26) 75-90 years 995 (20) Male sex, n (%) 2601 (52) Tumour grade, n (%) Well/moderately differentiated 3542 (71) Poorly differentiated/undifferentiated 1239 (25) Unknown 190 (4) Tumour location, n (%) Right 2460 (50) Left 2332 (47) Other/not specified 180 (4) Receipt of chemotherapy, n (%) 3829 (77) Co-morbidity score, n (%) 0 3854 (78) 1 897 (18) 2 221 (4) No resection n=1763 Age at diagnosis, n (%) 18-49 years 298 (17) 50-64 years 710 (40) 65-74 years 427 (24) 75-90 years 328 (19) Male sex, n (%) 957 (54) Tumour grade, n (%) Well/moderately differentiated 771 (44) Poorly differentiated/undifferentiated 208 (12) Unknown 784 (45) Tumour location, n (%) Right 667 (38) Left 701 (40) Other/not specified 395 (22)		the American Cancer Society that serves as a surveillance tool to assess patterns of care for patients with cancer. The NCDB collects and reports patient data on over 70% of cancers diagnosed from over 1500 CoC-accredited cancer programs in the United States.") Prognostic factors controlled for: Age, sex, race, year of diagnosis, tumour histology, tumour grade, tumour location, receipt of chemotherapy, insurance status, median income quartile, proportion without a high school degree by residence zip code, population density of residence, facility location, facility type, and co-morbidity score Outcomes: Overall survival Follow up: median 6.4 years (IQR 5.5-7.2) Data analysis: Kaplan-Meier and multivariate Cox regression analyses	sex, race, year of diagnosis, tumour histology, tumour grade, tumour location, receipt of chemotherapy, insurance status, median income quartile, proportion without a high school degree by residence zip code, population density of residence, facility location, facility type, and co-morbidity	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Receipt of chemotherapy, n (%) 1322 (75) Co-morbidity score, n (%) 0 1501 (85) 1 210 (12) 2 52 (3) **Inclusion criteria** Adult patients who had stage IV colon adenocarcinoma diagnosed between 2003 and 2005. **Exclusion criteria** Patients who underwent tumour-directed surgery within 24 hours of diagnosis (considered to have undergone non-elective resection) and those who underwent surgery for cancer of other sites (for example metastectomy).				
Full citation Benoist, S., Pautrat, K., Mitry, E., Rougier, P., Penna, C., Nordlinger, B., Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases, British Journal of Surgery, 92, 1155-60, 2005 **Ref Id** 845903 **Country/ies where the study was carried out** France **Study type** Case-matched cohort study	**Sample size** N=59 **Characteristics** Surgery, n=32 Age, years, mean (SD)= 60 (13) Male sex, n= 19 WHO performance status ≥ 1, n= 19 Site of primary lesion, n Right colon=6 Transverse colon=3 Left or sigmoid colon=14 Rectum=9 Chemotherapy, n=27 Age, years, mean (SD)=61 (12) Male sex, n=18 WHO performance status ≥ 1, n=19 Site of primary lesion, n Right colon=6	**Interventions** Surgery= Initial resection of the primary tumour Chemotherapy= no initial resection of primary tumour; treated with chemotherapy "Systemic chemotherapy was started less than 21 days after the diagnosis in all patients. Systemic chemotherapy was started at least 3 weeks after an uneventful surgical procedure. First-line chemotherapy consisted of a modified de Gramont regimen in 20 patients (11 in the resection group and nine in the chemotherapy	**Details** Definition of asymptomatic: No or minimal symptoms related to the primary tumour Data collection: Between 1997 and 2002; data on patients treated for liver metastases from colorectal cancer were prospectively collected. Each patient treated by chemotherapy without primary resection was matched with all (one or more) similar patients with asymptomatic colorectal cancer and unresectable synchronous liver metastases from the database of patients who underwent initial resection	**Results** Overall survival Surgery 24 events, n=32 Chemotherapy 21 events, n=27 log rank p=0.753 Survival time, months, median (range) Surgery= 23 (3-42) Chemotherapy= 22 (1-38) Post-operative complications, n Surgery= 6/32 Chemotherapy= N/A Grade 3/4 chemotherapy-related toxicity, n Surgery= 16/32 Chemotherapy= 10/27	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (confounding expected, but was controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study The aim of the study was to assess the best treatment strategy for patients with asymptomatic colorectal cancer and unresectable synchronous liver metastases. **Study dates** 1997-2002 **Source of funding** Not reported	Transverse colon=3 Left or sigmoid colon=14 Rectum=4 **Inclusion criteria** Colorectal cancer patients treated for unresectable synchronous liver metastases and an asymptomatic primary tumour who also had a performance status that allowed treatment by systemic chemotherapy **Exclusion criteria** Not reported	group) corresponding to 5-FU in combination with leucovorin, in combination chemotherapy with 5- FU and oxaliplatin in 20 patients (ten in each group) or irinotecan in 17 (nine in the resection group and eight in the chemotherapy group)." "In both groups, the response to chemotherapy was evaluated every 2 months by chest and abdominal CT. A switch to second-line chemotherapy was made in cases of grade 3 or 4 toxicity, partial response (less than 25 per cent) or disease progression."	of the primary tumour. During the selection process, the investigators were blinded to the long-term oncological results. Prognostic factors controlled for: age, sex, performance status (World Health Organization classification), primary tumour location (colon or rectum), number of liver metastases, reasons for judging liver metastases as unresectable, and type of chemotherapy (drugs and number of cycles). Outcomes: Primary: overall survival at 2 years. Secondary= morbidity and mortality (defined as death or complications occurring in hospital or within 30 days) rates after surgical resection of the primary tumour (resection group only), complications related to the primary tumour (chemotherapy group only), toxicity of chemotherapy, overall duration of hospital stay and rate of curative liver resection after tumour downstaging by chemotherapy. Follow up: Death or to the end of the study period Data analysis: The analysis was made on an intent-to-treat basis. Groups were compared by the X^2 test with Yates' correction,	Tumour related complications, n Surgery= N/A Chemotherapy= 4/27	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 **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Mann–Whitney U test or Student's t test as appropriate. Actuarial survival was calculated using the Kaplan–Meier method and was analysed using the log rank test. P < 0.05 was considered statistically significant.		
Full citation Galizia, G., Lieto, E., Orditura, M., Castellano, P., Imperatore, V., Pinto, M., Zamboli, A., First-line chemotherapy vs bowel tumour resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases, Archives of Surgery, 143, 352-358, 2008 **Ref Id** 846918 **Country/ies where the study was carried out** Italy **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess the effectiveness of bowel resection plus chemotherapy compared to first-line chemotherapy for patients with	**Sample size** N=65 **Characteristics** Surgery, n=42 Age, years, mean (SD)=62 (13) Male sex, n=28 Site of bowel tumour, n Right colon=12 Left colon=23 Rectum=7 Performance status, n 0=13 1=18 2=11 0/1=31 Chemotherapy, n=23 Age, years, mean (SD)=59 (14) Male sex, n=15 Site of bowel tumour, n Right colon=6 Left colon=12 Rectum=5 Performance status, n 0=6 1=11 2=6 0/1=17 **Inclusion criteria**	**Interventions** Chemotherapy regimen for both arms: "First-line systemic chemotherapy based on intravenous fluorouracil plus folinic acid or, after 2001, fluorouracil, folinic acid, and oxaliplatin or fluorouracil, folinic acid, and irinotecan hydrochloride. The response to systemic therapy was evaluated every 3 months and metastases were restaged with regard to their resectability. A switch to second-line chemotherapy, with the eventual addition of new biological therapies such as bevacizumab and cetuximab, was decided in cases of partial response (metastatic reduction <25%) or disease progression." Surgery= Resection of the bowl cancer. Chemotherapy was started at least 3 weeks after surgery.	**Details** Definition of asymptomatic: Complaining only of constitutional symptoms such as fatigue or anorexia Data collection: Clinical records were assessed from the Division of Surgical Oncology from January 4, 1995 to December 23, 2005. Prognostic factors controlled for: Performance status > 1, LDH > 450 U/L, ALP > 128 U/L, liver involvement H3, 50% of whole liver volume, no curative resection, treatment chemotherapy first Outcomes: Overall survival Follow up: Until end of study, mean follow up 21 months Data analysis: Univariate statistical analysis related to survival was determined by the log-rank test (Mantel-Cox). Curves were plotted using the product-limit method (Kaplan-Meier) and analysed using the generalized Savage test or	**Results** Overall survival (median 16 months of follow-up) Surgery 28 events, n=42 Control 21 events, n=23 p=0.03 Postoperative complications, n Surgery= 9/42 Control= N/A Tumour-related complications, n Surgery= N/A Control= 7/23	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (confounding expected, but was 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 due Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
asymptomatic colorectal cancer with unresectable metastases in the liver. **Study dates** January 4, 1995 to December 23, 2005 **Source of funding** No funding received	Patients with stage IV bowel cancer and unresectable liver-only metastases **Exclusion criteria** Patients with symptomatic primary tumours	Chemotherapy= Chemotherapy was started immediately after diagnosis.	the Mantel-Cox test. The independent significance of prognostic variables related to overall survival was determined by multivariate analysis, using the Cox proportional hazards model		
Full citation He, W. Z., Rong, Y. M., Jiang, C., Liao, F. X., Yin, C. X., Guo, G. F., Qiu, H. J., Zhang, B., Xia, L. P., Palliative primary tumour resection provides survival benefits for the patients with metastatic colorectal cancer and low circulating levels of dehydrogenase and carcinoembryonic antigen, Chinese journal of cancer, 35, 58, 2016 **Ref Id** 871508 **Country/ies where the study was carried out** China **Study type** Retrospective cohort study	**Sample size** N= 210 N surgery=135 Non-surgery=75 **Characteristics** Surgery, n= 387 Age, years, ≤ 60, n=135 Age, years, > 60, n=119 Male sex, n=169 Primary tumour location, n Right colon=132 Left colon=124 Rectum=131 Non-surgery, n= 133 Age, years, ≤ 60, n=75 Age, years, > 60, n=58 Male sex, n=90 Primary tumour location, n Right colon=45 Left colon=35 Rectum=53 **Inclusion criteria** Were admitted between 2005 and 2012, were diagnosed with metastatic colorectal cancer at	**Interventions** Surgery: had primary tumour resection Non-surgery: no primary tumour resection, had chemotherapy All patients received first-line chemotherapy that was either oxaliplatin or irinotecan-based	**Details** Definition of asymptomatic: No intestinal obstruction, enterobiasis or bleeding at the time of first presentation Data collection: Patient records from the database from Sun Yat-sen University Cancer Centre were reviewed. Prognostic factors controlled for: age, sex, primary tumour location, metastatic site, regimen of first-line chemotherapy, ALP, LDH, and CEA levels Outcomes: Median survival, progression free survival after first line chemotherapy Follow up: Death or last follow up (October 31, 2014) Data analysis: "The Kaplan–Meier method was used to plot the survival curves, and the differences were compared using the log-rank test. Multivariate analysis and the Cox proportional hazards model were used to determine	**Results** Survival time, months, median Surgery= 20.8 Non-surgery= 14.8 p< 0.001	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (confounding expected, but was controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias due Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study The aim of the study was to assess whether palliative primary tumour resection could provide survival benefits for patients with metastatic colorectal cancer with unresectable metastases. **Study dates** January 2005 to December 2012 **Source of funding** Natural Science Foundation of Guangdong, China (2015A030313010), Science and Technology Program of Guangzhou, China (1563000305) and National Natural Science Foundation of China (81272641 and 81572409).	first diagnosis, they had an ECOG status ≤2 and their follow-up information was available **Exclusion criteria** Those who had evidence of intestinal obstruction, enterobiasis, or bleeding at the time of first presentation, a second primary tumour and those who had all visible tumours removed.		independent significance. A P value less than or equal to 0.05 was considered significant."		
Full citation Matsumoto, T., Hasegawa, S., Matsumoto, S., Horimatsu, T., Okoshi, K., Yamada, M., Kawada, K., Sakai, Y., Overcoming the	**Sample size** N=88 N surgery= 41 N chemotherapy= 47 **Characteristics** Surgery, n=41	**Interventions** Upfront primary tumour resection Upfront chemotherapy The decision about the upfront treatment was made by a	**Details** Definition of asymptomatic: both no subjective symptoms and no obvious evidence of objective findings, such as bowel obstruction, perforation,	**Results** Overall survival Adjusted HR 0.72 95% CI 0.42 to 1.25 (upfront chemotherapy as reference) (Adjusted for age, sex, performance status,	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Challenges of Primary Tumour Management in Patients With Metastatic Colorectal Cancer Unresectable for Cure and an Asymptomatic Primary Tumour, Diseases of the Colon and Rectum, 57, 679-686, 2014 **Ref Id** 871814 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess the rate of symptom-directed surgery after systemic chemotherapy and to estimate the impact of initial primary tumour resection on survival in patients with unresectable metastatic colorectal cancer and an asymptomatic primary tumour **Study dates**	Male sex, n=16 Age, years, median (IQR)=67 (59-72) ECOG-PS, n 0=34 1=4 2=1 3=2 Cancer site, n Right colon=8 Left colon=21 Rectum=12 Chemotherapy, n=47 Male sex, n=33 Age, years, median (IQR)=62 (57-68) ECOG-PS, n 0=40 1=4 2=3 3=0 Cancer site, n Right colon=11 Left colon=25 Rectum=11 **Inclusion criteria** Synchronous stage IV colon or rectal adenocarcinoma clinically unresectable for cure and asymptomatic primary tumour **Exclusion criteria** Resectable metastatic colorectal cancer; symptomatic primary tumour; patients who received a non-resective surgical operation (diversion).	multidisciplinary team consisting of colorectal and hepatobiliary surgeons, oncologists, gastrointestinal physicians and radiologists taking into account all pre-treatment examination findings, patient performance status, and comorbidities. The most common chemotherapy regimen was FOLFOX in both groups. 85% of the resection group received postoperative chemotherapy. Biological agents were administered to both groups at similar rates (52% in the upfront chemotherapy group and 42% in the upfront resection group). None of the patients received radiotherapy.	primary tumour-related pain, or active bleeding requiring a transfusion. Data collection: Hospital records from the Kyoto University Hospital Prognostic factors controlled for: Age, sex, performance status, comorbidities, colonoscopic traversability, CEA level and number of metastatic organs Outcomes: Median survival time Follow up: median 21.3 months (IQR 12.2-32.9) Data analysis: Survival was calculated using the Kaplan-Meier method with differences between groups tested with the log-rank test. Adjusted survival was estimated using Cox proportional hazard model controlling for age, sex, performance status, comorbidities, colonoscopic traversability, CEA level and number of metastatic organs.	comorbidity, colonoscopic traversability, CEA level, and number of metastatic organs.) Median survival time, months Resection 23.9 (n=41) Chemotherapy 22.6 (n=47) Grade 3 or 4 postoperative complications Resection 8/41 Chemotherapy (who later received surgery) 2/11 p=0.92 Symptom-related surgery required Resection N/A Chemotherapy 12/47 Symptom-related surgery rate at 1 year Resection N/A Chemotherapy 19.1% Symptom-related surgery rate at 2 years Resection N/A Chemotherapy 26.1%	bias (confounding expected, but was controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Moderate risk of bias (Unclear whether information used to define intervention groups was specified at the start of the intervention. Intervention groups were clearly defined.) Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias due Bias in measurement of outcomes: Low risk of bias (Outcomes were objective and measured by health care professionals, not participant recall) Bias in selection of the reported result: Low risk of bias **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2005-2011 **Source of funding** Not reported					
Full citation Michel, P., Roque, I., Di Fiore, F., Langlois, S., Scotte, M., Teniere, P., Paillot, B., Colorectal cancer with non-resectable synchronous metastases: Should the primary tumour be resected?, Gastroenterologie Clinique et Biologique, 28, 434-437, 2004 **Ref Id** 871840 **Country/ies where the study was carried out** France **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to compare survival of patients with metastatic colorectal cancer who underwent elective resection of the primary tumour compared to those who did not. **Study dates**	**Sample size** N=54 **Characteristics** Surgery, n=31 Male sex, n=54.8 Age, years, mean=59.8 Primary rectal tumour, %=9.7 WHO health status class 0-1, %=80.5 Non-surgery, n=23 Male sex, n=69.6 Age, years, mean=58.9 Primary rectal tumour, n=34.7 WHO health status class 0-1, %=913 **Inclusion criteria** Patients with stage IV colon or rectal cancer with unresectable liver metastases **Exclusion criteria** Patients who underwent first-line surgery as a result of serious complications related to the primary tumour	**Interventions** Surgery: Elective surgery of the primary tumour Non-surgery: No elective surgery of the primary tumour "Postoperative chemotherapy was performed in all 30 patients who survived one month after surgery. Oxaliplatin and/or irinotecan was administered in 80% and 33% of patients given two chemotherapy regimens. In the group not undergoing elective surgery of the primary (group 2), all 23 patients were given chemotherapy. Oxaliplatin and/or irinotecan was administered in 82% and 40%, respectively. At least two chemotherapy regimens were given to 70% of patients in group 2."	**Details** Definition of asymptomatic: No intestinal obstruction, pain or haemorrhage Data collection: Medical records of patients admitted to the Gastrointestinal Disease Unit of Rouen University Hospital were assessed between June 1, 1996 and December 31, 1999 using the French disease group coding system. Prognostic factors controlled for: Number of metastases Outcomes: Overall survival, median survival, mean survival, hospital stay, at least three treatments, secondary surgery for GI complication Follow up: Until death or end of follow-up (October 1, 2002) Data analysis: "The Mann-Whitney test was used to compare quantitative variables and non-parametric tests or the exact Fischer test as appropriate to compare qualitative variables.	**Results** Survival time, months, median Surgery= 21 Non-surgery= 14 p= not significant Time to tumour-related intestinal obstruction, months, mean (range) Surgery N/A Non-surgery 4 (2-8) Tumour-related complications requiring surgery Surgery 0/31 Non-surgery 5/23	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Serious risk of bias (confounding expected, important potential confounders such as age, performance status or comorbidities not controlled for; statistically significant difference between groups at baseline in terms of primary rectal tumour) 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 due Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
June 1996 to December 1999 **Source of funding** Not reported			Kaplan-Meier survival plots were compared with the logrank test."		
Full citation Miyamoto, Y., Watanabe, M., Sakamoto, Y., Shigaki, H., Murata, A., Sugihara, H., Etoh, K., Ishimoto, T., Iwatsuki, M., Baba, Y., Iwagami, S., Yoshida, N., Baba, H., Evaluation of the necessity of primary tumour resection for synchronous metastatic colorectal cancer, Surgery Today, 1-6, 2014 **Ref Id** 871846 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess the need for primary tumour resection in patients with colorectal cancer and synchronous unresectable metastases who underwent chemotherapy, and identified the	**Sample size** N= 131 N surgery= 68 N non-surgery= 63 **Characteristics** Surgery, n=68 Age, years, mean (SD)=61.6 (12.8) Male sex, n=42 Location of the tumour, n Right colon=18 Left colon=21 Rectum=29 Non-surgery, n=63 Age, years, mean (SD)=64.4 (9.9) Male sex, n=43 (67) Location of the tumour, n Right colon=20 Left colon=25 Rectum=18 **Inclusion criteria** Patients with unresectable stage IV colorectal cancer treated at Kumamoto University Hospital; no or moderate primary tumour related symptoms at diagnosis **Exclusion criteria** Patients who had evidence of manifestations that required urgent surgical treatment; had symptomatic tumours	**Interventions** "All patients received up-front chemotherapy, using fluorouracil, leucovorin and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), with or without bevacizumab or anti-EGFR antibodies, as initial chemotherapy" Surgery: primary tumour resection Non-surgery: chemotherapy without initial primary tumour resection	**Details** Definition of asymptomatic: No evidence of manifestations that required urgent surgical treatment Data collection: Consecutive patient records at the Kumamoto University Hospital were reviewed Prognostic factors controlled for: histology, CEA level, tumour site, circumferential rate, Bormann classification, tumour size Outcomes: Overall survival, median survival time, postoperative complications, need for surgical intervention for complications during chemotherapy in the non-resection group Follow up: Data analysis: "A univariate analysis was conducted using the X^2 test and Mann–Whitney U test. Actuarial survival was calculated using the Kaplan–Meier method, and was analyzed using the logrank test. A multivariate Cox regression analysis was performed with the six statistically significant variables. A value of p< 0.05 was	**Results** Survival time, months, median Surgery= 30.4 (n=68) Non-surgery= 24.1 (n=63) p= 0.530 Post-operative complications, n Surgery= 12/68 Non-surgery= N/A Tumour-related complications, n Surgery= N/A Non-surgery= 16/63	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (confounding expected, but was 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: Unclear risk of bias (some graphs did were reported incorrectly (figure 1)) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
associations between the primary tumour characteristics and risk of intestinal obstruction or perforation. **Study dates** April 2005 to December 2011 **Source of funding** Not reported			considered to be significant."		
Full citation Ruo, L., Gougoutas, C., Paty, P. B., Guillem, J. G., Cohen, A. M., Wong, W. D., Elective bowel resection for incurable stage IV colorectal cancer: Prognostic variables for asymptomatic patients, Journal of the American College of Surgeons, 196, 722-728, 2003 **Ref Id** 849496 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess which prognostic factors would help determine which patients should undergo the elective resection of	**Sample size** N=127 **Characteristics** Surgery, n=127 Age, years, median (IQR)= 64 (22-87) Male sex, n=81 Tumour site, n Right colon=58 Left colon=31 Rectum=37 No-surgery, n=103 Age, years, median (IQR)=61 Male sex, n=57 Tumour site, n Right colon=29 Left colon=35 Rectum=37 **Inclusion criteria** Patients with asymptomatic stage IV metastatic colorectal cancer **Exclusion criteria** Patients with asymptomatic primary tumours	**Interventions** Surgery: bowel resection to remove the primary tumour, some also underwent a metastasectomy Non-surgery: did not undergo resection and received chemotherapy or radiation to the primary tumour	**Details** Definition of asymptomatic: No obstruction, perforation, bleeding, pain Data collection: Patient records were reviewed from hospital and colorectal service databases between 1996 and 1999. Prognostic factors controlled for: No of distant sites, metastases to liver only, extent of liver disease, LDH, CEA Outcomes: Overall survival, surgical intervention in patients initially managed without resection, postoperative complications Follow up: Until death or study end Data analysis: "The chi-square test was used for analysis of categorical data. Student's t-test was used for continuous variables. Survival was determined by the Kaplan-Meier method and distributions compared by the log rank test.	**Results** Survival time, months, median Surgery= 16 Non-surgery= 9 p < 0.001 Post-operative complications, n Surgery= 26/127 Non-surgery= N/A Tumour-related complications, n Surgery= N/A Non-surgery= 30/103	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Serious risk of bias (confounding expected, it was controlled for but not for some important potential confounders such as performance status or comorbidities) 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: Moderate risk of bias (missing data for baseline characteristics) Bias in measurement of outcomes: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
an asymptomatic primary tumour. **Study dates** 1996-1999 **Source of funding** Not reported			Multivariate analysis was performed using the Cox proportional hazards model."		Bias in selection of the reported result: Low risk of bias **Other information**
Full citation Samalavicius, N. E., Dulskas, A., Baltruskeviciene, E., Smailyte, G., Skuciene, M., Mikelenaite, R., Venslovaite, R., Aleknavicius, E., Samalavicius, A., Lunevicius, R., Asymptomatic primary tumour in incurable metastatic colorectal cancer: Is there a role for surgical resection prior to systematic therapy or not?, Wideochirurgia I Inne Techniki Maloinwazyjne, 11, 274-282, 2016 **Ref Id** 845018 **Country/ies where the study was carried out** Lithuania **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess the effect of the resection of an	**Sample size** N= 183 N surgery= 120 N chemotherapy= 63 **Characteristics** Surgery, n=120 Age < 70, n=76 Age ≥ 70, n=44 Male sex, n=67 Tumour site, n Colon=71 Rectum=49 Tumour differentiation grade, n G1-2=101 G3=15 Not available=4 Chemotherapy, n=63 Age < 70, n=43 Age ≥ 70, n=20 Male sex, n=104 Tumour site, n Colon=25 Rectum=38 Tumour differentiation grade, n G1-2=55 G3=6 Not available=2 **Inclusion criteria** Patients with stage IV colorectal cancer treated at the Lithuanian National Cancer Institute from January 1, 2008 to December 31,	**Interventions** Surgery= primary tumour resection Chemotherapy= chemotherapy without surgery All patients received chemotherapy: "Patients with clinically (metastases) and histologically (primary tumour) verified stage IV colorectal cancer... with asymptomatic primary tumour, and at least one cycle of palliative chemotherapy (FOLFOX, FOLFIRI or fluoropyrimidine, including the De Gramont and Mayo regimen or capecitabine) were included in this study"	**Details** Definition of asymptomatic: Not defined Data collection: Patient records were reviewed from the Lithuanian National Cancer Institute and were coded with the ICD-10. Prognostic factors controlled for: Initial treatment strategy, tumour site, regional lymph nodes, grade of differentiation of adenocarcinoma and application of biotherapy Outcomes: Overall survival Follow up: 4.5 years Data analysis: Kaplan-Meier curves for overall survival with log-rank tests to compare between groups. Cox regression analysis was employed to assess the effects of variables on patient survival.	**Results** Overall survival, hazard ratio (95% CI), p-value Surgery= reference Chemotherapy= 1.76 (1.16-2.68), 0.008 1-year survival, rate (95% CI) Surgery= 71.2 (62.1-78.5) Chemotherapy= 43.9 (31.4-55.7) 2-year survival, rate (95% CI) Surgery= 24.5 (17.1-32.6) Chemotherapy= 15.6 (7.8-25.6) 3-year survival, rate (95% CI) Surgery=10.3 (5.5-16.7) Chemotherapy= 1.7 (0.1-8.1) 5-year survival, rate (95% CI) Surgery= 4.0 (1.0-10.5) Chemotherapy= 1.7 120(0.1-8.1)	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: High risk of bias (confounding expected and was controlled for but important potential confounders such as age, performance status and comorbidity no 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 due Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
asymptomatic primary colorectal cancer in patients with incurable disease. **Study dates** 2008-2012 **Source of funding** Not reported	2012. Clinically and histologically verified stage IV colorectal cancer with asymptomatic primary tumour and at least one cycle of palliative chemotherapy FOLFOX, FOLFIRI or fluoropyrimidine). **Exclusion criteria** Not reported				
Full citation Seo, G. J., Park, J. W., Yoo, S. B., Kim, S. Y., Choi, H. S., Chang, H. J., Shin, A., Jeong, S. Y., Kim, D. Y., Oh, J. H., Intestinal complications after palliative treatment for asymptomatic patients with unresectable stage IV colorectal cancer, Journal of Surgical Oncology, 102, 94-99, 2010 **Ref Id** 872102 **Country/ies where the study was carried out** South Korea **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to compare the rates of major intestinal complications in asymptomatic patients who received palliative treatment for	**Sample size** N=227 **Characteristics** Surgery, n=144 Age, years, mean=58.0 Male sex, %=64.9 Performance status (ECOG) ≥ 2=7.7 Site of primary tumour, % Right colon=20.8 Left colon=28.5 Rectum=50.7 Tumour grade, % Low grade=86.8 High grade= 1.2 Chemotherapy, n=83 Age, years, mean=56.0 Male sex, %=20.5 Performance status (ECOG) ≥ 2=15.1 Site of primary tumour, % Right colon=31.4 Left colon=36.1 Rectum=32.5 Tumour grade, % Low grade=83.1 High grade= 16.9 **Inclusion criteria** Patients with asymptomatic and unresectable colorectal cancer	**Interventions** "All patients received 5-fluorouracil-based palliative chemotherapy with or without the addition of other chemotherapeutic agents. All patients received systemic chemotherapy." Surgery: palliative bowel resection Chemotherapy: received first line chemotherapy	**Details** Definition of asymptomatic: did not define Data collection: Patient records from the National Cancer Center of the Republic of Korea from March 2001 to January 2008 were retrospectively reviewed. Prognostic factors controlled for: first-line chemotherapy, high-grade differentiation, no of liver nodules ≥ 5, oxaliplatin Outcomes: Intestinal complications and gastrointestinal toxicity, postoperative mortality, 5 year survival Follow up: 5 years Data analysis: "The overall survival rate for prognostic factors was estimated using the Kaplan–Meier method and univariate analysis of significance was evaluated for each factor by a log-rank test. Multivariate analysis of overall survival time was performed using Cox's proportional hazards model.	**Results** Median survival time, months Surgery 22.0 Chemotherapy 14.0 Tumour-related complications, n Surgery=29/144 Chemotherapy=17/83 Postoperative complications, n Surgery= 50/144 Chemotherapy= N/A Postoperative complications requiring intensive care or surgery, n Surgery= 2/144 Chemotherapy= N/A	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: High risk of bias (confounding expected, not clear if median overall survival time was controlled for) Bias in selection of participants into the study: Moderate risk of bias (did not define asymptomatic) 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 due Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
unresectable stage IV colorectal cancer. **Study dates** March 2001 to January 2008 **Source of funding** Not reported	**Exclusion criteria** Symptomatic, did not receive chemotherapy, underwent diversion or bypass procedures, combined extra-colonic tumour, pathological diagnosis of neuroendocrine tumour, or insufficient medical records.		Any variable reaching a P-value of <0.10 in the univariate analysis was introduced in the multivariate analysis to identify independent predictors. All P-values were two-sided. A P-value of <0.05 was considered statistically significant."		
Full citation Yun, J. A., Huh, J. W., Park, Y. A., Cho, Y. B., Yun, S. H., Kim, H. C., Lee, W. Y., Chun, H. K., The role of palliative resection for asymptomatic primary tumour in patients with unresectable stage IV colorectal cancer, Diseases of the Colon and Rectum, 57, 1049-1058, 2014 **Ref Id** 859270 **Country/ies where the study was carried out** South Korea **Study type** Retrospective cohort/case-match study **Aim of the study** To compare the prognostic role of surgical resection of asymptomatic primary tumours in patients with unresectable synchronous	**Sample size** Matched cohort N=226; n=113 resection of primary tumour; n=113 no resection (chemotherapy with or without radiotherapy) (Total cohort N=416; n=218 resection of primary tumour; n=198 no resection (chemotherapy with or without radiotherapy)) **Characteristics** Matched cohort: Resection n=113 Age in years, median (range) 59 (23-87) Male sex, n (%) Resection 73 (65) BMI, median (range) 22.8 (16.9-31.7) Location of tumour Right colon 22 (20) Left colon 48 (43) Rectum 43 (38) Site of metastasis Liver 96 (85) Lung 32 (28) Distant lymph node 9 (8)	**Interventions** Resection of the primary tumour (with selected postoperative chemotherapy) No resection but chemo(radio)therapy A multidisciplinary team consisting of a surgeon, oncologist, radiation oncologist, radiologist, and endoscopist made the final determination regarding palliative resection after considering the potential for tumour growth, the possibility of emergent operation, and chemosensitivity in patients with unresectable metastases. Chemotherapy regimen for the non-resection group varied and included the following: 1) oxaliplatin-based chemotherapy with or without targeted agents 2) irinotecan-based	**Details** Definition of asymptomatic: Absence of obstruction, perforation, or bleeding Data collection: Retrospective chart review of medical records of patients admitted to the Samsung Medical Center in Seoul Prognostic factors controlled for: The groups were matched according to the following variables: age, sex, BMI, ASA score, tumour location, type of operation, preoperative CEA level, tumour size, depth of invasion, and lymph node metastasis. The regression model considered the following variables for inclusion in the multivariate model if univariate model showed statistical significance: sex, age, BMI, location of tumour, pretreatment CEA level, clinical T stage, clinical M stage, site of metastasis, cell type.	**Results** Overall survival at 5 years Resection 4.9% (n=113) Non-resection 3.5% (n=113) p=0.27 Overall survival according to the site of the metastasis Liver p=0.20 Lung p=0.79 Peritoneum p=0.16 Median survival period, months Resection 17.2 (mean 21.6, range 0.9-133.6) (n=113) Non-resection 14.4 (mean 18.3, range 0.4-67.9) (n=113) p=0.16 Surgery required for obstruction or perforation of the primary tumour Resection N/A Non-resection 7/113 30-day mortality Resection 1/113	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (confounding was controlled for by propensity-scored matching and by performing multivariate analysis) 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 **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
metastases with nonresection. **Study dates** January 2000 to December 2008 **Source of funding** None reported.	Peritoneum 14 (12) Bone 1 (1) Other 5 (4) Clinical T stage T2 2 (2) T3 103 (91) T4 8 (7) Clinical N stage N0 15 (13) N1 52 (46) N2 46 (41) M stage M1a 71 (63) M1b 42 (37) No resection (chemo(radio)therapy) n=113 Age in years, median (range) 60 (25-77) Male sex, n (%) 68 (60) BMI, median (range) 23.5 (17.1-35.2) Location of tumour Right colon 25 (23) Left colon 51 (46) Rectum 34 (31) Site of metastasis Liver 100 (89) Lung 33 (29) Distant lymph node 7 (6) Peritoneum 15 (13) Bone 1 (1) Other 5 (4) Clinical T stage T2 6 (5) T3 101 (89) T4 6 (5) Clinical N stage N0 17 (15) N1 58 (51) N2 38 (34) M stage	chemotherapy with or without targeted agents 3) 5-fluorouracil-based chemotherapy with or without targeted agents 4) other regimens Some patients in the resection group also received chemotherapy after the surgery. The regimen varied and included the ones listed above.	Outcomes: overall survival, median survival time Follow up: Patients were monitored every 3 months with serum CEA level testing and CT of the chest and abdominopelvic region to assess disease status. Other examinations such as MRI or PET were performed as needed for further evaluation. For patients who did not return for observation after 1 year, information was obtained by letter or telephone. Data analysis: Cox regression method with multivariate analysis, Kaplan-Meier analysis with a log-rank test for analysing survival	Non-resection 3/113	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	M1a 69 (61) M1b 44 (39) **Inclusion criteria** Unresectable stage IV colorectal cancer with asymptomatic primary tumour (defined as the absence of obstruction, perforation, or bleeding). N=113 patients who underwent resection of the primary tumour were matched with equal number of patients who did not undergo resection of the primary tumour but received chemotherapy with or without radiotherapy, the matching was done based on the following characteristics: age, sex, BMI, ASA score, tumour location, type of operation, preoperative CEA level, tumour size, depth of invasion, and lymph node metastasis. **Exclusion criteria** Not asymptomatic primary tumour; patients who underwent bypass surgery without resection of the primary tumour, diverting enterostomy, and open and closure.				
Full citation Zhang, R. X., Ma, W. J., Gu, Y. T., Zhang, T. Q., Huang, Z. M., Lu, Z. H., Gu, Y. K., Primary tumour location as a predictor of the benefit of palliative resection for colorectal cancer with unresectable metastasis, World	**Sample size** N=194 total; n=125 primary tumour resection; n=69 no resection **Characteristics** Not reported according to resection/no resection. **Inclusion criteria**	**Interventions** Resection of the primary tumour No resection of the primary tumour Most patients received chemotherapy but the number not reported according to the resection/no resection.	**Details** Definition of asymptomatic: No signs and symptoms of intestinal obstruction, perforation, or bleeding. Data collection: Patient records were reviewed from the Sun Yat-sen University Cancer Center	**Results** All-cause mortality, median follow-up 12 months Resection n=125, number of events not reported No resection n=69, number of events not reported RR 1.034 95% CI 0.973 to 1.098, p=0.285,	**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 in the analysis)

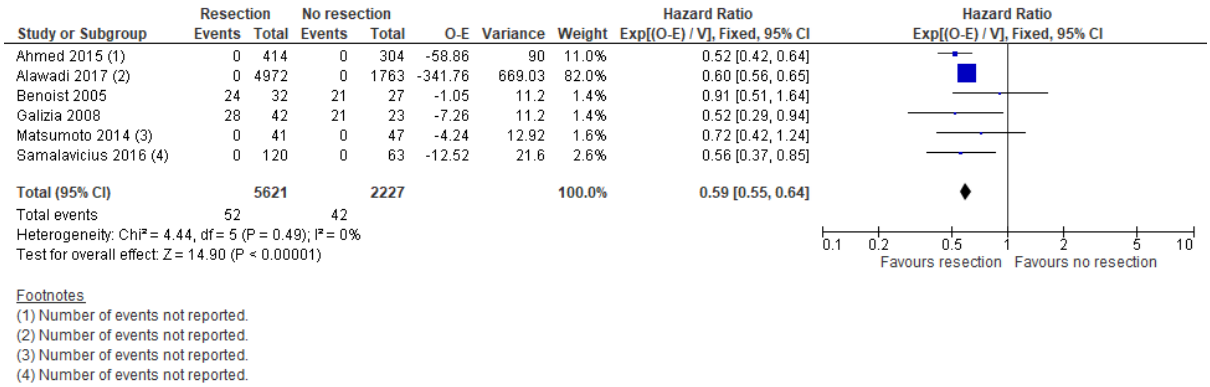
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal of Surgical Oncology, 15 (1) (no pagination), 2017 **Ref Id** 850875 **Country/ies where the study was carried out** China **Study type** Retrospective cohort study **Aim of the study** To assess whether the site of colorectal cancer is a predictor of palliative resection in asymptomatic colorectal cancer patients with unresectable metastasis. **Study dates** January 1st 2007 to December 31st 2013 **Source of funding** National Natural Science Foundation of China	Age 18–75 years; pathologically confirmed colorectal cancer; unresectable synchronous metastases, as assessed by two experienced hepatobiliary surgeons; resectable primary tumour; ECOG performance status of 0, 1, or 2; no signs and symptoms of intestinal obstruction, perforation, or bleeding; having received a full colonoscopy **Exclusion criteria** Rectal tumours below 12 cm from the anal verge; symptomatic primary tumour (severe bleeding, bowel obstruction, or tumour perforation); peritoneal or brain metastasis; history of another primary cancer	Most patients did not receive any targeted therapy.	Prognostic factors controlled for: The following variables were considered in the analysis and included in the multivariate model if found significant in the univariate analysis: primary location, T stage, lymphovascular invastion, perineural invasion, N stage, regional lymph nodes, metastasis lymph nodes, sex, diameter of liver metastasis, neoadjuvant chemotherapy, histological type, CA 119 level, number of liver metastases, CEA level, systemic chemotherapy received, if palliative resection of the primary tumour was done Outcomes: Overall survival, survival time Follow up: median 12 months (range 1 to 79 months) Data analysis: "… multivariate Cox proportional hazards regression model and the univariate Kaplan–Meier method were used to evaluate prognosis factors of OS."	controlled for primary location, diameter of liver metastasis, histological type, number of liver metastasis, CEA level, systemic chemotherapy. Survival time, months, median Subpopulation with left-sided colon cancer Resection 22 No resection 14 p=0.009 Subpopulation with right-sided colon cancer Resection 12 No resection 10 p=0.910	Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Moderate risk of bias (Interventions not described in detail and the number of patients in each group who received chemotherapy or other treatment not reported.) 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 **Other information**

5-FU: fluorouracil; ALP: Alkaline phosphatase; ASA: American Society of Anesthesiologists; BMI: body mass index; CEA: carcinoembryonic antigen; CI: confidence interval; CoC: Commission on Cancer; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; FOLFIRI: folinic acid, fluorouracil and irinotecan; FOLFOX: folinic acid, fluorouracil and oxaliplatin; G: tumour grade; GI: gastrointestinal; HR: hazard ratio; ICD-10: International Statistical Classification of Diseases and Related Health Problems (10th revision); IQR: interquartile range; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; N/A: not applicable; NCDB: National Cancer Database; OS: overall survival; PET: positron emission tomography; PTR: primary tumour resection; ROBINS-I: Risk of bias in non-randomised studies - of intervention; RR: relative risk; SD: standard deviation; TNM: cancer classification system, standing for tumour, nodal and metastasis stages; WHO: World Health Organization

Appendix E – Forest plots

Forest plots for review question: Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?

Figure 2: Resection versus no resection for asymptomatic primary tumour – Overall survival (median 1.3 to 6.4 years of follow-up; event is death from any cause)



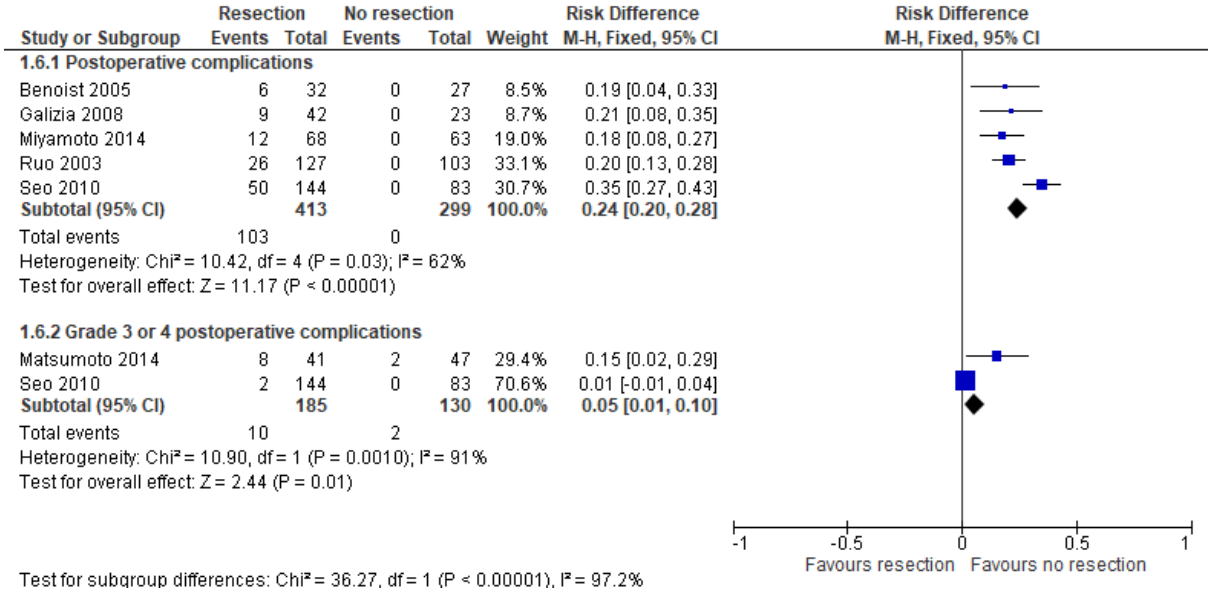
Study or Subgroup	Resection Events	Resection Total	No resection Events	No resection Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Ahmed 2015 (1)	0	414	0	304	-58.86	90	11.0%	0.52 [0.42, 0.64]
Alawadi 2017 (2)	0	4972	0	1763	-341.76	669.03	82.0%	0.60 [0.56, 0.65]
Benoist 2005	24	32	21	27	-1.05	11.2	1.4%	0.91 [0.51, 1.64]
Galizia 2008	28	42	21	23	-7.26	11.2	1.4%	0.52 [0.29, 0.94]
Matsumoto 2014 (3)	0	41	0	47	-4.24	12.92	1.6%	0.72 [0.42, 1.24]
Samalavicius 2016 (4)	0	120	0	63	-12.52	21.6	2.6%	0.56 [0.37, 0.85]
Total (95% CI)		**5621**		**2227**			**100.0%**	**0.59 [0.55, 0.64]**
Total events	52		42					

Heterogeneity: Chi² = 4.44, df = 5 (P = 0.49); I² = 0%
Test for overall effect: Z = 14.90 (P < 0.00001)

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

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

Figure 3: Resection versus no resection for asymptomatic primary tumour – Postoperative complications



Study or Subgroup	Resection Events	Resection Total	No resection Events	No resection Total	Weight	Risk Difference M-H, Fixed, 95% CI
1.6.1 Postoperative complications						
Benoist 2005	6	32	0	27	8.5%	0.19 [0.04, 0.33]
Galizia 2008	9	42	0	23	8.7%	0.21 [0.08, 0.35]
Miyamoto 2014	12	68	0	63	19.0%	0.18 [0.08, 0.27]
Ruo 2003	26	127	0	103	33.1%	0.20 [0.13, 0.28]
Seo 2010	50	144	0	83	30.7%	0.35 [0.27, 0.43]
Subtotal (95% CI)		**413**		**299**	**100.0%**	**0.24 [0.20, 0.28]**
Total events	103		0			

Heterogeneity: Chi² = 10.42, df = 4 (P = 0.03); I² = 62%
Test for overall effect: Z = 11.17 (P < 0.00001)

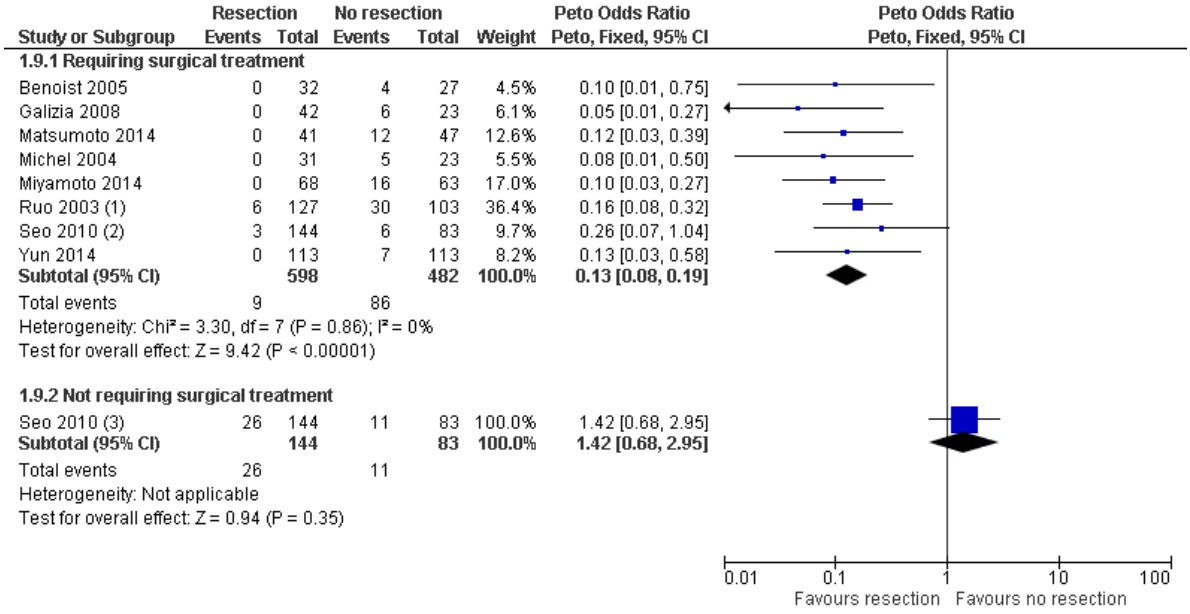
1.6.2 Grade 3 or 4 postoperative complications						
Matsumoto 2014	8	41	2	47	29.4%	0.15 [0.02, 0.29]
Seo 2010	2	144	0	83	70.6%	0.01 [-0.01, 0.04]
Subtotal (95% CI)		**185**		**130**	**100.0%**	**0.05 [0.01, 0.10]**
Total events	10		2			

Heterogeneity: Chi² = 10.90, df = 1 (P = 0.0010); I² = 91%
Test for overall effect: Z = 2.44 (P = 0.01)

Test for subgroup differences: Chi² = 36.27, df = 1 (P < 0.00001), I² = 97.2%

CI: confidence interval; M-H: Mantel Haenszel

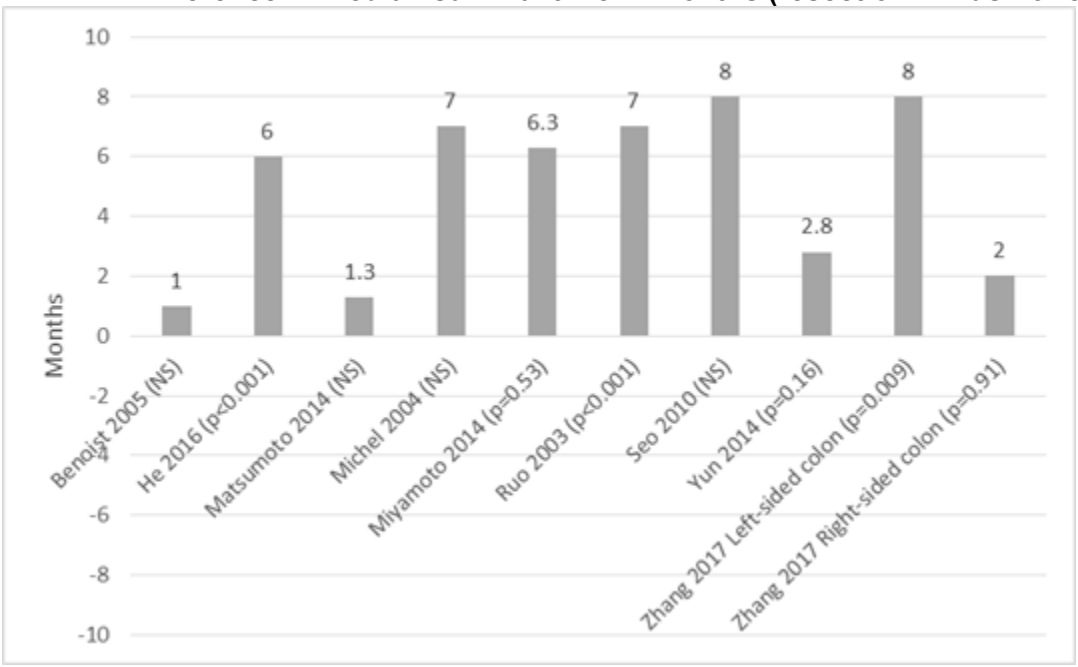
Figure 4: Resection versus no resection for asymptomatic primary tumour – Tumour-related complications



Footnotes
(1) 2 patients in the resection group developed anastomotic leak and had to be operated and 4 patients developed intestinal pobstruction...
(2) 3 patients in the resection group developed instestinal obstruction requiring surgery.
(3) RR 1.36 (0.71 to 2.61). 18 patients in the resection group developed obstruction that did not require surgery, 1 developed fistula, 7...

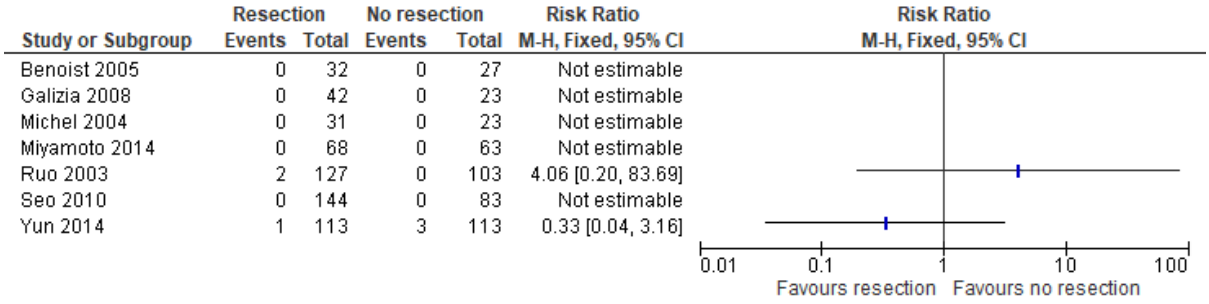
CI: confidence interval

Figure 5: Resection versus no resection for asymptomatic primary tumour – Difference in median survival time in months (resection minus no resection)



NS: not significant

Figure 6: Resection versus no resection for asymptomatic primary tumour – 30-day mortality



CI: confidence interval; M-H: Mantel Haenszel

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Appendix F – GRADE tables

GRADE tables for review question: Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?

Table 5: Clinical evidence profile for comparison primary tumour resection to no primary tumour resection

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Primary tumour resection	No resection	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Overall survival (median 1.3 to 6.4 years of follow-up; event is death from any cause)												
6	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	5621	2227	HR 0.59 (0.55 to 0.64)	At 3 years no resection 20%[1], resection 38.7% (35.7% to 41.3%)	LOW	CRITICAL
Overall survival at 2 years (event is death from any cause)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	95/127 (74.8%)	97/103 (94.2%)	HR not reported	At 2 years no resection 6%, resection 25% (p<0.001)	VERY LOW	CRITICAL
Overall survival at 5 years (event is death from any cause)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	113	113	HR not reported	At 5 years no resection 3.5%, resection 4.9% (p=0.27)	VERY LOW	CRITICAL
All-cause mortality (median 12 months of follow-up)												
1	observational studies	no serious	no serious inconsistency	no serious indirectness	serious[3]	none	122/125 (97.6%)	65/69 (94.2%)	RR 1.04 (0.97 to 1.11)	38 more per 1000 (from 28	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Primary tumour resection	No resection	Relative (95% CI)	Absolute (95% CI)		
		risk of bias								fewer to 104 more)		
Quality of life												
0	no evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Postoperative complications												
5	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103/413 (24.9%)	0/299 (0%)	Risk difference 24% (20% to 28%)	240 more per 1000 (from 200 more to 280 more)	LOW	CRITICAL
Grade 3 or 4 postoperative complications												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	10/185 (5.4%)	2/130 (1.5%)	Risk difference 5% (1% to 10%)	50 more per 1000 (from 10 more to 100 more)	VERY LOW	CRITICAL
Tumour-related complications - Requiring surgical treatment												
8	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/598 (1.5%)	86/482 (17.8%)	Peto OR 0.13 (0.08 to 0.19)	151 fewer per 1000 (from 139 fewer to 161 fewer)	LOW	CRITICAL
Tumour-related complications - Not requiring surgical treatment												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	26/144 (18.1%)	11/83 (13.3%)	RR 1.36 (0.71 to 2.61)	48 more per 1000 (from 38 fewer to 213 more)	VERY LOW	CRITICAL
Median survival time, months (Better indicated by higher values)												
9	observational studies	serious[2]	serious[4]	no serious indirectness	not assessed[5]	none	816	603	-	Median survival time in the resection group ranged from 1	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Primary tumour resection	No resection	Relative (95% CI)	Absolute (95% CI)		
										month more to 8 months more than in the no resection group		
30-day mortality												
7	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	3/557 (0.5%)	3/435 (0.7%)	Not pooled[6]	-	VERY LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; RR: relative risk
1 Survival percentage at 3 years in the control group estimated using 3-year survival data from Alawaldi 2017.
2 Some important potential confounding factors such as age, performance status and comorbidities not adjusted for in the analysis.
3 Less than 300 events.
4 Heterogeneity in results as some studies found a statistically significant difference between the arms and some did not.
5 No information available to assess imprecision.
6 Not pooled - could not adjust for potential confounders.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?

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

Appendix H – Economic evidence tables

Economic evidence tables for review question: Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?

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

Appendix J – Economic analysis

Economic evidence analysis for review question: Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative intent?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: Does surgery for the asymptomatic 3 primary tumour improve outcomes for people with metastatic colorectal 4 cancer, which cannot be treated with curative intent?

5 **Table 6: Excluded studies and reasons for their exclusion**

Study	Reason for exclusion
Ahmed, S., K. Shahid R, Pahwa, P., Kanthan, S., Reeder, B., Yadav, S., Sami, A., Haider, K., Leis, A., Survival benefit and complications of primary tumour resection (PTR) in patients with stage IV colorectal cancer (CRC) in the era of modern chemotherapy: A systematic review and meta-analysis, Journal of Clinical Oncology. Conference, 31, 2013	A conference abstract
Ahmed, S., Leis, A., Chandra-Kanthan, S., Fields, A., Reeder, B., Iqbal, N., Haider, K., Le, D., Pahwa, P., Surgical management of the primary tumour in stage IV colorectal cancer: A confirmatory retrospective cohort study, Journal of Cancer, 7, 837-845, 2016	Population partially indirect, 40% symptomatic
Ahmed, S., Leis, A., Fields, A., Chandra-Kanthan, S., Haider, K., Alvi, R., Reeder, B., Pahwa, P., Survival impact of surgical resection of primary tumour in patients with stage IV colorectal cancer: Results from a large population-based cohort study, Cancer, 120, 683-691, 2014	Population partially indirect, 40% symptomatic
Ahmed, S., Pahwa, P., Kanthan, S., Fields, A. L. A., Le, D. M., Haider, K., Reeder, B., Ahmed, O., Alvi, R., Iqbal, N., Abbas, T., Zaidi, A., Arnold, F., Yadav, S., Sami, A., Leis, A., Surgical management of the primary tumour in stage IV colorectal cancer: A validation study, Journal of Clinical Oncology. Conference, 33, 2015	A conference abstract
Ahmed, S., Shahid, R. K., Leis, A., Haider, K., Kanthan, S., Reeder, B., Pahwa, P., Should noncurative resection of the primary tumour be performed in patients with stage IV colorectal cancer? A systematic review and meta-analysis, Current Oncology, 20, e420-e441, 2013	studies assessed individually
Ahmed, S., Shahid, R. K., Leis, A., Haider, K., Pahwa, P., Should palliative resection of primary tumour be performed in patients with advanced colorectal cancer? a systematic review & meta-analysis, Annals of Oncology, 9), ix182, 2012	A conference abstract
Alawadi, Z., Phatak, U., Hu, C. Y., Bailey, C. E., Kao, L., You, Y. N., Chang, G. J., Comparative effectiveness of primary tumour resection in metastatic colon cancer: An instrumental variable analysis, Journal of Clinical Oncology. Conference, 33, 2015	A conference abstract
Alawadi, Z., Phatak, U., Hu, C., Bailey, C., Kao, L., You, Y., Chang, G. J., Comparative effectiveness of primary tumour resection in metastatic colon cancer: An instrumental variable analysis, Annals of Surgical Oncology, 1), S9, 2015	A conference abstract
Ando, T., Ayumu, H., Shunsuke, T., Hiroki, Y., Naokatsu, N., Sohachi, N., Akira, U., Hiroshi, M., Haruka, F., Shinya, K., Yoshiaki, M., Kohei, O., Toshiro, S., Clinical factors associated with acute progression of metastatic tumours after resection of the primary tumour in patients with unresectable colorectal cancer, European Journal of Cancer, 3), S82, 2015	A conference abstract
Anwar, S., Peter, M. B., Dent, J., Scott, N. A., Palliative excisional surgery for primary colorectal cancer in patients with	Studies assessed individually

incurable metastatic disease. Is there a survival benefit? A systematic review, Colorectal Disease, 14, 920-930, 2012	
Arredondo, J., Martinez, P., Baixauli, J., Pastor, C., Rodriguez, J., Pardo, F., Rotellar, F., Chopitea, A., Hernandez-Lizoain, J. L., Analysis of surgical complications of primary tumour resection after neoadjuvant treatment in stage IV colon cancer, Journal of Gastrointestinal Oncology, 5, 148-153, 2014	No comparison group
Aslam, M. I., Kelkar, A., Sharpe, D., Jameson, J. S., Ten years experience of managing the primary tumours in patients with stage IV colorectal cancers, International Journal of Surgery, 8, 305-313, 2010	Unclear if primary tumour is asymptomatic and if metastasis is incurable
Ayez, N., Alberda, W. J., Verheul, H. M., Burger, J. W., de Wilt, J. H., Verhoef, C., Surgery of the primary tumour in stage iv colorectal cancer with unresectable metastases, European Oncology and Haematology, 8, 27-31, 2012	Narrative review
Bajwa, A., Blunt, N., Vyas, S., Suliman, I., Bridgewater, J., Hochhauser, D., Ledermann, J. A., O'Bichere, A., Primary tumour resection and survival in the palliative management of metastatic colorectal cancer, European Journal of Surgical Oncology, 35, 164-167, 2009	Surgery was performed for symptomatic primary tumours.
Beham, A., Rentsch, M., Pulmann, K., Mantouvalou, L., Spatz, H., Schlitt, H. J., Obed, A., Survival benefit in patients after palliative resection vs non-resection colon cancer surgery, World Journal of Gastroenterology, 12, 6634-6638, 2006	Indirect population, 60% with symptomatic primary tumour
Benefits of upfront primary tumour resection (UPTR) according to sidedness in mCRC: retrospective analyses of TTD MACRO-2 and PLANET randomised trials, Annals of Oncology, Conference: 42nd ESMO Congress, ESMO 2017. Spain. 28, v167, 2017	Conference abstract
Birkett, R. T., O'Donnell, M. M. T., Epstein, A. J., Saur, N. M., Bleier, J. I. S., Paulson, E. C., Elective colon resection without curative intent in stage IV colon cancer, Surgical Oncology, 28, 110-115, 2019	Predictive factors for receiving or not receiving elective resection of the primary tumour.
Boselli, C., Renzi, C., Gemini, A., Castellani, E., Trastulli, S., Desiderio, J., Corsi, A., Barberini, F., Cirocchi, R., Santoro, A., Parisi, A., Redler, A., Noya, G., Surgery in asymptomatic patients with colorectal cancer and unresectable liver metastases: The authors' experience, OncoTargets and Therapy, 6, 267-272, 2013	Not clear what variables were accounted for the in the multivariate model, also not clear if overall mortality/survival was analysed with Cox regression (hazard ratio) or logistic regression (RR)
Breugom, A. J., Bastiaannet, E., Guren, M. G., Korner, H., Boelens, P. G., Dekker, F. W., Kapiteijn, E., Gelderblom, H., Larsen, I. K., Liefers, G. J., Van De Velde, C. J., Resection of the primary tumour for asymptomatic incurable metastatic colorectal cancer - A EURECCA international comparison, European Journal of Surgical Oncology, 42 (9), S86-S87, 2016	A conference abstract
Cao, G., Zhou, W., Song, Z., Huang, X., Novel scoring system evaluating palliative primary tumour resection provides survival benefits for patients with unresectable metastatic colorectal cancer, Diseases of the Colon and Rectum, 61 (5), e248-e249, 2018	A conference abstract
Cellini, C., Hunt, S. R., Fleshman, J. W., Birnbaum, E. H., Bierhals, A. J., Mutch, M. G., Stage IV Rectal Cancer with Liver Metastases: Is There a Benefit to Resection of the Primary Tumour?, World Journal of Surgery, 1-7, 2010	Population not relevant, majority had a curable metastatic disease
Cetin, B., Kaplan, M. A., Berk, V., Tufan, G., Benekli, M., Isikdogan, A., Ozkan, M., Coskun, U., Buyukberber, S., Bevacizumab-containing chemotherapy is safe in patients with	Did not control for confounders

unresectable metastatic colorectal cancer and a synchronous asymptomatic primary tumour, Japanese Journal of Clinical Oncology, 43, 28-32, 2013	
Chafai, N., Chan, C. L. H., Bokey, E. L., Dent, O. F., Sinclair, G., Chapuis, P. H., What factors influence survival in patients with unresected synchronous liver metastases after resection of colorectal cancer?, Colorectal Disease, 7, 176-181, 2005	Population indirect/unclear but appears to be mostly with symptomatic primary tumour
Chan, T. W., Brown, C., Ho, C. C., Gill, S., Primary tumour resection in patients presenting with metastatic colorectal cancer: Analysis of a provincial population-based cohort, American Journal of Clinical Oncology: Cancer Clinical Trials, 33, 52-55, 2010	Population not relevant, symptomatic primary tumour
Chang, H. S., Lee, K. Y., Lau, J. W. L., Gwee, Y. X., Chong, C. S., Modern day palliative chemotherapy for metastatic colorectal cancer (MCRC) in an Asian population. Does colonic resection affect survival? and a retrospective cohort study, Gastroenterology, 152 (5 Supplement 1), S1258, 2017	A conference abstract
Chen, G., Zhang, R. X., Li, Y. H., Lin, J. Z., Kong, L. H., Wang, Z., Ding, P. R., Wan, D., Pan, Z. Z., Deng, Y., Wang, H., Peng, J., Qiu, M., Wang, C., Zhang, J., Li, W., Yuan, Y., Wang, W., Multi-center, randomized, controlled, open-label effectiveness study of primary tumour resection or not in asymptomatic colorectal cancer with unresectable metastatic disease, Journal of Clinical Oncology. Conference, 33, 2015	A conference abstract of a trial protocol. This trial (NCT02149784) is still recruiting (according to clinicaltrials.gov)
Chew, M. H., Teo, J. Y., Kabir, T., Koh, P. K., Eu, K. W., Tang, C. L., Stage IV Colorectal Cancers: An Analysis of Factors Predicting Outcome and Survival in 728 cases, Journal of Gastrointestinal Surgery, 16, 603-612, 2012	No relevant comparison, population unclear
Cirocchi, Roberto, Trastulli, Stefano, Abraha, Iosief, Vettoretto, Nereo, Boselli, Carlo, Montedori, Alessandro, Parisi, Amilcare, Noya, Giuseppe, Platell, Cameron, Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable Stage IV colorectal cancer, Cochrane Database of Systematic Reviews, 2012	Cochrane review not sufficiently reported; included studies were extracted individually
Clancy, C., Burke, J. P., Barry, M., Calvin Coffey, J., The effect of resection of the primary tumour for stage IV colorectal cancer on patient survival: A systematic review and meta-analysis, Colorectal Disease, 2), 16, 2014	A conference abstract
Clancy, C., Burke, J. P., Barry, M., Kalady, M. F., Calvin Coffey, J., A Meta-Analysis to Determine the Effect of Primary Tumour Resection for Stage IV Colorectal Cancer with Unresectable Metastases on Patient Survival, Annals of Surgical Oncology, 21, 3900-3908, 2014	Studies assessed individually
Cook, A. D., Single, R., McCahill, L. E., Surgical resection of primary tumours in patients who present with stage IV colorectal cancer: An analysis of surveillance, epidemiology, and end results data, 1988 to 2000, Annals of Surgical Oncology, 12, 637-645, 2005	Population unclear, the study did not differentiate between asymptomatic and symptomatic primary tumour
Costi, R., Mazzeo, A., Di Mauro, D., Veronesi, L., Sansebastiano, G., Violi, V., Roncoroni, L., Sarli, L., Palliative resection of colorectal cancer: Does it prolong survival?, Annals of Surgical Oncology, 14, 2567-2576, 2007	Comparison is non-resective surgery and thus not according to review protocol. Also, 35% of the patients had symptomatic primary tumours
Cotte, E., Passot, G., Glehen, O., GRECCAR 8: Impact on survival of the primary tumour resection in rectal cancer with unresectable metastasis: A randomized multicentre study, Colorectal Disease, 15, 118, 2013	A conference abstract of a trial protocol. This trial (NCT02314182) is still recruiting (according to clinicaltrials.gov)

Cotte, E., Villeneuve, L., Passot, G., Boschetti, G., Bin-Dorel, S., Francois, Y., Glehen, O., Rullier, E., Rouanet, P., Panis, Y., Tuech, J. J., De Chaisemartin, C., Sielezneff, I., Kirzin, S., Faucheron, J. l, Pezet, D., Mariette, C., Regimbeau, J. M., Rivoire, M., Lefevre, J., Meunier, B., Deplanque, G., Porcheron, J., Ortega-Deballon, P., Pocard, M., Bereder, J. M., Baranger, B., Evrard, S., Paineau, J., Kianmanesh, R., Tougeron, D., GRECCAR 8: Impact on survival of the primary tumour resection in rectal cancer with unresectable synchronous metastasis: A randomized multicentre study, BMC Cancer, 15 (1) (no pagination), 2015	A trial protocol, this trial (NCT02314182) is still recruiting (according to clinicaltrials.gov)
Cummins, E. R., Vick, K. D., Poole, G. V., Incurable colorectal carcinoma: the role of surgical palliation, American Surgeon, 70, 433-7, 2004	Population not relevant, symptomatic primary tumour
Daskalakis, K., Karakatsanis, A., Hessman, O., Stuart, H. C., Welin, S., Tiensuu Janson, E., Oberg, K., Hellman, P., Norlen, O., Stalberg, P., Association of a Prophylactic Surgical Approach to Stage IV Small Intestinal Neuroendocrine Tumours With Survival, JAMA oncology, 4, 183-189, 2018	Population not relevant: neuroendocrine tumours.
de Mestier, L., Manceau, G., Neuzillet, C., Bachet, J. B., Spano, J. P., Kianmanesh, R., Vaillant, J. C., Bouche, O., Hannoun, L., Karoui, M., Primary tumour resection in colorectal cancer with unresectable synchronous metastases: A review, World Journal of Gastrointestinal Oncology, 6, 156-69, 2014	Studies assessed individually
De Mestier, L., Neuzillet, C., Pozet, A., Desot, E., Deguelte-Lardiere, S., Volet, J., Karoui, M., Kianmanesh, R., Bonnetain, F., Bouche, O., Is primary tumour resection associated with a longer survival in colon cancer and unresectable synchronous metastases? A 4-year multicentre experience, European Journal of Surgical Oncology, 40, 685-691, 2014	Relevance of population unclear, not reported if primary tumour is symptomatic or asymptomatic. Inclusion was based on first-line chemotherapy received.
De Wilt, J. H. W., Verhoef, C., Punt, C. J. A., T'Lam-Boer, J. H. W., Yilmaz, M., Mol, L., Koopman, M., The CAIRO4 study: The role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer-A randomized phase III study of the Dutch Colorectal Cancer Group (DCCG), Journal of Clinical Oncology. Conference, 34, 2016	A conference abstract. This trial (NCT01606098) is still recruiting (according to clinicaltrials.gov)
Desot, E., Delmas, C., Marquis, E., Garcia, B., Geoffroy, P., Abdelli, N., Dubroeucq, O., Lagarde, S., Bouche, O., Should the primary tumour be resected in patients with unresectable synchronous metastasis of colorectal cancer? Prognostic retrospective multicentric study of 128 patients, Annals of Oncology, 8), viii204, 2010	A conference abstract
Dorajoo, S. R., Tan, W. J. H., Koo, S. X., Tan, W. S., Chew, M. H., Tang, C. L., Wee, H. L., Yap, C. W., A scoring model for predicting survival following primary tumour resection in stage IV colorectal cancer patients with unresectable metastasis, International Journal of Colorectal Disease, 31, 235-245, 2016	No relevant comparison
Duraker, N., Civelek Caynak, Z., Hot, S., The impact of primary tumour resection on overall survival in patients with colorectal carcinoma and unresectable distant metastases: A prospective cohort study, International Journal of Surgery, 12, 737-741, 2014	Population unclear/not relevant, all patients had an operation but not all of the operations were resections of the primary tumour. At least 15% had symptomatic primary tumours that required urgent operation
Eisenberger, A., Whelan, R. L., Neugut, A. I., Survival and symptomatic benefit from palliative primary tumour resection in	Studies assessed individually

patients with metastatic colorectal cancer: A review, International Journal of Colorectal Disease, 23, 559-568, 2008	
Elagili, F., Stocchi, L., Kalady, M., Dietz, D., Management of asymptomatic stage IV rectal cancer: Should the primary tumour be resected?, Colorectal Disease, 2), 119, 2014	full text is an abstract
Faron, M., Bourredjem, A., Pignon, J. P., Bouche, O., Douillard, J. Y., Adenis, A., Elias, D., Ducreux, M., Impact on survival of primary tumour resection in patients with colorectal cancer and unresectable metastasis: Pooled analysis of individual patients' data from four randomized trials, Journal of Clinical Oncology. Conference, 30, 2012	Full text is an abstract
Faron, M., Pignon, J. P., Malka, D., Bourredjem, A., Douillard, J. Y., Adenis, A., Elias, D., Bouche, O., Ducreux, M., Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials, European Journal of Cancer, 51, 166-176, 2015	Population unclear/not relevant, does not differentiate between symptomatic and asymptomatic primary tumour
Ferrand, F., Malka, D., Bourredjem, A., Allonier, C., Bouche, O., Louafi, S., Boige, V., Mousseau, M., Raoul, J. L., Bedenne, L., Leduc, B., Deguiral, P., Faron, M., Pignon, J. P., Ducreux, M., Impact of primary tumour resection on survival of patients with colorectal cancer and synchronous metastases treated by chemotherapy: Results from the multicenter, randomised trial Federation Francophone de Cancerologie Digestive 9601, European Journal of Cancer, 49, 90-97, 2013	Population unclear/not relevant, does not differentiate between symptomatic and asymptomatic primary tumour
Ferreira, M. B. A., Castro, N. C., Peres, S. V., Viana, L. S., Analysis of overall survival among patients with metastatic colorectal cancer, with and without undergoing elective colectomy, Annals of Oncology, 8), viii205, 2010	A conference abstract
Fields, A. C., Lu, P., Vierra, B. M., Hu, F., Irani, J., Bleday, R., Goldberg, J. E., Nash, G. M., Melnitchouk, N., Survival in Patients with High-Grade Colorectal Neuroendocrine Carcinomas: The Role of Surgery and Chemotherapy, Annals of Surgical Oncology, 31, 31, 2019	Population not relevant: neuroendocrine tumours.
Frago, R., Kreisler, E., Espin-Basany, E., Biondo, S., Basany, E. E., Pons, L. V., Carrion, J. A., de Laspra, E. C. D., de la Portilla de Juan, F., Roman, M. P., Calvo, A. P. C. P., Navascues, J. M. E., Sanz, C. M., Marquez, M. F., Lozano, M. A. C., Ausas, I. C., Gallego, M. A., Cazador, A. C., Macias, A. E., Lopez, L. M., Alvarado, N. C., Impact of resection versus no resection of the primary tumour on survival in patients with colorectal cancer and synchronous unresectable metastases: protocol for a randomized multicenter study (CR4), International Journal of Colorectal Disease, 32, 1085-1090, 2017	A trial protocol, trial (NCT02015923) not yet completed (according to clinicaltrials.gov). Population unclear, does not differentiate between symptomatic and asymptomatic primary tumour
Furuhata, T., Okita, K., Nishidate, T., Hirata, K., Ohnishi, H., Kobayashi, H., Kotake, K., Sugihara, K., Oncological benefit of primary tumour resection with high tie lymph node dissection in unresectable colorectal cancer with synchronous peritoneal metastasis: a propensity score analysis of data from a multi-institute database, International Journal of Clinical Oncology, 20, 922-927, 2015	No comparison group
Gresham, G., Renouf, D. J., Chan, M., Kennecke, H. F., Lim, H. J., Brown, C., Cheung, W. Y., Association between palliative resection of the primary tumour and overall survival in a population-based cohort of metastatic colorectal cancer patients, Annals of Surgical Oncology, 21, 3917-23, 2014	Population unclear/not relevant, does not differentiate between symptomatic and asymptomatic primary tumour

Gulack, B. C., Nussbaum, D. P., Keenan, J. E., Ganapathi, A. M., Sun, Z., Worni, M., Migaly, J., Mantyh, C. R., Surgical Resection of the Primary Tumour in Stage IV Colorectal Cancer Without Metastasectomy Is Associated with Improved Overall Survival Compared with Chemotherapy/Radiation Therapy Alone, Diseases of the Colon and Rectum, 59, 299-305, 2016	Population unclear/not relevant, does not differentiate between symptomatic and asymptomatic primary tumour
Ha, G. W., Kim, J. H., Lee, M. R., Meta-analysis of oncologic effect of primary tumour resection in patients with unresectable stage IV colorectal cancer in the era of modern systemic chemotherapy, Annals of surgical treatment and research, 95, 64-72, 2018	Includes patients with symptomatic primary tumours.
Huh, J. W., Cho, C. K., Kim, H. R., Kim, Y. J., Impact of resection for primary colorectal cancer on outcomes in patients with synchronous colorectal liver metastases, Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, 14, 1258-1264, 2010	No relevant comparison and population not relevant, metastatic disease was resectable in most of the patients
Ichikawa, Y., Goto, A., Kobayashi, N., Ota, M., Tokuhisa, M., Ishibe, A., Watanabe, J., Watanabe, K., Ishikawa, T., Tanaka, K., Akiyama, H., Fujii, S., Endo, I., Does resection of primary lesions show survival benefit for stage IV colorectal cancer patients with unresectable metastases?, Hepato-Gastroenterology, 60, 1945-1949, 2013	Population unclear, not clear if primary tumour symptomatic or asymptomatic
Ishihara, S., Hayama, T., Yamada, H., Nozawa, K., Matsuda, K., Miyata, H., Yoneyama, S., Tanaka, T., Tanaka, J., Kiyomatsu, T., Kawai, K., Nozawa, H., Kanazawa, T., Kazama, S., Yamaguchi, H., Sunami, E., Kitayama, J., Hashiguchi, Y., Sugihara, K., Watanabe, T., Prognostic impact of primary tumour resection and lymph node dissection in stage IV colorectal cancer with unresectable metastasis: A propensity score analysis in a multicenter retrospective study, Annals of Surgical Oncology, 21, 2949-2955, 2014	Population unclear/not relevant, does not differentiate between symptomatic and asymptomatic primary tumour
Ishihara, S., Nishikawa, T., Tanaka, T., Tanaka, J., Kiyomatsu, T., Kawai, K., Hata, K., Nozawa, H., Kazama, S., Yamaguchi, H., Sunami, E., Kitayama, J., Sugihara, K., Watanabe, T., Benefit of primary tumour resection in stage IV colorectal cancer with unresectable metastasis: a multicenter retrospective study using a propensity score analysis, International Journal of Colorectal Disease., 29, 2015	Population unclear/not relevant, does not differentiate between symptomatic and asymptomatic primary tumour
Jang, H. S., Ju, J. K., Kim, C. H., Lee, S. Y., Kim, H. R., Kim, Y. J., Palliative resection of a primary tumour in patients with unresectable colorectal cancer: could resection type improve survival?, Annals of surgical treatment and research, 91, 172-177, 2016	No relevant comparison, all patients underwent some type of resection
Jimenez, F., Conde, M., Cerdan, C., Garcia, M., Ortega, M., Zuloaga, J., Esteban, F., Sanz, R., Sanz, G., Cerdan, J., Rectal cancer with synchronous liver metastasis: Is surgical resection of the primary tumour justified? 15-year results, Colorectal Disease, 2), 51, 2012	A conference abstract
Ju, J., Yeo, K. H., Kim, K. T., Palliative resection of primary tumour in incurable colorectal cancer: A case-controlled study as to whether complete or excision, European Journal of Surgical Oncology, 40 (11), S116-S117, 2014	A conference abstract
Julien, L., Ternent, C., Nelson, R., Beaty, J., Thorson, A., Reyes, J., Blatchford, G., Shashidharan, M., Is there a survival advantage for elective primary tumour resection in asymptomatic patients with incurable stage IV colorectal cancer?, Diseases of the Colon and Rectum, 53 (4), 667, 2010	A conference abstract

Kang, W., Kim, C., Palliative resection of primary tumour in incurable colorectal cancer: A case-controlled study as to whether complete or excision, Colorectal Disease, 2), 69, 2015	A conference abstract
Karoui, M., Roudot-Thoraval, F., Mesli, F., Mitry, E., Aparicio, T., DesGuetz, G., Louvet, C., Landi, B., Tiret, E., Sobhani, I., Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: Results of a multicentric study, Diseases of the Colon and Rectum, 54, 930-938, 2011	Patients were symptomatic
Kaufman, M. S., Radhakrishnan, N., Roy, R., Gecelter, G., Tsang, J., Thomas, A., Nissel-Horowitz, S., Mehrotra, B., Influence of palliative surgical resection on overall survival in patients with advanced colorectal cancer: a retrospective single institutional study, Colorectal DisColorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland, 10, 498-502, 2008	Patients were symptomatic
Kim, C. W., Baek, J. H., Choi, G. S., Yu, C. S., Kang, S. B., Park, W. C., Lee, B. H., Kim, H. R., Oh, J. H., Kim, J. H., Jeong, S. Y., Ahn, J. B., Baik, S. H., The role of primary tumour resection in colorectal cancer patients with asymptomatic, synchronous unresectable metastasis: Study protocol for a randomized controlled trial, Trials, 17 (1) (no pagination), 2016	A trial protocol. The RCT (NCT01978249) was terminated early because of difficulty recruiting (according to clinicaltrials.gov)
Kim, M. S., Chung, M., Ahn, J. B., Kim, C. W., Cho, M. S., Shin, S. J., Baek, S. J., Hur, H., Min, B. S., Baik, S. H., Kim, N. K., Clinical significance of primary tumour resection in colorectal cancer patients with synchronous unresectable metastasis, Journal of Surgical OncologyJ Surg Oncol, 110, 214-221, 2014	26% of the patients in the resection group symptomatic
Kim, S. K., Lee, C. H., Lee, M. R., Kim, J. H., Multivariate analysis of the survival rate for treatment modalities in incurable stage IV colorectal cancer, Journal of the Korean Society of Coloproctology, 28, 35-41, 2012	Patients were symptomatic
Kleespies, A., Fuessl, K. E., Seeliger, H., Eichhorn, M. E., Muller, M. H., Rentsch, M., Thasler, W. E., Angele, M. K., Kreis, M. E., Jauch, K. W., Determinants of morbidity and survival after elective non-curative resection of stage IV colon and rectal cancer, International Journal of Colorectal Disease, 24, 1097-1109, 2009	No relevant population or comparison, all had resections of the primary tumour
Kodaz, H., Erdogan, B., Hacibekiroglu, I., Turkmen, E., Tozkir, H., Albayrak, D., Uzunoglu, S., Cicin, I., Primary Tumour Resection Offers Higher Survival Advantage in KRAS Mutant Metastatic Colorectal Cancer Patients, Hepato-Gastroenterology, 62, 876-879, 2015	Unclear whether patients were asymptomatic
Konyalian, V. R., Rosing, D. K., Haukoos, J. S., Dixon, M. R., Sinow, R., Bhaheetharan, S., Stamos, M. J., Kumar, R. R., The role of primary tumour resection in patients with stage IV colorectal cancer, Colorectal Disease, 9, 430-437, 2007	Population not relevant, more than half of the patients with symptomatic primary tumour
Korkmaz, L., Coskun, H., Dane, F., Karabulut, B., Karaagac, M., Cabuk, D., Karabulut, S., Aykan, N. F., Doruk, H., Avci, N., Turhal, N. S., Artac, M., Kras-mutation influences outcomes for palliative primary tumour resection in advanced colorectal cancer-a Turkish Oncology Group study, Surgical Oncology, 27, 485-489, 2018	Unclear whether patients had symptomatic primary tumours.
Kuo, L. J., Leu, S. Y., Liu, M. C., Jian, J. J. M., Cheng, S. H., Chen, C. M., How Aggressive Should We Be in Patients with Stage IV Colorectal Cancer?, Diseases of the Colon and Rectum, 46, 1646-1652, 2003	Population not relevant, metastatic disease not necessarily incurable and primary tumour not necessarily asymptomatic

Lau, J. W. L., Chang, H. S. Y., Lee, K. Y., Gwee, Y. X., Lee, W. Q., Chong, C. S., Survival outcomes following primary tumour resection for patients with incurable metastatic colorectal carcinoma: Experience from a single institution, Journal of Digestive Diseases, 19, 550-560, 2018	Unclear whether patients had symptomatic primary tumours.
Lau, J. W. L., Chang, H. S., Lee, K. Y., Lee, W. Q. S., Chong, C. S., Primary tumour resection confers benefit on the overall survival of patients with metastatic colorectal cancer (MCRC) and unresectable metastases, Gastroenterology, 152 (5 Supplement 1), S1302, 2017	A conference abstract
Lee, K. C., Ou, Y. C., Hu, W. H., Liu, C. C., Chen, H. H., Meta-analysis of outcomes of patients with stage IV colorectal cancer managed with chemotherapy/ radiochemotherapy with and without primary tumour resection, OncoTargets and Therapy, 9, 7059-7069, 2016	Studies assessed individually
Lewis, A., Nelson, R. A., Lai, L. L., Resection of primary tumour in patients who present with stage IV colon cancer may result in improved survival, Journal of Clinical Oncology. Conference, 33, 2015	A conference abstract
Li, L. T., Cormier, J. N., Feig, B. W., Petersen, N. J., Sansgiry, S., Artinyan, A., Berger, D. H., Anaya, D. A., Defining the role of primary tumour resection and chemotherapy in patients 75 and over presenting with metastatic colon cancer, Annals of Surgical Oncology, 1), S140-S141, 2012	A conference abstract
Lim, C., Doussot, A., Osseis, M., Esposito, F., Salloum, C., Calderaro, J., Tournigand, C., Azoulay, D., Bevacizumab improves survival in patients with synchronous colorectal liver metastases provided the primary tumour is resected first, Clinical and Translational Oncology, 1-6, 2018	Intervention not relevant - addition of bevacizumab
Lin, B. S., Ziogas, A., Seery, T. E., Stamos, M. J., Zell, J. A., Role of surgical resection among chemotherapy-treated patients with colorectal cancer stage IV disease: A survival analysis, Journal of Clinical Oncology. Conference: ASCO Annual Meeting, 29, 2011	A conference abstract
Lourdes, C. U., Isabel, P., Ana, C., De Eulate Vanesa, A., Raquel, J., Itziar, T. G., Carmen, V., De Pace Laura, A., Lourdes, G., Fernando, R., Surgical resection of primary tumours in patients with stage IV colorectal cancer and unresectable liver metastases, Annals of Oncology, 28 (Supplement 3), iii121-iii122, 2017	A conference abstract
Maeda, K., Shibutani, M., Otani, H., Nagahara, H., Sugano, K., Ikeya, T., Amano, R., Kimura, K., Sakurai, K., Kubo, N., Muguruma, K., Tanaka, H., Inoue, T., Hirakawa, K., Prognostic value of preoperative inflammation-based prognostic scores in patients with stage IV colorectal cancer who undergo palliative resection of asymptomatic primary tumours, Anticancer Research, 33, 5567-5574, 2013	No comparison group, all patients had a resective surgery
Maeda, K., Shibutani, M., Otani, H., Nagahara, H., Sugano, K., Ikeya, T., Kubo, N., Amano, R., Kimura, K., Muguruma, K., Tanaka, H., Hirakawa, K., Low nutritional prognostic index correlates with poor survival in patients with stage IV colorectal cancer following palliative resection of the primary tumour, World Journal of Surgery, 38, 1217-1222, 2014	No comparison group, all patients had a resective surgery
Manceau, G, Karoui, M, Bachet, J-B, Spano, J-P, Bardier, A, Dubreuil, O, Wagner, M, Vaillant, J-C, Hannoun, L, Asymptomatic colon cancer with unresectable synchronous liver metastases: should the primary tumour be resected?, Hepato-Gastro and Oncologie Digestive, 20, 424-430, 2013	Full text in French

Maroney, S., Chavez De Paz, C., Mark, R. E., Garberoglio, C., Raskin, E., Maheswari, S., Solomon, N., Benefit of surgical resection of the primary tumour in stage iv colorectal cancer with unresectable metastasis, Annals of Surgical Oncology, 1), S95, 2016	A conference abstract
Maroney, S., de Paz, C. C., Reeves, M. E., Garberoglio, C., Raskin, E., Senthil, M., Namm, J. P., Solomon, N., Benefit of Surgical Resection of the Primary Tumour in Patients Undergoing Chemotherapy for Stage IV Colorectal Cancer with Unresected Metastasis, Journal of Gastrointestinal Surgery, 22, 460-466, 2018	A conference abstract
Mege, D., Manceau, G., Bridoux, V., Venara, A., Voron, T., Brunetti, F., Sielezneff, I., Karoui, M., Berger, A., Ouaissi, M., Codjia, T., Dazza, M., Gagnat, G., Hamel, S., Mallet, L., Martre, P., Philouze, G., Roussel, E., Tortajada, P., Dumaine, A. S., Heyd, B., Lakkis, Z., Paquette, B., de' Angelis, N., Esposito, F., Lizzi, V., Michot, N., Denost, Q., Tresallet, C., Tetard, O., Sabbagh, C., Rivier, P., Fayssal, E., Collard, M., Moszkowicz, D., Peschaud, F., Etienne, J. C., loge, L., Beyer-Berjot, L., Bege, T., Corte, H., Bonnet, J., D'Annunzio, E., Humeau, M., Issard, J., Munoz, N., Abba, J., Jafar, Y., Lacaze, L., Sage, P. Y., Susoko, L., Trilling, B., Arvieux, C., Mauvais, F., Severino, B. U., Pitel, S., Vauchaussade de Chaumont, A., Badic, B., Blanc, B., Bert, M., Rat, P., Ortega-Deballon, P., Chau, A., Dejeante, C., Mariette, C., Piessen, G., Gregoire, E., Alfarai, A., Lefevre, J., Cabau, M., David, A., Kadoche, D., Dufour, F., Goin, G., Goudard, Y., Pauleau, G., Sockeel, P., De la Villeon, B., Pautrat, K., Eveno, C., Brouquet, A., Couchard, A. C., Balbo, G., Mabrut, J. Y., Bellinger, J., Bertrand, M., Aumont, A., Duchalais, E., Messiere Adrien Tranchart, A. S., Cazauran, J. B., Pichot-Delahaye, V., Dubuisson, V., Maggiori, L., Boumediene, B. D., Fuks, D., Kahn, X., Huart, E., Catheline, J. M., Lailler, G., Baraket, O., Baque, P., Diaz de Cerio, J. M., Bernard Maes, P. M., Fernoux, P., Guillem, P., Chatelain, E., de Saint Roman, C., Fixot, K., Surgical management of obstructive right-sided colon cancer at a national level results of a multicenter study of the French Surgical Association in 776 patients, European Journal of Surgical Oncology, 44, 1522-1531, 2018	Symptomatic colon cancer.
Mehta, H. B., Vargas, G. M., Adhikari, D., Dimou, F., Riall, T. S., Comparative effectiveness of chemotherapy vs resection of the primary tumour as the initial treatment in older patients with Stage IV colorectal cancer, Colorectal Disease, 19, O210-O218, 2017	The curability status of the metastasis not clear but 25% of the patients in the resection group had metastesectomy, therefore, not relevant
Mehta, H. B., Vargas, G. M., Tamirisa, N. P., Adhikari, D., Brown, K. M., Riall, T. S., Comparative effectiveness of chemotherapy versus resection of the primary tumour as the initial treatment modality in older patients with stage IV colorectal cancer, Pharmacoepidemiology and Drug Safety, 1), 224-225, 2015	A conference abstract
Mik, M., Dziki, L., Galbfach, P., Trzcinski, R., Sygut, A., Dziki, A., Resection of the primary tumour or other palliative procedures in incurable stage IV colorectal cancer patients?, Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland, 12, e61-67, 2010	Comparison is non-resective surgical procedures such as loop colostomy and therefore not according to the review protocol
Okazaki, S., Yasui, H., Fukuda, M., Yamaguchi, T., Impact of primary tumour resection on survival for incurable and asymptomatic stage iv colorectal cancer and incidence of primary tumour related complications in unresected patients:	A conference abstract

Results of a single-institution retrospective study, Annals of Oncology, 11), xi160-xi161, 2012	
Oweira, H., Giryes, A., Mannhart, M., Decker, M., Abdel-Rahman, O., Impact of Time to Start Systemic Therapy on the Outcomes of Patients with Metastatic Colorectal Cancer Treated with First Line FOLFOX Chemotherapy; a Patient-Level Pooled Analysis of Two Clinical Trials, Expert review of gastroenterology & hepatology, 12, 1069â□□1074, 2018	Comparison not in PICO.
Park, E. J., Baek, J. H., Choi, G. S., Park, W. C., Kang, S. B., Lee, B. H., Kim, H. R., Oh, J. H., Kim, J. H., Jeong, S. Y., Baik, S. H., Lee, K. Y., Ahn, J. B., Kim, N. K., The role of primary tumour resection in colorectal cancer patients with asymptomatic, synchronous unresectable metastasis: A multicenter, randomized controlled trial, Colorectal Disease, 19 (Supplement 2), 5, 2017	A conference abstract. This RCT (NCT01978249) was terminated early due to difficulty recruiting patients
Phatak, U. R., Hu, C., You, Y., Feig, B. W., Skibber, J. M., Rodriguez-Bigas, M. A., Cormier, J. M., Kao, L. S., Chang, G. J., Primary tumour resection inmetastatic colon cancer: A propensity score analysis of the national cancer data base, Journal of Surgical Research, 186 (2), 641, 2014	A conference abstract
Platell, C., Gebski, V., Solomon, M., Hewett, P., Price, T., Quiene, S., Wilson, K., Tebbutt, N., The super study- Multicentre study of evaluating the role of palliative surgical resection of the primary tumour in patients with metastatic colorectal cancer, Asia-Pacific Journal of Clinical Oncology, 6, 187, 2010	A conference abstract
Poultsides, G. A., Paty, P. B., Reassessing the need for primary tumour surgery in unresectable metastatic colorectal cancer: Overview and perspective, Therapeutic Advances in Medical Oncology, 3, 35-42, 2011	Narrative review
Rahbari, N. N., Lordick, F., Fink, C., Bork, U., Stange, A., Jager, D., Luntz, S. P., Englert, S., Rossion, I., Koch, M., Buchler, M. W., Kieser, M., Weitz, J., Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS - a randomised controlled multicentre trial (ISRCTN30964555), BMC Cancer, 12 (no pagination), 2012	A trial protocol, the trial (ISRCTN30964555) recruitment has ended but no publications with results have been identified
Royle, T., Evison, F., Wilkie, R., Keh, C., Survival after primary colorectal cancer resection with liver metastases at diagnosis: Should octogenarians be counselled not to have surgery? A UK population observational study, Colorectal Disease, 2), 62, 2014	A conference abstract
Sada, Y., Duan, Z., El-Serag, H., Davila, J., Utilization and outcomes of primary tumour surgery for stage IV colon cancer in the United States: A population-based study, Journal of Clinical Oncology. Conference, 30, 2012	A conference abstract
Scabini, S., Rimini, E., Massobrio, A., Romairone, E., De Marini, L., Ferrando, V., Resective surgery of primary tumour in patients with Stage IV colorectal cancer: A retrospective study in a single institution, Colorectal Disease, 2), 58, 2012	A conference abstract
Scheer, M. G. W., Sloots, C. E. J., Van der Wilt, G. J., Ruers, T. J. M., Management of patients with asymptomatic colorectal cancer and synchronous irresectable metastases, Annals of Oncology, 19, 1829-1835, 2008	Studies assessed individually
Scoggins, C. R., Meszoely, I. M., Blanke, C. D., Beauchamp, R. D., Leach, S. D., Nonoperative management of primary colorectal cancer in patients with stage IV disease, Annals of Surgical Oncology, 6, 651-657, 1999	Did not control for confounders

Semple, C., Fitzpatrick, D., Campbell, J., Gavin, A., Does resection of the primary tumour in metastatic colorectal cancer confer a survival benefit?, Colorectal Disease, 6), 42, 2011	A conference abstract
Shida, D., Boku, N., Tanabe, T., Yoshida, T., Tsukamoto, S., Takashima, A., Kanemitsu, Y., Primary Tumour Resection for Stage IV Colorectal Cancer in the Era of Targeted Chemotherapy, Journal of Gastrointestinal Surgery, 27, 27, 2018	Includes patients with symptomatic primary tumours.
Shida, D., Hamaguchi, T., Ochiai, H., Tsukamoto, S., Takashima, A., Boku, N., Kanemitsu, Y., Prognostic Impact of Palliative Primary Tumour Resection for Unresectable Stage 4 Colorectal Cancer: Using a Propensity Score Analysis, Annals of Surgical Oncology, 23, 3602-3608, 2016	20-30% of the patients with symptomatic primary tumour
Simillis, C., Kalakouti, E., Afxentiou, T., Kontovounisios, C., Adamina, M., Cunningham, D., Tekkis, P., A meta-analysis comparing outcomes of primary tumour resection versus no resection in patients with stage IV colorectal cancer, Colorectal Disease, 19 (Supplement 2), 31, 2017	A conference abstract
Somasundar, P. S., Olszewski, A., Khan, H., Surgical management of metastatic colon cancer in the elderly, Hpb, 2), 138, 2014	A conference abstract
Stillwell, A. P., Buettner, P. G., Ho, Y. H., Meta-Analysis of Survival of Patients with Stage IV Colorectal Cancer Managed with Surgical Resection Versus Chemotherapy Alone, World Journal of Surgery, 1-11, 2010	Studies assessed individually
Stillwell, A. P., Ho, Y. H., Veitch, C., Systematic review of prognostic factors related to overall survival in patients with stage IV colorectal cancer and unresectable metastases, World Journal of Surgery, 35, 684-692, 2011	A systematic review of factors associated with better survival in people with stage IV colorectal cancer and unresectable metastases. Some of the included studies relevant but no relevant data presented
Stoss, C., Nitsche, U., Stecher, L., Wilhelm, D., Friess, H., Ceyhan, G. O., Primary tumour resection in metastasized colorectal cancer-a meta-analysis, United European Gastroenterology Journal, 4 (5 Supplement 1), A471-A472, 2016	A conference abstract
t Lam-Boer, J., Van der Geest, L. G., Verhoef, C., Elferink, M. E., Koopman, M., de Wilt, J. H., Palliative resection of the primary tumour is associated with improved overall survival in incurable stage IV colorectal cancer: A nationwide population-based propensity-score adjusted study in the Netherlands, International Journal of Cancer, 139, 2082-2094, 2016	Population unclear/not relevant, does not differentiate between symptomatic and asymptomatic primary tumour
t, Lam-Boer J, Mol, L, Verhoef, C, Haan, Af, Yilmaz, M, Punt, Cj, Wilt, Jh, Koopman, M, The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer--a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG), BMC Cancer, 14, 741, 2014	A trial protocol. This trial (NCT01606098) is still recruiting patients (according to clinicaltrials.gov)
Tan, W. J., Chew, M. H., Tan, I. B. H., Law, J. H., Zhao, R., Acharyya, S., Mao, Y. L., Fernandez, L. G., Loi, C. T., Tang, C. L., Palliative surgical intervention in metastatic colorectal carcinoma: A prospective analysis of quality of life, Colorectal Disease, 18, 357-363, 2016	Population not relevant, patients with symptomatic primary tumour
Tarantino, I., Warschkow, R., Worni, M., Cerny, T., Ulrich, A., Schmied, B. M., Guller, U., Prognostic relevance of palliative primary tumour removal in 37,793 metastatic colorectal cancer patients: A population-based, propensity score-adjusted trend analysis, Annals of Surgery, 262, 112-120, 2015	Population unclear/not relevant, does not differentiate between symptomatic and asymptomatic primary tumour

Tebbutt, N. C., Norman, A. R., Cunningham, D., Hill, M. E., Tait, D., Oates, J., Livingston, S., Andreyev, J., Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases, Gut, 52, 568-573, 2003	Population unclear, symptomatic patients included but not clear what proportion
Temple, L. K. F., Hsieh, L., Wong, W. D., Saltz, L., Schrag, D., Use of surgery among elderly patients with stage IV colorectal cancer, Journal of Clinical Oncology, 22, 3475-3484, 2004	Retrospective study could not determine what proportion of patients were asymptomatic
Tierney, J. F., Chivukula, S. V., Wang, X., Pappas, S. G., Schadde, E., Hertl, M., Poirier, J., Keutgen, X. M., Resection of primary tumour may prolong survival in metastatic gastroenteropancreatic neuroendocrine tumours, Surgery, 2018	Population not relevant - neuroendocrine tumours.
T'Lam-Boer, J., Van Der Geest, L., Verhoef, C., Koopman, M., Elferink, M., De Wilt, J., Palliative resection of the primary tumour is associated with increased survival in patients with synchronous metastatic colorectal cancer: A nationwide population-based study from the Netherlands, Annals of Oncology, 25 (Supplement 2), ii110, 2014	A conference abstract, full text retrieved
Tsang, W. Y., Ziogas, A., Lin, B. S., Seery, T. E., Karnes, W., Stamos, M. J., Zell, J. A., Role of Primary Tumour Resection Among Chemotherapy-Treated Patients with Synchronous Stage IV Colorectal Cancer: A Survival Analysis, Journal of Gastrointestinal Surgery, 18, 592-598, 2014	Population not relevant, metastatic disease not necessarily incurable, primary tumour not necessarily asymptomatic
Van Der Pool, A. E., De Wilt, J. H., Lalmahomed, Z. S., Eggermont, A. M., Ijzermans, J. N., Verhoef, C., Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases, British Journal of Surgery, 97, 383-390, 2010	Population and intervention not relevant, this study considers the sequence of resection for synchronous metastatic colorectal cancer, that is, the population is not with metastasis not amenable to curative treatment
van Rooijen, K. L., Shi, Q., Goey, K. K. H., Meyers, J., Heinemann, V., Diaz-Rubio, E., Aranda, E., Falcone, A., Green, E., de Gramont, A., Sargent, D. J., Punt, C. J. A., Koopman, M., Prognostic value of primary tumour resection in synchronous metastatic colorectal cancer: Individual patient data analysis of first-line randomised trials from the ARCAD database, Eur J Cancer, 91, 99-106, 2018	Unclear whether patients had symptomatic primary tumours.
Vatandoust, S., Roy, A. C., Price, T. J., Ullah, S., Beeke, C., Townsend, A. R., Padbury, R., Roder, D., Maddern, G., Karapetis, C. S., Survival impact of primary tumour resection in patients (pts) with unresectable metastatic colorectal cancer (mCRC): Findings from the South Australian Metastatic Colorectal Cancer Registry (SAMCRC), Journal of Clinical Oncology. Conference, 33, 2015	A conference abstract
Venderbosch, S., De Wilt, J. H., Teerenstra, S., Loosveld, O. J., Van Bochove, A., Sinnige, H. A., Creemers, G. J. M., Tesselaar, M. E., Mol, L., Punt, C. J. A., Koopman, M., Prognostic value of resection of primary tumour in patients with stage IV colorectal cancer: Retrospective analysis of two randomized studies and a review of the literature, Annals of Surgical Oncology, 18, 3252-3260, 2011	Studies assessed individually
Verberne, C. J., de Bock, G. H., Pijl, M. E. J., Baas, P. C., Siesling, S., Wiggers, T., Palliative resection of the primary tumour in stage IV rectal cancer, Colorectal Disease, 14, 314-319, 2012	Did not specify whether primary tumours were asymptomatic
Verberne, C., De Bock, G. H., Pijl, M. E. J., Wiggers, T., Outcomes of surgical and chemotherapeutic palliative treatment	A conference abstract

strategies in patients with metastasized rectal cancer, Annals of Oncology, 1), i51, 2010	
Wang, Z., Lian, L., Zhou, Y., Liu, T. S., The value of primary tumour resection in patients with metastatic colorectal cancer received chemotherapy plus bevacizumab: Results from the single center, retrospective study, Journal of Clinical Oncology. Conference, 33, 2015	A conference abstract
Wang, Z., Liang, L., Yu, Y., Wang, Y., Zhuang, R., Chen, Y., Cui, Y., Zhou, Y., Liu, T., Primary Tumour Resection Could Improve the Survival of Unresectable Metastatic Colorectal Cancer Patients Receiving Bevacizumab-Containing Chemotherapy, Cellular Physiology and Biochemistry, 39, 1239-1246, 2016	Did not control for confounders
Watanabe, A., Yamazaki, K., Kinugasa, Y., Tsukamoto, S., Yamaguchi, T., Shiomi, A., Tsushima, T., Yokota, T., Todaka, A., Machida, N., Fukutomi, A., Onozawa, Y., Yasui, H., Influence of primary tumour resection on survival in asymptomatic patients with incurable stage IV colorectal cancer, International Journal of Clinical Oncology, 19, 1037-1042, 2014	Analysis on the relationship between primary tumour resection and survival was unadjusted, no other outcomes of interest reported
Wilkinson, K. J., Chua, W., Ng, W., Roohullah, A., Management of asymptomatic primary tumours in stage IV colorectal cancer: Review of outcomes, World Journal of Gastrointestinal Oncology, 7, 513-23, 2015	Studies assessed individually
Wong, S. F., Field, K. M., Kosmider, S., Tie, J., Wong, H. L., Tran, B., Tacey, M., Shapiro, J. D., McKendrick, J. J., Gibbs, P., Metastatic colorectal cancer (mCRC) with primary in situ: An Australian registry, Journal of Clinical Oncology. Conference, 31, 2013	A conference abstract
Wong, S. F., Wong, H. L., Field, K. M., Kosmider, S., Tie, J., Wong, R., Tacey, M., Shapiro, J., Nott, L., Richardson, G., Cooray, P., Jones, I., Croxford, M., Gibbs, P., Primary Tumour Resection and Overall Survival in Patients With Metastatic Colorectal Cancer Treated With Palliative Intent, Clinical Colorectal Cancer, 15, e125-e132, 2016	Unclear whether patients had asymptomatic tumours
Xu, H., Xia, Z., Jia, X., Chen, K., Li, D., Dai, Y., Tao, M., Mao, Y., Primary Tumour Resection Is Associated with Improved Survival in Stage IV Colorectal Cancer: An Instrumental Variable Analysis, Scientific Reports, 5, 16516, 2015	Unclear whether patients had asymptomatic tumours
Yamauchi, M., Shinozaki, K., Ikeda, S., Nitta, T., Doi, M., Comparison between primary tumour resection and primary chemotherapy for patients with unresectable colorectal cancer, Annals of Oncology, 9), ix55, 2013	A conference abstract
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Appendix L – Research recommendations

Research recommendations for review question: Does surgery for the asymptomatic primary tumour improve outcomes for people with metastatic colorectal cancer, which cannot be treated with curative

No research recommendations were made for this review question.