National Institute for Health and Care Excellence

Draft for consultation

Colorectal cancer (update)

[D3] Treatment for metastatic colorectal cancer in the lung amenable to local treatment

NICE guideline TBC

Evidence reviews

July 2019

Draft for Consultation

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

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN:

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Optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment

This evidence review supports recommendations 1.5.7 to 1.5.8 and the research recommendation on the cost effectiveness and safety of non-surgical ablation and stereotactic body radiotherapy compared to resection for people with metastatic colorectal cancer in the lung amenable to local treatment.

Review question

What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment?

Introduction

People who have been successfully treated for colorectal cancer sometimes develop metastases in other parts of their body, often in the liver or lungs. While pulmonary metastasectomy is commonly used for treating lung metastases, there is a wide variation in practice (Fiorentino 2010). Radiotherapy, including stereotactic body radiation therapy (SBRT) or percutaneous ablation are less invasive treatment alternatives. Therefore, the aim of this review was to determine the most effective combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung that is potentially curable with local treatments such as surgery or stereotactic radiotherapy.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	Adults with colorectal cancer with metastases in the lung who are candidates to receive local treatment for their lung metastasis/metastases. Subgroups: • Metachronous or synchronous metastasis • Synchronous primary tumour that is symptomatic or asymptomatic
Intervention	• Surgery • Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) (only for patients with controlled primary tumour) • Percutaneous ablation (including radiofrequency (RF), microwave and irreversible electroporation (IRE))

Comparison	• Individual local interventions (with or without systemic anti-cancer treatment) or combinations of interventions will be compared to each other (groups of treatment compared to each other) or to: • Systemic anti-cancer treatment (SACT) alone • Supportive care (symptom-directed treatment, for example pain management, palliative radiotherapy)
Outcomes	**Critical** • Lung progression-free survival • Overall survival • Quality of life **Important** • Disease-free survival • Symptomatic radiation pneumonitis • Treatment-related 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

Two retrospective cohort studies were included this review (Filippi 2016; Kim 2012).

The included studies are summarised in Table 2.

One study (Filippi 2016) compared surgery to stereotactic body radiation therapy (SBRT) and the other study (Kim 2012) compared surgery to chemotherapy or supportive care.

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
Filippi 2016 Retrospective cohort study Italy	N=170 patients with colorectal cancer with their first diagnosis of lung metastases	Surgery (wedge resection, anatomical resection) versus SBRT (3D-CRT or IG-VMAT)	• Lung progression-free survival • Overall survival • Treatment-related mortality
Kim 2012 Retrospective cohort study South Korea	N=105 patients who underwent curative resection for colorectal cancer and had pulmonary metastases as the initial distant metastasis	Surgery (wedge resection, lobectomy, lymph node dissection) versus chemotherapy or best supportive care* *94/104 patients received chemotherapy (did not specify how many surgical patients received chemotherapy)	• Overall survival

3D-CRT: three dimensional conformal radiation therapy; IG-VMAT: image-guided volumetric modulated arc therapy; N: number; SBRT: stereotactic body radiation therapy

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no 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

Comparison 1: Surgery versus stereotactic body radiation therapy (SBRT)

Critical outcomes

Lung-progression free survival

- Very low quality evidence from 1 retrospective cohort study (N=170) showed a clinically important increase in lung progression-free survival at 2.5 years between those receiving surgery compared to those receiving SBRT.

Overall survival

- Very low quality evidence from 1 retrospective cohort study (N=170) showed no clinically important difference in overall survival at 2.5 years between those receiving surgery compared to those receiving SBRT.

Quality of life

No evidence was identified to inform this outcome.

Important outcomes

Disease-free survival

No evidence was identified to inform this outcome.

Symptomatic radiation pneumonitis

No evidence was identified to inform this outcome.

Treatment-related mortality

- Very low quality evidence from 1 retrospective cohort study (N=170) showed no clinically important difference in treatment-related mortality between those receiving surgery compared to those receiving SBRT.

Comparison 2: Surgery versus chemotherapy or best supportive care

Critical outcomes

Lung-progression free survival

No evidence was identified to inform this outcome.

Overall survival

- Very low quality evidence from 1 retrospective cohort study (N=105) showed a clinically important increase in overall survival at 5 years between those receiving surgery compared to those receiving chemotherapy or best supportive care.

Quality of life

No evidence was identified to inform this outcome.

Important outcomes

Disease-free survival

No evidence was identified to inform this outcome.

Symptomatic radiation pneumonitis

No evidence was identified to inform this outcome.

Treatment-related mortality

No evidence was identified to inform this outcome.

Economic evidence statements

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

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

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

Disease-free survival was an important outcome because it suggests ineffective control of the lung metastases. Additionally, symptomatic radiation pneumonitis and treatment-related mortality were also important outcomes, as they are indicative of the short-term side effects of treatments.

The quality of the evidence

Evidence was available from 2 retrospective cohort studies that compared surgery to stereotactic body radiation therapy (SBRT) and surgery to chemotherapy or best supportive care. Evidence was available for lung progression-free survival, overall survival and treatment-related mortality. There was no evidence for quality of life, disease-free survival or symptomatic lung pneumonitis.

The quality of the evidence was assessed using GRADE and was of very low quality. The quality of the evidence was downgraded because of methodological limitations affecting the risk of bias and imprecision of the risk estimate.

There was high risk of bias for the lung progression-free survival outcome due to different follow-up protocols used for the two cohorts, uncertain definition of local failure, lack of analysis of baseline differences, and lack of information regarding the number of patients in the surgery cohort who also received chemotherapy.

Uncertainty around the risk estimate was attributable to low event rates and small sample sizes.

Benefits and harms

The very low quality of the evidence and lack of evidence for many comparisons and outcomes impacted the decision-making of the committee and the committee based the recommendations largely on their clinical expertise. There was insufficient clinical evidence

to recommend one type of treatment over another, therefore, the committee recommended that surgical resection (metastasectomy), ablation or SBRT should be considered for people with colorectal lung metastases who are amenable for local treatment. The consideration of the treatment options should be based on a discussion in a MDT which includes thoracic surgeon and a specialist in non-surgical ablative techniques. The committee acknowledged the inherent risk of complications of surgery, ablation or SBRT. MDT discussion should be held to mitigate the risks of overtreatment in people unlikely to benefit.

The committee agreed that with the appropriate specialists being available in MDTs, more people will be referred for active treatment for lung metastases and will potentially benefit from increased lung progression-free survival and overall survival.

Considering biopsies for patients with a solitary lung lesion will provide histological data that would not otherwise be available and guide optimal treatment options and to rule out primary lung cancer. However, the committee noted that there are potential risks associated with biopsies, including biopsy-related dissemination.

Because of the limited, poor quality evidence and the lack of randomised trials, the committee made a research recommendation comparing surgical and non-surgical treatment for people with colorectal lung metastases suitable for local treatment. See appendix L for more details.

Cost effectiveness and resource use

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

The recommendations are not anticipated to have a significant resource impact as they are likely to reflect current practice for larger centres. However, the recommendations may encourage more active treatment for metastatic disease in some centres. While there are increased costs associated with the active treatment options (pulmonary metastectomy, ablation or SBRT) there are potential benefits in terms of progression-free survival and overall survival meaning that the interventions could be cost-effective in cost per QALY terms. Furthermore, the recommendation to consider active treatment only after multi-disciplinary team discussion should ensure that treatment is only considered in those patients that are most likely to benefit and reduce the potential for overtreatment (and associated costs).

Other factors the committee took into account

The committee acknowledged the PulMiCC trial (PulMiCC 2012), a randomised controlled feasibility trial of the effectiveness of pulmonary metastesectomy in patients previously treated for colorectal cancer that has a study completion date of June 2020. Outcomes include 5-year overall survival, relapse free survival, lung function and patient-reported quality of life. These results will help to establish a further randomised and comparative evidence base and provide data on patient-reported outcomes that could help determine the best treatments for patients.

References

Filippi 2016

Filippi A, Guerrera F, Badellino S, et al. (2016) Exploratory analysis on overall survival after either surgery or stereotactic radiotherapy for lung oligometastases from colorectal cancer. Clinical Oncology 28(8): 505-12

Fiorentino 2010

Fiorentino F, Hunt I, Teoh K, et al. (2010) Pulmonary metastasectomy in colorectal cancer: A systematic review and quantitative synthesis. Journal of the Royal Society of Medicine 103(2): 60-66

Intermullo 2010

Internullo E, Cassivi S, Van Raemdonck D, et al. (2008) Pulmonary metastasectomy: a survey of current practice amongst members of the European Society of Thoracic Surgeons. Journal of Thoracic Oncology 3(11): 1257-66

Kim 2012

Kim C, Huh J, Kim H, et al. (2012) Factors influencing oncological outcomes in patients who develop pulmonary metastases after curative resection of colorectal cancer. Diseases of the Colon and Rectum 55(4): 459-464

PulMiCC 2012

Treasure T, Fallowfield L, Lees B, et al. (2012) Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial. Thorax 67(2): 185-187

Tan 2009

Tan K, Lopes Gde L and R Sim (2009) How uncommon are isolated lung metastases in colorectal cancer? A review from database of 754 patients over 4 years. Journal of Gastrointestinal Surgery 13(4): 642-48

Treasure 2008

Treasure T (2008) Pulmonary metastasectomy for colorectal cancer: weak evidence and no randomised trials. European Journal of Cardio-Thoracic Surgery 33(2): 300-02

Appendices

Appendix A – Review protocol

Review protocol for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment?

Table 3: Review protocol for optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment

Field (based on PRISMA-P)	Content
Review question	What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment?
Type of review question	Intervention
Objective of the review	To determine the most effective combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung that is potentially curable with local treatments such as surgery or stereotactic radiotherapy. Previously, localised treatments for lung metastases were limited to patients with a solitary lung tumour, however the definition of oligometastatic disease has changed over time as it became clear that patients with multiple lung metastases can also benefit from localised treatments. For this reason we have not used the term 'oligometastatic' in our review question due to the changing meaning of this term over time.
Eligibility criteria – population/disease/condition/issue/ domain	Adults with colorectal cancer with metastases in the lung who are candidates to receive local treatment for their lung metastasis/metastases. **Subgroups:** • Metachronous or synchronous metastasis • Synchronous primary tumour that is symptomatic or asymptomatic
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Surgery • Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) (only for patients with controlled primary tumour) • Percutaneous ablation (including radiofrequency (RF), microwave and irreversible electroporation (IRE))
Eligibility criteria – comparator(s)/control or reference (gold) standard	• Individual local interventions (with or without systemic anti-cancer treatment) or combinations of interventions will be compared to each other (groups of treatment compared to each other), or to

	• Systemic anti-cancer treatment (SACT) alone (i.e. chemotherapy, immunotherapy, biological agents) • Supportive care (symptom-directed treatment, for example pain management, palliative radiotherapy)
Outcomes and prioritisation	**Critical outcomes:** • Lung progression-free survival • Overall survival • Quality of life (measured using validated scales only) **Important outcomes:** • Disease-free survival • Symptomatic radiation pneumonitis • Treatment-related mortality MIDs: statistical significance for all outcomes except quality of life, which will use values from the literature 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 *Confirmed with guideline committee.
Eligibility criteria – study design	• Systematic reviews • RCTs • Comparative prospective and retrospective observational studies (minimum 10 patients in each arm) Only published full texts in English language will be considered.
Other inclusion exclusion criteria	Inclusion: • English-language • Published full text papers • All settings will be considered that consider medications and treatments available in the UK

	• Studies published post 2000 Studies published 2000 onwards will be considered for this review question because the guideline committee agreed that treatments for lung oligometastases were not defined prior to 2000.
Proposed sensitivity/sub-group analysis, or meta-regression	In case of high heterogeneity, the following factors will be considered: • With or without local interventions for the primary colorectal tumour • Subtype of treatment Observational studies should include at least one of the following adjustments: • Age • Synchronous or metachronous • Number of metastases • CEA level • Unilateral or bilateral metastasis
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search. 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.
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 systematic reviews, RCTs, and comparative prospective and retrospective observational studies in first instance, but download all results • Dates: post-2000
Identify if an update	Not an update

Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual **Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs 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 for 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 NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CEA: carcinoembryonic antigen; 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; MID: minimal important difference; NHS: National Health Service; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; PROSPERO: International prospective register of systematic reviews; RCT: randomised controlled trial; 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

1 Appendix B – Literature search strategies

2 Literature search strategies for review question: What is the optimal combination 3 and sequence of treatments in patients presenting with metastatic colorectal 4 cancer in the lung amenable to local treatment?

5 Databases: Embase/Medline

6 Last searched on: 16/05/2018

#	Searches
1	(exp colorectal cancer/ or exp colon tumor/ or exp rectum tumor/) use emez
2	exp colorectal neoplasms/ use ppez
3	((colorect* or colo rect* or colon or colonic or rectal or rectum) adj3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)).tw.
4	or/1-3
5	Lung metastasis/ use emez
6	exp neoplasm metastasis/ use ppez
7	exp lung/ use ppez
8	6 and 7
9	((lung* or pulmonary) adj3 (disseminat* or metasta* or migrat*)).tw.
10	((colorect* or colo rect* or colon or colonic or rectal or rectum) adj3 pulmonary metasta*).tw.
11	5 or 8 or 9
12	4 and 11
13	12 or 10
14	(Lung resection/ or metastasis resection/) use emez
15	(Metastasectomy/ or pneumonectomy/ or thoracic surgery, video-assisted/) use ppez
16	metastasectom*.tw.
17	((lung* or pulmonary) adj3 (excis* or metastasectom* or resect* or surg*)).tw.
18	or/14-17
19	13 and 18
20	exp antineoplastic agent/ use emez or exp antineoplastic agents/ use ppez
21	exp Antineoplastic Protocols/ use ppez
22	exp chemotherapy/ use emez
23	Cancer Vaccines/ use ppez
24	cancer vaccine/ use emez
25	cancer immunotherapy/ use emez
26	exp antibodies, monoclonal/ use ppez
27	monoclonal antibody/ use emez
28	((anti canc* or anticanc* or anticarcinogen* or anti neoplas* or antineoplas* or cytotoxic*) adj3 (agent* or drug* or protocol* or regimen* or treatment* or therap*)).ti.
29	(SACT or chemotherap* or immunotherap* or biological agent* or biological therap*).ti.
30	or/20-29
31	13 and 30
32	(radiosurgery/ or stereotactic body radiation therapy/ or stereotactic radiosurgery/ or cyberknife/) use emez
33	radiosurgery/ use ppez
34	(Stereotactic* adj2 (irradiation* or RT or radiation* or radioablation* or radiosurg* or radiotherap* or therap* or treat*)).tw.
35	(SBRT or SABRT or SABR or cyberknife or cyber knife).tw.
36	or/32-35
37	13 and 36
38	radiofrequency ablation/ use emez or ablation techniques/ use ppez
39	microwave thermotherapy/ use emez
40	irreversible electroporation/ use emez or electroporation/ use ppez

#	Searches
41	((percutaneous* or radiofrequen* or radio-frequen* or RF or microwave*) adj3 ablat*).tw.
42	electroporat*.tw.
43	(RFA or MWA or IRE).tw.
44	or/38-43
45	13 and 44
46	18 or 30 or 36 or 44
47	13 and 46
48	Letter/ use ppez
49	letter.pt. or letter/ use emez
50	note.pt.
51	editorial.pt.
52	Editorial/ use ppez
53	News/ use ppez
54	exp Historical Article/ use ppez
55	Anecdotes as Topic/ use ppez
56	Comment/ use ppez
57	Case Report/ use ppez
58	case report/ or case study/ use emez
59	(letter or comment*).ti.
60	or/48-59
61	randomized controlled trial/ use ppez
62	randomized controlled trial/ use emez
63	random*.ti,ab.
64	or/61-63
65	60 not 64
66	animals/ not humans/ use ppez
67	animal/ not human/ use emez
68	nonhuman/ use emez
69	exp Animals, Laboratory/ use ppez
70	exp Animal Experimentation/ use ppez
71	exp Animal Experiment/ use emez
72	exp Experimental Animal/ use emez
73	exp Models, Animal/ use ppez
74	animal model/ use emez
75	exp Rodentia/ use ppez
76	exp Rodent/ use emez
77	(rat or rats or mouse or mice).ti.
78	or/65-77
79	limit 47 to (english language and yr="2000-current")
80	79 not 78
81	remove duplicates from 80

1 **Database: Cochrane Library**

2 Last searched on: 16/05/2018

#	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 (Word variations have been searched)
3	#1 or #2
4	MeSH descriptor: [Neoplasm Metastasis] explode all trees
5	MeSH descriptor: [Lung] explode all trees
6	#4 and #5
7	((lung* or pulmonary) near/3 (disseminat* or metasta* or migrat*)):ti,ab,kw (Word variations have been searched)

#	Search
8	((colorect* or colo rect* or colon or colonic or rectal or rectum) near/3 pulmonary metasta*):ti,ab,kw (Word variations have been searched)
9	#6 or #7
10	#3 and #9
11	#10 or #8
12	MeSH descriptor: [Metastasectomy] this term only
13	MeSH descriptor: [Pneumonectomy] this term only
14	MeSH descriptor: [Thoracic Surgery, Video-Assisted] this term only
15	metastasectom*:ti,ab,kw (Word variations have been searched)
16	((lung* or pulmonary) near/3 (excis* or metastasectom* or resect* or surg*)):ti,ab,kw (Word variations have been searched)
17	{or #12-#16}
18	MeSH descriptor: [Antineoplastic Agents] explode all trees
19	MeSH descriptor: [Antineoplastic Protocols] explode all trees
20	MeSH descriptor: [Cancer Vaccines] this term only
21	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
22	((anti canc* or anticanc* or anticarcinogen* or anti neoplas* or antineoplas* or cytotoxic*) near/3 (agent* or drug* or protocol* or regimen* or treatment* or therap*)):ti,ab,kw (Word variations have been searched)
23	(SACT or chemotherap* or immunotherap* or biological agent* or biological therap*):ti,ab,kw (Word variations have been searched)
24	{or #18-#23}
25	MeSH descriptor: [Radiosurgery] this term only
26	(Stereotactic* near/2 (irradiation* or RT or radiation* or radioablation* or radiosurg* or radiotherap* or therap* or treat*)):ti,ab,kw (Word variations have been searched)
27	(SBRT or SABRT or SABR or cyberknife or cyber knife):ti,ab,kw (Word variations have been searched)
28	{or #25-#27}
29	MeSH descriptor: [Ablation Techniques] explode all trees
30	MeSH descriptor: [Electroporation] this term only
31	((percutaneous* or radiofrequen* or radio-frequen* or RF or microwave*) near/3 ablat*):ti,ab,kw (Word variations have been searched)
32	electroporat*:ti,ab,kw (Word variations have been searched)
33	(RFA or MWA or IRE):ti,ab,kw (Word variations have been searched)
34	{or #29-#33}
35	#17 or #24 or #28 or #34
36	#11 and #35 Publication Year from 2000 to 2018

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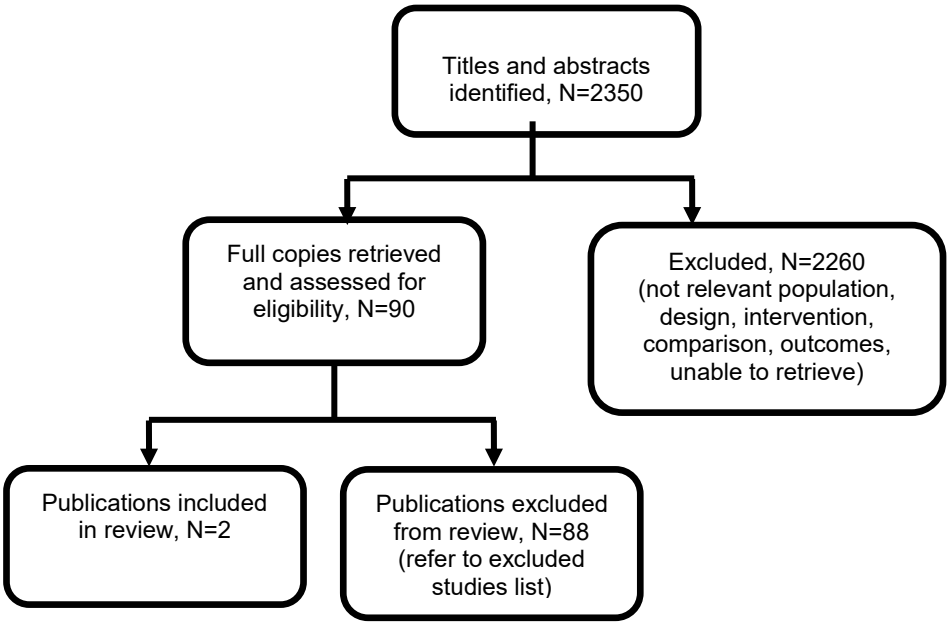
2

Appendix C – Clinical evidence study selection

Clinical study selection for: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment?

Figure 1: Study selection flow chart



1 Appendix D – Clinical evidence tables

2 Clinical evidence tables for review question: What is the optimal combination and sequence of treatments in patients 3 presenting with metastatic colorectal cancer in the lung amenable to local treatment?

4 Table 4: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Filippi, A. R., Guerrera, F., Badellino, S., Ceccarelli, M., Castiglione, A., Guarneri, A., Spadi, R., Racca, P., Ciccone, G., Ricardi, U., Ruffini, E., Exploratory Analysis on Overall Survival after Either Surgery or Stereotactic Radiotherapy for Lung Oligometastases from Colorectal Cancer, Clinical Oncology (Royal College of Radiologists), 28, 505-12, 2016 **Ref Id** 828116 **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	**Sample size** N= 170. n surgery= 142 n SBRT= 28 **Characteristics** Surgery, n=142 Male sex, n=87 Age at treatment, years, median (IQR)=66.37 (59.29-72.38) Charlson score, n 0= 71 ≥1= 71 Previous metastases, n No= 96 Yes= 46 Number of metastases, n 1=78 > 1= 64 Maximum size of metastases, mm, median (IQR)= 15 (12-25) CEA, ng/ml 0-5= 68 >5= 30 Unknown= 44 Lung metastases diagnosis, n Synchronous=21	**Interventions** "Lung metastases were defined as the new appearance of nodules ≥ 8 mm in the lung parenchyma. SBRT or surgery was proposed to patients at the discretion of the treating physician, often after discussion within a multidisciplinary team, without applying any specific selection criteria for surgery or SBRT." Surgery vs SBRT Surgery= The surgical approach was chosen "according to the number, the location and the laterality of the lesions: usually, muscle-sparing axillary thoracotomy was the access of choice. In case of synchronous bilateral lesions, the surgical timing was personalised on each patient characteristic. Complete palpation of the lung was carried out in all cases, except in the case of thoracoscopic procedures. Wedge resection was accomplished in the case of	**Details** Data collection= Retrospective cohort study the Piedmont Health Service Register (including patients covered by the Regional Health Service) of patients who underwent surgery or SBRT from 2005 to 2012. Follow up= Follow up time depended on the treatment received. Overall survival assessed at 1 and 2 years. Follow up was kept at a minimum for patients who received surgery and 6 weeks after SBRT and then every 3 months for SBRT patients. Outcomes= Local progression for SBRT (radiologically defined as regrowth of a treated lesion, excluding radiation-induced fibrosis) and local progression for surgery was defined as intra-lobar	**Results** Progression-free survival, adjusted effect (multivariable), HR (95% CI), p-value Surgery= reference SBRT= 2.78 (1.67-4.62), < 0.001 Progression-free survival, adjusted effect (IPTW, multivariable), HR (95% CI), p-value Surgery= reference SBRT= 3.04 (1.88-4.92), < 0.001 Overall survival, adjusted effect (multivariable), HR (95% CI), p-value Surgery= reference SBRT= 1.71 (0.82-3.54), 0.139 Overall survival, adjusted effect (IPTW, multivariable), HR (95% CI), p-value Surgery= reference	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Low risk of bias (study controlled for potential confounding variables) Bias in selection of participants into the study: Unclear risk of selection bias (the cohorts were unbalanced regarding numbers (surgery= 142; SBRT= 28), but baseline characteristics were similar) 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: High risk of bias (low validity of the progression-free survival

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
assess the effect of surgery compared to stereotactic radiotherapy for lung oligomestases from colorectal cancer on overall survival and progression-free survival. **Study dates** 2005 to 2012 **Source of funding** Not reported	Metachronous= 121 SBRT, n=28 Male sex, n= 14 Age at treatment, years, median (IQR)= 72.07 (66.06-77.03) Charlson score, n 0=12 ≥1=16 Previous metastases, n No=17 Yes=11 Number of metastases, n 1=17 > 1=11 Maximum size of metastases, mm, median (IQR)= 15.5 (11.5-22.5) CEA, ng/ml 0-5=15 >5=6 Unknown=7 Lung metastases diagnosis, n Synchronous=2 Metachronous=26 **Inclusion criteria** All patients treated at the time with their first diagnosis of lung metastases with either surgery or SBRT. Patients had to fulfil the inclusion criteria of: "(i) histological diagnosis of primary colorectal adenocarcinoma previously treated with radical surgery; (ii) number of lung metastases ≤5; (iii)maximum tumour	peripherally located pulmonary nodules; anatomical resections (segmentectomy or lobectomy) were carried out in the case of multiple nodules in the same pulmonary segment or lobe, of large lesions or in the case of metastases deeply located in the pulmonary parenchyma. Lymph node assessment included hilar and mediastinal node sampling." SBRT= "Lung metastases were either treated with three dimensional conformal radiation therapy (3D-CRT) 2005-2010) or, more recently, with image-guided volumetric modulated arc therapy (IG-VMAT; 2010-2012)."	recurrences, independently from the number of incomplete resections (R1). Treatment-related mortality= death within 30 days of treatment. Data analysis= Kaplan-Meier survival functions assessed with the Log-rank test with univariate and multivariate Cox proportional hazard models to assess the effect of clinical characteristics on overall survival. Calculated a propensity score for SBRT treatment by weighting each patient in the Cox model with the inverse probability of treatment weighting (IPTW) to obtain an adjusted estimate of the treatment effect. Factors controlled for= gender, age, Charlson's comorbidity score, carcinoembryonic antigen levels, maximum size of metastases, disease-free intervals	SBRT= 1.28 (0.58-2.82), 0.547 Treatment-related mortality (death within 30 days), n Surgery= 1/142 SBRT= 0/28	outcome due to different follow-up protocols used for the two cohorts and the uncertain definition of local failure, typical of surgery versus SBRT and the lack of standardised data on toxicity) Bias in selection of the reported result: Low risk of bias **Other information** "It is impossible to disentangle the effect of differences between the follow-up protocols and sample sizes of the two cohorts from a potential negative impact of SBRT on the risk of local or distant recurrences. For this reason, we believe that overall survival was the only robust and reliable end point for comparative analyses, whereas PFS results should be interpreted with caution, being at a high risk of biases."

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	diameter ≤50mm;(iv) adequate pulmonary function (forced expiratory volume in the first second (FEV_1) > 40% predicted and diffusion capacity of the lung for carbon monoxide (DLCO) > 40% predicted); (v) Eastern Cooperative Oncology Group (ECOG) performance status 0-1; (vi) controlled primary tumour (no evidence of recurrent disease in the abdomen) and/or controlled extra lung metastases (metastases successfully controlled by local therapies and/or previous systemic therapies)." **Exclusion criteria** Not reported				
Full citation Kim, C. H., Huh, J. W., Kim, H. J., Lim, S. W., Song, S. Y., Kim, H. R., Na, K. J., Kim, Y. J., Factors influencing oncological outcomes in patients who develop pulmonary metastases after curative resection of colorectal cancer, Diseases of the Colon and Rectum, 55, 459-464, 2012	**Sample size** N=105 n surgery= 48 n chemotherapy or best supportive care, n=57 **Characteristics** n= 105 Age, years, mean (SD)= 67.2 (10.4) Male sex, n= 64 ASA score, n 1= 22 2= 75 3= 8	**Interventions** Surgery vs chemotherapy or supportive care Surgery= "The decision to proceed with the surgical resection of pulmonary metastases was determined by a multidisciplinary committee comprising the thoracic surgeon, radiologist, medical oncologist, and colorectal surgeon. Selection criteria for pulmonary metastasectomy were defined as controlled primary colorectal	**Details** Data collection: Patient data from a prospectively collected register with a tertiary care hospital/referral centre in South Korea was reviewed. Outcomes: Overall survival at 5 years Follow up: 3 month intervals for 2 years, and then 6 month intervals for	**Results** Overall survival at 5 years, multivariate analysis controlling for (age, sex, BMI, ASA score, tumour location, T category, N category, M category, tumour diameter, differentiation, adjuvant chemotherapy, pulmonary metastesectomy location, bilaterality, number, diameter,	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Low risk of bias Bias in selection of participants into the study: High risk of selection bias (did not assess potential differences in baseline characteristics and noted that "… the group of patients with lung metastases

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 844357 **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 identify the predicting factors for oncological outcomes after curative resection in patients with colorectal cancer and pulmonary metastases **Study dates** January 2000 to June 2010 **Source of funding** No funding received	Primary tumour characteristics Tumour location, n Colon= 18 Rectum= 87 T category, n 1= 2 2=7 3= 87 4= 9 N category, n 0= 41 1= 37 2= 27 TNM category, n I= 6 II= 31 III= 62 IV= 6 Adjuvant chemotherapy, n= 79 Pulmonary metastasectomy Number, n 1= 44 2=21 3= 7 4=5 ≥5= 28 Diameter of metastasis, cm, mean (SD)= 1.64 (1.19) Lung resection, n= 48 Adjuvant chemotherapy, n= 94 **Inclusion criteria** Patients who underwent curative resection for colorectal	cancer technically resectable metastatic pulmonary lesions, absence of extrathoracic metastasis, with the exception of potentially curable local recurrence of primary cancer or hepatic metastasis, sufficient cardiopulmonary reserve, and no contraindication because of comorbidity. Wedge resection was the treatment of choice in those lesions that were discreet, small, subpleural nodules. Lobectomy was sometimes technically necessary to allow complete resection of centrally located metastases. Lymph node dissection, as performed for primary lung cancer, was not indicated routinely and was performed when lymph node involvement was suspected in the preoperative radiological studies. Chemotherapy following diagnosis of pulmonary metastases was given to 94 (89.5%) patients and not given to 10 (9.5%) patients for economic reasons or patient refusal." Non-surgery= Chemotherapy or best supportive care	the next 3 years and then annually thereafter Data analysis= Kaplan-Meier survival was calculated with log-rank tests used to assess differences in the curves. Variables with a univariate significance of $p \leq 0.10$ were included in the multivariate analysis. Cox proportional hazard regression analyses using the forward stepwise method was performed to assess which variables remained independently (p value ≤ 0.05 was considered statistically significant). Factors controlled for: age, sex, BMI, ASA score, tumour location, T category, N category, M category, tumour diameter, differentiation, prelaparotomy CEA level, adjuvant chemotherapy, pulmonary metastesectomy location, bilaterality, number, diameter, extrapulmonary metastases, disease free interval, prethoractomy CEA level, adjuvant chemotherapy for treatment of pulmonary metastasectomy	disease free interval, prethoractomy CEA level), HR (95% CI), p-value Surgery= reference No surgery= 2.184 (1.009-4.731), 0.048	that fulfilled the criteria for operation probably comprised a select group with the nonaggressive tumour biology.)" At intervention Bias in classification of interventions: Unclear risk of bias ("Chemotherapy following diagnosis of pulmonary metastases was given to 94 patients and not given to 10 patients for economic reasons or patient refusal.") Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

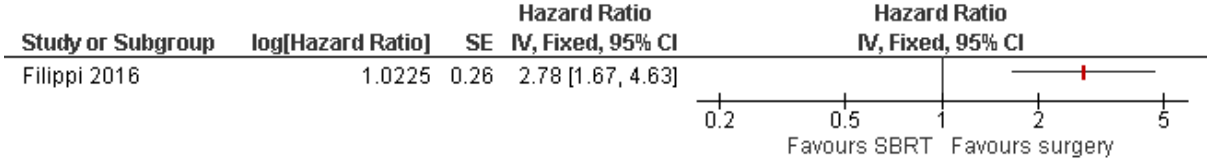
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	cancer and had pulmonary metastases as the initial distant metastasis **Exclusion criteria** Other distant metastases diagnosed before the pulmonary metastasis				

ASA: American Society of Anesthesiologists; BMI: body mass index; CEA: carcinoembryonic antigen; *CI: confidence interval; Charlson score: a comorbidity index; ECOG: Eastern Cooperative On-cology Group; HR: Hazard ratio; IPTW: inverse probability of treatment weighting; IQR: interquartile range; N: number; PFS: progression-free survival; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions; SBRT: Stereotactic body radiation therapy; TNM: cancer classification system, standing for tumour, nodal and metastasis stages.*

Appendix E – Forest plots

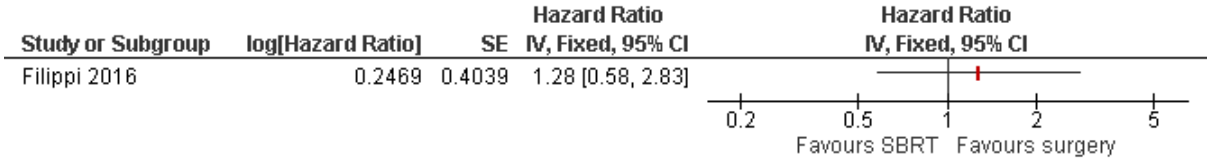
Forest plots for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment?

Figure 2: Comparison 1: Surgery versus stereotactic body radiation therapy (SBRT) - lung progression-free survival, adjusted effect (IPTW, multivariable)



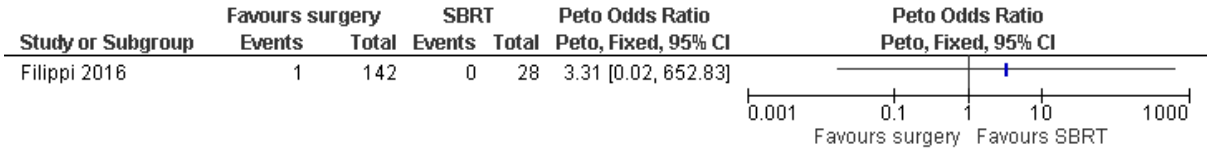
CI: confidence interval; IPTW: inverse probability of treatment weighting; IV: inverse variance; SE: standard error

Figure 3: Comparison 1: Surgery versus stereotactic body radiation therapy (SBRT) – 2.5-year overall survival, adjusted effect (IPTW, multivariable)



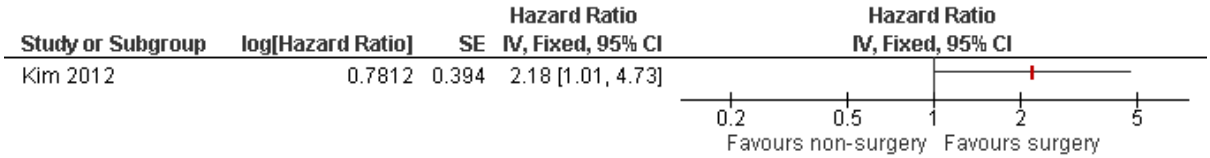
CI: confidence interval; IPTW: inverse probability of treatment weighting; IV: inverse variance; SE: standard error

Figure 4: Comparison 1: Surgery versus stereotactic body radiation therapy (SBRT) Treatment-related mortality (death within 30 days)



CI: confidence interval

Figure 5: Comparison 2: Surgery versus chemotherapy or supportive care – 5-year overall survival, multivariate analysis*



CI: confidence interval; IV: inverse variance; SE: standard error

*Multivariate analysis controlling for (age, sex, BMI, ASA score, tumour location, T category, N category, M category, tumour diameter, differentiation, adjuvant chemotherapy, pulmonary metastesectomy location, bilaterality, number, diamteter, disease free interval, prethoractomy CEA level).

1 Appendix F – GRADE tables

2 GRADE tables for review question: What is the optimal combination and sequence of treatments in patients presenting with 3 metastatic colorectal cancer in the lung amenable to local treatment?

4 Table 5: Clinical evidence profile for comparison 1: surgery versus stereotactic body radiation therapy (SBRT)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	SBRT	Relative (95% CI)	Absolute	Quality	Importance
2.5-year lung progression-free survival, adjusted effect (IPTW, multivariable)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	142	28	HR 2.78 (1.67 to 4.63)	At 2.5 years surgery[a] 72.5%, SBRT 40.9% (22.6% to 58.4%)	VERY LOW	CRITICAL
2.5-year overall survival, adjusted effect (IPTW, multivariable)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37/142	10/28	HR 1.28 (0.58 to 2.83)	At 2.5 years surgery[a] 38.0%, SBRT 29% (6.5% to 57.1%)	VERY LOW	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Symptomatic radiation pneumonitis												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	SBRT	Relative (95% CI)	Absolute		
Treatment-related mortality (death within 30 days)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/142 (0.7%)	0/28 (0%)	Peto OR 3.31 (0.02 to 652.83)	not estimable[3]	VERY LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; IPTW: inverse probability of treatment weighting; OR: odds ratio; SBRT: stereotactic body radiation therapy
1 Quality of evidence downgraded by 1 because of high risk of bias for the lung progression-free survival outcome due to different follow-up protocols used for the two cohorts and the uncertain definition of local failure) (Filippi 2016)
2 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (< 300 events for dichotomous outcomes or < 400 patients for continuous outcomes).
3 Not estimable due to 0 events in the control arm
a The absolute risk at 2.5 years in the control group taken from Filippi 2016

Table 6: Clinical evidence profile for comparison 2: surgery versus chemotherapy or best supportive care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	CT or supportive care	Relative (95% CI)	Absolute		
Lung progression-free survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
5-year overall survival, multivariate analysis												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48	57	HR 2.18 (1.01 to 4.73)	not calculable[e]	VERY LOW	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Symptomatic radiation pneumonitis												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	CT or supportive care	Relative (95% CI)	Absolute		
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Treatment-related mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; CT: chemotherapy; HR: hazard ratio

1 Quality of evidence downgraded by 1 because study did not assess differences in baseline characteristics and did not state how many patients in the surgery cohort also received chemotherapy (Kim 2012)

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

a The absolute risk at 5 years was not calculable because the study did not report event rates (Kim 2012)

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment?

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

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment?

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

Appendix J – Economic analysis

Economic evidence analysis for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

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

5 **Table 7: Excluded studies and reasons for their exclusion**

Study	Reason for exclusion
Agolli, L., Bracci, S., Nicosia, L., Valeriani, M., De Sanctis, V., Osti, M. F., Lung Metastases Treated With Stereotactic Ablative Radiation Therapy in Oligometastatic Colorectal Cancer Patients: Outcomes and Prognostic Factors After Long-Term Follow-Up, Clinical Colorectal Cancer, 16, 58-64, 2017	Not comparative
Andres, A., Mentha, G., Adam, R., Gerstel, E., Skipenko, O. G., Barroso, E., Lopez-Ben, S., Hubert, C., Majno, P. E., Toso, C., Surgical management of patients with colorectal cancer and simultaneous liver and lung metastases, The British journal of surgery, 102, 691-699, 2015	Population not relevant - resected liver metastases vs resected simultaneous liver and lung metastases vs simultaneous resected liver and unresected lung metastases
Bin Traiki, T. A., Fisher, O. M., Valle, S. J., Parikh, R. N., Kozman, M. A., Glenn, D., Power, M., Liauw, W., Alzahrani, N. A., Morris, D. L., Percutaneous lung ablation of pulmonary recurrence may improve survival in selected patients undergoing cytoreductive surgery for colorectal cancer with peritoneal carcinomatosis, European Journal of Surgical Oncology, 43, 1939-1948, 2017	No adjustment for any confounding factors in the analysis
Cardillo, G., Treasure, T., Recurrent Lung Metastases: Evidence of Benefit From Surgery Requires a Randomized Trial, Annals of Thoracic Surgery, 104, 1435, 2017	Editorial
Cassano, A., Congedo, M. T., D'Argento, E., Pozzo, C., Rossi, E., Margaritora, S., Nachira, D., Orlandi, A., Schinzari, G., Quirino, M., Bagala, C., Granone, P., Barone, C., Resection of lung metastases from colorectal cancer: Analysis of outcome and prognostic factors, European Journal of Cancer, 3), S355-S356, 2015	Conference abstract
Chao, Y. K., Management of lung metastases from colorectal cancer: Video-assisted thoracoscopic surgery versus thoracotomy a case-matched study, Lung Cancer, 1), S42, 2013	Conference abstract
De Baere, T., Auperin, A., Deschamps, F., Chevallier, P., Gaubert, Y., Boige, V., Fonck, M., Escudier, B., Palussiere, J., Radiofrequency ablation is a valid treatment option for lung metastases: Experience in 566 patients with 1037 metastases, Annals of Oncology, 26, 987-991, 2015	Not comparative

Study	Reason for exclusion
Douillard, Jy, Siena, S, Cassidy, J, Tabernero, J, Burkes, R, Barugel, M, Humblet, Y, Bodoky, G, Cunningham, D, Jassem, J, Rivera, F, Kocákova, I, Ruff, P, B?asi?ska-Morawiec, M, Smakal, M, Canon, Jl, Rother, M, Oliner, Ks, Tian, Y, Xu, F, Sidhu, R, Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer, Annals of oncology : official journal of the european society for medical oncology, 25, 1346-1355, 2014	Population not relevant - did not have lung metastases
Duraker, N., Civelek Caynak, Z., Hot, S., The impact of primary tumor 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 not relevant - only 3/188 patients had lung metastases
Embun, R., Royo, I., Hernandez, J., Ramirez, E., Menal, P., Recuero, J. L., Garcia Tirado, F. J., Rivas, J. J., Surgical approach for pulmonary metastasectomy. Does it really matter?, Interactive Cardiovascular and Thoracic Surgery, 1), S46, 2010	Conference abstract
Faisal, M., Uthman, I., Abo Bakr, A., Combined pulmonary metastasectomy and chemotherapy in patients with colorectal lung metastases and concurrent extrapulmonary disease, Journal of Thoracic Oncology, 13 (4 Supplement 1), S121-S122, 2018	Conference abstract
Ferguson, C. D., Luis, C. R., Steinke, K., Safety and efficacy of microwave ablation for medically inoperable colorectal pulmonary metastases: Single-centre experience, Journal of Medical Imaging and Radiation Oncology, 61, 243-249, 2017	Not comparative
Ferguson, J., Alzahrani, N., Zhao, J., Glenn, D., Power, M., Liauw, W., Morris, D. L., Long term results of RFA to lung metastases from colorectal cancer in 157 patients, European Journal of Surgical Oncology, 41, 690-695, 2015	Comparison not relevant - complete remission vs local control and systemic progression vs local progression and systemic progression
Filippi, A. R., Guerrera, F., Badellino, S., Ceccarelli, M., Castiglione, A., Guarneri, A., Spadi, R., Racca, P., Ciccone, G., Ricardi, U., Ruffini, E., Stereotactic radiotherapy versus surgery: Comparison of survival in lung metastases from colo-rectal cancer, Radiotherapy and Oncology, 115, S382, 2015	Conference abstract
Fiorentino, F., Hunt, I., Teoh, K., Treasure, T., Utley, M., Pulmonary metastasectomy in colorectal cancer: A systematic review and quantitative synthesis, Journal of the Royal Society of Medicine, 103, 60-66, 2010	Systematic review - included studies were case series and not comparative
Fossum, C. C., Alabbad, J. Y., Romak, L. B., Hallemeier, C. L., Haddock, M. G., Huebner, M., Dozois, E. J., Larson, D. W., The role of neoadjuvant radiotherapy for locally-advanced	Population not relevant - only 11/93 patients had lung metastases

Study	Reason for exclusion
rectal cancer with resectable synchronous metastasis, Journal of Gastrointestinal Oncology, 8, 650-658, 2017	
Franko, J., Shi, Q., Goldman, C. D., Pockaj, B. A., Nelson, G. D., Goldberg, R. M., Pitot, H. C., Grothey, A., Alberts, S. R., Sargent, D. J., Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: A pooled analysis of North Central Cancer Treatment Group phase III trials N9741 and N9841, Journal of Clinical Oncology, 30, 263-267, 2012	Interventions not relevant - did not include surgery, SBRT, SABR or percutaneous ablation
Gadot, M., Lawrence, Y., Aderka, D., Golan, T., Shani, A., Halpern, N., Margalit, O., Shmueli, E., Colorectal cancer patients with lung-only metastases have a favorable prognosis irrespective of treatment, Annals of Oncology, 27 (Supplement 2), ii43, 2016	Conference abstract
Gamelin, E., Mineur, L., Chevelle, C., Cailleux, P., Martin, L., Bastit, L., Roullet, B., Hasbini, A., Savary, J., Cellier, P., Neoadjuvant radiotherapy +/- tegafur-uracil plus leucovorin in rectal adenocarcinoma: Final results of a French multicenter phase III study, Journal of Clinical Oncology, 1), 4104, 2009	Conference abstract
Gervaz, P., Delgadillo, X., Gonzalez, M., A meta analysis of risk factors for survival after lung metastasectomy in colorectal cancer patients, Colorectal Disease, 2), 9, 2012	Conference abstract
Greenwood, A., West, D., Is a thoracotomy rather than thoracoscopic resection associated with improved survival after pulmonary metastasectomy?, Interactive Cardiovascular and Thoracic Surgery, 17, 720-724, 2013	Systematic review - interventions not relevant (i.e. thoracotomy vs thoracoscopic)
Guerrera, F., Falcoz, P. E., Renaud, S., Massard, G., Does perioperative chemotherapy improve survival in patients with resectable lung metastases of colorectal cancer?, Interactive Cardiovascular and Thoracic Surgery, 24, 789-791, 2017	Systematic review - included studies assessed individually
Hawkes, E. A., Ladas, G., Cunningham, D., Nicholson, A. G., Wassilew, K., Barbachano, Y., Ratnayake, G., Rao, S., Chau, I., Peri-operative chemotherapy in the management of resectable colorectal cancer pulmonary metastases, BMC Cancer, 12 (no pagination), 2012	Intervention not relevant - surgery alone vs surgery peri-operative chemotherapy
Hernandez, J., Molins, L., Fibla, J. J., Heras, F., Embun, R., Rivas De Andres, J. J., Video-assisted thoracoscopic surgery is as effective as the open approach for resection of pulmonary metastases of colorectal origin and anatomical resection and shows improved survival over wedge resection in a spanish prospective multicentre study (GECMP-CCR), Interactive Cardiovascular and Thoracic Surgery. Conference: 23rd European Conference on	Conference abstract

Study	Reason for exclusion
General Thoracic Surgery. Lisbon Portugal. Conference Publication:, 21, 2015	
Hernandez, J., Molins, L., Fibla, J. J., Heras, F., Embun, R., Rivas, J. J., Rivas, F., Mier, J. M., de la Cruz, J., Rubio, M., Fernandez, E., Carbajo, M., Penalver, R., Jarabo, J. R., Gonzalez-Rivas, D., Bolufer, S., Pages, C., Call, S., Smith, D., Wins, R., Arnau, A., Arroyo, A., Carmen Marron, M., Tamura, A., Blanco, M., de Olaiz, B., Munoz, G., Garcia Prim, J. M., Rombola, C., Barajas, S. G., Rodriguez, A., Freixinet, J., Ruiz, J., Carriquiry, G., Rosenberg, M., Canalis, E., Role of major resection in pulmonary metastasectomy for colorectal cancer in the Spanish prospective multicenter study (GECMP-CCR), Annals of Oncology, 27, 850-855, 2016	Comparison not relevant - video-assisted thoracoscopic surgery vs open resection; intervention not relevant - all patients received surgery
Hou, Z., Zhang, H., Gui, L., Wang, W., Zhao, S., Video-assisted thoracoscopic surgery versus open resection of lung metastases from colorectal cancer, International Journal of Clinical and Experimental Medicine, 8, 13571-13577, 2015	Comparison not relevant - video-assisted thoracoscopic surgery vs open resection
Huang, L., Li, T. J., Zhang, J. W., Liu, S., Fu, B. S., Liu, W., Neoadjuvant chemotherapy followed by surgery versus surgery alone for colorectal cancer: Meta-analysis of randomized controlled trials, Medicine (United States), 93, e231, 2014	Systematic review - none of the included studies were relevant
Hunt, S. L., McKay, A., Kelly, L. M., Kirk, A. J. B., A case series of pulmonary resection for metastatic colorectal cancer in a UK regional thoracic center, Future Oncology, 11, 35-36, 2015	Case series
Ibrahim, T., Tselikas, L., Yazbeck, C., Kattan, J., Systemic Versus Local Therapies for Colorectal Cancer Pulmonary Metastasis: What to Choose and When?, Journal of Gastrointestinal Cancer, 47, 223-231, 2016	Systematic review - none of the included studies were relevant
Ihn, M. H., Kim, D. W., Cho, S., Oh, H. K., Jheon, S., Kim, K., Shin, E., Lee, H. S., Chung, J. H., Kang, S. B., Curative resection for metachronous pulmonary metastases from colorectal cancer: Analysis of survival rates and prognostic factors, Cancer Research and Treatment, 49, 104-115, 2017	Comparison not relevant - synchronous vs metachronous
Ina, K., Furuta, R., Kataoka, T., Sugiura, S., Kayukawa, S., Kanamori, T., Kikuchi, T., Kabeya, M., Hibi, S., Yuasa, S., Adverse effects of bevacizumab during treatment for metastatic colorectal cancer, Journal of Analytical Oncology, 4, 24-29, 2015	Comparison not relevant - chemotherapy vs no chemotherapy
Inoue, Y., Miki, C., Hiro, J., Ojima, E., Yamakado, K., Takeda, K., Kusunoki, M., Improved survival using multi-modality therapy in patients with lung metastases from colorectal cancer: a preliminary study, Oncology Reports, 14, 1571-1576, 2005	No adjustment for any confounding factors in the analysis

Study	Reason for exclusion
Jarabo, J. R., Gomez, A. M., Calatayud, J., Fraile, C. A., Fernandez, E., Pajuelo, N., Embun, R., Molins, L., Rivas, J. J., Hernando, F., Combined Hepatic and Pulmonary Metastasectomies From Colorectal Carcinoma. Data From the Prospective Spanish Registry 2008-2010, Archivos de Bronconeumologia, 54, 189-197, 2018	Comparison group not relevant - had liver metastectomies
Javed, M. A., Sheel, A., Sheikh, A. A., Adu, J., Page, R. D., Rooney, P., Surgical management of pulmonary metastases from colorectal cancer - The Mersey experience, Colorectal Disease, 5), 35, 2011	Conference abstract
Kaira, K., Okumura, T., Ohde, Y., Takahashi, T., Murakami, H., Kondo, H., Nakajima, T., Yamamoto, N., Prognostic significance of thymidylate synthase expression in the adjuvant chemotherapy after resection for pulmonary metastases from colorectal cancer, Anticancer Research, 31, 2763-2771, 2011	Comparison not relevant - surgery alone vs surgery neoadjuvant chemotherapy
Kawakatsu, S., Mise, Y., Inoue, Y., Ishizawa, T., Ito, H., Takahashi, Y., Saiura, A., Staged resection optimizes patient selection for aggressive surgery in patients with synchronous liver and lung colorectal metastases, Hpb, 19 (Supplement 1), S33, 2017	Conference abstract
Landes, U., Robert, J., Morel, P., Gervaz, P., Delgadillo, X., Predicting survival after resection of pulmonary metastases from colorectal cancer: A history of previous liver metastases matters, Colorectal Disease, 3), 12, 2010	Conference abstract
Lee, D., Kang, Y., Kang, J., Wang, Y., Kim, S., Kim, Y., Yoo, I., Han, D., Stereotactic body radiotherapy for primary or metastatic lung tumors: Analysis of long-term single center experience, Journal of Thoracic Oncology, 4), S247-S248, 2012	Conference abstract
Lee, H. P., Chong, B. K., Lee, K. H., Bok, J. S., Choi, S. H., Kim, H. R., Kim, Y., Park, S. I., Kim, D. K., Clinical outcomes of double metastasis in lung and liver from colorectal cancer, Interactive Cardiovascular and Thoracic Surgery, 25 (Supplement 1), i54, 2017	Conference abstract
Lencioni, R., Crocetti, L., Cioni, R., Suh, R., Glenn, D., Regge, D., Helmberger, T., Gillams, A. R., Frilling, A., Ambrogi, M., Bartolozzi, C., Mussi, A., Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study), The Lancet Oncology, 9, 621-628, 2008	Comparisons not relevant - non-small-cell lung cancer vs CRC metastases vs other metastases (from primary malignancy other than colorectal carcinoma)
Lyons, N, Pathak, S, Daniels, I, Spiers, A, Smart, N, Percutaneous management of pulmonary metastases arising from colorectal cancer; a systematic review, Gut., 64, A544, 2015	Systematic review - included studies assessed individually

Study	Reason for exclusion
Mazzola, R., Levra, N. G., Ricchetti, F., Fersino, S., Fiorentino, A., Aiello, D., Alongi, F., Increased efficacy of stereotactic ablative radiation therapy in combination with bevacizumab in lung oligopersistent/oligoprogressive metastases from colon cancer, International Journal of Radiation Oncology Biology Physics, 99 (2 Supplement 1), E437, 2017	Conference abstract
Mazzola, R., Tebano, U., Aiello, D., Di Paola, G., Giaj-Levra, N., Ricchetti, F., Fersino, S., Fiorentino, A., Ruggieri, R., Alongi, F., Increased Efficacy of Stereotactic Ablative Radiation Therapy after Bevacizumab in Lung Oligometastases from Colon Cancer, Tumori, tj5000701, 2017	Unavailable from the British Library
Meimarakis, G., Spelsberg, F., Angele, M., Preissler, G., Fertmann, J., Crispin, A., Reu, S., Kalaitzis, N., Stemmler, M., Giessen, C., Heinemann, V., Stintzing, S., Hatz, R., Winter, H., Resection of pulmonary metastases from colon and rectal cancer: Factors to predict survival differ regarding to the origin of the primary tumor, Annals of Surgical Oncology, 21, 2563-2572, 2014	Comparison not relevant - middle/lower rectum vs upper colon
Migliore, M., Milosevic, M., Lees, B., Treasure, T., Maria, G. D., Finding the evidence for pulmonary metastasectomy in colorectal cancer: The PulMicc trial, Future Oncology, 11, 15-18, 2015	Supplement to Migliore 2015
Mitry, E., Fields, A. L. A., Bleiberg, H., Labianca, R., Portier, G., Tu, D., Nitti, D., Torri, V., Elias, D., O'Callaghan, C., Langer, B., Martignoni, G., Bouche, O., Lazorthes, F., Van Cutsem, E., Bedenne, L., Moore, M. J., Rougier, P., Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: A pooled analysis of two randomized trials, Journal of Clinical Oncology, 26, 4906-4911, 2008	Population not relevant - only 13/278 patients had lung metastases
Nakajima, J., Survival prognosis of pulmonary metastasectomy for colorectal cancer has been improved with combination of new chemotherapy, Interactive Cardiovascular and Thoracic Surgery. Conference: 21st European Conference on General Thoracic Surgery. Birmingham United Kingdom. Conference Publication:, 17, 2013	Conference abstract
Navarria, P., Ascolese, A. M., Tomatis, S., Cozzi, L., De Rose, F., Mancosu, P., Alongi, F., Clerici, E., Lobefalo, F., Tozzi, A., Reggiori, G., Fogliata, A., Scorsetti, M., Stereotactic body radiotherapy (sbrt) in lung oligometastatic patients: Role of local treatments, Radiation Oncology, 9 (1) (no pagination), 2014	Not comparative
Oztas, M., Urkan, M., Indications of pulmonary resection as a part of curative intent surgical treatment in patients with simultaneous liver and	Conference abstract

Study	Reason for exclusion
pulmonary metastases arising from colorectal cancer: What Does Cumulative Evidence Say?, European Surgical Research, 1), 138-139, 2015	
Park, H. S., Jung, M., Shin, S. J., Heo, S. J., Kim, C. G., Lee, M. G., Beom, S. H., Lee, C. Y., Lee, J. G., Kim, D. J., Ahn, J. B., Benefit of Adjuvant Chemotherapy After Curative Resection of Lung Metastasis in Colorectal Cancer, Annals of Surgical Oncology, 23, 928-935, 2016	Comparison not relevant - no chemotherapy vs adjuvant chemotherapy
Park, J. H., Kim, T. Y., Lee, K. H., Han, S. W., Oh, D. Y., Im, S. A., Kang, G. H., Chie, E. K., Ha, S. W., Jeong, S. Y., Park, K. J., Park, J. G., The beneficial effect of palliative resection in metastatic colorectal cancer, British Journal of Cancer, 108, 1425-1431, 2013	Population not relevant - only 20.4% had lung metastases
Park, S., Kang, B. W., Lee, S. J., Yoon, S., Chae, Y. S., Kim, J. G., Lee, K. H., Koh, S. A., Song, H. S., Park, K. U., Kim, J. Y., Heo, M. H., Ryoo, H. M., Cho, Y. Y., Jo, J., Lee, J. L., Lee, S. A., Clinical significance of systemic chemotherapy after curative resection of metachronous pulmonary metastases from colorectal cancer, Cancer Chemotherapy and Pharmacology, 80, 187-193, 2017	Comparison not relevant - chemotherapy vs observation
Perini, M. V., Yeo, D., Muralidharan, V., Christophi, C., Approach to colorectal liver/ Lung metastases, Hpb, 3), 150, 2011	Conference abstract
Petre, E. N., Jia, X., Thornton, R. H., Sofocleous, C. T., Alago, W., Kemeny, N. E., Solomon, S. B., Treatment of pulmonary colorectal metastases by radiofrequency ablation, Clinical Colorectal Cancer, 12, 37-44, 2013	Not comparative
Pfannschmidt, J., Dienemann, H., Hoffmann, H., Surgical Resection of Pulmonary Metastases From Colorectal Cancer: A Systematic Review of Published Series, Annals of Thoracic Surgery, 84, 324-338, 2007	Systematic review - none of the included studies were comparative
Pfannschmidt, J., Egerer, G., Bischof, M., Thomas, M., Dienemann, H., Surgical intervention for pulmonary metastases. [German, English], Deutsches Arzteblatt, 109, 645-651, 2012	Systematic review - none of the included studies were comparative
Price, T. J., Tomita, Y., Beeke, C., Padbury, R., Townsend, A. R., Maddern, G., Roy, A., Roder, D., Karapetis, C. S., Survival for patients with resectable lung metastatic colorectal cancer (mCRC), Journal of Clinical Oncology. Conference, 33, 2015	Conference abstract
Qiu, H., Katz, A. W., Chowdhry, A. K., Usuki, K. Y., Singh, D. P., Metcalfe, S., Cheruvu, P., Chen, Y., Okunieff, P., Milano, M. T., Stereotactic Body Radiotherapy for Lung Metastases from Colorectal Cancer: Prognostic Factors for Disease Control and Survival,	Not comparative

Study	Reason for exclusion
American journal of clinical oncology, 41, 53-58, 2018	
Ricco, A., Davis, J., Rate, W., Yang, J., Perry, D., Pablo, J., D'Ambrosio, D., Sharma, S., Sundararaman, S., Kolker, J., Creach, K. M., Lanciano, R., Lung metastases treated with stereotactic body radiotherapy: The RSSearch patient Registry's experience, Radiation Oncology, 12 (1) (no pagination), 2017	Not comparative
Rieber, J., Andratschke, N., Blanck, O., Duma, M., Ganswindt, U., Imhoff, D., Kahl, H., Klaas, D., Petersen, C., Wittig, A., Guckenberger, M., Sterzing, F., SBRT for lung metastases: Detailed subgroup analysis of 700 patients diagnosed with 963 lung metastases, Radiotherapy and Oncology, 1), S27-S28, 2015	Conference abstract
Schefter, T. E., Kavanagh, B. D., Raben, D., Kane, M., Chen, C., Stuhr, K., Kelly, K., Mitchell, J. D., Bunn, P. A., Gaspar, L. E., A phase I/II trial of stereotactic body radiation therapy (SBRT) for lung metastases: Initial report of dose escalation and early toxicity, International Journal of Radiation Oncology Biology Physics, 66, S120-S127, 2006	Not comparative; population not relevant - only 4/12 had primary colorectal cancer
Schlijper, R. C. J., Grutters, J. P. C., Houben, R., Dingemans, A. M. C., Wildberger, J. E., Raemdonck, D. V., Cutsem, E. V., Haustermans, K., Lammering, G., Lambin, P., Ruysscher, D. D., What to choose as radical local treatment for lung metastases from colo-rectal cancer: Surgery or radiofrequency ablation?, Cancer Treatment Reviews, 40, 60-67, 2014	Systematic review - none of the included studies were comparative
Shin, J. W., Lee, S. I., Moon, H. Y., Significance of follow-up in detection of pulmonary metastasis of colorectal cancer, Journal of the Korean Society of Coloproctology, 26, 293-297, 2010	Intervention not relevant - effectiveness of interventions for detecting pulmonary metastases
Shiono, S., Okumura, T., Boku, N., Hishida, T., Ohde, Y., Sakao, Y., Yoshiya, K., Higashiyama, M., Kameyama, K., Adachi, H., Shiomi, K., Kanzaki, M., Yoshimura, M., Matsuura, M., Hata, Y., Chen, F., Yoshida, K., Sasaki, H., Horio, H., Takenoyama, M., Yamashita, M., Hashimoto, T., Fujita, A., Okumura, M., Funai, K., Asano, H., Suzuki, M., Shiraishi, Y., Nakayama, M., Yamada, S., Hoshi, E., Yamazaki, N., Matsuo, T., Miyazawa, H., Sato, Y., Takao, M., Nakamura, H., Nakayama, H., Shimizu, K., Watanabe, T., Suzuki, H., Kataoka, M., Tsunezuka, Y., Akamine, S., Kadokura, M., Hyodo, I., Nakata, M., Mori, K., Kondo, H., Outcomes of segmentectomy and wedge resection for pulmonary colorectal cancer metastases, Interactive Cardiovascular and Thoracic Surgery, 23 (Supplement 1), i24-i25, 2016	Conference abstract

Study	Reason for exclusion
Subbiah, I. M., Blackmon, S. H., Correa, A. M., Kee, B., Vaporciyan, A. A., Swisher, S. G., Eng, C., Preoperative chemotherapy prior to pulmonary metastasectomy in surgically resected primary colorectal carcinoma, Oncotarget, 5, 6584-6593, 2014	Intervention not relevant - Surgery alone vs surgery preoperative chemotherapy
Terezakis, S., Morikawa, L., Wu, A., Zhang, Z., Shi, W., Weiser, M. R., Paty, P. B., Guillem, J., Temple, L., Nash, G. M., Zelefsky, M. J., Goodman, K. A., Long-Term Survival After High-Dose-Rate Brachytherapy for Locally Advanced or Recurrent Colorectal Adenocarcinoma, Annals of Surgical Oncology, 22, 2168-2178, 2015	Comparison not relevant - locally advanced vs locally recurrent
Treasure, T, Fallowfield, L, Lees, B, Farewell, V, Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial, Thorax, 67, 185-187, 2012	Study protocol
Treasure, T., Pulmonary metastasectomy in colorectal cancer (PulMiCC), Lung Cancer, 1), S78-S79, 2014	Conference abstract
Treasure, T., Pulmonary metastasectomy in colorectal cancer (PulMiCC) A surgeon friendly randomised trial design, Lung Cancer, 1), S66-S67, 2013	Conference abstract
Treasure, T., PulMiCC (Pulmonary Metastasectomy in Colorectal Cancer) trial, European Journal of Surgical Oncology, 37 (11), 1010, 2011	Study protocol
Treasure, T., Pulmonary Metastasectomy in Colorectal Cancer: The PulMiCC trial, Lung Cancer, 91 (Supplement 1), S67-S68, 2016	Conference abstract
Treasure, T., The PulMiCC (Pulmonary Metastasectomy in Colorectal Cancer) trial, Lung Cancer, 1), S64, 2012	Study protocol
Treasure, T., Milosevic, M., Fiorentino, F., Macbeth, F., Pulmonary metastasectomy: What is the practice and where is the evidence for effectiveness?, Thorax., 09, 2014	Narrative review
Trillet-Lenoir, V., Freyer, G., Kaemmerlen, P., Fond, A., Pellet, O., Lombard-Bohas, C., Gaudin, J. L., Lledo, G., Mackiewicz, R., Gouttebel, M. C., Moindrot, H., Boyer, J. D., Chassignol, L., Stremsdoefer, N., Desseigne, F., Moreau, J. M., Hedelius, F., Moraillon, A., Chapuis, F., Bleuse, J. P., Barbier, Y., Heilmann, M. O., Valette, P. J., Assessment of tumour response to chemotherapy for metastatic colorectal cancer: Accuracy of the RECIST criteria, British Journal of Radiology, 75, 903-908, 2002	Not comparative
Tsitsias, T., Toufektzian, L., Routledge, T., Pilling, J., Are there recognized prognostic factors for patients undergoing pulmonary metastasectomy for colorectal carcinoma?, Interactive Cardiovascular and Thoracic Surgery, 23, 962-969, 2016	Literature review - included studies assessed individually

Study	Reason for exclusion
Turan, N., Benekli, M., Dane, F., Unal, O. U., Kara, H. V., Koca, D., Balvan, O., Eren, T., Tastekin, D., Helvaci, K., Berk, V., Demirci, U., Ozturk, S. C., Dogan, E., Cetin, B., Kucukoner, M., Tonyali, O., Tufan, G., Oztop, I., Gumus, M., Coskun, U., Uner, A., Ozet, A., Buyukberber, S., Adjuvant systemic chemotherapy with or without bevacizumab in patients with resected pulmonary metastases from colorectal cancer, Thoracic Cancer, 5, 398-404, 2014	Intervention not relevant - chemotherapy vs bevacizumab
Vidarsdottir, H., Moller, P. H., Jonasson, J. G., Pfannschmidt, J., Gudbjartsson, T., Indications and surgical outcome following pulmonary metastasectomy: a nationwide study, Thoracic & Cardiovascular Surgeon, 60, 383-9, 2012	Not comparative
Vogl, T. J., Eckert, R., Naguib, N. N. N., Beeres, M., Gruber-Rouh, T., Nour-Eldin, N. E. A., Thermal ablation of colorectal lung metastases: Retrospective comparison among laser-induced thermotherapy, radiofrequency ablation, and microwave ablation, American Journal of Roentgenology, 207, 1340-1349, 2016	Intervention not relevant - laser-induced thermotherapy vs radiofrequency ablation vs microwave ablation
Vogl, T. J., Lehnert, T., Zangos, S., Eichler, K., Hammerstingl, R., Korkusuz, H., Lindemayr, S., Transpulmonary chemoembolization (TPCE) as a treatment for unresectable lung metastases, European Radiology, 18, 2449-2455, 2008	Not comparative
Vogl, T. J., Naguib, N. N. N., Gruber-Rouh, T., Koitka, K., Lehnert, T., Nour-Eldin, N. E. A., Microwave ablation therapy: Clinical utility in treatment of pulmonary metastases, Radiology, 261, 643-651, 2011	Not comparative
Vogl, T. J., Naguib, N. N. N., Lehnert, T., Nour-Eldin, N. E. A., Radiofrequency, microwave and laser ablation of pulmonary neoplasms: Clinical studies and technical considerations - Review article, European Journal of Radiology, 77, 346-357, 2011	Narrative review
Wang, Z., Wang, X., Yuan, J., Zhang, X., Zhou, J., Lu, M., Liu, D., Li, J., Shen, L., Survival Benefit of Palliative Local Treatments and Efficacy of Different Pharmacotherapies in Colorectal Cancer With Lung Metastasis: Results From a Large Retrospective Study, Clinical Colorectal Cancer., 2018	Population not relevant - received palliative treatments
Weber-Donat, G., Boronat, A., Boucherie, J. C., Amouyal, G., Hubsh, J. P., Piracchio, R., Cholley, B. P., Sapoval, M. R., Pellerin, O., Lung metastases of colorectal carcinoma: Percutaneous radiofrequency ablation under C-arm cone-beam CT guidance, CardioVascular and Interventional Radiology, 1), S244, 2014	Conference abstract
Widder, J., Klinkenberg, T. J., Ubbels, J. F., Wiegman, E. M., Groen, H. J., Langendijk, J. A., Pulmonary oligometastases: metastasectomy or stereotactic ablative radiotherapy?, Radiother OncolRadiotherapy and oncology : journal of the	No adjustment for any confounding factors in the analysis

Study	Reason for exclusion
European Society for Therapeutic Radiology and Oncology, 107, 409-13, 2013	
Wong, E. Y. T., Tan, G. H. C., Ng, D. W. J., Koh, T. P. T., Kumar, M., Teo, M. C. C., Surgical Management of Metastatic Colorectal Cancer: A Single-Centre Experience on Oncological Outcomes of Pulmonary Resection vs Cytoreductive Surgery and HIPEC, Journal of Gastrointestinal Cancer, 48, 353-360, 2017	Population not relevant - patients with CRC lung metastases vs CRC peritoneal metastases
Yamakado, K., Hase, S., Matsuoka, T., Tanigawa, N., Nakatsuka, A., Takaki, H., Takao, M., Kanazawa, S., Inoue, Y., Sawada, S., Kusunoki, M., Takeda, K., Radiofrequency Ablation for the Treatment of Unresectable Lung Metastases in Patients with Colorectal Cancer: A Multicenter Study in Japan, Journal of Vascular and Interventional Radiology, 18, 393-398, 2007	Not comparative
Yamakado, K., Inoue, Y., Takao, M., Takaki, H., Nakatsuka, A., Uraki, J., Kashima, M., Kusunoki, M., Shimpo, H., Takeda, K., Long-term results of radiofrequency ablation in colorectal lung metastases: Single center experience, Oncology Reports, 22, 885-891, 2009	Not comparative
Yokota, M., Kobayashi, A., Nomura, S., Nishizawa, Y., Ito, M., Nagai, K., Saito, N., Patterns and treatment of recurrence following pulmonary resection for colorectal metastases, World journal of surgery, 39, 1758-1766, 2015	Population not relevant - patients had previously been treated for their pulmonary metastases (with surgery) and then experienced recurrence (brain, lung, liver)

1

Appendix L – Research recommendations

Research recommendations for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the lung amenable to local treatment?

Research recommendation in question format:

What is the cost effectiveness and safety of non-surgical ablation and stereotactic body radiotherapy compared to resection for people with metastatic colorectal cancer in the lung amenable to local treatment?

Rationale

Most deaths from colorectal cancer are due to metastatic disease. The most common sites of metastasis are the regional lymph nodes, the liver, the peritoneum and the lungs, with estimates suggesting that between 1.7% and 7.2% of people with colorectal cancer will develop an isolated lung metastasis (Tan 2009). Removal of a lung metastasis through pulmonary metastasectomy has become established practice on the basis that it can increase survival and is potentially curative, however evidence on the effectiveness of this intervention is limited (Treasure 2008) and is mostly based on data from case series. Whilst results from a randomised trial (PulMICC) trial are expected to be published soon (PulMiCC 2012), no other evaluations of this intervention using a randomised design have been conducted.

Less invasive methods for removal of a pulmonary metastasis include ablation and stereotactic radiotherapy, both of which have increased in popularity; however as with pulmonary metastasectomy it is not clear whether either of these interventions are effective.

Research recommendation rationale:

Research question	What is the best local treatment for metastatic colorectal cancer in the lung?
Importance to 'patients' or the population	Evidence in relation to interventions for pulmonary metastasis is lacking. In the past patients with a pulmonary metastasis were offered surgery; and whilst pulmonary metastasectomy is most commonly offered currently, newer, less invasive treatments such as stereotactic radiotherapy (SBRT) and percutaneous ablative techniques are increasing in popularity. However, none of these interventions have a clear evidence base there is little evidence comparing the three treatment modalities.
Relevance to NICE guidance	When drafting recommendations on interventions for pulmonary metastasis the committee were constrained by the nature of the evidence base with only limited and low quality data available. A high-quality clinical trial in this area would allow clearer recommendations to be made.
Relevance to NHS	Ensuring people with pulmonary metastasis receive the best treatment, leading to better outcomes is important to the NHS, particularly as - practice can vary across the country.

Research question	What is the best local treatment for metastatic colorectal cancer in the lung?
National priorities	The NHS is committed to improving the care, treatment and support for everyone diagnosed with cancer. Determining the optimal treatment for pulmonary metastasis will contribute towards this goal.
Current evidence base	The evidence base for local treatment of pulmonary metastasis is of very low quality. There are currently no randomised trials published. Most of the evidence base is derived from retrospective cohort studies with no comparison group made between the effectiveness of the different techniques outlined above.
Equality	N/A

1 **PICO table:**

Population	Patients with previous colorectal cancer with lung metastases amenable to local treatment (*including* patients with metastatic disease at other sites that have been treated with curative intent)
Intervention	Non-surgical ablation • ablation • stereotactic body radiotherapy
Comparison	Resection (pulmonary metastasectomy)
Outcomes	Primary: • 5-year survival Secondary: • quality of life • procedure-related morbidity • disease-free survival • cost-effectiveness
Study design	Randomised controlled trial
Timeframe	5 years

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