National Institute for Health and Care Excellence

Final

Colorectal cancer (update)

[E1] Follow-up to detect recurrence after treatment for non-metastatic colorectal cancer

NICE guideline NG151

Evidence reviews

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Final

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

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Follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer

This evidence review supports recommendation 1.6.1.

Review question

What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

Introduction

People who have potentially curative surgery for colorectal cancer are typically followed-up for a number of years, with the aim of detecting and treating any recurrences at the earliest possible stage. The effectiveness of follow-up to detect treatable recurrences could depend on factors including: the frequency of testing, the type of tests used, the duration of follow-up and the personnel who carry out the tests. Frequent follow-up testing however is resource intensive and could lead to patient anxiety. It also is unclear whether early detection of recurrence consistently leads to better outcomes. This review aimed to determine the optimal follow-up protocol, by comparing the outcomes of patients on different follow-up protocols.

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 who have undergone surgical or endoscopic resection for non-metastatic colorectal cancer (colon cancer or rectal cancer) with curative intent (with or without adjuvant therapy). • T any • N any • M0
Intervention	Follow-up strategy taking into consideration one or more of the following elements: • Intensity/frequency of follow-up • Duration of follow-up • Content of follow-up (for example clinical examination, serum CEA level, colonoscopy, liver-focused imaging, chest x-ray) • Setting of follow-up (for example primary care or hospital) • Personnel in charge of running clinic (for example consultant led or nurse led)
Comparison	• Follow-up strategies compared to each other, for example: ○ intensive versus less intensive ○ hospital-based versus GP-based • No follow-up
Outcomes	**Critical** • Overall survival • Colorectal cancer-specific survival

	Important • Local recurrence • Distant metastasis • Metachronous colorectal cancer • Resectability of recurrent local or metastatic disease • Overall quality of life • Procedure-related morbidity

CEA: carcinoembryonic antigen; GP: General Practitioner; TNM: cancer classification system, standing for tumour, nodal and metastasis stages.

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

Seventeen randomised controlled trials (RCTs) reported in 3 publications were included (CEAwatch 2017; COLOFOL 2018; Jeffrey 2016). Fifteen of the RCTs were reported in a systematic review (Jeffrey 2016). The meta-analyses of Jeffrey 2016 were updated with 2 additional RCTs (COLOFOL 2018 and CEAwatch 2017).

The included studies are summarised in Table 2. The follow-up protocols compared in the trials are summarised in Figure 1.

Nine RCTs compared more follow-up visits or tests to fewer visits or tests (CEAwatch 2017; COLOFOL 2018; Kjeldsen 1997; Mäkelä 1995; Pietra 1998; Rodríguez-Moranta 2006; Secco 2002; Treasure 2014; Wang 2009). Four RCTs compared formal follow-up to minimal or no follow-up up (FACS 2014; Ohlsson 1995; Schoemaker 1998; Secco 2002). Five RCTs compared more liver imaging to less liver imaging (CEAwatch 2017; FACS 2014; GILDA 1998; Rodríguez-Moranta 2006; Schoemaker 1998). Four RCTs compared carcinoembryonic antigen (CEA) tests to no CEA tests (FACS 2014; Kjeldsen 1997; Ohlsson 1995; Treasure 2014). Three RCTs compared surgeon-led to GP (Augestad 2013; Wattchow 2006) or nurse-led follow-up (Strand 2011).

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

Excluded studies

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

1 Summary of clinical studies included in the evidence review

2 Summaries of the studies that were included in this review are presented in Table 2.
3 Summaries of the follow-up protocols compared in the trials are presented in Figure 1.

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

Trial	N	Intervention	Control	Follow-up for survival (months)	Formal follow-up period	Outcomes
Augestad 2013 (reported in Jeffery 2016) RCT Norway	110	GP led follow-up	Surgeon led follow-up	Median 24	2 years	• Overall survival • Colorectal cancer-specific survival • Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease • Overall quality of life
CEAwatch 2017 RCT The Netherlands	3223	CEA every 2 months, and annual CT of chest/abdomen during the first 3 years. Annual outpatient visits. CEA every 3 months in the 4th and fifth years.	Netherlands (2008) follow-up guidelines: outpatient visits every 6 months for the first 3 years and annual visits in years 4 and 5. Liver US and CXR at each visit. CEA every 3–6 months in the first 3 years and annually in following 2 years.	60	5 years (step down after 3)	• Overall survival • Colorectal cancer-specific survival • Resectability of recurrent local or metastatic disease
COLOFOL 2018 RCT International	2509	CEA 1 month Postoperatively then CEA; CT or MRI of the liver or PET scans, or both; as well as X-ray or CT of the lungs at 6, 12, 18, 24, and 36 months	CEA 1 month postoperatively then CEA; CT or MRI of the liver, or both; and X-ray/CT of the lungs 12 and 36 months after surgery	60	3 years	• Overall survival • Colorectal cancer-specific survival • Local recurrence/Distant metastasis (colorectal cancer-specific recurrence)

Trial	N	Intervention	Control	Follow-up for survival (months)	Formal follow-up period	Outcomes
FACS 2014 (reported in Jeffery 2016) RCT UK	1202	• CEA follow-up group: CEA testing every 3 months for 2 years, then every 6 months for 3 years with a single CT scan of the chest/ abdomen/ pelvis if requested at study entry by clinician • CT follow-up group: CT scan of the chest/ abdomen/ pelvis every 6 months for 2 years, then annually for 3 years, plus colonoscopy at 2 years • CEA+CT follow-up group: both blood and imaging as above, plus colonoscopy at 2 years	No scheduled follow-up except a single CT scan of the chest/ abdomen /pelvis if requested at study entry by a clinician	Median 41	5 years (step down at 2 years)	• Overall survival • Colorectal cancer-specific survival • Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease
GILDA 1998 (reported in Jeffery 2016) RCT International	1228	Clinic visits at 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, and 60 months, with history and clinical examination, FBC, CEA, and CA 19-9. Colonoscopy and CXR at 12, 24, 36, 48, and 60 months. Liver US at 4, 8, 12, 16, 24, 36, 48, and 60 months. For rectal participants, pelvic CT at 4, 12, 24, and 48 months	Clinic visits at 4, 8, 12, 16, 20, 24, 30, 42, 48, and 60 months, including history, examination, and CEA. Colonoscopy at 12 and 48 months. Liver US at 4 and 16 months. Rectal cancer participants in addition had rectoscopy at 4 months, CXR at 12 months, and liver US at 8 and 16 months. A single pelvic CT was allowed if required as a	Median 62	5 years	• Overall survival • Colorectal cancer-specific survival • Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease • Overall quality of life

Trial	N	Intervention	Control	Follow-up for survival (months)	Formal follow-up period	Outcomes
			baseline after adjuvant treatment			
Kjeldsen 1997 (reported in Jeffery 2016) RCT Denmark	597	Clinic visits at 6, 12, 18, 30, 36, 48, 60, 120, 150, and 180 months after radical surgery. Tests included medical history, clinical examination, DRE, gynaecological examination, Haemoccult-II test, colonoscopy, CXR, haemoglobin level, ESR, and liver enzymes	Clinic visits at 60, 120, and 180 months. Tests included medical history, clinical examination, DRE, gynaecological examination, Haemoccult-II test, colonoscopy, CXR, haemoglobin level, ESR, and liver enzymes	NR	15 years	• Overall survival • Colorectal cancer-specific survival • Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease • Overall quality of life
Mäkelä 1995 (reported in Jeffery 2016) RCT Finland	106	Flexible sigmoidoscopy with video imaging every 3 months, colonoscopy at 3 months (if not done pre-op), then annually. US of the liver and primary site at 6 months, then annually.	Annual rigid sigmoidoscopy and barium enema for those with rectal or sigmoid cancers.	Median 60	5 years	• Overall survival • Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease
Ohlsson 1995 (reported in Jeffery 2016) RCT Sweden	107	Clinic visits at 3-, 6-, 9-, 12-, 15-, 18-, 21-, 24-, 30-, 36-, 42-, 48-, and 60-month intervals. Performed at each visit were clinical exam, rigid proctosigmoidoscopy, CEA, alkaline phosphatase, gamma-glutaryl transferase, faecal haemoglobin, and CXR.	No follow-up visits planned.	66 to 106	5 years	• Overall survival • Colorectal cancer-specific survival • Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease

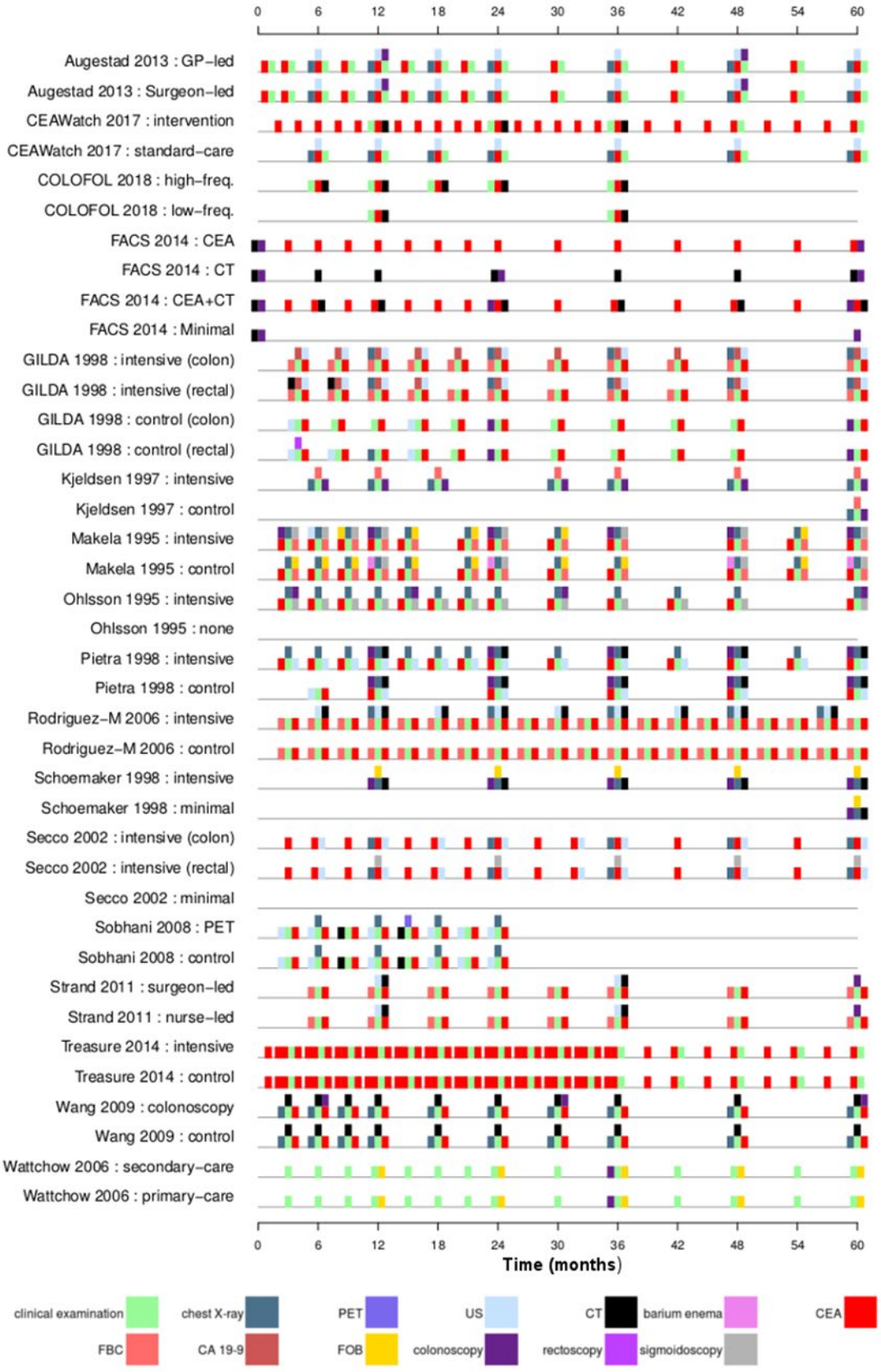
Trial	N	Intervention	Control	Follow-up for survival (months)	Formal follow-up period	Outcomes
		Examination of anastomosis (flexible sigmoidoscopy or colonoscopy) done at 9, 21, and 42 months. Colonoscopy at 3, 15, 30, and 60 months. CT of the pelvis at 3, 6, 12, 18, and 24 months.				
Pietra 1998 (reported in Jeffery 2016) RCT Italy	207	Clinic visits at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 months, then annually thereafter. Clinical examination, ultrasound, CEA, and CXR at each visit. Annual CT of the liver and colonoscopy.	Clinic visits at 6 and 12 months, then annually. At each visit, clinical examination, CEA, and US. Annual CXR, colonoscopy, and CT.	60	5 years	• Overall survival • Colorectal cancer-specific survival • Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease
Rodríguez-Moranta 2006 (reported in Jeffery 2016) RCT Spain	259	Tests: history, examination, and bloods (including CEA), US/CT, CXR, and colonoscopy.	Tests: history, examination, and bloods (including CEA)	48	5 years	• Overall survival • Colorectal cancer-specific survival • Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease
Schoemaker 1998 (reported in	325	Annual CXR, CT of the liver, and colonoscopy	CXR, CT of the liver, and colonoscopy done at 5 years or if indicated	60	5 years	• Overall survival • Local recurrence/ distant metastasis (relapse-free survival)

Trial	N	Intervention	Control	Follow-up for survival (months)	Formal follow-up period	Outcomes
Jeffery 2016) RCT Australia						• Resectability of recurrent local or metastatic disease
Secco 2002 (reported in Jeffery 2016) RCT Italy	337	Clinic visits and serum CEA, abdomen/pelvic US scans, and CXR. Those with rectal carcinoma had rigid sigmoidoscopy and CXR.	Minimal follow-up programme done by physicians	62	5 years	• Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease
Sobhani 2008 (reported in Jeffery 2016) RCT France	130	PET performed at 9 and 15 months in addition to the conventional follow-up tests	Conventional follow-up	24	1.25 years	• Resectability of recurrent local or metastatic disease
Strand 2011 (reported in Jeffery 2016) RCT	110	Nurse led 6 monthly visits for 3 years, then annually up to 5 years. Symptom enquiry occurred at each visit (bloods and CEA as indicated)	Surgeon led 6 monthly visits for 3 years, then annually up to 5 years. Tests were the same as for nurse-led.	60	5 years	• Overall survival • Local recurrence/ distant metastasis (relapse-free survival)

Trial	N	Intervention	Control	Follow-up for survival (months)	Formal follow-up period	Outcomes
Sweden		Abdomen US and CXR (replaced by CT in latter half of the study) at 1 and 3 years				
Treasure 2014 (reported in Jeffery 2016) RCT UK	216	A significant CEA rise triggered “second-look” surgery, with intention to remove any recurrence discovered	No action taken on significant CEA rise	NR	5 years	• Overall survival • Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease
Wang 2009 (reported in Jeffery 2016) RCT China	326	Colonoscopy at each visit	Colonoscopy at six months, 30 months, and 60 months	64-79	5 years	• Overall survival • Local recurrence/ distant metastasis (relapse-free survival) • Resectability of recurrent local or metastatic disease • Procedure-related morbidity
Wattchow 2006 (reported in Jeffery 2016) RCT Australia	203	Primary care follow-up	Secondary care follow-up	24	5 years	• Overall quality of life

CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CXR: chest X-ray; CT: computed tomography; DRE: digital rectal examination; ESR: erythrocyte sedimentation rate; FBC: full blood count; GP: General Practitioner; MRI: magnetic resonance imaging; NR: not reported; PET: positron emission tomography; RCT: randomised controlled trial; US: ultrasound

Figure 1: Summary of follow-up protocols compared in trials



CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CT: computed tomography; FBC: full blood count; FOB: faecal occult blood; PET: positron emission tomography; US: ultrasound

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

Comparison 1: More intensive follow-up versus less intensive follow-up

Critical outcomes

Overall survival

- High quality evidence from 14 RCTs including 10532 participants with colorectal cancer (with follow-up ranging from 24 to 66 months) indicated a clinically important improvement in overall survival with a more intensive follow-up schedule compared to less intensive follow-up.

Colorectal cancer-specific survival

- Moderate quality evidence from 10 RCTs including 9775 participants with colorectal cancer (with follow-up ranging from 24 to 66 months) indicated no clinically important difference in colorectal cancer-specific survival with a more intensive follow-up schedule compared to less intensive follow-up.

Important outcomes

Relapse-free survival

- Moderate quality evidence from 14 RCTs including 8746 participants with colorectal cancer (with follow-up ranging from 24 to 66 months) indicated no clinically important difference in relapse-free survival with a more intensive follow-up schedule compared to less intensive follow-up.

Local recurrence

No evidence was identified to inform this outcome.

Distant metastasis

No evidence was identified to inform this outcome.

Metachronous colorectal cancer

No evidence was identified to inform this outcome.

Resectability of recurrent local or metastatic disease

- High quality evidence from 13 RCTs including 5157 participants with colorectal cancer (with follow-up ranging from 24 to 66 months) indicated resectable recurrences were more likely with a more intensive follow-up schedule compared to less intensive follow-up.

Overall quality of life

No evidence was identified to inform this outcome.

Procedure-related morbidity

- Low quality evidence from one RCT including 1561 follow-up colonoscopies for colorectal cancer showed no clinically important difference in the rates of colonoscopy complications between more versus less intensive follow-up.

Comparison 2: More visits or tests versus fewer visits or tests

Critical outcomes

Overall survival

- High quality evidence from 8 RCTs including 7436 participants with colorectal cancer (with follow-up ranging from 41 to 64 months) indicated a clinically important improvement in overall survival with more follow-up visits or tests compared to fewer visits or tests.

Colorectal cancer-specific survival

- Moderate quality evidence from 8 RCTs including 7114 participants with colorectal cancer (with follow-up ranging from 41 to 64 months) indicated there may be a clinically important improvement in colorectal cancer-specific survival with more follow-up visits or tests compared to fewer visits or tests, but there was uncertainty in the estimate.

Important outcomes

Relapse-free survival

- Moderate quality evidence from 9 RCTs including 6397 participants with colorectal cancer (with follow-up ranging from 41 to 64 months) indicated no clinically important difference relapse-free survival with more follow-up visits or tests compared to fewer visits or tests.

Local recurrence

No evidence was identified to inform this outcome.

Distant metastasis

No evidence was identified to inform this outcome.

Metachronous colorectal cancer

No evidence was identified to inform this outcome.

Resectability of recurrent local or metastatic disease

- Moderate quality evidence from 7 RCTs including 2041 participants with colorectal cancer (with follow-up ranging from 41 to 64 months) indicated resectable recurrences were more likely with more follow-up visits or tests compared to fewer visits or tests.

Overall quality of life

- Low quality evidence from 1 RCT including 350 participants with colorectal cancer indicated a small increase in quality of life, as measured by the Nottingham Health Profile, associated with more frequent follow-up visits compared with less frequent follow-up.

Procedure-related morbidity

- Low quality evidence from 1 RCT including 1561 follow-up colonoscopies for colorectal cancer showed no clinically important difference in the rates of colonoscopy complications between more versus less intensive follow-up.

Comparison 3: Visits or tests versus minimal or no follow-up

Critical outcomes

Overall survival

- High quality evidence from 3 RCTs including 1634 participants with colorectal cancer (with follow-up ranging from 41 to 66 months) indicated no clinically important difference in overall survival with follow-up visits or tests compared to minimal or no follow-up.

Colorectal cancer-specific survival

- High quality evidence from 2 RCTs including 1309 participants with colorectal cancer (with follow-up ranging from 41 to 66 months) indicated no clinically important difference in colorectal cancer-specific survival with follow-up visits or tests compared to minimal or no follow-up.

Important outcomes

Relapse-free survival

- Low quality evidence from 4 RCTs including 1971 participants with colorectal cancer (with follow-up ranging from 41 to 66 months) indicated no clinically important difference in relapse-free survival with follow-up visits or tests compared to minimal or no follow-up.

Local recurrence

No evidence was identified to inform this outcome.

Distant metastasis

No evidence was identified to inform this outcome.

Metachronous colorectal cancer

No evidence was identified to inform this outcome.

Resectability of recurrent local or metastatic disease

- Moderate quality evidence from 4 RCTS including 1971 participants with colorectal cancer (with follow-up ranging from 41 to 66 months) indicated resectable recurrences were more likely with follow-up visits or tests compared to minimal or no follow-up.

Overall quality of life

No evidence was identified to inform this outcome.

Procedure-related morbidity

No evidence was identified to inform this outcome.

Comparison 4: More liver imaging versus less liver imaging

Critical outcomes

Overall survival

- Moderate quality evidence from 4 RCTs including 5036 participants with colorectal cancer (with follow-up ranging from 48 to 60 months) indicated no clinically important difference in overall survival with more liver imaging during follow-up compared to less liver-imaging.

Colorectal cancer-specific survival

- Moderate quality evidence from 3 RCTs including 4724 participants with colorectal cancer (with follow-up ranging from 48 to 60 months) indicated no clinically important difference in colorectal cancer-specific survival with more liver imaging during follow-up compared to less liver-imaging.

Important outcomes

Relapse-free survival

- Moderate quality evidence from 3 RCTs including 3026 participants with colorectal cancer (with follow-up ranging from 48 to 60 months) indicated no clinically important difference in relapse-free survival with more liver imaging during follow-up compared to less liver imaging.

Local recurrence

No evidence was identified to inform this outcome.

Distant metastasis

No evidence was identified to inform this outcome.

Metachronous colorectal cancer

No evidence was identified to inform this outcome.

Resectability of recurrent local or metastatic disease

- Low quality evidence from 4 RCTs including 3026 participants with colorectal cancer (with follow-up ranging from 48 to 60 months) indicated resectable recurrences were more likely with more liver imaging during follow-up compared to less liver-imaging.

Overall quality of life

- Moderate quality evidence from 1 RCT including 1228 participants with colorectal cancer followed up for 60 months indicated no clinically important differences among the three main quality of life scales (SF-12 mental component, SF-12 physical component, and PGWB Index) between follow-up with more liver imaging compared to less liver-imaging.

Procedure-related morbidity

No evidence was identified to inform this outcome.

Comparison 5: CEA tests versus no CEA tests

Critical outcomes

Overall survival

- Moderate quality evidence from 3 RCTs including 920 participants with colorectal cancer (with 66 months follow-up) indicated no clinically important difference in overall survival with follow-up involving CEA tests compared to follow-up without CEA tests.

Colorectal cancer-specific survival

- Moderate quality evidence from 2 RCTs including 704 participants with colorectal cancer (with 66 months follow-up) indicated no clinically important difference in colorectal cancer-specific survival with follow-up involving CEA tests compared to follow-up without CEA tests.

Important outcomes

Relapse-free survival

- Moderate quality evidence from 3 RCTs including 920 participants with colorectal cancer (with 66 months follow-up) indicated no clinically important difference in relapse-free survival with follow-up involving CEA tests compared to follow-up without CEA tests.

Local recurrence

No evidence was identified to inform this outcome.

Distant metastasis

No evidence was identified to inform this outcome.

Metachronous colorectal cancer

No evidence was identified to inform this outcome.

Resectability of recurrent local or metastatic disease

- Very low quality evidence from 4 RCTs including 2120 participants with colorectal cancer (with follow-up ranging from 41 to 66 months) indicated resectable recurrence was more likely with follow-up involving CEA tests than with follow-up without CEA tests.

Overall quality of life

No evidence was identified to inform this outcome.

Procedure-related morbidity

No evidence was identified to inform this outcome.

Comparison 6: Nurse or GP led follow-up versus surgeon led follow-up

Critical outcomes

Overall survival

- Moderate quality evidence from 2 RCTs including 220 participants with colorectal cancer (with follow-up ranging from 24 to 60 months) indicated no clinically important difference in overall survival with nurse or GP led follow-up compared to surgeon led follow-up.

Colorectal cancer-specific survival

- Moderate quality evidence from 1 RCT including 110 participants with colorectal cancer (with 24 months follow-up) indicated no clinically important difference in overall survival with GP led follow-up compared to surgeon led follow-up.

Important outcomes

Relapse-free survival

- Moderate quality evidence from 2 RCTs including 220 participants with colorectal cancer (with follow-up ranging from 24 to 60 months) indicated no clinically important difference in relapse-free survival with nurse or GP led follow-up compared to surgeon led follow-up.

Local recurrence

No evidence was identified to inform this outcome.

Distant metastasis

No evidence was identified to inform this outcome.

Metachronous colorectal cancer

No evidence was identified to inform this outcome.

Resectability of recurrent local or metastatic disease

- Moderate quality evidence from 1 RCT including 110 participants with colorectal cancer (with 24 months follow-up) indicated no clinically important difference in the likelihood of resectable recurrences with GP led follow-up compared to surgeon led follow-up.

Overall quality of life

- Moderate quality evidence from 1 RCT including 110 participants with colorectal cancer (with 24 months follow-up) indicated no significant effect on quality of life main outcome measures with GP led follow-up compared to surgeon led follow-up. For EORTC QLQ-C30, significant effects in favour of GP led follow-up were reported for role functioning, emotional functioning, and pain. A second RCT including 203 participants found no important differences between health-related quality of life in primary versus secondary care follow-up.

Procedure-related morbidity

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

The critical outcomes for decision making were overall and cancer-specific survival because the aim of follow-up for detection of recurrence is to prolong survival by early treatment of any recurrences found. Recurrence (both local and distant) and metachronous primary disease were important outcomes and any follow-up test needs be able to detect these. Resectability of recurrent disease was also an important outcome, because recurrence has to be detected at an early and treatable stage if follow-up is to be worthwhile. Finally quality of life and procedure related morbidity were important outcomes because some patients experience anxiety related to follow-up testing and the tests themselves can have adverse effects.

The quality of the evidence

Evidence was available for the comparison of intensity of follow-up, content of the follow-up and setting/personnel in charge of the follow-up. No evidence was identified for duration of follow-up. Evidence was available for critical outcomes on all comparisons. No evidence was identified for the outcomes local recurrence, distant metastases and metachronous colorectal cancer. Evidence about procedure related morbidity and quality of life was limited to a single trial in each case.

The quality of the evidence was assessed using GRADE, and varied from low to high quality. Evidence was downgraded for lack of blinding, inadequate allocation concealment, for inconsistency and for imprecision.

Benefits and harms

The recommendation to offer follow-up for the first 3 years that includes serum CEA and CT (of the chest, abdomen and pelvis) for people who have had potentially curative surgical treatment for non-metastatic colorectal cancer is based on evidence that recurrent disease was more likely to be resectable when patients received regular follow-up tests than with minimal or no follow-up. The evidence also showed recurrent disease was more likely to be resectable when follow-up tests included CEA and liver imaging. The committee agreed that the ability to completely resect recurrent disease would lead to improved survival in the longer term.

Evidence about test-related morbidity was limited to a single randomised trial, which did not find an increased risk with more intense follow-up. The committee agreed that the evidence did not indicate the optimal frequency of CEA or CT testing and so they did not recommend how often these tests should be done during the first 3 years of follow-up. Following the 2011 guideline the committee considered standard practice would be a minimum of two CTs of the chest, abdomen, and pelvis in the first 3 years and with CEA tests at least every 6 months in the first 3 years. The committee thought that recommending a more intense follow-up protocol than that recommended in the 2011 guideline was not justified due to the costs, patient anxiety, potential test related-morbidity and consequences of false positive tests.

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 represent current practice. There will therefore be no associated resource impact.

Other factors the committee took into account

The use of follow-up colonoscopy was not covered in the recommendations as this has a different purpose to CEA or CT testing and is covered by guidance from the British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland (ACPGBI). Where CEA testing and CT scanning is used to detect recurrence, colonoscopy is used to prevent and detect further tumours.

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Sobhani I, Tiret E, Labtahi R, et al. (2008) Early detection of recurrence by 18FDG-PET in the follow-up of patients with colorectal cancer. British Journal of Cancer 98(5): 875-880

Strand 2011

Strand E, Nygren I, Bergkvist L, et al. (2011) Nurse or surgeon follow-up after rectal cancer: a randomized trial. Colorectal Disease 13(9): 999-1003

Treasure 2014

Treasure T, Monson K, Fiorentino F et al. (2014) The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer. BMJ Open 4(5): e004385

Wang 2009

Wang T, Cui Y, Huang W, et al. (2009) The role of postoperative colonoscopic surveillance after radical surgery for colorectal cancer: a prospective, randomized clinical study. Gastrointestinal Endoscopy 69(3 Pt 2): 609-615

Wattchow 2006

Wattchow D, Weller D, Esterman A, et al. (2006) General practice vs surgical-based follow-up for patients with colon cancer: randomised controlled trial. British Journal of Cancer 94(8): 1116-1121

Appendices

Appendix A – Review protocol

Review protocol for review question: What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

Table 3: Review protocol for the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer

Field (based on PRISMA-P)	Content
Review question	What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?
Type of review question	Intervention
Objective of the review	To determine the optimal methods and frequencies of follow-up after potentially curative surgical treatment to detect recurrence for people who have had non-metastatic colorectal cancer.
Eligibility criteria – population/disease/condition/issue /domain	Adults who have undergone surgical or endoscopic resection for non-metastatic colorectal cancer (colon cancer or rectal cancer) with curative intent (with or without adjuvant therapy): • T any • N any • M0
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Follow-up strategy taking into consideration one or more of the following elements: o Intensity/frequency of follow-up o Duration of follow-up o Content of follow-up (for example clinical examination, serum CEA level, colonoscopy, liver-focused imaging, chest x-ray) o Setting of follow-up (for example primary care or hospital) o Personnel in charge of running clinic (for example consultant led or nurse led)
Eligibility criteria – comparator(s)/control or reference (gold) standard	• Follow-up strategies compared to each other, for example: o intensive versus less intensive o hospital-based versus GP-based • No follow-up
Outcomes and prioritisation	**Critical outcomes** • Overall survival (MID: any statistically significant difference) • Colorectal cancer-specific survival (MID: any statistically significant difference) **Important outcomes**

Field (based on PRISMA-P)	Content
	• Local recurrence (MID: any statistically significant difference) • Distant metastasis (MID: any statistically significant difference) • Metachronous colorectal cancer (MID: any statistically significant difference) • Resectability of recurrent local or metastatic disease (MID: any statistically significant difference) • Overall quality of life measured using validated scales (MID: from published literature) • Procedure-related morbidity (MID: any statistically significant difference) 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 of RCTs • RCTs • Comparative observational studies if eligible RCTs are not available
Other inclusion exclusion criteria	Inclusion criteria: • 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 considered that follow-up methods have evolved and evidence published prior to 2000 would no longer be relevant.
Proposed sensitivity/sub-group analysis, or meta-regression	None identified.
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.

Field (based on PRISMA-P)	Content
	Quality control will be performed by the senior systematic reviewer
Data management (software)	Pairwise meta-analyses was performed using Cochrane Review Manager (RevMan5). 'GRADEpro' was be used to assess the quality of evidence for each outcome. NGA STAR software was 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 (to be confirmed by Information Scientist): 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 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: • CASP 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'

Field (based on PRISMA-P)	Content
	developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	**Synthesis of data:** Pairwise meta-analysis of randomised trials will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled if baselines are comparable. If any studies report both, the method used in the majority of studies will be analysed. **Minimally important differences:** The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except quality of life for which published MIDs from literature will be used (see outcomes section for more information).
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	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 NGA 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 Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by 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 with PROSPERO

CASP: critical appraisal skills programme; CCTR: Cochrane controlled trials register; 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 Re-search 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); GP: General Practitioner; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimal important difference; NGA: National Guidelines Alliance; NHS: National Health Service; NICE: National Institute for Health and Clinical Excellence; PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols; PROSPERO: International prospective register of systematic reviews; RCT: randomised controlled trial; 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 are the optimal methods 3 and frequencies of follow-up to detect recurrence after potentially curative 4 surgical treatment for non-metastatic colorectal cancer?

5 Database: Embase/Medline

6 Last searched on: 12/02/2019

#	Search
1	(exp colorectal cancer/ or exp colon tumor/ or exp rectum tumor/) use emez
2	exp colorectal neoplasms/ use ppez
3	((colorect* or colo rect* or colon or colonic or rectal or rectum) adj3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)).tw.
4	or/1-3
5	exp recurrence/ use ppez
6	Neoplasm recurrence, local/ use ppez
7	Disease progression/ use ppez
8	Cancer recurrence/ use emez
9	Recurrent disease/ use emez
10	Tumor recurrence/ use emez
11	postoperative care/
12	(Recurr* or relaps* or reappear* or post-operat* or postoperat* or post-surg* or postsurg* or post-hosp* or posthosp*).tw.
13	or/5-12
14	4 and 13
15	exp aftercare/ use ppez
16	exp *aftercare/ use emez
17	(follow up or followup).ti.
18	((follow up or followup) adj3 (hospital* or post-hospital*or operat* or post-operat* or resection* or surg* or post-surg* or therap* or post-therap* or postherp* or posttherap* or treatment* or post-treatment or posttreatment)).tw.
19	((follow up or followup) adj3 (plan* or program* or protocol* or regime* or schedule* or strateg*)).tw.
20	exp patient monitoring/ use emez
21	exp Monitoring, Physiologic/ use ppez
22	population surveillance/ use ppez
23	(surveill* adj3 (colonoscop* or guideline* or follow up or followup or plan* or post-operat* or postoperat* or post-treatment* or posttreatment* or practice* or program* or protocol* schedule* or strateg*)).tw.
24	(re-examin* or reexamin* or periodic examin* or regular examin* or checkup* or check-up*).tw.
25	or/15-24
26	14 and 25
27	Letter/ use ppez
28	letter.pt. or letter/ use emez
29	note.pt.
30	editorial.pt.
31	Editorial/ use ppez
32	News/ use ppez
33	exp Historical Article/ use ppez
34	Anecdotes as Topic/ use ppez
35	Comment/ use ppez
36	Case Report/ use ppez
37	case report/ or case study/ use emez
38	(letter or comment*).ti.
39	or/27-38
40	randomized controlled trial/ use ppez
41	randomized controlled trial/ use emez
42	random*.ti,ab.
43	or/40-42
44	39 not 43
45	animals/ not humans/ use ppez
46	animal/ not human/ use emez
47	nonhuman/ use emez
48	exp Animals, Laboratory/ use ppez
49	exp Animal Experimentation/ use ppez
50	exp Animal Experiment/ use emez
51	exp Experimental Animal/ use emez
52	exp Models, Animal/ use ppez

#	Search
53	animal model/ use emez
54	exp Rodentia/ use ppez
55	exp Rodent/ use emez
56	(rat or rats or mouse or mice).ti.
57	or/44-56
58	26 not 57
59	limit 58 to (english language and yr="2000-current")
60	remove duplicates from 59

1 **Database: Cochrane Library**

2 Last searched on: 12/02/2019

#	Search
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees
2	((colorect* or colo rect* or colon or colonic or rectal or rectum) near/3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)):ti,ab,kw
3	#1 or #2
4	MeSH descriptor: [Recurrence] explode all trees
5	MeSH descriptor: [Neoplasm Recurrence, Local] this term only
6	MeSH descriptor: [Disease Progression] this term only
7	MeSH descriptor: [Postoperative Care] this term only
8	(Recurr* or relaps* or reappear* or post-operat* or postoperat* or post-surg* or postsurg* or post-hosp* or posthosp*):ti,ab,kw
9	{or #4-#8}
10	#3 and #9
11	MeSH descriptor: [Aftercare] explode all trees
12	(follow up or followup):ti
13	((follow up or followup) near/3 (hospital* or post-hospital*or operat* or post-operat* or resection* or surg* or post-surg* or therap* or post-therap* or postherp* or posttherap* or treatment* or post-treatment or posttreatment)):ti,ab,kw
14	((follow up or followup) near/3 (plan* or program* or protocol* or regime* or schedule* or strateg*)):ti,ab,kw
15	MeSH descriptor: [Monitoring, Physiologic] explode all trees
16	MeSH descriptor: [Population Surveillance] this term only
17	(surveill* near/3 (colonoscop* or guideline* or follow up or followup or plan* or post-operat* or postoperat* or post-treatment* or posttreatment* or practice* or program* or protocol* schedule* or strateg*)):ti,ab,kw
18	(re-examin* or reexamin* or periodic examin* or regular examin* or checkup* or check-up*):ti,ab,kw
19	{or #11-#18}
20	#10 and #19 Publication Year from 2000 to 2018

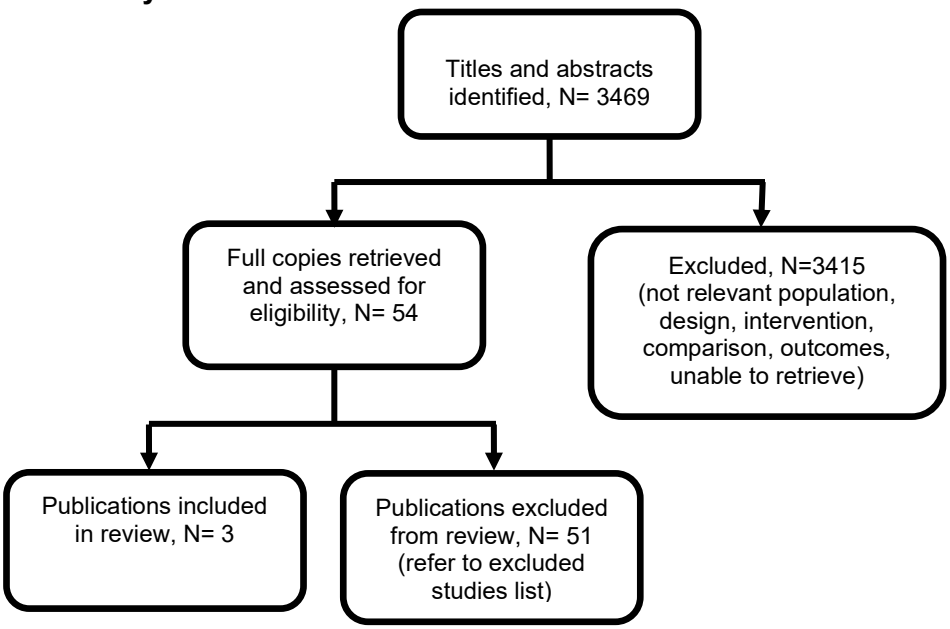
3

4

Appendix C – Clinical evidence study selection

Clinical study selection for: What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

Figure 2: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

Table 4: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Jeffery, Mark, Hickey, Brigid E, Hider, Phil N, See, Adrienne M, Follow-up strategies for patients treated for non-metastatic colorectal cancer, Cochrane Database of Systematic Reviews, 2016 **Ref Id** 625345 **Country/ies where the study was carried out** Not applicable **Study type** Systematic review **Aim of the study** To assess the effectiveness of intensive follow-up after treatment with curative intent for non-metastatic colorectal cancer	**Sample size** 15 RCTs included (N=5403 participants) **Characteristics** 7 studies included Dukes' stage A, B, and C colon and rectal cancer (Augestad 2013; FACS 2014; Kjeldsen 1997; Mäkelä 1995; Ohlsson 1995; Rodríguez-Moranta 2006; Wang 2009). 2 studies excluded Dukes' A participants (GILDA 1998; Pietra 1998), 2 studies excluded participants with rectal cancer (Pietra 1998; Wattchow 2006), 1 study included only rectal cancer participants (Strand 2011). **Inclusion criteria** RCTs were included if they compared different follow-up strategies for people with histologically	**Interventions** The studies were grouped according to comparisons as follows: • More visits and tests versus fewer visits and tests (Kjeldsen 1997; Mäkelä 1995; Pietra 1998; Rodríguez-Moranta 2006; Secco 2002; Treasure 2014; Wang 2009); • Formal follow-up versus minimal/no follow-up (FACS 2014; Ohlsson 1995; Schoemaker 1998; Secco 2002); • More liver imaging versus less liver imaging (FACS 2014; GILDA 1998; Rodríguez-Moranta 2006; Schoemaker 1998); • Carcinoembryonic antigen (CEA) versus no CEA (FACS 2014; Kjeldsen 1997; Ohlsson 1995; Treasure 2014); and	**Details** This review used standard methods for Cochrane intervention reviews: 2 authors sifted the literature searches and 2 authors did data extraction independently. Risk of bias was assessed using the Cochrane risk of bias tool. GRADEPro was used to evaluate the overall quality of the evidence. Subgroup analyses to investigate heterogeneity included: use of CEA, CT, and PET/CT in the intensive follow-up strategy when compared with no use or less frequent use (twice at most) in the control arm, and setting for follow-up (general practitioner (GP)- or nurse-led follow-up compared with hospital follow-up and "dose" of follow-up, i.e. studies that compared the use of	**Results** • 12 RCTs reported overall survival (Augestad 2013; FACS 2014; GILDA 1998; Kjeldsen 1997; Mäkelä 1995; Ohlsson 1995; Pietra 1998; Rodríguez-Moranta 2006; Schoemaker 1998; Strand 2011; Treasure 2014; Wang 2009). • 7 RCTs reported colorectal cancer-specific survival (measured from the time of randomisation in the study) (Augestad 2013; FACS 2014; GILDA 1998; Kjeldsen 1997; Ohlsson 1995; Rodríguez-Moranta 2006; Wang 2009). • 14 RCTs reported relapse-free survival (measured from the time of randomisation in the study) (Augestad 2013; FACS 2014; GILDA 1998; Kjeldsen 1997; Mäkelä 1995; Ohlsson 1995; Pietra 1998; Rodríguez-Moranta 2006; Schoemaker 1998; Secco	**Limitations** CASP systematic review checklist 1. Did the review address a clearly focused question? Yes 2. Did the authors look for the right type of papers? Yes 3. Do you think all important & relevant studies were included? Yes 4. Did the authors do enough to assess quality of the included studies? Yes 5. If the results of the review have been combined, was it reasonable to do so? Yes 6. What are the overall results? (See Forest plots)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Literature searched in May 2016 **Source of funding** Princess Alexandra Hospital Cancer Collaborative Group, Australia supported on of the authors.	proven adenocarcinoma of the colon or rectum, stage T1-4N0-2M0, treated surgically with curative intent (with or without adjuvant treatment). These trials included comparisons of follow-up versus no follow-up, follow-up strategies of varying intensity (differing frequency or quantity of testing, or both), and follow-up in different healthcare settings (e.g. primary care versus hospital). There was no language restriction on the literature search which was done in May 2016 **Exclusion criteria** Not reported	• Setting for follow-up (where frequency of visits and tests were identical in both arms): general practitioner (GP)-led follow-up, Augestad 2013; Wattchow 2006, or nurse-led follow-up, Strand 2011, compared with surgeon-led follow-up.	more visits and tests with fewer visits and tests). Sensitivity analyses were done to test the strength of the conclusions by excluding studies at high risk of bias for the particular outcome concerned (Kjeldsen 1997; Mäkelä 1995; Pietra 1998; Schoemaker 1998; Wang 2009), and by study age (excluding the older studies that completed accrual by 1996) (Kjeldsen 1997; Mäkelä 1995; Ohlsson 1995; Pietra 1998; Schoemaker 1998; Treasure 2014).	2002; Sobhani 2008; Strand 2011; Treasure 2014; Wang 2009). • 13 RCTs reported salvage surgery (surgery performed with curative intent for relapse of colorectal cancer) (Augestad 2013; FACS 2014; GILDA 1998; Kjeldsen 1997; Mäkelä 1995; Ohlsson 1995; Pietra 1998; Rodríguez-Moranta 2006; Schoemaker 1998; Secco 2002; Sobhani 2008; Treasure 2014; Wang 2009). • 8 RCTs reported interval recurrences (relapse of colorectal cancer detected between follow-up visits or symptomatic recurrences) (FACS 2014; Kjeldsen 1997; Mäkelä 1995; Secco 2002; Sobhani 2008; Wang 2009; Wattchow 2006; Augestad 2013). • 4 RCTs assessed quality of life (Augestad 2013; GILDA 1998; Kjeldsen 1997; Wattchow 2006). • 4 studies evaluated costs of surveillance (including investigations) (Augestad 2013; Secco 2002; Rodríguez-Moranta 2006; Strand 2011). Rodríguez-Moranta 2006 and Augestad 2013 performed	7. How precise are the results? (See Forest plots & GRADE imprecision assessment) 8. Can the results be applied to the local population? Yes 9. Were all important outcomes considered? Yes 10. Are the benefits worth the harms and costs? Probably, but limited information about harms

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				cost=minimisation analyses.	
Full citation Verberne, C. J., Zhan, Z., van den Heuvel, E. R., Oppers, F., de Jong, A. M., Grossmann, I., Klaase, J. M., de Bock, G. H., Wiggers, T., Survival analysis of the CEAwatch multicentre clustered randomized trial, British Journal of Surgery, 104, 1069-1077, 2017 **Ref Id** 751306 **Country/ies where the study was carried out** Netherlands **Study type** RCT - multi-centre stepped wedge design. **Aim of the study** To determine whether the earlier detection and increased curative treatment rates demonstrated by the CEAwatch trial (intesive CEA monitoring vs usual care) are associated with increases in overall survival and disease-specific survival. The	**Sample size** Patients included in CEAwatch trial N=3223; included in final analysis n=3182; recurrent disease detected during trial period n=238 (care as usual n=112; CEAwatch protocol n=126). **Characteristics** Male 56%, female 44%; Median age 70 years (range 26 to 95); Colon primary 63%, rectum primary 37%; 70% had adjuvant chemotherapy; AJCC stage I 28%, II 39%, III 33% **Inclusion criteria** Primary colorectal cancer, AJCC stage I–III disease, R0 resection between 2007 and July 2012. **Exclusion criteria** Unclear.	**Interventions** Care as usual following national guidance - outpatient clinic visits every 6 months for 3 years, and annually for the fourth and fifth year; and CEA measurement every 3 - 6 months in the first 3 years, and annually in the fourth and fifth year; with recommendations for liver ultrasonography and chest x-ray at each visit. Follow-up started after curative resection and adjuvant therapy (if this had been included in the patients treatment programme). CEAwatch intensive follow-up protocol (optimised for sensitivity/specificity) - CEA measurement every 2 months and annual CT imaging of thorax and abdomen for the first three years; CEA measurement in the fourth and fifth years. If the patient's absolute CEA level was greater than 2.5 ng/ml and there was a 20% increase in the CEA levels when compared to the previous reading, another sample was taken 4 weeks later.	**Details** Randomisation. Multi-centre, stepped-wedge RCT using a unidirectional crossover design. Five clusters were created by randomly grouping together 11 teaching hospitals into 5 clusters. Each cluster started the trial by providing care as usual, however every three months one cluster switched to the CEAwatch follow-up protocol. Randomisation was used to determine in what order the clusters switched. No further details provided. Follow-up/outcomes. The study compared (in patients with recurrence) the effects of method of follow-up on overall survival and disease specific survival rates. Statistical analysis. A Cox Markov model was used to compare the transition from recurrence to death in patients for whom recurrence was detected via the CEAwatch protocol vs those for whom recurrence was detected via the care as usual protocol. The	**Results** Outcome: Overall survival. CEAwatch vs care as usual - HR 0.73, 95% CI 0.46 to 1.17, p = 0.191. Interaction between detection method and follow-up protocol - p = 0.496. CEA testing vs CT imaging - HR 1.34, 95% CI 0.83 to 2.17. CEA testing vs patient self-report - HR 0.39, 95% CI 0.25 to 0.63. CT imaging vs patient self-report - HR 0.29, 95% CI 0.17 to 0.51. Outcome: Colorectal cancer-specific survival CEAwatch vs care as usual - HR 0.78, 95% CI 0.48 to 1.28. CEA testing vs CT imaging - HR 1.28, 95% CI 0.76 to 2·14. CT imaging vs patient self-report - HR 0.26, 95% CI 0.14 to 0.47.	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (Insufficient information reported.) Allocation concealment: high risk (cluster randomised – staff would know what protocol would be received before patients were entered) Performance bias Blinding of participants and personnel: high risk (No blinding; Control intervention was national guidelines of Netherlands in 2008 - but adherence to this guideline was poor) Detection bias Blinding of outcome assessment: low/high risk (No blinding. Risk of bias depends on the outcomes, high risk for subjective outcomes.) Attrition bias Incomplete outcome data: unclear risk

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
study also aimed to explore whether differences in survival relate to the detection method (i.e. CEA based blood tests, CT imaging, or self-report. **Study dates** October 2015 to March 2015. **Source of funding** Netherlands Organization for Health Research and Development.		If this CEA level was greater than the previous reading, abdomen and chest CTs were recommended.	model was adjusted for age at diagnosis, gender, hospital, and primary tumour stage.	CEA testing vs patient self-report - HR 0.33, 95% CI 0.20 to 0.55.	Reporting bias Selective reporting: low risk Other bias Other sources of bias: - The trial had a stepped-wedge cluster randomized design, so some most patients received both types of follow-up. The switch was always from conventional follow-up to the intensive schedule - so there could be bias if early recurrences have different natural history to later ones. Hazard ratios for survival outcomes could only be estimated using a Cox Markov model adjusted for age, sex, primary tumour stage and hospital. This model assumed that the different follow-up strategies would only affect outcomes in those with recurrence.
Full citation Wille-Jørgensen, P., Syk, I., Smedh, K., et al.,, Effect of more vs less frequent follow-up testing on overall and colorectal cancer–specific mortality in patients with stage ii or iii colorectal cancer: The colofol randomized clinical	**Sample size** N=2555 randomised; n=1275 allocated to receive follow-up at 6, 12, 18, 24 and 36 months after surgery (high-frequency follow-up); n=1280 allocated to receive follow-up at 12 and 36 months after surgery (low-frequency follow-up)	**Interventions** High-frequency follow-up versus low-frequency follow-up High-frequency follow-up Multislice contrast enhanced CT of the thorax and abdomen and CEA at 6, 12, 18, 24, and 36 months after surgery.	**Details** Randomisation and allocation concealment Block randomisation in block sizes of 10 was done, allocation by computer. No other details provided. Blinding No blinding.	**Results** Outcome: Overall survival (5 years of follow-up; event is death from any cause) High-frequency 161 events, n=1253 Low-frequency 174 events, n=1256 log-rank p=0.43 Outcome: Colorectal cancer-specific survival (5	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (Insufficient information reported.) Allocation concealment: unclear risk (Insufficient information reported.)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
trial, Jama, 319, 2095-2103, 2018 **Ref Id** 864237 **Country/ies where the study was carried out** Denmark, Sweden and Uruguay **Study type** RCT (COLOFOL trial) **Aim of the study** To examine overall mortality, colorectal cancer–specific mortality, and colorectal cancer–specific recurrence rates among patients with stage II or III colorectal cancer who were randomised after curative surgery to 2 alternative schedules for follow-up testing with computed tomography and carcinoembryonic antigen. **Study dates** January 2006 to December 2010 **Source of funding** Nordic Cancer Union, A. P. Møller Foundation,	**Characteristics** Age in years, median (IQR) High-frequency 65.2 (59.6-69.7) Low-frequency 64.7 (58.6-69.9) Male sex, n (%) High-frequency 706 (56) Low-frequency 675 (54) Type of cancer, n (%) Rectal High-frequency 428 (34) Low-frequency 456 (36) Right-sided colon High-frequency 355 (28) Low-frequency 357 (28) Transverse colon High-frequency 68 (5) Low-frequency 47 (4) Left-sided colon High-frequency 416 (33) Low-frequency 419 (33) Type of treatment, n (%) Preoperative radiotherapy High-frequency 247 (20) Low-frequency 276 (22) Adjuvant chemotherapy High-frequency 591 (47) Low-frequency 581 (46) Cancer stage II (T3-4N0M0), n (%) High-frequency 675 (54) Low-frequency 677 (54)	Low-frequency follow-up Multi-slice contrast-enhanced CT of the thorax and abdomen and CEA at 12 and 36 months after surgery. Pelvic CT was not required. Endoscopy and examination for pelvic recurrence were allowed in both groups at the discretion of the treating physician. Although permitted in the study, no department used magnetic resonance imaging or chest radiography as part of its surveillance program.	Follow-up/outcomes At each follow-up, data were collected on symptoms, CT scans, and CEA test results and additional examinations were performed if recurrence was suspected. Up to 3 months' variability in follow-up intervals was allowed to accommodate local needs for prioritisation and patient preferences. If the participant experienced symptoms between follow-up examinations, an interval examinations were done and recorded. If a recurrence was not detected during an interval follow-up examination, the participant was allowed to continue in the study. If a recurrence was suspected during any follow-up examination, the case was discussed in a local multidisciplinary team and further diagnostic assessment and treatment was provided as recommended. All participants had to be followed-up with surveillance examinations until 3 years after surgery and the participating centres	years of follow-up; event is death from colorectal cancer) High-frequency 128 events, n=1248 Low-frequency 137 events, n=1250 log-rank p=0.52 Outcome: Colorectal cancer-specific recurrence (5 years of follow-up; event is colorectal recurrence) High-frequency 265 events, n=1248 Low-frequency 238 events, n=1250 log-rank p=0.15	Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: low/high risk (No blinding. Risk of bias depends on the outcomes, high risk for subjective outcomes.) Attrition bias Incomplete outcome data: unclear risk (Participants who received allocated intervention were included in the intention-to-treat analysis for survival and recurrence outcomes but 22/1275 and 24/1280 participants in high-frequency and low-frequency groups, respectively, were excluded from intention-to-treat analysis because "did not receive intervention as randomised".) Reporting bias Selective reporting: low risk Other bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Beckett Foundation, Grosserer Chr. Andersen og hustru bursary, Sigvald og Edith Rasmussens Memorial Fund, Martha Margrethe og Christian Hermansens Fund, the Danish Medical Association, the Danish Cancer Society, the Danish Council for Independent Research/Medical Sciences, Swedish Cancer Foundation	**Inclusion criteria** Surgical resection with curative intent for colorectal adenocarcinoma (with or without adjuvant treatment); ≤75 years of age; written informed consent; a colon and rectum free of neoplasia verified by perioperative barium enema or a colonoscopy within 3 months after surgery; tumour stage II or III (T3-T4, N0,M0, any N1-N2, M0). **Exclusion criteria** Clinical diagnosis of hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis; local resection of colorectal cancer; life expectancy of <2 years due to comorbid conditions (for example cardiac disease, advanced multiple sclerosis with systemic complications, or liver cirrhosis); inability or refusal to provide informed consent; inability to comply with study requirements; inability to tolerate surgery for recurrence; other or previous malignancies		reported outcomes until 5 years after surgery. Primary outcome was 5-year overall mortality and 5-year colorectal cancer-specific mortality. Five-year colorectal cancer-specific recurrence was a secondary outcome. Adverse events were not recorded. Statistical analysis Intention-to-treat analysis done (although 22/1275 and 24/1280 excluded from high-frequency and low-frequency follow-up groups, respectively, because "did not receive intervention as randomised") for survival and recurrence outcomes.		Other sources of bias: -

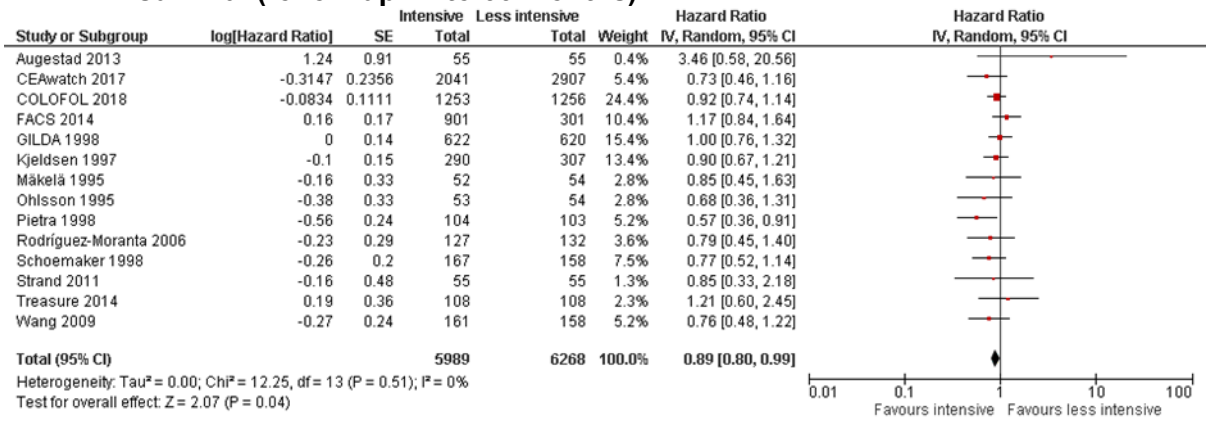
Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	(except for non-melanoma skin cancer); participation in another clinical trial that was incompatible with this study's follow-up regimens.				

AJCC: American Joint Committee on Cancer; CASP: Critical Appraisal Skills Programme CEA: carcinoembryonic antigen; CI: confidence interval; CT: computed tomography; GP: General Practitioner; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: hazard ratio; IQR: inter-quartile range; MRI: magnetic resonance imaging; N: number; PET: positron emission tomography; R(0): complete resection; RCT: randomised controlled trial; TNM: cancer classification system, standing for tumour,nodal and metastasis stages

Appendix E – Forest plots

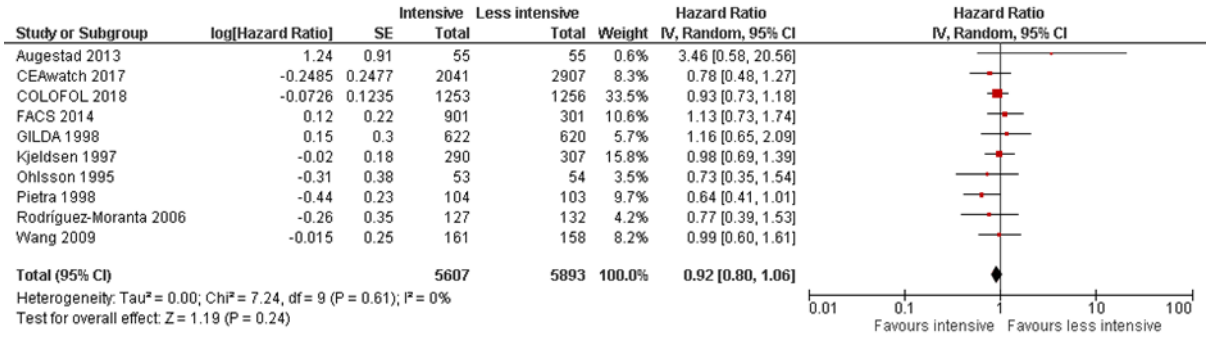
Forest plots for review question: What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

Figure 3: Comparison 1: More intensive versus less intensive follow-up – Overall survival (follow-up 24 to 66 months)



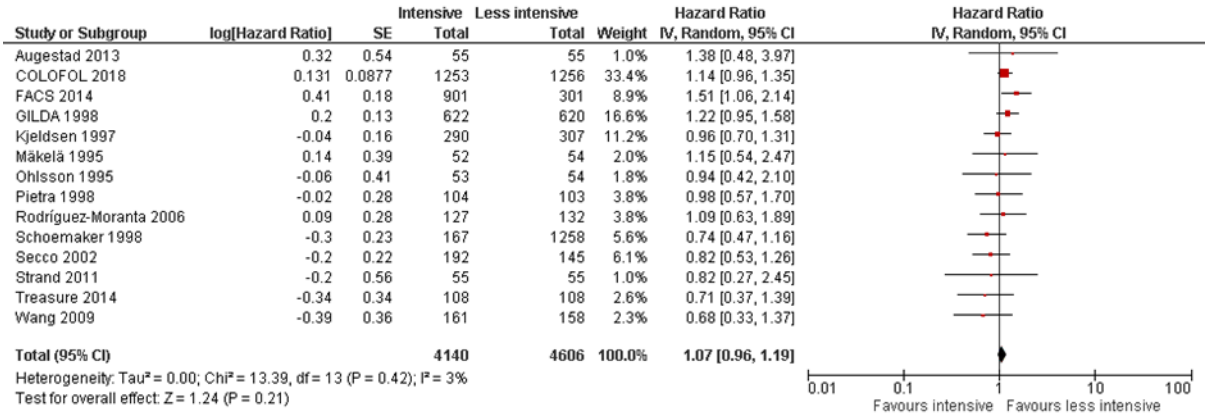
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 4: Comparison 1: More intensive versus less intensive follow-up – Colorectal cancer-specific survival (follow-up 24 to 66 months)



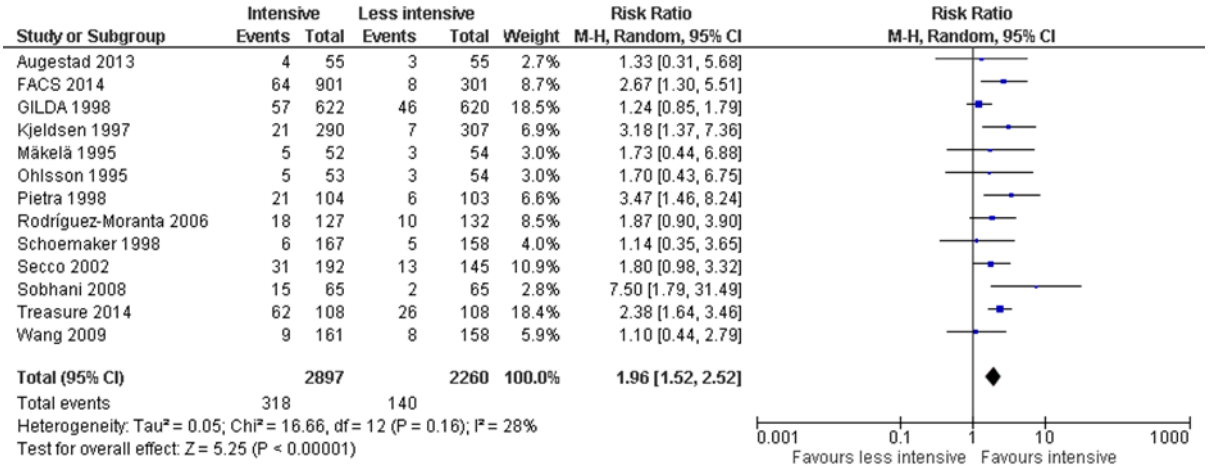
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 5: Comparison 1: More intensive versus less intensive follow-up – Relapse-free survival (follow-up 24 to 66 months)



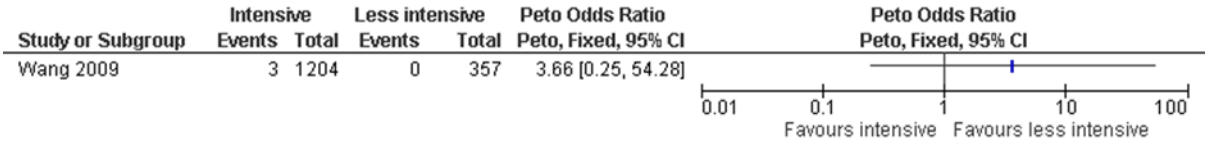
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 6: Comparison 1: More intensive versus less intensive follow-up – Resectable recurrent disease (follow-up 24 to 66 months)



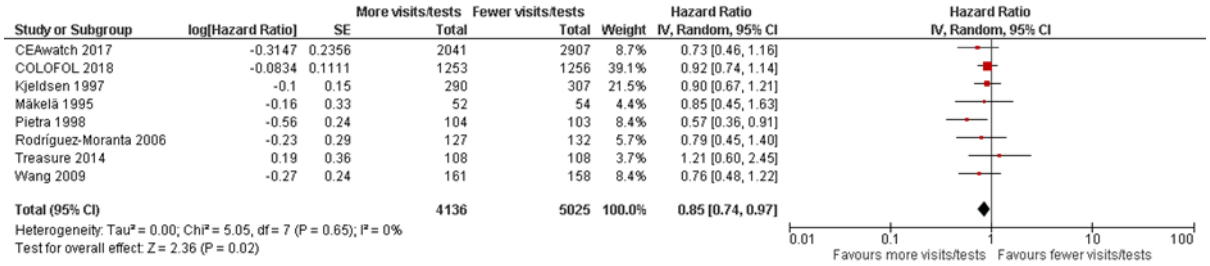
CI: confidence interval; M-H: Mantel-Haenszel

Figure 7: Comparison 1: More intensive versus less intensive follow-up – Procedure-related morbidity (follow-up 64 months)



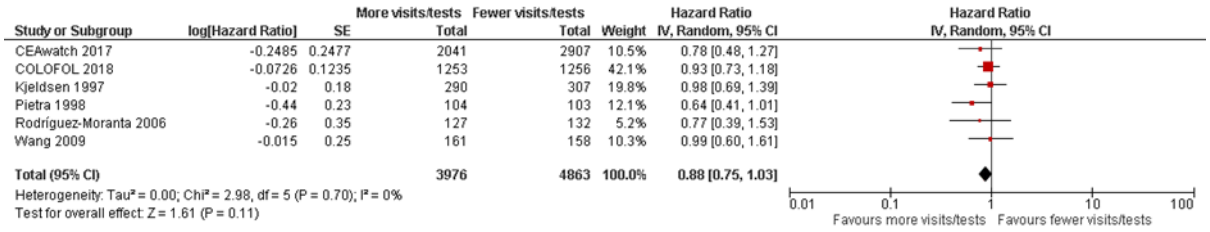
CI: confidence interval;

Figure 8: Comparison 2: More visits or tests versus fewer visits or tests – Overall survival (follow-up 41 to 64 months)



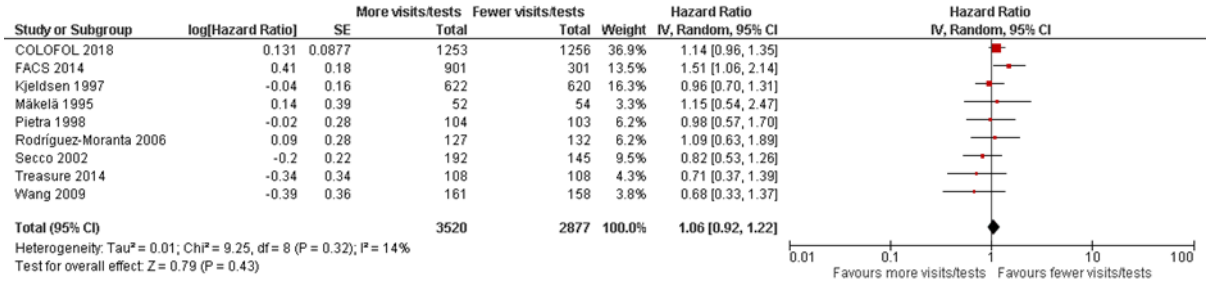
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 9: Comparison 2: More visits or tests versus fewer visits or tests – Colorectal cancer-specific survival (follow-up 41 to 64 months)



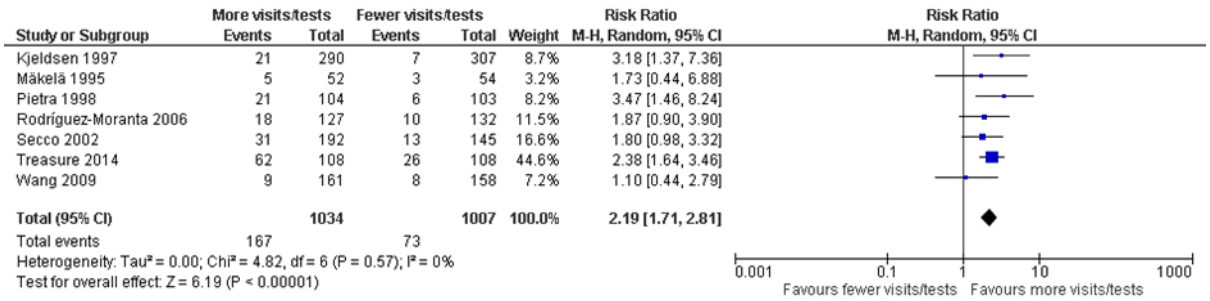
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 10: Comparison 2: More visits or tests versus fewer visits or tests – Relapse-free survival (follow-up 41 to 64 months)



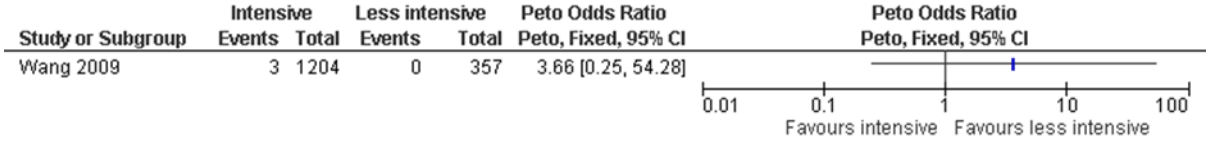
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 11: Comparison 2: More visits or tests versus fewer visits or tests – Resectable recurrent disease (follow-up 41 to 64 months)



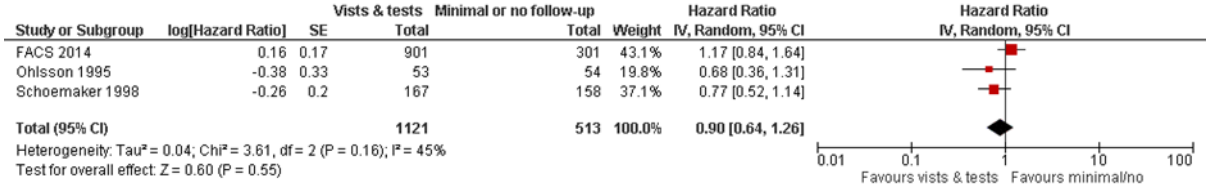
CI: confidence interval; M-H: Mantel-Haenszel

Figure 12: Comparison 2: More visits or tests versus fewer visits or tests – Procedure-related morbidity (follow-up 64 months)



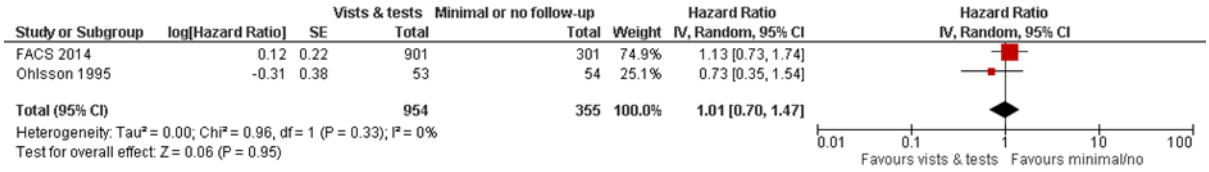
CI: confidence interval

Figure 13: Comparison 3: Visits or tests versus minimal or no follow-up – Overall survival (follow-up 41 to 66 months)



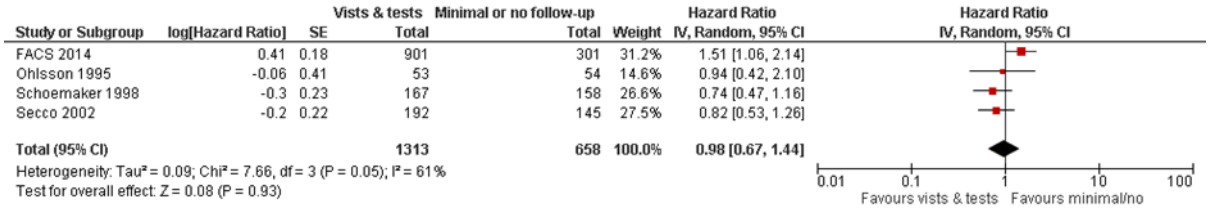
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 14: Comparison 3: Visits or tests versus minimal or no follow-up – Colorectal cancer-specific survival (follow-up 41 to 66 months)



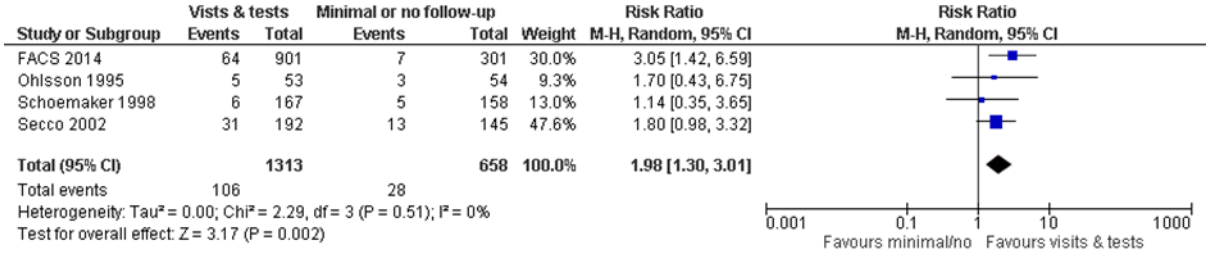
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 15: Comparison 3: Visits or tests versus minimal or no follow-up – Relapse-free survival (follow-up 41 to 66 months)



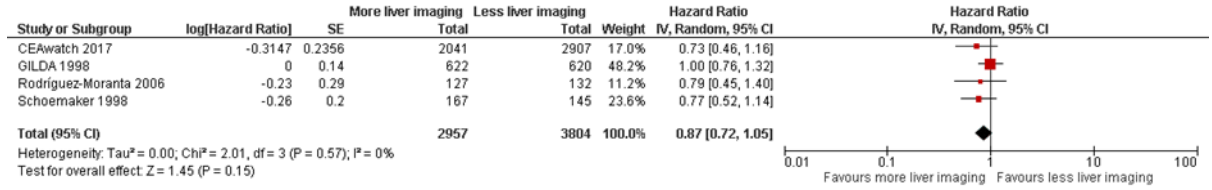
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 16: Comparison 3: Visits or tests versus minimal or no follow-up – Resectable recurrent disease (follow-up 41 to 66 months)



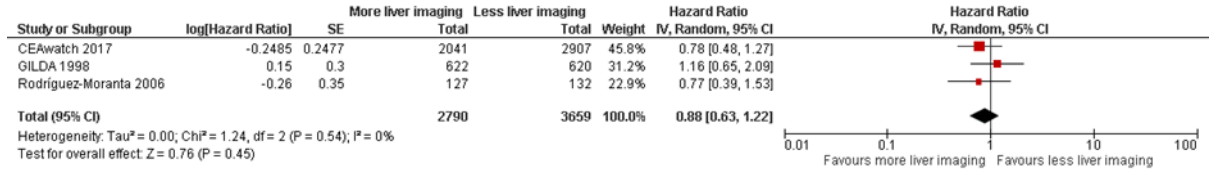
CI: confidence interval; M-H: Mantel-Haenszel

Figure 17: Comparison 4: More liver imaging versus less liver imaging – Overall survival (follow-up 48 to 60 months)



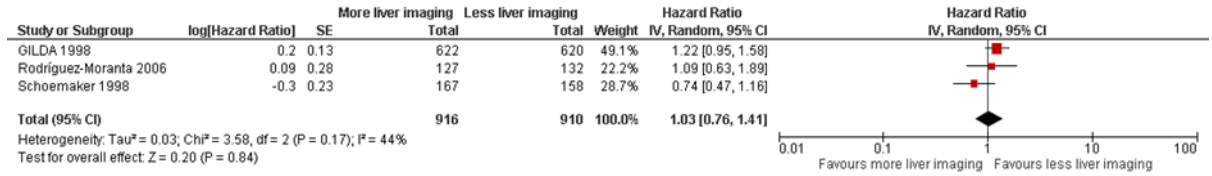
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 18: Comparison 4: More liver imaging versus less liver imaging – Colorectal cancer-specific survival (follow-up 48 to 60 months)



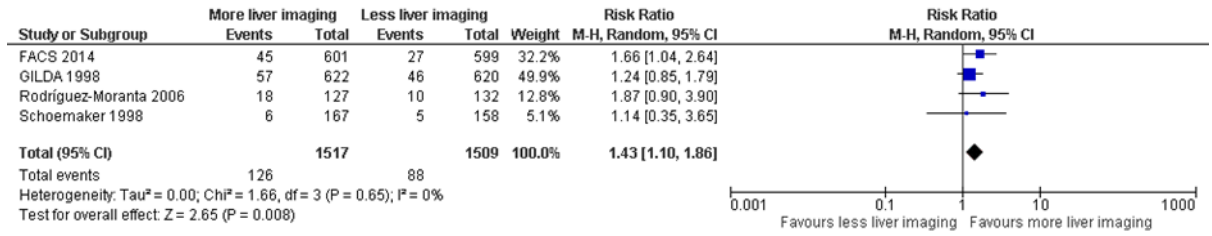
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 19: Comparison 4: More liver imaging versus less liver imaging – Relapse-free survival (follow-up 48 to 60 months)



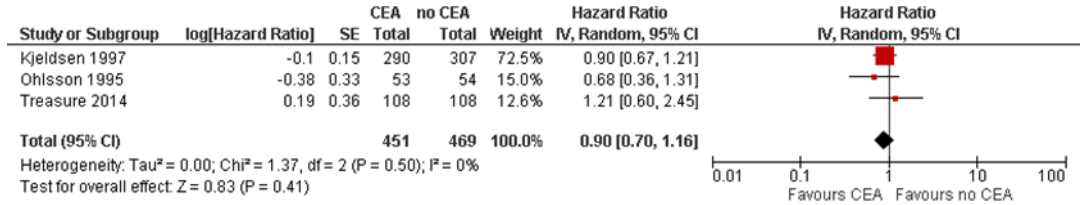
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 20: Comparison 4: More liver imaging versus less liver imaging – Resectable recurrent disease (follow-up 48 to 60 months)



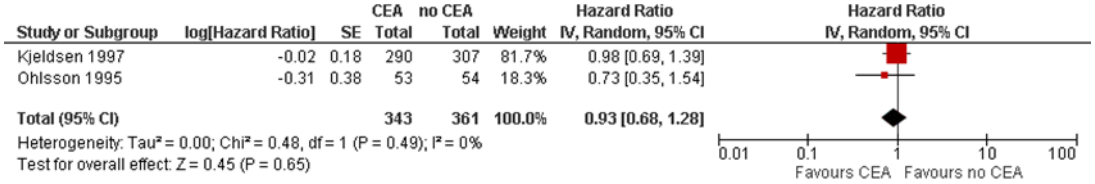
CI: confidence interval; M-H: Mantel-Haenszel

Figure 21: Comparison 5: CEA tests versus no CEA tests – Overall survival (follow-up 66 months)



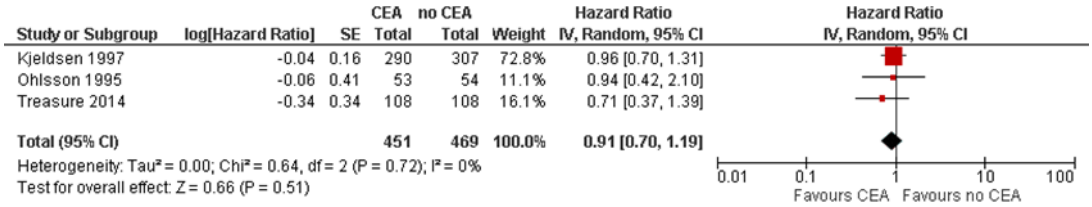
CEA: carcinoembryonic antigen; CI: confidence interval; IV: inverse variance; SE: standard error

Figure 22: Comparison 5: CEA tests versus no CEA tests – Colorectal cancer-specific survival (follow-up 66 months)



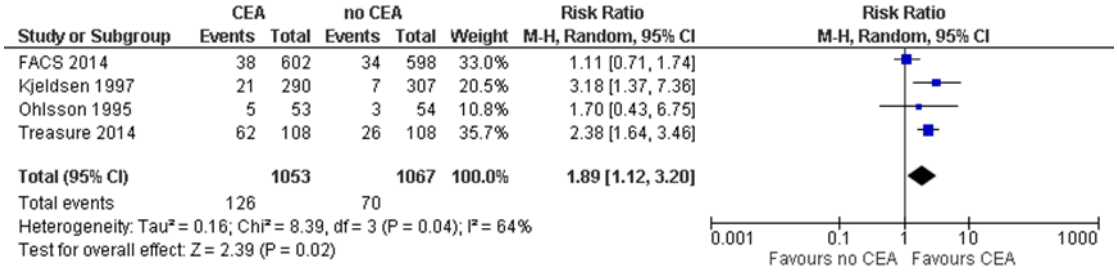
CEA: carcinoembryonic antigen; CI: confidence interval; IV: inverse variance; SE: standard error

Figure 23: Comparison 5: CEA tests versus no CEA tests – Relapse-free survival (follow-up 66 months)



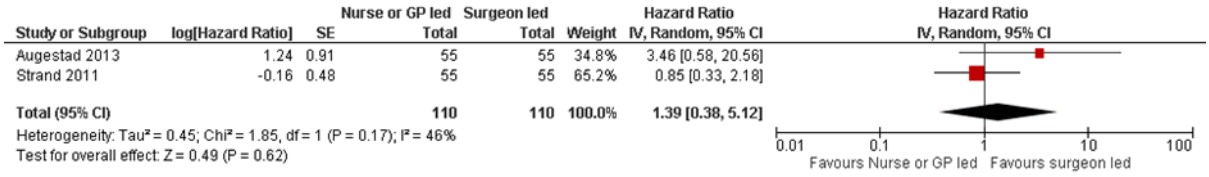
CEA: carcinoembryonic antigen; CI: confidence interval; IV: inverse variance; SE: standard error

Figure 24: Comparison 5: CEA tests versus no CEA tests – Resectable recurrent disease (follow-up 41 to 66 months)



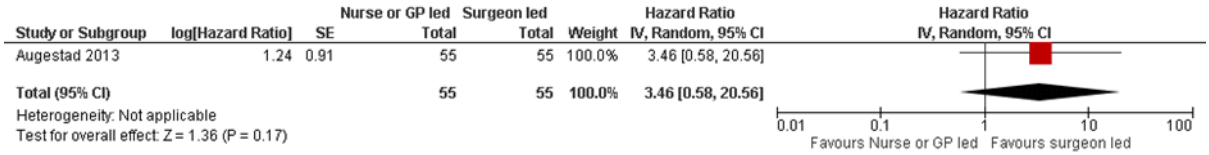
CEA: carcinoembryonic antigen; CI: confidence interval; M-H: Mantel-Haenszel

Figure 25: Comparison 6: Nurse or GP led follow-up versus surgeon led follow-up – Overall survival (follow-up 24 to 60 months)



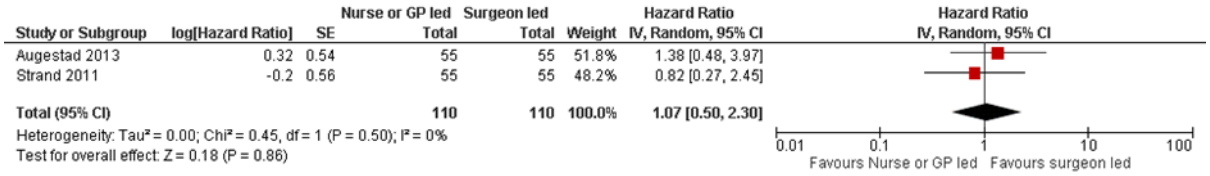
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 26: Comparison 6: Nurse or GP led follow-up versus surgeon led follow-up – Colorectal cancer-specific survival (follow-up 24 months)



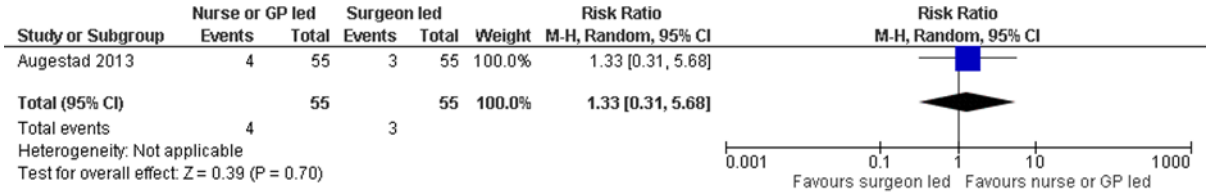
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 27: Comparison 6: Nurse or GP led follow-up versus surgeon led follow-up – Relapse-free survival (follow-up 24 to 60 months)



CI: confidence interval; df: degrees of freedom; IV: inverse variance; SE: standard error

Figure 28: Comparison 6: Nurse or GP led follow-up versus surgeon led follow-up – Resectable recurrent disease (follow-up 24 months)



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

Appendix F – GRADE tables

GRADE tables for review question: What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

Table 5: Clinical evidence profile for comparison 1: More intensive versus less intensive follow-up

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intensive follow-up	Less intensive follow-up	Relative (95% CI)	Absolute (95% CI)		
Overall survival (event is death from any cause; follow-up 24 months to 66 months)												
14	randomised trials	not serious	not serious	not serious	not serious	none	5989	6268	HR 0.89 (0.80 to 0.99)	At 5 years: 87% (86% to 89%) overall survival with intensive versus 86% without[5]	HIGH	CRITICAL
Colorectal cancer-specific survival (event is death from colorectal cancer; follow-up 24 months to 66 months)												
10	randomised trials	serious [1]	not serious	not serious	not serious	none	5607	5893	HR 0.92 (0.80 to 1.06)	At 5 years: 90% (88% to 91%) colorectal cancer-specific survival with intensive versus 89% without[5]	MODERATE	CRITICAL
Relapse-free survival (event is any colorectal cancer recurrence; follow-up 24 months to 66 months)												
14	randomised trials	serious [2]	not serious	not serious	not serious	none	4140	4606	HR 1.07 (0.96 to 1.19)	At 5 years: 80% (78% to 82%) relapse with intensive versus 81% without[5]	MODERATE	IMPORTANT
Local recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Distant recurrence												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intensive follow-up	Less intensive follow-up	Relative (95% CI)	Absolute (95% CI)		
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Metachronous colorectal cancer												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Resectable recurrent disease (Salvage surgery; follow-up 24 months to 66 months)												
13	randomised trials	not serious	not serious	not serious	not serious	none	318/2897 (11.0%)	140/2260 (6.2%)	RR 1.96 (1.52 to 2.52)	59 more per 1,000 (from 32 more to 94 more)	HIGH	IMPORTANT
Overall quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Procedure-related complications (Colonoscopy complications; follow-up 64 months)												
1	randomised trials	serious [1]	not serious	not serious	serious [4]	none	3/1204 (0.2%)	0/357 (0.0%)	OR 3.66 (0.25 to 54.28)	3 more per 1,000 (from 1 fewer to 51 more)[6]	LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; OR: odds ratio; RR: relative risk
1 Downgraded due to lack of blinding in 5 trials leading to high risk of ascertainment bias for cause of death.
2 Downgraded due to lack of blinding in 4 trials and lack of allocation concealment in 3 trials.
3 High risk of bias due to lack of blinding of participants and outcome assessment
4 Number of events <300
5 Control group rates take from COLOFOL 2018 trial
6 Assumed control group risk of 0.1%

Table 6: Clinical evidence profile for comparison 2: More visits or tests versus fewer visits or tests

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	More visits or tests	Fewer visits or tests	Relative (95% CI)	Absolute (95% CI)		
Overall survival (event is death from any cause; follow-up 41 months to 64 months)												
8	randomised trials	not serious	not serious	not serious	not serious	none	4136	5025	HR 0.85 (0.74 to 0.97)	At 5 years: 88%	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	More visits or tests	Fewer visits or tests	Relative (95% CI)	Absolute (95% CI)		
										(86% to 89%) overall survival with more visits versus 86% with fewer[6]		
Colorectal cancer-specific survival (event is death from colorectal cancer; follow-up 41 months to 64 months)												
6	randomised trials	serious [1]	not serious	not serious	not serious	none	3976	4863	HR 0.88 (0.75 to 1.03)	At 5 years: 90% (89% to 92%) cancer-specific survival with more visits versus 89% with fewer[6]	MODERATE	CRITICAL
Relapse-free survival (event is any colorectal cancer recurrence; follow-up 41 months to 64 months)												
9	randomised trials	serious [2]	not serious	not serious	not serious	none	3520	2877	HR 1.06 (0.92 to 1.22)	At 5 years: 80% (77% to 82%) relapse-free survival with more visits versus 81% with fewer[6]	MODERATE	IMPORTANT
Local recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Distant metastasis												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	More visits or tests	Fewer visits or tests	Relative (95% CI)	Absolute (95% CI)		
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Metachronous colorectal cancer												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Resectable recurrent disease (Salvage surgery; follow-up 41 months to 64 months)												
7	randomised trials	not serious	not serious	not serious	serious [3]	none	167/1034 (16.2%)	73/1007 (7.2%)	RR 2.19 (1.71 to 2.81)	86 more per 1,000 (from 51 more to 131 more)	MODERATE	IMPORTANT
Overall quality of life (follow-up not reported)												
1	randomised trials	very serious [4,5]	not serious	not serious	not serious	none	Kjeldsen 1997 (N=350) reported a small increase in quality of life, as measured by the Nottingham Health Profile, associated with more frequent follow-up visits compared with virtually no follow-up				LOW	IMPORTANT
Procedure-related complications (Colonoscopy complications; follow-up 64 months)												
1	randomised trials	serious [4]	not serious	not serious	serious [3]	none	3/1204 (0.2%)	0/357 (0.0%)	OR 3.66 (0.25 to 54.28)	3 more per 1,000 (from 1 fewer to 51 more)[7]	LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; OR: odds ratio; RR: relative risk
1 Downgraded 4 trials were not blinded which could cause ascertainment bias for cause of death.
2 Downgraded because 3 trials were not blinded and 1 lacked allocation concealment.
3 Number of events <300
4 Downgraded due to lack of blinding
5 HRQoL only measured in 350/597 participants in the trial
6 Control group rates take from COLOFOL 2018 trial
7 Assumed control group risk of 0.1%

Table 7: Clinical evidence profile for comparison 3: Visits or tests versus minimal or no follow-up

Quality assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Visits and tests	Minimal or no follow-up	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Overall survival (event is death from any cause; follow-up 41 months to 66 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	1121	513	HR 0.90 (0.64 to 1.26)	At 5 years: 83% (77% to 87%) overall survival with visits & tests versus 81% with minimal follow-up[4]	HIGH	CRITICAL
Colorectal cancer-specific survival (event is death from colorectal cancer; follow-up 41 months to 66 months)												
2	randomised trials	not serious	not serious	not serious	not serious	none	954	355	HR 1.01 (0.70 to 1.47)	At 5 years: 87% (81% to 91%) cancer-specific survival with visits & tests versus 87% with minimal follow-up[4]	HIGH	CRITICAL
Relapse-free survival (event is any colorectal cancer recurrence; follow-up 41 months to 66 months)												
4	randomised trials	serious [1]	serious [2]	not serious	not serious	none	1313	658	HR 0.98 (0.67 to 1.44)	At 5 years: 86% (80% to 91%) relapse-free survival with visits & tests versus	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Visits and tests	Minimal or no follow-up	Relative (95% CI)	Absolute (95% CI)		
										86% with minimal follow-up[4]		
Local recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Distant recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Metachronous colorectal cancer												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Resectablility of recurrent disease (Salvage surgery; follow-up 41 months to 66 months)												
4	randomised trials	not serious	not serious	not serious	serious [3]	none	106/1313 (8.1%)	28/658 (4.3%)	RR 1.98 (1.30 to 3.01)	42 more per 1,000 (from 13 more to 86 more)	MODERATE	IMPORTANT
Overall quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Procedure-related complications												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; HR: hazard ratio; RR: relative risk
1 Downgraded due to high risk of bias due to allocation concealment in one of the trials.
2 Serious heterogeneity (I2 = 61%). Random effects model used, but there were no pre-specified subgroups to allow for further exploration of the causes of heterogeneity.
3 Number of events <300
4 Control group rate taken from symptomatic follow-up only arm of FACS 2014 trial

Table 8: Clinical evidence profile for comparison 4: More liver imaging versus less liver imaging

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	More liver imaging	less liver imaging	Relative (95% CI)	Absolute (95% CI)		
Overall survival (event is death from any cause; follow-up 48 months to 60 months)												
4	randomised trials	serious [1]	not serious	not serious	not serious	none	2957	3804	HR 0.87 (0.72 to 1.05)	At 5 years: 81% (78% to 84%) overall survival with more imaging versus 79% with less[4]	MODERATE	CRITICAL
Colorectal cancer-specific survival (event is death from colorectal cancer; follow-up 48 months to 60 months)												
3	randomised trials	serious [1]	not serious	not serious	not serious	none	2790	3659	HR 0.88 (0.63 to 1.22)	At 5 years: 88% (84% to 92%) cancer-specific survival with more imaging versus 87% with less[4]	MODERATE	CRITICAL
Relapse-free survival (event is any colorectal cancer recurrence; follow-up 48 months to 60 months)												
3	randomised trials	serious [1]	not serious	not serious	not serious	none	916	910	HR 1.03 (0.76 to 1.41)	At 5 years: 83% (77% to 87%) relapse-free survival with more imaging versus 83% with less[4]	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	More liver imaging	less liver imaging	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Local recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Distant recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Metachronous colorectal cancer												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Resectablility of recurrent disease (Salvage surgery; follow-up 48 months to 60 months)												
4	randomised trials	serious [1]	not serious	not serious	serious [2]	none	126/1517 (8.3%)	88/1509 (5.8%)	RR 1.43 (1.10 to 1.86)	25 more per 1,000 (from 6 more to 50 more)	LOW	IMPORTANT
Overall quality of life (follow-up 60 months)												
1	randomised trials	not serious	not serious	not serious	serious [3]	none	No clinically important differences among the three main quality of life scales (SF-12 mental component, SF-12 physical component, and PGWB Index) between the two study arms (N=1228).				MODERATE	IMPORTANT
Procedure-related complications												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; HR: hazard ratio; PGWB Index: psychological general well-being index; RR: relative risk; SF-12: 12-Item Short Form Survey

1 Downgraded because 2 trials were at high risk of bias due to lack of allocation concealment

2 Number of participants <300

3 Unclear imprecision as no figures were presented in Jeffrey 2016

4 Control group rates taken from no-CT arms of the FACS 2014 trial

1 **Table 9: Clinical evidence profile for comparison 5: CEA tests versus no CEA tests**

Quality assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CEA	no CEA	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Overall survival (event is death from any cause; follow-up 66 months)												
3	randomised trials	serious [1]	not serious	not serious	not serious	none	451	469	HR 0.90 (0.70 to 1.16)	At 5 years: 81% (76% to 85%) overall survival with CEA versus 79% with no CEA[4]	MODERATE	CRITICAL
Colorectal cancer-specific survival (event is death from colorectal cancer; follow-up 66 months)												
2	randomised trials	serious [1]	not serious	not serious	not serious	none	343	361	HR 0.93 (0.68 to 1.28)	At 5 years: 88% (84% to 91%) cancer-specific survival with CEA versus 87% with no CEA[4]	MODERATE	CRITICAL
Relapse-free survival (event is any colorectal cancer recurrence; follow-up 66 months)												
3	randomised trials	serious [1]	not serious	not serious	not serious	none	451	469	HR 0.91 (0.70 to 1.19)	At 5 years: 84% (80% to 88%) relapse-free survival with CEA versus 83% with no CEA[4]	MODERATE	IMPORTANT
Local recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CEA	no CEA	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Distant recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Metachronous colorectal cancer												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Resectablility of recurrent disease (Salvage surgery; follow-up 41 months to 66 months)												
4	randomised trials	serious [1]	serious [2]	not serious	serious [3]	none	126/1053 (12.0%)	70/1067 (6.6%)	RR 1.89 (1.12 to 3.20)	58 more per 1,000 (from 8 more to 144 more)	VERY LOW	IMPORTANT
Overall quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Procedure-related complications												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CEA: carcinoembryonic antigen; CI: confidence interval; HR: hazard ratio; RR: relative risk
1 One trial at high risk of bias due to lack of allocation concealment and blinding
2 Considerable heterogeneity (I2=64%). Random effects model used- but no subgroups were specified for exploration of heterogeneity.
3 Number of events < 300
4 Control group rates taken from no-CEA arms of the FACS 2014 trial

Table 10: Clinical evidence profile for comparison 6: Nurse or GP led follow-up versus surgeon led follow-up

Quality assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nurse or GP led	Surgeon led	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Overall survival (event is death from any cause; follow-up: range 24 months to 60 months)												
2	randomised trials	not serious	not serious	not serious	serious [1]	none	110	110	HR 1.39 (0.38 to 5.12)	NR[2]	MODERATE	CRITICAL
Colorectal cancer-specific survival (event is death from colorectal cancer; follow-up 24 months)												

Quality assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nurse or GP led	Surgeon led	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1	randomised trials	not serious	not serious	not serious	serious [1]	none	55	55	HR 3.46 (0.58 to 20.56)	NR[2]	MODERATE	CRITICAL
Relapse-free survival (event is any colorectal cancer recurrence; follow-up 24 months to 60 months)												
2	randomised trials	not serious	not serious	not serious	serious [1]	none	110	110	HR 1.07 (0.50 to 2.30)	NR[2]	MODERATE	IMPORTANT
Local recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Distant recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Metachronous colorectal cancer												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Resectablility of recurrent disease (Salvage surgery; follow-up 24 months)												
1	randomised trials	not serious	not serious	not serious	serious [1]	none	4/55 (7.3%)	3/55 (5.5%)	RR 1.33 (0.31 to 5.68)	18 more per 1,000 (from 38 fewer to 255 more)	MODERATE	IMPORTANT
Overall quality of life (follow-up 24 months)												
2	randomised trials	not serious	not serious	not serious	serious [1]	none	Augestad 2013 (N=110) reported no significant effect on quality of life main outcome measures. For EORTC QLQ-C30, significant effects in favour of GP-led follow-up were reported for role functioning (P= 0.02), emotional functioning (P = 0.01), and pain (P = 0.01). Wattchow 2006 (N=203) found no important differences between HRQoL in primary versus secondary care follow-up.					MODERATE	IMPORTANT
Procedure-related complications												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items; GP: General Practitioner; HR: hazard ratio: HrQoL: Health-related Quality of Life; NR: not reported; RR: relative risk

1 Number of events <300

2 Insufficient information to calculate absolute survival rates

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

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 are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

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

Appendix J – Economic analysis

Economic evidence analysis for review question: What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: What are the optimal methods and 3 frequencies of follow-up to detect recurrence after potentially curative surgical 4 treatment for non-metastatic colorectal cancer?

5 **Table 11: Excluded studies and reasons for their exclusion**

Study	Reason for exclusion
A randomised controlled trial to assess the cost-effectiveness of intensive versus no scheduled follow-up in patients who have undergone resection for colorectal cancer with curative intent (The FACS Trial) (Project record), Health Technology Assessment Database, 2005	HTA Database entry for the FACS trial
Adams, K., Higgins, L., Beazley, S., Ryan, S., Papagrigoriadis, S., Efficacy of a nurse-led colorectal cancer follow-up clinic-long-term outcomes, Diseases of the Colon and Rectum, Conference, Annual Meeting of the American Society of Colon and Rectal Surgeons, ACSRS 2011. Vancouver, BC Canada. Conference Publication: (var.pagings). 54 (5) (pp e165), 2011	Non comparative study
Andersson, P. H., Wille-Jorgensen, P., Horvath-Puho, E., Petersen, S. H., Martling, A., Sorensen, H. T., Syk, I., The COLOFOL trial: Study design and comparison of the study population with the source cancer population, Clinical Epidemiology, 8, 15-21, 2016	Describes COLOFOL trial protocol
Augestad, K. M., Norum, J., Dehof, S., Aspevik, R., Ringberg, U., Nestvold, T., Vonen, B., Skrovseth, S. O., Lindsetmo, R. O., Cost-effectiveness and quality of life in surgeon versus general practitioner-organised colon cancer surveillance: A randomised controlled trial, BMJ Open, 3 (4) (no pagination), 2013	Included in Cochrane review.
Augestad, K. M., Vonen, B., Aspevik, R., Nestvold, T., Ringberg, U., Johnsen, R., Norum, J., Lindsetmo, R. O., Should the surgeon or the general practitioner (GP) follow up patients after surgery for colon cancer? A randomized controlled trial protocol focusing on quality of life, cost-effectiveness and serious clinical events, BMC Health Services Research, 8, 2008	Included in Cochrane review.
Baca, B., Beart Jr, R. W., Etzioni, D. A., Surveillance after colorectal cancer resection: A systematic review, Diseases of the Colon and Rectum, 54, 1036-1048, 2011	All relevant studies included in Cochrane review
Bastiaenen, V. P., Hovdenak Jakobsen, I., Labianca, R., Martling, A., Morton, D. G., Primrose, J. N., Tanis, P. J., Laurberg, S., Consensus and controversies regarding follow-up after treatment with curative intent of nonmetastatic colorectal cancer: a synopsis of guidelines used in countries represented in the European Society of Coloproctology, Colorectal Disease., 2019	Exclude - summary of guidelines
Belderbos, T. D., Leenders, M., Moons, L. M., Siersema, P. D., Local recurrence and timing of follow-up colonoscopy after emr for non-pedunculated colorectal lesions: Systematic review and meta-analysis, Gastrointestinal Endoscopy, Conference, Digestive Disease Week 2013, DDW 2013. Orlando, FL United States. Conference Publication: (var.pagings). 77 (5 SUPPL. 1) (pp AB535-AB536), 2013	Conference abstract
Belderbos, T., Leenders, M., Moons, L., Siersema, P., Local recurrence after EMR for non-pedunculated colorectal lesions: Systematic review and metaanalysis, United European Gastroenterology Journal, Conference, 21st United European	Conference abstract

Study	Reason for exclusion
Gastroenterology Week. Berlin Germany. Conference Publication: (var.pagings). 1 (1 SUPPL. 1) (pp A329), 2013	
Byung, W. M., Jun, W. U., Hong, Y. M., Role of regular follow-up after curative surgery for colorectal cancer, Hepato Gastroenterology, 54, 63-66, 2007	Abstract only
Coebergh Van Den Braak, R. R. J., Lalmahomed, Z. S., Buttner, S., Hansen, B. E., Ijzermans, J. N. M., Nonphysician Clinicians in the Follow-Up of Resected Patients with Colorectal Cancer, Digestive Diseases, 36, 17-25, 2017	Not an RCT
Figueredo, A., Rumble, R. B., Maroun, J., Earle, C. C., Cummings, B., McLeod, R., Zuraw, L., Zwaal, C., Agboola, O., Citron, M., DeNardi, F. G., Fine, S., Fisher, B., Germond, C., Jonker, D., Khoo, K., Kocha, W., Lethbridge, M., Lofters, W., Malthaner, R., Moore, M., Tandan, V., Wong, R., Follow-up of patients with curatively resected colorectal cancer: A practice guideline, BMC Cancer, 3, 2003	All relevant studies included in Cochrane review
Gage, M. M., Hueman, M. T., Colorectal Cancer Surveillance: What Is the Optimal Frequency of Follow-up and Which Tools Best Predict Recurrence?, Current Colorectal Cancer Reports, 13, 316-324, 2017	Expert review
Grossmann, E. M., Johnson, F. E., Virgo, K. S., Longo, W. E., Fossati, R., Follow-up of colorectal cancer patients after resection with curative intent - The GILDA trial, Surgical Oncology, 13, 119-124, 2004	Included in Cochrane review.
Jeffery, G. M., Hickey, B. E., Hider, P., Follow-up strategies for patients treated for non-metastatic colorectal cancer, Cochrane Database of Systematic Reviews, 1, 2002	Earlier version of Cochrane review
Jeyarajah, S., Adams, K. J., Higgins, L., Ryan, S., Leather, A. J. M., Papagrigoriadis, S., Prospective evaluation of a colorectal cancer nurse follow- up clinic, Colorectal DiseaseColorectal Dis, 13, 31-38, 2011	Not an RCT
Lee-Ying, R. M., Kennecke, H. F., Nguyen, L., Cheung, W. Y., Cost-effectiveness of surveillance after curative resection (CR) of metastatic colorectal cancer (CRC), Journal of Clinical Oncology, Conference, 2017 Gastrointestinal Cancers Symposium. United States. 35 (4 Supplement 1) (no pagination), 2017	Abstract only
Lepage, C, Phelip, J-M, Cany, L, Maillard, E, Lievre, A, Chatellier, T, Faroux, R, Duchmann, J-C, Ben, Abdelghani M, Breysacher, G, Geoffroy, P, Pere-Verge, D, Pelaquier, A, Pillon, D, Ezenfis, J, Rinaldi, Y, Darut-Jouve, A, Duluc, M, Adenis, A, Bouche, O, Effect of 5 years of imaging and CEA follow-up to detect recurrence of colorectal cancer-PRODIGE 13 a FFCD and Unicancer phase III trial: baseline characteristics, Annals of oncology. Conference: 41st european society for medical oncology congress, ESMO 2016. Denmark. Conference start: 20161007. Conference end: 20161011, 27, 2016	Ongoing trial, abstract only
Lopez-Kostner, F., Zarate, A., Kronberg, U., Sanguineti, A., Pinto, E., Wainstein, C., Long-term functional and oncologic outcome in patients undergoing intersphincteric resection with handsewn coloanal anastomosis for very low rectal cancer, Diseases of the Colon and Rectum, Conference, Annual Meeting of the American Society of Colon and Rectal Surgeons, ACSRS 2011. Vancouver, BC Canada. Conference Publication: (var.pagings). 54 (5) (pp e170), 2011	Abstract only
Mant, D, Perera, R, Gray, A, Rose, P, Fuller, A, Corkhill, A, George, S, Little, L, Regan, S, Mellor, J, Pugh, Sa, Northover, J, Weaver, A,	FACS trial 5 year resultsâ□“ already

Study	Reason for exclusion
Barsoum, G, Tan, Lt, Mortensen, N, Scholefield, J, Wasan, H, Ferry, D, Primrose, Jn, Effect of 3-5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: FACS randomized controlled trial, Journal of Clinical Oncology, 31, 2013	included in Cochrane Review
Mant, D., Gray, A., Pugh, S., Campbell, H., George, S., Fuller, A., Shinkins, B., Corkhill, A., Mellor, J., Dixon, E., Little, L., Perera-Salazar, R., Primrose, J., A randomised controlled trial to assess the cost-effectiveness of intensive versus no scheduled follow-up in patients who have undergone resection for colorectal cancer with curative intent, Health Technology Assessment, 21, 2017	FACS trial 5 year resultsâ□“ already included in Cochrane Review
Mercado, M., Hart, R., Scheer, A., Tricco, A., Hamid, J., Brezden-Masley, C., Impact of CEA alone or as part of a high intensity surveillance strategy in detecting curative colorectal cancer recurrence: A systematic review and meta-analysis, Journal of Clinical Oncology, Conference, 2017 Gastrointestinal Cancers Symposium. United States. 35 (4 Supplement 1) (no pagination), 2017	Abstract only
Mokhles, S., Macbeth, F., Farewell, V., Fiorentino, F., Williams, N. R., Younes, R. N., Takkenberg, J. J., Treasure, T., Meta-analysis of colorectal cancer follow-up after potentially curative resection, British Journal of Surgery, 103, 1259-68, 2016	Relevant included studies are reported in Cochrane review
Papagrigoriadis, S., Follow-up of patients with colorectal cancer: The evidence is in favour but we are still in need of a protocol, International Journal of Surgery, 5, 120-128, 2007	All relevant studies included in Cochrane review
Patel, K., Hadar, N., Lee, J., Siegel, B. A., Hillner, B. E., Lau, J., The Lack of Evidence for PET or PET/CT Surveillance of Patients with Treated Lymphoma, Colorectal Cancer, and Head and Neck Cancer: A Systematic Review, Journal of Nuclear MedicineJ Nucl Med, 54, 1518-1527, 2013	Only diagnostic accuracy data are presented
Pita-Fernandez, S, Alhayek-Ai, M, Gonzalez-Martin, C, Lopez-Calvino, B, Seoane-Pillado, T, Pertega-Diaz, S, Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis (Provisional abstract), Database of Abstracts of Reviews of Effects, epub, 2014	DARE database entry for Pita-Fernandez 2015
Pita-Fernandez, S., Alhayek-Ai, M., Gonzalez-Martin, C., Lopez-Calvino, B., Seoane-Pillado, T., Pertega-Diaz, S., Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: A systematic review and meta-analysis, Annals of OncologyAnn Oncol, 26, 644-656, 2015	Relevant included studies are reported in Cochrane review
Primrose, J. N., Fuller, A., Rose, P., Perera-Salazar, R., Mellor, J., Corkhill, A., George, S., Mant, D., Follow-up after colorectal cancer surgery: Preliminary observational findings from the UK FACS trial, Journal of Clinical Oncology, Conference, ASCO Annual Meeting 2011. Chicago, IL United States. Conference Publication: (var.pagings). 29 (15 SUPPL. 1) (no pagination), 2011	Included in Cochrane review
Primrose, J. N., Perera, R., Gray, A., Effect of 3 to 5 years of scheduled CEA and CT followup to detect recurrence of colorectal cancer: The FACS randomized clinical trial, Diseases of the Colon and Rectum, 57, e421-e422, 2014	Included in Cochrane review
Primrose, Jn, Perera, R, Gray, A, Rose, P, Fuller, A, Corkhill, A, George, S, Mant, D, Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial, Jama, 311, 263-270, 2014	Included in Cochrane review

Study	Reason for exclusion
Pugh, S. A., Fuller, A., Perera, R., George, S., Mant, D., Primrose, J., The follow-up after colorectal cancer surgery trial: Randomised trial of follow-up after colorectal cancer surgery and outcome following recurrence, Journal of the American College of Surgeons, 1), e46-e47, 2014	Abstract only
Pugh, S. A., Mant, D., Shinkins, B., Mellor, J., Perera, R., Primrose, J., Scheduled use of CEA and CT follow-up to detect recurrence of colorectal cancer: 6-12 year results from the FACS randomised controlled trial, Annals of Oncology. Conference: 41st European Society for Medical Oncology Congress, ESMO, 27, 2016	Conference abstract of FACS trial 8 year results, insufficient detail to extract survival data
Renehan, A. G., Egger, M., Saunders, M. P., O'Dwyer, S. T., Impact on survival of intensive follow up after curative resection for colorectal cancer: Systematic review and meta-analysis of randomised trials, British Medical Journal, 324, 813-816, 2002	All relevant studies reported in Cochrane review
Rodriguez-Moranta, F, Castells, A, Salo, J, Arcusa, A, Boadas, J, Besssa, V, Pinol, V, Balaguer, F, Cuardrado, R, Delgado, S, Lacy, A, Batiste-Alentorn, E, Pique, Jm, Efficacy Of Postoperative Surveillance After Radical Surgery for Colorectal Cancer (CRC). Analysis Of a Prospective, Multicenter, Randomized Controlled Trial, Journal of Gastroenterology, 128, Abstract W967, 2005	Included in the Jeffrey 2016 Cochrane Review
Rodriguez-Moranta, F., Salo, J., Arcusa, A., Boadas, J., Pinol, V., Bessa, X., Batiste-Alentorn, E., Lacy, A. M., Delgado, S., Maurel, J., Pique, J. M., Castells, A., Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: A prospective, multicenter, randomized, controlled trial, Journal of Clinical Oncology, 24, 386-393, 2006	Already included in Jeffrey 2016 systematic review
Rosati, G., Ambrosini, G., Barni, S., Andreoni, B., Corradini, G., Luchena, G., Daniele, B., Gaion, F., Oliverio, G., Duro, M., Martignoni, G., Pinna, N., Sozzi, P., Pancera, G., Solina, G., Pavia, G., Pignata, S., Johnson, F., Labianca, R., Apolone, G., Zaniboni, A., Monteforte, M., Negri, E., Torri, V., Mosconi, P., Fossati, R., A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma, Annals of Oncology, 27, 274-280, 2016	GILDA trial - already included in Jeffrey 2016 Cochrane review
Secco, G. B., Fardelli, R., Gianquinto, D., Bonfante, P., Baldi, E., Ravera, G., Derchi, L., Ferraris, R., Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: A prospective, randomized and controlled trial, European Journal of Surgical Oncology, 28, 418-423, 2002	Included in Cochrane review
Shinkins, B., Nicholson, B. D., James, T., Pathiraja, I., Pugh, S., Perera, R., Primrose, J., Mant, D., What carcinoembryonic antigen level should trigger further investigation during colorectal cancer follow-up? A systematic review and secondary analysis of a randomised controlled trial, Health Technology Assessment, 21, 2017	Secondary analysis of FACS trial
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Study	Reason for exclusion
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Study	Reason for exclusion
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Appendix L – Research recommendations

Research recommendations for review question: What are the optimal methods and frequencies of follow-up to detect recurrence after potentially curative surgical treatment for non-metastatic colorectal cancer?

No research recommendations were made for this review question.