National Institute for Health and Care Excellence

Final

Colorectal cancer (update)

[C6] Endoscopic resection alone for early colon cancer

NICE guideline NG151

Evidence reviews

January 2020

Final

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

Disclaimer

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

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

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ISBN: 978-1-4731-3657-1

Contents

Endoscopic resection alone for people with early colon cancer

No recommendations were made from this evidence review.

Review question

Which people with early colon cancer can be treated with endoscopic resection alone?

Introduction

Increasing use of endoscopy for the resection of polyps has led to improvements in the detection of early colorectal cancer and an increase in the numbers of people identified as having malignant polyps. However, malignancy is not usually confirmed until a histological examination of the resected polyp has been conducted. For some people, subsequent resection of the bowel will be required, whereas for others a 'watch and wait' strategy may be sufficient. There is a lack of clarity on which people should go on to have a bowel resection after endoscopy as it is not clear in which groups this will lead to improved survival. Therefore, the objective of this review was to determine which people with early colon cancer can be treated with endoscopic resection alone.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	Adults after endoscopic resection of a pedunculated or sessile polyp with invasive cancer. Early colon cancer defined as: • T1 • N0 • M0 <u>Subgroups (analysed separately):</u> • sessile versus pedunculated tumour/polyp • single versus fragmented specimen • low grade tumours (grade 1) versus high grade (grade 2 or 3) • lymphovascular infiltration • positive versus negative resection margin • Haggitt or kikuchi level
Intervention	Observation/deferred of surgery
Comparison	Further surgical resection
Outcomes	**Critical** • Overall survival • Local recurrence • Disease-free survival **Important**

	• Quality of life • Distant metastasis • Treatment-related morbidity

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

Four observational studies were included in this review (Kouyama 2018; Levic 2018; Tamaru 2017; Yoshii 2014).

The included studies are summarised in Table 2.

The studies compared endoscopic resection alone to endoscopic resection plus surgery.

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

Excluded studies

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

Summary of clinical studies included in the evidence review

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

Table 2: Summary of included studies

Study	Population	Intervention/comparison	Outcomes
Kouyama 2018 Retrospective cohort study Japan	N= 930 T1 colorectal cancer patients treated by ER or ER and surgical resection (with lymph node dissection)	ER only versus ER + surgery with lymph node dissection	• Local recurrence • Disease-free survival • Distant metastasis
Levic 2018 Retrospective cohort study Denmark	N=304 (after propensity score matching) patients with colorectal cancer with a malignant colorectal polyp with submucosal invasion completely resected at	Polypectomy only (i.e. patients for whom it was decided not to perform subsequent bowel resection due to confirmed histological diagnosis of a malignant polyp) versus	• Overall survival • Local recurrence • Disease-free survival • Distant metastasis • Treatment-related morbidity

Study	Population	Intervention/comparison	Outcomes
	a primary endoscopic procedure.	polypectomy + bowel resection.	
Tamaru 2017 Retrospective cohort study Japan	N=359 T1 colorectal cancer patients treated between January 1992 and December 2008 at Hiroshima University Hospital and 10 affiliated hospitals (Hiroshima Gastrointestinal Endoscopy Research Group) and followed up for >5 years.	ER (e.g. polypectomy, EMR, ESD) alone versus ER + surgery (indication for additional surgery was determined according to Japanese Classification of Colorectal Carcinoma guidelines.)	• Local recurrence • Distant metastasis
Yoshii 2014 Retrospective cohort study Japan	N=389 patients with histologically confirmed T1 colorectal cancer (defined as carcinoma that only invaded submucosa, corresponding to a T1 lesion under the American Joint Committee on Cancer classification guidelines.)	ER (e.g. snare polypectomy, EMR) alone versus ER + surgery (defined as radical resection (e.g. bowel resection) and regional lymph node dissection). Patients were selected for subsequent surgery on the basis of risk factors according to Japanese Society for Cancer of the Colon and Rectum criteria.	• Local recurrence • Disease-free survival • Distant metastasis

EMR: endoscopic mucosal resection; ER: endoscopic resection; ESD: endoscopic submucosal dissection; T: tumour stage

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: Endoscopic resection alone versus endoscopic resection plus surgery

Critical outcomes

Overall survival

- Very low quality evidence from 1 retrospective cohort study (N=304) showed no clinically important difference in overall survival between those receiving ER alone compared to those receiving ER + surgery.

Local recurrence

All patients

- Very low quality evidence from 3 retrospective cohort studies (N=1399) showed a clinically important increased risk of local recurrence in those receiving ER alone compared to those receiving ER + surgery.

Low risk patients

- Very low quality evidence from 1 retrospective cohort study (N=164) showed no clinically important difference in local recurrence between low risk patients receiving ER alone compared to those receiving ER + surgery.

High risk patients

- Very low quality evidence from 2 retrospective cohort studies (N=386) was inconsistent about the effect of ER alone compared to ER + surgery on local recurrence. One study showed a clinically important increased risk of in local recurrence in high risk patients receiving ER alone compared to those receiving ER + surgery, but the other showed no difference.

Disease free survival

All patients

- Very low quality evidence from 2 retrospective cohort studies (N=1234) showed no clinically important difference in disease free survival between those receiving ER alone compared to those receiving ER + surgery.

Low risk patients

- Very low quality evidence from 1 retrospective cohort study (N=164) showed no clinically important difference in disease free survival between low risk patients receiving ER alone compared to those receiving ER + surgery.

High risk patients

- Very low quality evidence from 1 retrospective cohort study (N=112) showed no clinically important difference in disease free survival between high risk patients receiving ER alone compared to those receiving ER + surgery.

Important outcomes

Quality of life

No evidence was identified to inform this outcome.

Distant metastasis

All patients

- Very low quality evidence from 3 retrospective cohort studies (N=1389) showed no clinically important difference in distant metastasis between those receiving ER alone compared to those receiving ER + surgery.

Low risk patients

- Very low quality evidence from 1 retrospective cohort study (N=164) showed no clinically important difference in distant metastasis between low risk patients receiving ER alone compared to those receiving ER + surgery.

High risk patients

- Very low quality evidence from 2 retrospective cohort studies (N=386) showed no clinically important difference in distant metastasis between high risk patients receiving ER alone compared to those receiving ER + surgery.

Treatment-related morbidity

- Very low quality evidence from 1 retrospective cohort study (N=304) showed a clinically important reduction in intraoperative surgical complications in those receiving ER alone compared to those receiving ER + surgery.
- Very low quality evidence from 1 retrospective cohort study (N=304) showed a clinically important reduction in postoperative surgical complications in those receiving ER alone compared to those receiving ER + surgery.
- Very low quality evidence from 1 retrospective cohort study (N=304) showed a clinically important reduction in postoperative medical complications in those receiving ER alone compared to those receiving ER + surgery.
- Very low quality evidence from 1 retrospective cohort study (N=304) showed a clinically important reduction in grade 3 or 4 complications in those receiving ER alone compared to those receiving ER + surgery.

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

Disease-free survival and overall survival were considered critical outcomes for decision-making because the aim of cancer treatment is to control the disease and improve survival.

Local recurrence and distant metastasis were critical outcomes because they typically lead to further treatment with associated treatment related adverse effects and because they indicate that the disease was not controlled by the surgical treatment.

Quality of life was an important outcome because of the impact that different treatment options can have on patients' functioning and their potential long term adverse effects. Treatment-related mortality was identified as an important outcome because it is indicative of the short-term side effects of treatment.

The quality of the evidence

Evidence was available for the comparison of endoscopic resection alone versus endoscopic resection + surgery. Evidence was available for all of the outcomes except quality of life. The quality of the clinical evidence was assessed using GRADE and was of very low quality.

The quality of evidence was downgraded because of methodological limitations affecting the risk of bias and imprecision in the risk estimate. Indirectness was also an issue as all four studies included patients with tumours located in the rectum. Uncertainty around the risk estimate was generally attributable to low event rates and small sample sizes.

Benefits and harms

The low quality of the evidence and lack of evidence for some comparisons and outcomes impacted the decision-making and the strength of the recommendations as there was insufficient evidence to recommend one type of treatment over another.

The committee agreed that they were unable to make any recommendations due to the very low quality of the studies reviewed and the inclusion of both high and low risk patients in a number of samples.

The committee discussed current practice and noted that risk scoring systems (using histopathological criteria) were already well established and had been disseminated by organisations such as the British Society of Gastroenterology and the Association of Coloproctology for Great Britain and Ireland.

The committee went on to discuss the expansion of research into the genetic markers of recurrence and the benefit that this was likely to have on treatment decision-making. It was agreed that if this guideline were to be updated in future this question might be better addressed through a review of predictive studies focusing on the biomarkers of recurrence. As a result of this discussion the committee agreed that it would not be appropriate to draft a research recommendation in relation to this review.

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.

References

Kouyama 2018

Kouyama Y, Kudo S, Miyachi H, et al. (2018) Risk factors of recurrence in T1 colorectal cancers treated by endoscopic resection alone or surgical resection with lymph node dissection. International Journal of Colorectal Disease 33(8): 1029-1038

Levic 2018

Levic K, Bulut O, Hansen T, et al. (2018) Malignant colorectal polyps: endoscopic polypectomy and watchful waiting is not inferior to subsequent bowel resection. A nationwide propensity score-based analysis. Langenbeck's Archives of Surgery 404(2): 231-242

Tamaru 2017

Tamaru Y, Oka S, Tanaka S, et al. (2017) Long-term outcomes after treatment for T1 colorectal carcinoma: a multicenter retrospective cohort study of Hiroshima GI Endoscopy Research Group. Journal of Gastroenterology 52(11): 1169-1179

Yoshii 2014

1 Yoshii S, Nojima M, Nosho K, et al. (2014) Factors associated with risk for colorectal cancer
2 recurrence after endoscopic resection of T1 tumors, Clinical Gastroenterology and
3 Hepatology 12(2): 292-302

1 Appendices

2 Appendix A – Review protocol

3 Review protocol for review question: Which people with early colon cancer 4 can be treated with endoscopic resection alone?

5 **Table 3: Review protocol for endoscopic resection alone for early colon cancer**

Field (based on PRISMA-P)	Content
Review question	Which people with early colon cancer can be treated with endoscopic resection alone?
Type of review question	Intervention
Objective of the review	To determine which people with early colon cancer can be treated with endoscopic resection alone.
Eligibility criteria – population/disease/condition/issue/domain	Adults after endoscopic resection of a pedunculated or sessile polyp with invasive cancer Early colon cancer defined as: • T1 • N0 • M0 A priori subgroups according to (specific definitions depending on the available evidence): • sessile versus pedunculated tumour/polyp • single versus fragmented specimen • low grade tumours (grade 1) versus high grade (grade 2 or 3) • lymphovascular infiltration • positive versus negative resection margin • Haggitt or kikuchi level
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Observation/deferral of surgery
Eligibility criteria – comparator(s)/control or reference (gold) standard	Further surgical resection
Outcomes and prioritisation	Critical outcomes: • Overall survival (MID: statistical significance) • Local recurrence • Disease-free survival Important outcomes: • Quality of life (measured using validated scales) • Distant metastasis

Field (based on PRISMA-P)	Content
	• Treatment-related morbidity 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 (MCS) and > 3.29 for the physical component summary (PCS) of the Short Form SF-12 (SF-12) • SF-36: > 7.1 for the physical functioning scale, > 4.9 for the bodily pain scale, and > 7.2 for the physical component summary
Eligibility criteria – study design	• Systematic reviews of RCTs • RCTs • Prospective and retrospective comparative observational studies
Other inclusion exclusion criteria	Inclusion: • English-language • All settings will be considered that consider medications and treatments available in the UK • Studies published post 2005 • Observational studies should include multivariate analysis controlling for the following confounding factors: ○ Age ○ Sex ○ Race ○ Functional status Studies conducted post 2005 will be considered for this review question because the guideline committee considered that treatment techniques have evolved and evidence prior to 2005 would not be relevant any longer.
Proposed sensitivity/sub-group analysis, or meta-regression	In case of heterogeneity, the following subgroup analyses will be conducted: • sessile versus pedunculated tumour/polyp • single versus fragmented specimen • tumour grade • lymphovascular infiltration • positive vs negative resection margin • Haggitt or kikuchi level
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor.

Field (based on PRISMA-P)	Content
	Quality control will be performed by the senior systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Potential sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance, but download all results Dates: from 1995
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual **Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs • ROBINS-I for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. The risk of bias across all available evidence was evaluated for each outcome using an adaptation

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

ASA: American Society of Anesthesiologists; CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; EQ-5D: EuroQol five dimensions questionnaire; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items; EORTC QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (29 items); EORTC QLQ-CR38: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (38 items); FACT-C: Functional Assessment of Cancer Therapy questionnaire (colorectal cancer); FACT-G: Functional Assessment of Cancer Therapy questionnaire (general); GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; M0: distant metastasis stage; MCS: mental component summary; MID: minimally important difference; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; PCS: physical component summary; RCT: randomised controlled trial; RevMan5: Review Manager version 5; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions; ROBIS: a tool for assessing risk of bias in systematic reviews; SF-12: 12-Item Short Form Survey; SF-36: 36-Item Short Form Survey

1 Appendix B – Literature search strategies

2 Literature search strategies for review question: Which people with early colon 3 cancer can be treated with endoscopic resection alone?

4 Databases: Embase/Medline

5 Last searched on: 09/11/2018

#	Search
1	exp colorectal neoplasms/ use ppez
2	(exp colorectal cancer/ or exp colon tumor/) use emez
3	((colorect* or colo rect* or colon or colonic) adj3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)).tw.
4	or/1-3
5	colonic polyps/ use ppez
6	(exp colon polyp/ or colorectal polyp/) use emez
7	((colorect* or colo rect* or colon or colonic) adj2 (adenocarcinoma or polyp or polyps or polypoid)).tw.
8	(t1 or n0 or M0 or (early adj2 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*))).tw.
9	or/5-8
10	endoscopic mucosal resection/ use ppez
11	(endoscopic surgery/ or endoscopic mucosal resection/ or endoscopic polypectomy/ or polypectomy/) use emez
12	(endoscopic adj3 (excision or management or polypectom* or resect* or therap*)).tw.
13	(colonoscopic adj2 polypectom*).tw.
14	or/10-13
15	4 and 9 and 14
16	Letter/ use ppez
17	letter.pt. or letter/ use emez
18	note.pt.
19	editorial.pt.
20	Editorial/ use ppez
21	News/ use ppez
22	exp Historical Article/ use ppez
23	Anecdotes as Topic/ use ppez
24	Comment/ use ppez
25	Case Report/ use ppez
26	case report/ or case study/ use emez
27	(letter or comment*).ti.
28	or/16-27
29	randomized controlled trial/ use ppez
30	randomized controlled trial/ use emez
31	random*.ti,ab.
32	or/29-31
33	28 not 32
34	animals/ not humans/ use ppez
35	animal/ not human/ use emez
36	nonhuman/ use emez
37	exp Animals, Laboratory/ use ppez
38	exp Animal Experimentation/ use ppez
39	exp Animal Experiment/ use emez
40	exp Experimental Animal/ use emez
41	exp Models, Animal/ use ppez
42	animal model/ use emez
43	exp Rodentia/ use ppez

#	Search
44	exp Rodent/ use emez
45	(rat or rats or mouse or mice).ti.
46	or/33-45
47	15 not 46
48	limit 47 to (yr="2005 - current" and english language)
49	remove duplicates from 48

1 **Database: Cochrane Library**

2 Last searched on: 12/11/2018

#	Search
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees
2	(((colorect* or colo rect* or colon or colonic) 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: [Colonic Polyps] this term only
5	((colorect* or colo rect* or colon or colonic) near/2 (adenocarcinoma* or polyp or polyps or polypoid)):ti,ab,kw
6	(t1 or n0 or M0 or (early near/2 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*))):ti,ab,kw
7	{or #4-#6}
8	MeSH descriptor: [Endoscopic Mucosal Resection] this term only
9	(endoscopic near/3 (excision or management or polypectom* or resect* or therap*)):ti,ab,kw
10	(colonoscopic near/2 polypectom*):ti,ab,kw
11	{or #8-#10}
12	#3 and #7 and #11 with Cochrane Library publication date Between Jan 2005 and Dec 2018

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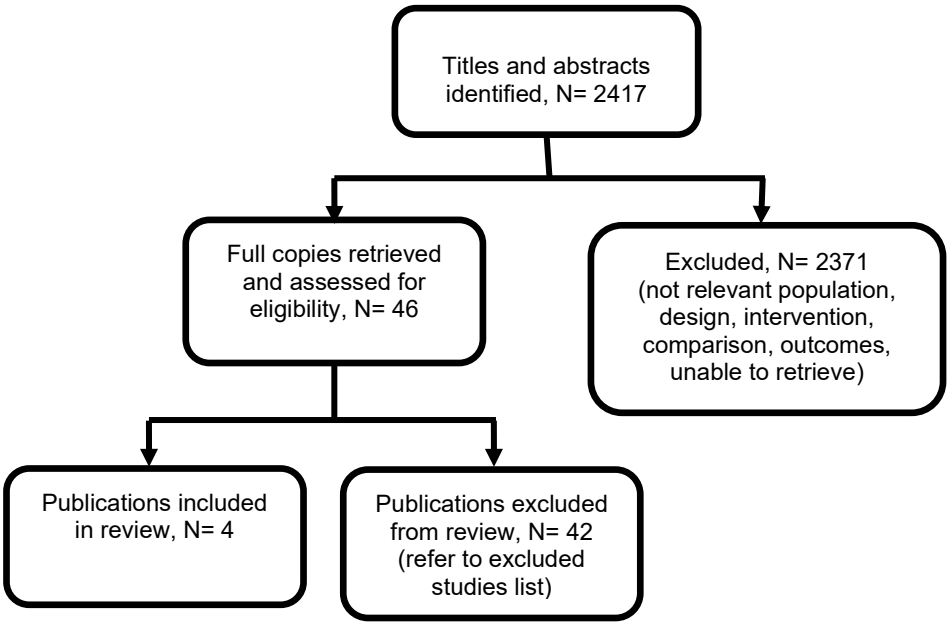
4

1 Appendix C – Clinical evidence study selection

2 Clinical study selection for: Which people with early colon cancer can be treated 3 with endoscopic resection alone?

Figure 1: Study selection flow chart



4

Appendix D – Clinical evidence tables

Clinical evidence tables for review question: Which people with early colon cancer can be treated with endoscopic resection alone?

Table 4: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kouyama, Y., Kudo, S. E., Miyachi, H., Ichimasa, K., Matsudaira, S., Misawa, M., Mori, Y., Kudo, T., Hayashi, T., Wakamura, K., Ishida, F., Hamatani, S., Risk factors of recurrence in T1 colorectal cancers treated by endoscopic resection alone or surgical resection with lymph node dissection, International Journal of Colorectal Disease, 33, 1029-1038, 2018 **Ref Id** 928018 **Country/ies where the study was carried out** Japan. **Study type** Retrospective cohort study. **Aim of the study** To "… clarify the risk factors for	**Sample size** N=930. Intervention n=298; control n=632. **Characteristics** Patient characteristics - intervention Age, years, mean: 67.7 ± 12.0 Male sex, n=199 (66.8%) Location - rectum n=50 (16.8%) Morphological type - depressed n=27 (9.1%) Pit pattern - type VN, n=11 (3.7%) Mean tumour size: 21.0mm ± 15.3 SM depth (mean): 3148.36µm ± 2200.8 Vertical margin of ER (+): n=13 (14.4%) Horizontal margin of ER (-): n=5 (1.7%) Histologic type (Por or Muc): n=23 (7.7%) Lymphatic invasion (+): n=34 (11.4%) Vascular invasion (+): n=21	**Interventions** Intervention – Endoscopic resection only. After endoscopic resection, physical examinations, blood tests including carcinoembryonic antigen level and carbohydrate antigen 19–9, computed tomography of the chest, abdomen and pelvis, and a full colonoscopy were performed every year for 5 years." Control - Surgical resection (initial or additional) with lymph node dissection. "After surgical resection, physical examinations and blood tests, including carcinoembryonic antigen and carbohydrate antigen 19–9 levels, were performed (in principle) every 3 months for first 3 years after surgical resection, and every 6 months for the next 2 years in accordance with the JSCCR guidelines [14]. In addition, computed tomography scans of the chest, abdomen, and pelvis were performed every	**Details** Data collection: Retrospective review of records relating to T1 patients undergoing endoscopic or local resection, and/or surgery with regional lymph node dissection at a single institution (Yokohama hospital) between April 2001 and June 2015. Outcomes: Recurrence free survival. Local recurrence defined as recurrence within the surgical field for colon cancer or within the pelvis for rectal cancer. Distant recurrence was defined as the occurrence of metastasis of colorectal origin associated with the index tumour. Follow-up (months, mean): 52.3 ± 37.2	**Results** Local recurrence: ER group 0/248; SR group 0/513. Disease-free survival: ER group 4/298; SR group 6/632. Distant metastasis: ER group 1/248; SR group 1/513. Recurrence free survival (distant metastasis): ER group n=4/298 (1.34%); SR group n=6/632 (0.95%); p =	**Limitations** Risk of bias assessed using the ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Low risk of bias. Bias in selection of participants into the study: Low risk of bias Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
recurrence in patients with T1 colorectal cancers treated by endoscopic resection (ER) alone or surgical resection (SR) with lymph node dissection …" **Study dates** 2001 - 2015. **Source of funding** None.	(7.1%) Tumour budding (+): 23 (7.7%) Follow-up (months, mean): 41.5 ± 34.7 Patient characteristics - control Age, years, mean: 64.8 ± 11.2 Male sex, n=387 (61.2%) Location - rectum n=119 (18.8%) Morphological type - depressed n=188 (29.4%) Pit pattern - type VN, n=186 (29.4%) Mean tumour size: 21.2mm ± 12.5 SM depth (mean): 3915.8 ± 2259.7 Vertical margin of ER (+): n =46 (7.3%) Horizontal margin of ER (-): n=18 (2.8%) Histologic type (Por or Muc): n=110 (17.4%) Lymphatic invasion (+): n=258 (40.8%) Vascular invasion (+): n=226 (35.8%) Tumour budding (+): n=184 (29.1%) Follow-up (months), mean ± SD: 57.5 ± 37.2 **Inclusion criteria** T1 patients undergoing	6 months, and a full colonoscopy was performed every year for 5 years." "Lesions observed to have III, IV, or VI low-grade pit patterns (i.e., adenomas, intramucosal colorectal carcinomas, and slightly invasive submucosal colorectal carcinomas) were resected endoscopically. Patients with lesions exhibiting a VI high-grade or VN pit pattern (i.e., massively invasive submucosal colorectal carcinomas) were referred for surgery. No biopsy was performed before treatment. Patients with complications and/or old age, or who refused surgery underwent endoscopic resection as a first-line treatment."	Statistical analysis: Kaplan Meier analysis and log rank test.	0.324 (log rank test). Prognostic risk factors for recurrence: Treatment (endoscopic resection vs surgical resection) HR 4.36 (95% CI 1.13 to 16.90), p = 0.033.	Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias Other information Study included patients with rectal cancer. Comparison group included patients who had surgery as an initial treatment. Age, SM depth, depressed-type lesions, VN pit pattern, and histopathological risk factors were higher/more frequent in the SR group compared to that in the ER group. (p < 0.001)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	endoscopic or local resection, and/or surgery with regional lymph node dissection. None of these patients had received preoperative radiotherapy or neoadjuvant chemotherapy. **Exclusion criteria** Patients with - advanced cancers in the colon or rectum, familial adenomatous polyposis, Lynch syndrome, inflammatory bowel disease. Patients who underwent transanal endoscopic microsurgery or had specimens that were impossible to pathologically evaluate in detail due to damage or loss were also excluded.				
Full citation Levic, K., Bulut, O., Hansen, T. P., Gogenur, I., Bisgaard, T., Malignant colorectal polyps: endoscopic polypectomy and watchful waiting is not inferior to subsequent bowel resection. A nationwide propensity score-based analysis, Langenbeck's Archives of Surgery., 2018 **Ref Id** 928112	**Sample size** Before propensity score matching N=962. ER alone/watchful waiting n=424; subsequent bowel resection n=268. After propensity score matching n=304; ER/watchful waiting n=152; subsequent bowel resection n=152. **Characteristics** Intervention - before propensity score matching Age (mean, years): 71.3	**Interventions** Intervention - Watchful waiting - Patients in this group were defined as those where it was decided not to perform subsequent bowel resection due to confirmed histological diagnosis of a malignant polyp. No other details provided e.g. in relation to other treatments received. Control - Subsequent bowel resection -Patients in this group were defined as those where it was decided to perform	**Details** Data collection: The study sample was comprised of consecutive patients diagnosed with malignant polyps (non-screened) between January 2001 and December 2011 (selected from the Danish Colorectal Cancer Group [DCCG] database). In order to deal with the potential for missing patients, data were also extracted from	**Results** After propensity score matching (n=304; watchful waiting n=152; subsequent bowel resection n=152) Total overall survival, odds	**Limitations** Risk of bias assessed using the ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (histological information was not used in matching process

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Denmark. **Study type** Retrospective controlled cohort study. **Aim of the study** To compare outcomes of watchful waiting or subsequent bowel resection in colorectal cancer patients who have previously had a polypectomy. **Study dates** 2001 - 2016. **Source of funding** Not reported.	(10.9 ± SD) Male sex, n = 242 (57%) Mean BMI (±SD), kg/m2 26.5 (5%) ASA score - 1: n = 87 (20.6%); 2: n = 164 (38.8%); 3: n = 64 (15.1%); 4: n = 5 (1.2%); missing data: 103 (24.3%) CCI score - 0: n = 282 (66.5%); 1 - 2 n = 111 (26.2%); ≥ 3 n = 31 (7.3%) Adenocarcinoma, n (%): colon =291 (68.6); rectum =133 (31.4) Polyp size, mean, mm (±SD): 19.34 (10) Polyp size: ≤ 10 mm n=78 (18.4%); 11 - 20 mm n =211 (49.9%); > 20 mm n=134 (31.7%) Polyp morphology, n (%): Pedunculated=304 (71.7); sessile=80 (18.9); missing data=40 (9.4) Polypectomy technique, n (%): En bloc=332 (78.3); piecemeal=92 (21.7) Histological type, n (%): Adenocarcinoma, common type=414 (97.6); mucinous adenocarcinoma=10 (2.4) Differentiation, n (%): Well=36 (8.5); moderate=121 (28.5); poor=6 (1.4); missing data=261 (61.6) Resection margin, n (%):	subsequent bowel resection after confirmed histological diagnosis of a malignant polyp. No other details provided e.g. in relation to other treatments received.	the National Pathology Databank (Patobank) and the Danish National Patient Registry. Malignant polyps were identified using the subheadings of cancer in a polyp, cancer after polypectomy, cancer after Endoscopic Mucosal Resection (EMR), and cancer after local resection. Outcomes: Overall survival (measured as date of polypectomy until date of death, or date of last follow-up). Disease free survival (measured as date of polypectomy until date of recurrence, death or last follow-up). Local recurrence (defined as histologically verified adenocarcinoma at endoscopic resection site in polypectomy only/watchful waiting, and at the site of anastomosis in the case of subsequent bowel resection. Systemic recurrence/distant metastases (defined as	ratio (95% CI), watchful waiting n = 92/152 (60.5%), subsequent bowel resection n = 100/152, (65.8%), OR 1.196 (0.825 to 1.735 95% CI), p = .344 3 year overall survival, odds ratio (95% CI), watchful waiting n = 133/152 (87.5%), subsequent bowel resection n = 133/152, (87.5%), OR 0.985 (0.522 to 1.86 95% CI), p = .963 5 year overall survival, odds ratio (95% CI), watchful waiting n = 116/152 (76.3%), subsequent bowel	due to missing data) Bias in selection of participants into the study: Low risk of bias Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: serious risk of bias. "The follow-up after treatment also differed between patients with WW and SBR. There is a national follow-up program for patients undergoing bowel resection for colorectal cancer in Denmark, but not for patients with malignant polyps and WW. During chart review, it became clear that the strategy for the follow-up program for patients with

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Negative (> 1 mm)=273 (64.4); positive (≤ 1 mm)=60 (14.2); uncertain/missing data=91 (21.5) Lymphovascular invasion, n (%): yes=22 (5.2); no=140 (33); missing data=262 (61.8) Tumour budding, n (%): yes=45 (10.6); no=6 (1.4); missing data=373 (88) Haggitt level, n (%): 1=8 (2.3); 2=4 (1.2); 3=2 (0.6); 4=2 (0.6) Kikuchi level, n (%): Sm1=6 (7.5); Sm2=2 (2.5); Sm3 2 (2.5); missing data=70 (80) Intervention - after propensity score matching Age (mean, years: 68.1 (11.6 ± SD) Male sex, n = 77 (50. 7%) Mean BMI (±SD), kg/m2 27.6 (5.8%) ASA score - 1: n = 45 (29.6%); 2: n = 68 (44.7%); 3: n = 30 (19.7%); 4: n = 1 (0.7%); missing data: 8 (5.3%) CCI score - 0: n = 105 (69.1%); 1 - 2 n = 35 (23%); ≥ 3 n = 12 (7.9%) Adenocarcinoma, n (%): colon =103 (67.8); rectum =49 (32.2) Polyp size, mean, mm (±SD): 18.54 (9.5)		recurrence in other organs). Follow-up: Mean: 7.5 years (3-188 months). All patients followed from polypectomy until 31 December 2016 or until death. Statistical analysis: Survival and recurrence analysis - propensity score matching was used. Variables included age, gender, American Society of Anesthesiologists' score, location of polyp, resection margin, and polyp morphology. These were chosen on basis of clinical impact of variable on allocation to treatment group and outcome. Missing data categorised as unknown. As there were a large amount of missing data in relation to histological variables these were not included in propensity score matching. Patients in the watchful waiting group were matched with patients in the subsequent bowel resection group at a ratio of 1:1, using nearest neighbour approach, and	resection n = 121/152, (79.6%), OR 1.16 (0.718 to 1.875 95% CI), p = .545 Local recurrence and/or distant metastases - watchful waiting n = 11/152 (7.2%), subsequent bowel resection n = 3/152 (2%), p = .052 Total disease free survival, odds ratio (95% CI), watchful waiting n = 87/152 (57.2%), subsequent bowel resection n = 98/152 (64.5%), OR 1.278 (0.89 to 1.833 95% CI), p = .184	WW differed greatly between treating surgeons and/or institutions. Due to great heterogeneity, this could not be accounted for in the analysis. The non-uniformity of the WW follow-up strategy may have affected time to diagnosis of recurrences, and thereby treatment options and ultimately survival in the WW group." Bias due to missing data: Moderate risk of bias. Histological variables could not be included in propensity score matching due to missing data. Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Polyp size: mm: ≤ 10 mm=31 (20.5); 11 - 20 mm=75 (49.7); > 20 mm=45 (29.8) Polyp morphology, n (%): Pedunculated=97 (63.8); sessile=42 (27.6); missing data=13 (8.6) Polypectomy technique, n (%): En bloc=112 (73.7); piecemeal=40 (26.3) Histological type, n (%): Adenocarcinoma, common type=148 (97.4); mucinous adenocarcinoma=4 (2.6) Differentiation, n (%): Well=14 (9.2); moderate=44 (28.9); poor=3 (2); missing data=91 (59.9) Resection margin, n (%): Negative (> 1 mm)=46 (30.3); positive (≤ 1 mm)=45 (29.6); uncertain/missing data=61 (40.1) Lymphovascular invasion, n (%): yes=3 (2); no=6 (3.9); missing data=143 (94.1) Tumour budding, n (%): yes=4 (2.6); no=18 (11.8); missing data=130 (85.5) Haggitt level, n (%): 1=5 (4.5); 2=0 (0); 3=1 (0.9); 4=0 (0); missing data= 110 (94.5) Kikuchi level, n (%): Sm1=2 (4.8); Sm2=1 (2.4); Sm3=2 (4.8); missing data=37 (88.1)		caliper of 0.2 times SD of logit of propensity score. Before propensity score matching, survival and recurrence rates were compared between groups with a log-rank test and multivariate analysis was performed Cox's proportional hazards regression model. After propensity score matching, survival rates were compared with a Cox proportional hazard model and survival curves were plotted using Kaplan-Meier method.	3 year disease free survival, odds ratio (95% CI), watchful waiting n = 125/152 (82.2%), subsequent bowel resection n = 128/152, (84.2%), OR 1.121 (0.647 to 1.944 95% CI), p = .683 5 year disease free survival, odds ratio (95% CI), watchful waiting n = 109/152 (71.7%), subsequent bowel resection n = 118/152, (77.6%), OR 1.285 (0.82 to 2.015 95% CI), p = .274 Distant metastases only - watchful	Study included patients with rectal cancer. Histological information not included in propensity score matching due to missing data.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Control before propensity score matching Age, years, mean: 65 (10.3 ± SD) Male sex, n = 129 (48.1%) Mean BMI (±SD), kg/m2 26.3 (4.5%) ASA score - 1: n = 96 (35.8%); 2: n = 126 (47%); 3: n = 37 (13.8%); 4: n = 3 (1.1%); missing data: 6 (2.2%) CCI score - 0: n = 204 (76.1%); 1 - 2 n = 46 (17.2%); ≥ 3 n = 18 (6.7%) Adenocarcinoma, n (%): colon =203 (75.7); rectum =65 (24.3) Polyp size, mean, mm (±SD): 19.75 (10.5) Polyp size: ≤ 10 mm n=36 (13.7%); 11 - 20 mm n=148 (56.5%); > 20 mm n=78 (29.8%) Polyp morphology, n (%): Pedunculated=155 (57.8); sessile=89 (33.2); missing data=24 (9) Polypectomy technique, n (%): En bloc=196 (73.1); 72 (26.9) Histological type, n (%): Adenocarcinoma, common type=248 (92.5); mucinous adenocarcinoma=20 (7.5) Differentiation, n (%): Well=12 (4.5); moderate=69			waiting n = 5/152 (3.3%), subsequent bowel resection n = 7/152 (4.6%), p = .77 Treatment-related morbidity: Intraoperative surgical complications – watchful waiting 0/152; subsequent bowel resection 6/152. Postoperative surgical complications - watchful waiting 0/152; subsequent bowel resection 30/152. Postoperative medical complications - watchful waiting 0/152; subsequent bowel resection 15/152.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(25.7); poor=12 (4.5); missing data=175 (65.3) Resection margin, n (%): Negative (> 1 mm)=50 (18.7); positive (≤ 1 mm)=119 (44.4); uncertain/missing data=99 (36.9) Lymphovascular invasion, n (%): yes=18 (6.7); no=66 (24.6); missing data=184 (68.7) Tumour budding, n (%): yes=25 (9.3); no=8 (3); missing data= () Haggitt level, n (%): 1=3 (1.7); 2=1 (0.5); 3=3 (1.7); 4=0 (0); missing data n=172 (96.1) Kikuchi level, n (%): Sm1=1 (1.1); Sm2=4 (4.5); Sm3=0 (0); missing data=84 (94.4) Control after propensity score matching Age, years, mean: 66.6 (10.02 ± SD) Male sex, n = 76 (50%) Mean BMI (±SD), kg/m2 26.7 (4.4%) ASA score - 1: n = 48 (31.6%); 2: n = 69 (45.4%); 3: n = 27 (17.8%); 4: n = 2 (1.3%); missing data: 6 (3.9%) CCI score - 0: n = 115 (75.7%); 1 - 2 n = 26 (17.1%); ≥ 3 n = 11 (7.2%)			Grade 3 or 4 complications - watchful waiting 0/152; subsequent bowel resection 20/152	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Adenocarcinoma, n (%): colon =114 (75); rectum =38 (25) Polyp size, mean, mm (±SD): 20.15 (9.43) Polyp size: ≤ 10 mm=16 (10.9); 11 - 20 mm=85 (57.9); > 20 mm=46 (31.3) Polyp morphology, n (%): Pedunculated=96 (63.2); sessile=47 (30.9); missing data=9 (5.9) Polypectomy technique, n (%): En bloc=113 (74.3); piecemeal=39 (25.7) Histological type, n (%): Adenocarcinoma, common type=139 (91.4); mucinous adenocarcinoma=13 (8.6) Differentiation, n (%): Well=5 (3.3); moderate=41 (27); poor=7 (4.6); missing data=99 (65.1) Resection margin, n (%): Negative (> 1 mm)=49 (32.2); positive (≤ 1 mm)=52 (34.2); uncertain/missing data=51 (33.6) Lymphovascular invasion, n (%): yes=4 (2.6); no=5 (3.3); missing data=143 (94.1) Tumour budding, n (%): yes=8 (5.3); no=12 (7.9); missing data=132 (86.8) Haggitt level, n (%): 1=3 (2.9); 2=1 (1); 3=2 (1.9); 4=0 (0); missing data=99 (94.3)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Kikuchi level, n (%): Sm1=1 (2.1); Sm2=3 (6.4); Sm3=0 (0); missing data=43 (91.5) **Inclusion criteria** "... > 17 years of age with a malignant colorectal polyp with submucosal invasion completely resected at the primary endoscopic procedure. Incomplete polypectomy was defined as a biopsy of a polyp or macroscopic suspicion of residual polyp at the end of the endoscopic procedure, as stated in endoscopy reports." The study sample was comprised of consecutive patients diagnosed with malignant polyps between January 2001 and December 2011 (selected from the Danish Colorectal Cancer Group [DCCG] database). **Exclusion criteria** "... biopsy, incomplete polypectomy or multiple endoscopic resections for the same malignant polyp, resection with transanal endoscopic microsurgery (TEM) (as these patients are often investigated with TRUS and/or MRI prior to the TEM procedure, and a				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	full-thickness excision can, unlike a polypectomy, provide evaluation of penetration into the muscularis propria), patients with hereditary nonpolyposis colorectal cancer (HNPCC), patients with familial adenomatous polyposis (FAP), advanced disease (T4 tumors, distant metastases, and suspicious lymph nodes on CT scan), multiple malignant polyps or synchronous cancer, previous surgery for colorectal cancer, current cancer in other organs, neoadjuvant chemo- or radiation therapy, active inflammatory bowel disease, and pregnancy."				
Full citation Tamaru, Y., Oka, S., Tanaka, S., Nagata, S., Hiraga, Y., Kuwai, T., Furudoi, A., Tamura, T., Kunihiro, M., Okanobu, H., Nakadoi, K., Kanao, H., Higashiyama, M., Arihiro, K., Kuraoka, K., Shimamoto, F., Chayama, K., Long-term outcomes after treatment for T1 colorectal carcinoma: a multicenter retrospective cohort study of Hiroshima GI	**Sample size** N=359. Intervention (ER alone) n=121; control (ER + additional surgery) n=238. **Characteristics** Patient characteristics - intervention Age, years, mean: 69.3 (± SD 10.7, range 41-86) Male sex, n=79 (65.3%) Malignant diseases in other organs n=15 (12.4%) Tumour location - colon n =92 (76%), rectum n =29 (24%)	**Interventions** Intervention: ER only. Control: ER + additional surgery. Indication for additional surgery was determined according to Japanese Classification of Colorectal Carcinoma guidelines. Endoscopic resection methods included polypectomy, endoscopic mucosal resection, and ESD	**Details** Data collection: Patients with T1 CRC treated at Hiroshima University Hospital (and 10 affiliated hospitals - Hiroshima Gastrointestinal Endoscopy Research Group) between January 1992 and December 2008) Outcomes: Overall recurrence rate, local recurrence rate (defined as recurrence at the site of resected CRC	**Results** NB These data relate to 'non e-curable' patients. Local recurrence rate (defined as recurrence at the site of resected CRC in the case of ER, or within the surgical	**Limitations** Risk of bias assessed using the ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias. The study does not control for potential confounding

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Endoscopy Research Group, Journal of Gastroenterology, 52, 1169-1179, 2017 **Ref Id** 928781 **Country/ies where the study was carried out** Japan. **Study type** Retrospective cohort study. **Aim of the study** To "… analyze the long-term outcomes of patients with T1 CRC after treatment, including surgical resection alone." **Study dates** 1992 - 2013. **Source of funding** Japan Agency for Medical Research and Development.	Tumour size, mean: 18.5 mm (± 10.6) Gross type, n(%): Protruded n=97 (80.2%); superficial n=24 (19.8%) Adenomatous component positive n =84 (69.4%) Histology, n (%): tub/pap =120 (99.2); por/sig/muc = 1 (0.8%) Submucosal invasion depth (μm): <1000 n=21 (17.4%); ≥1000 n=100 (82.6%) Vertical margin positive, n = 12 (10%) Lymphatic invasion positive, n = 31 (25.6%) Venous invasion positive, n = 10 (8.3%) Budding high grade, n = 21 (17.4%) Lymph node metastasis, n (%) Patient characteristics - control Age, years, mean: 63.3 (± 10.7, range 32-86) Male sex, n= 149 (62.6%) Malignant diseases in other organs n=18 (7.6%) Tumour location - colon n = 182 (76.5%), rectum n = 56 (23.5%) Tumour size, mean: 18.3 mm (± 11.6) Gross type, n(%): Protruded n=202 (84.9); superficial		in the case of ER, or within the surgical field of colonic carcinoma or within the pelvis for rectal carcinoma in the case of surgical resection). Distant recurrence rate (defined as occurrence of metastasis of colorectal origin associated with the index tumour). Overall survival rate. Disease free survival rate. Disease specific survival rate. **Follow-up:** Mean 100.8 months; ± 46.8. Patients followed up for less than 5 years were not included in the study. "Physical examinations, chest radiography, contrast enhanced computed tomography of the abdomen and pelvis, and blood tests (including carcino-embryonic antigen level) were performed every 6 months postoperatively for the first 3 years, and thereafter every 12 months in principle. An annual total colonoscopy was performed. Confirmation of	field of colonic carcinoma or within the pelvis for rectal carcinoma in the case of surgical resection): ER only group 3.3%, 4/121 (95% CI 0.9 to 8.2); ER + additional surgery group 2.5%, 6/238 (95% CI 0.9 to 5.4). Reported as non significant, p value not included. Distant recurrence rate (defined as occurrence of metastasis of colorectal origin associated with the index tumour): ER only group 3.3%, 4/121 (95% CI 0.9 to 8.2); ER + additional	factors (although the results reported here relate only to those patients defined as non e-curable, i.e. high risk patients). However there were significant baseline differences between groups, for example in age, submucosal depth, and incidence of lymphatic invasion. Bias in selection of participants into the study: Low risk of bias Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	n=38 (15.1%) Adenomatous component positive n =154 (64.7%) Histology, n (%): tub/pap n=235 (98.7%); por/sig/muc n=3 (1.3%) Submucosal invasion depth (μm): <1000 n=19 (8%); ≥1000 n=219 (92%) Vertical margin positive: n=50 (21%) Lymphatic invasion positive: n=88 (37%) Venous invasion positive: n=37 (15.6%) Budding high grade: n=48 (20.1%) Lymph node metastasis: n=19 (8%) **Inclusion criteria** Patients with T1 CRC treated between January 1992 and December 2008 at Hiroshima University Hospital and 10 affiliated hospitals (Hiroshima GI Endoscopy Research Group) and followed up for >5 years. **Exclusion criteria** "Patients with previous or synchronous CRC, familial adenomatous polyposis, inflammatory bowel disease, or a follow-up period of < 5 years were		recurrence was based on imaging and/or pathological findings." **Statistical analysis:** Kaplan-Meier method.	surgery group 3.8%, 9/238 (95% CI 1.7 to 7.1). Overall recurrence rate: ER only group 5%, 6/121 (95% CI 1.8 to 10); ER + additional surgery group 5.5%, 13/238 (95% CI 2.9 to 9.2). Reported as non significant, p value not included. Mortality: ER only group 31%, 38/121 (95% CI 23 to 40); ER + additional surgery group 16%, 38/238 (95% CI 12 to 21); p < 0.01. Mortality from T1 colorectal cancer: ER only group 2.5%, 3/121 (95% CI 0.5 to	outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias **Other information** Study included patients with rectal cancer. The mean age in the ER only group (69.3 ± 10.7 years old) was significantly higher than in the ER + additional surgery group (63.3 ± 10.7 years old), p < 0.01. The incidence of submucosal invasion depth <1000 um in the ER only group (17.4%, 21/121) was significantly higher than in the ER + additional surgery group (8.0%, 19/238), p < 0.01. The incidence of lymphatic invasion in the ER + additional surgery

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	excluded. Patients who underwent surgical resection without lymph node dissection (transanal endoscopic microsurgery or local resection) as initial treatment for T1 CRC were also excluded."			7.1); ER + additional surgery group 2.9%, 7/238 (95% CI 1.2 to 6.0). Reported as non significant, p value not included. Overall survival rates in non e-curable patients: ER only 79.3%, ER + additional surgery 92.4%; p < 0.01. Disease free survival rates in non e-curable patients: ER only 98.1%; ER + additional surgery 97.9%, p = 0.51. Disease specific survival rates	group was significantly higher than that in the ER only group (37.0 vs. 25.6%, p < 0.05).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				in non e-curable patients: ER only 99.1%; ER + additional surgery 98.3%, p = 0.29.	
Full citation Yoshii, S., Nojima, M., Nosho, K., Omori, S., Kusumi, T., Okuda, H., Tsukagoshi, H., Fujita, M., Yamamoto, H., Hosokawa, M., Factors associated with risk for colorectal cancer recurrence after endoscopic resection of T1 tumors, Clinical Gastroenterology and Hepatology, 12, 292-302.e3, 2014 **Ref Id** 929017 **Country/ies where the study was carried out** Japan. **Study type** Retrospective cohort study. **Aim of the study** To investigate the long-term efficacy of subsequent surgery after endoscopic resection.	**Sample size** N=389. Endoscopic resection + surgery n=205; endoscopic resection only n=184. **Characteristics** Patient characteristics - intervention Age, years, mean: 66.4 (10.9 SD) Male sex: n=113 (61.4%) Body mass index (kg/m2) ≤ 18.4 n= 16 (8.7%); 18.5 - 24.9 n=112 (60.9%); ≥ 25 n=56 (30.4%) Performance status n (%): 0 n=105 (57.1); 1 n=56 (30.4); ≥ 2 n=23 (12.5) Charlson Comorbidity score n (%): 0 n=99 (53.8); 1 n=39 (21.2); ≥ n=46 (25.0) Location n (%): Right colon n=55 (29.9); left colon n=96 (52.2); rectum =33 (17.9) Configuration (classified according to Paris system) n (%): Pedunculated n=54 (29.3); sessile n=71 (38.6); flat elevated n=49 (26.6);	**Interventions** Intervention: Endoscopic resection + subsequent surgery. Control: Endoscopic resection only. Patients were selected for subsequent surgery on the basis of risk factors according to Japanese Society for Cancer of the Colon and Rectum criteria. All patients underwent endoscopic resection by snare polypectomy techniques or endoscopic mucosal resection. Piecemeal resection was performed for large lesions that could not be resected en bloc. Subsequent surgery was defined as radical resection (e.g. bowel resection) and regional lymph node dissection.	**Details** Data collection: Data were collected in relation to 467 patients with histologically confirmed T1 colorectal cancer who underwent endoscopic resection at the Keiyukai Sapporo Hospital between January 1989 and December 2008. Outcomes: Time to recurrence Time to local recurrence Time to distant metastasis Disease specific survival Follow-up: 0-84 months. Statistical analysis: Cox regression modelling and Kaplan-Meier, log rank test, PROs adjustment	**Results** Outcomes and results - stratified by risk status Cumulative risk of recurrence in low risk patients (n=164, patients with only deep submucosal invasion as a risk factor): endoscopic resection + surgery = endoscopic resection only p = 0.537 (log-rank test), p = 0.867 (PRoS-stratified log rank test).	**Limitations** Risk of bias assessed using the ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Low risk of bias Bias in selection of participants into the study: Low risk of bias Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 1989 - 2008 **Source of funding** Not reported.	depressed n=10 (5.4) Tumour size (mm) n (%): >20 n=124 (67.4); ≤20 n=60 (32.6) Resection method n (%): En bloc n=152 (82.6); piecemeal n=32 (17.4) Vertical margin n (%): negative n=168 (91.3); positive n=16 (8.7) Submucosal invasion n (%): Superficial n=97 (52.7); deep n=87 (47.3) Lymphatic invasion n (%): negative n=179 (97.3); positive n=5 (2.7) Venous invasion n (%): negative n=178 (96.7); positive n=6 (3.3) Histologic type (classified according to World Health Organization criteria) n (%): well, mod n=175 (95.1); por, sig, muc n=9 (4.9) Tumour budding n (%): Low grade n=173 (94.0); high grade n=11 (6.0) Surgical indication (JSCCR, 2010) n (%): no n=88 (47.8); yes n=96 (52.2) Probability of receiving subsequent surgery (calculated as probability of receiving subsequent surgery with listed variables by using logistic regression models) mean (SD), %: 36.6 (24.3)			Cumulative risk of recurrence in high risk patients (n=112, patients with one or more risk factors other than deep submucosal invasion): endoscopic resection + surgery = 5.8%; endoscopic resection only = 58.0%, p < 0.001 (log-rank test), p < 0.001 (PRoS stratified log-rank test). Cumulative risk of recurrence in low-risk patients with pedunculated configurations : ER only 0%, ER + surgery 3.3%, p =	Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias Other information Study included patients with rectal cancer.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Patient characteristics - control Age, years, mean: 61.8 (9.6 SD) Male sex: n=126 (61.8%) Body mass index (kg/m2) ≤ 18.4 n=12 (5.9%); 18.5 - 24.9 n=126 (61.5%); ≥ 25 n=67 (32.7%) Performance status n (%): 0 n =168 (82.4); 1 n=32 (15.7); ≥ 2 n=4 (2.0) Charlson Comorbidity score n (%): 0 n=124 (60.5); 1 n=49 (23.9); ≥ n=32 (15.6) Location n (%): Right colon n=42 (20.5); left colon n=141 (68.8); rectum n=22 (10.7) Configuration (classified according to Paris system) n (%): Pedunculated n=59 (28.8); sessile n=102 (49.8); flat elevated n=26 (12.7); depressed n=18 (8.8) Tumour size (mm) n (%): >20 n=145 (70.7); ≤20 n=60 (29.3) Resection method n (%): En bloc n=160 (78.0); piecemeal n=45 (22.0) Vertical margin n (%): negative n=170 (82.9); positive n=35 (17.1) Submucosal invasion n (%): Superficial n=34 (16.6); deep n=171 (83.4)			0.452 (log-rank test). Cumulative risk of recurrence in low-risk patients with non-pedunculated configurations : ER only 4.8%, ER + surgery 1.8%, p = 0.452 (log-rank test); HR 3.7% (95% CI 0.3 to 41.0), p = 0.252 (log-rank test); PRoS-adjusted HR 1.4 (95% CI 0.1 to 15.5), p = 0.795 (PRoS stratified log-rank test). Cumulative risk of distant metastasis in high-risk patients with pedunculated configurations : ER only 0%,	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Lymphatic invasion n (%): negative n=181 (91.7); positive n=17 (8.3) Venous invasion n (%): negative n=185 (90.2); positive n=20 (9.8) Histologic type (classified according to World Health Organization criteria) n (%): well, mod n=182 (88.8); por, sig, muc n=23 (11.2) Tumour budding n (%): Low grade n=189 (92.2); high grade n=16 (7.8) Surgical indication (JSCCR, 2010) n (%): no n=25 (12.2); yes n=180 (87.8) Probability of receiving subsequent surgery (calculated as probability of receiving subsequent surgery with listed variables by using logistic regression models) mean (SD), % 67.1 (22.0) **Inclusion criteria** Patients with histologically confirmed T1 colorectal cancer (defined as carcinoma that only invaded submucosa, corresponding to a T1 lesion under the American Joint Committee on Cancer classification guidelines. **Exclusion criteria** Patients with synchronous colorectal			ER + surgery 25%, p = 0.264). Cumulative risk of distant metastasis in high-risk patients with non-pedunculated configurations : ER only 42.5%, ER + surgery 7%; HR 8.0 (95% CI 1.6 to 39.4), p = 0.003 (log-rank test); PRoS adjusted HR 9.9 (95% CI 0.8 to 130.2), p = 0.056 (PRoS stratified log-rank test) Cumulative disease-specific survival in low-risk group: HR 2.0 (95% CI 0.1 to 32.5), p = 0.264 (log-	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	cancer or cancer of other origins, those lost to follow up, and patients with uncertain pathologic examinations or lesions with features "… strongly suggestive of carcinoma invasion near the muscularis propria ..."			rank test); PRoS adjusted HR 1.5 (95% CI 0.1 to 25.9), p = 0.780 (PRoS stratified log-rank test), cumulative disease specific death rate ER 5.6%, ER + surgery 3.1%. Cumulative disease-specific survival in high-risk group: HR 6.7 (95% CI 1.3 to 33.4), p = 0.007 (log-rank test); PRoS adjusted HR 5.5 (95% CI 0.4 to 68.4), p = 0.155 (PRoS stratified log-rank test), cumulative disease specific death rate ER	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				44.4%, ER + surgery 17.1%. Outcomes and results - stratified by indication for surgery Cumulative risk of recurrence in patients not indicated for surgery: endoscopic resection + surgery = 0% (0/25); endoscopic resection only = 2.3%, p = 0.577 (log-rank test). Cumulative risk of recurrence in patients with indication for surgery: endoscopic resection + surgery = 3.7%; endoscopic resection only	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				= 20.1%, p < 0.001 (log-rank test), p = 0.001 (PRoS-stratified log rank test). Outcomes and results - stratified by configuration Cumulative risk of recurrence in patients with pedunculated configurations indicated for surgery: p = 0.777 (log-rank test), p = 0.896 (PRoS-stratified log rank test). Cumulative risk of recurrence in patients with non-pedunculated configurations indicated for surgery: endoscopic resection + surgery =	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				4.0%; endoscopic resection only = 25.6%, p < 0.001 (log-rank test), p < 0.001 (PRoS-stratified log rank test). Outcomes and results for high risk group - stratified by configuration Cumulative risk of recurrence in high risk patients (with other risk factors except deep submucosal invasion) with pedunculated configurations : endoscopic resection + surgery = endoscopic resection only = %, p = 0.221 (log-rank test).	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Cumulative risk of recurrence in high risk patients (with other risk factors except deep submucosal invasion) with non pedunculated configurations : endoscopic resection + surgery = 6.6%; endoscopic resection only = 73.7%, p < 0.001 (log-rank test), p < 0.001 (PRoS stratified log-rank test).	

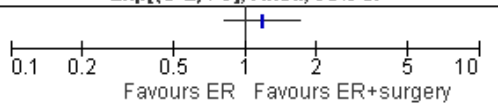
ASA: American Society of Anesthesiologists; BMI: body mass index; CCI: Charlson Comorbidity Index; CI: confidence interval; CRC: colorectal cancer; CT: computerised tomography; EMR: endoscopic mucosal resection; ER: endoscopic resection; ESD: endoscopic submucosal dissection; FAP: familial adenomatous polyposis; GI: gastrointestinal; HNPCC: hereditary nonpolyposis colorectal cancer; HR: hazard ratio; JSCCR: MRI: magnetic resonance imaging; N: number; OR: odds ratio; PRoS: propensity score; ROBINS-I: a tool for assessing risk of bias in non randomised studies of interventions; SBR: subsequent bowel resection; SD: standard deviation; SM: submucosal depth; SR: surgical resection; T: tumour stage; TEM: transanal endoscopic microsurgery; TRUS: Transanal endoscopic ultrasounds; WW: watchful waiting

Appendix E – Forest plots

Forest plots for review question: Which people with early colon cancer can be treated with endoscopic resection alone?

Figure 2: Comparison 1: endoscopic resection only versus endoscopic resection + surgery - overall survival

Study or Subgroup	Endoscopic resection Events	Total	Endo. resection + surgery Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Levic 2018 (1)	60	152	52	152	4.98	27.81	1.20 [0.82, 1.73]

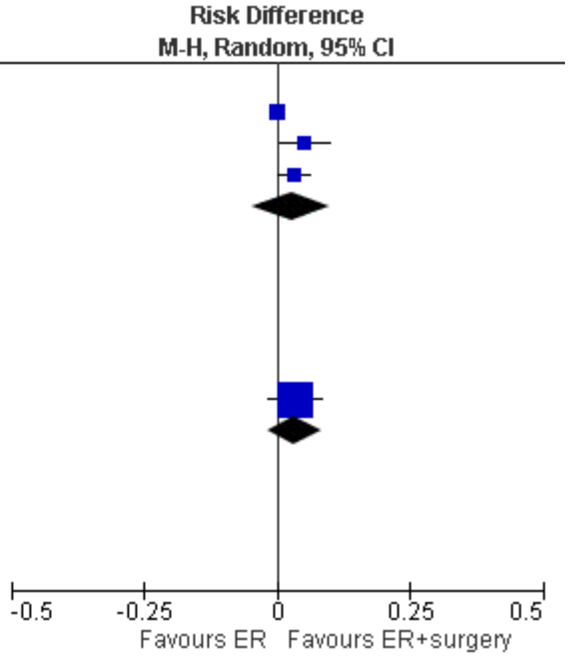


Footnotes
(1) Mean follow-up: 7.5 years (3-188 months)

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

Figure 3: Comparison 1: endoscopic resection only versus endoscopic resection + surgery - local recurrence in all patients and in low risk patients

Study or Subgroup	Endoscopic resection Events	Total	Endo. resection + surgery Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.2.1 All patients						
Kouyama 2018 (1)	0	248	0	513	35.5%	0.00 [-0.01, 0.01]
Levic 2018 (2)	11	152	3	152	31.0%	0.05 [0.01, 0.10]
Yoshii 2014 (3)	5	151	0	183	33.5%	0.03 [0.00, 0.06]
Subtotal (95% CI)		**551**		**848**	**100.0%**	**0.03 [-0.05, 0.10]**
Total events	16		3			
Heterogeneity: Tau² = 0.00; Chi² = 45.45, df = 2 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 0.74 (P = 0.46)						
1.2.2 Low risk patients						
Yoshii 2014	2	60	0	104	100.0%	0.03 [-0.02, 0.08]
Subtotal (95% CI)		**60**		**104**	**100.0%**	**0.03 [-0.02, 0.08]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						



Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%

Footnotes

(1) Mean follow-up 4.4 years. Colon cancer only

(2) Mean follow-up: 7.5 years (3-188 months)

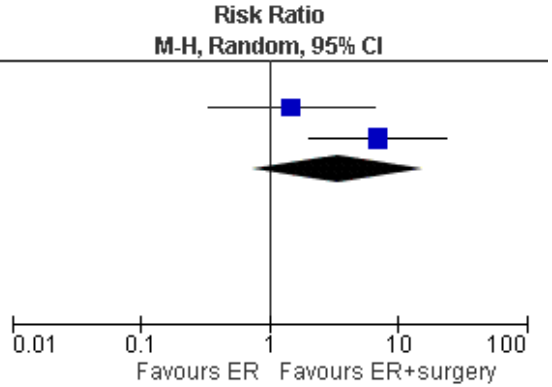
(3) Follow-up 0 to 7.1 years. Colon cancer patients only.

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

Figure 4: Comparison 1: endoscopic resection only versus endoscopic resection + surgery, outcome - local recurrence in high risk patients

Study or Subgroup	Endoscopic resection Events	Total	Endo. resection + surgery Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.3 High risk patients						
Tamaru 2017 (1)	3	92	4	182	46.4%	1.48 [0.34, 6.49]
Yoshii 2014	10	36	3	76	53.6%	7.04 [2.06, 24.02]
Subtotal (95% CI)		**128**		**258**	**100.0%**	**3.42 [0.75, 15.66]**
Total events	13		7			

Heterogeneity: Tau² = 0.73; Chi² = 2.53, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 1.58 (P = 0.11)



Test for subgroup differences: Not applicable

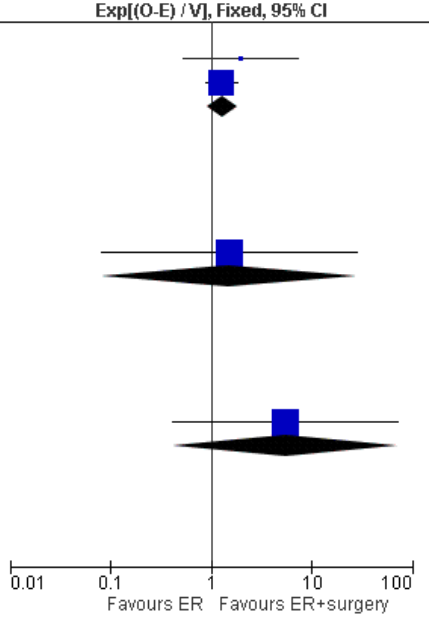
Footnotes

(1) Follow-up: Mean 8.4 years. Colon cancer only.

CI: confidence interval; ER: endoscopic resection; M-H: Mantel-Haenszel

Figure 5: Comparison 1: endoscopic resection only versus endoscopic resection + surgery - disease free survival

Study or Subgroup	Endoscopic resection Events	Total	Endo. resection + surgery Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.4.1 All patients								
Kouyama 2018 (1)	4	298	6	632	1.46	2.18	6.9%	1.95 [0.52, 7.37]
Levic 2018 (2)	65	152	54	152	7.22	29.44	93.1%	1.28 [0.89, 1.83]
Subtotal (95% CI)		**450**		**784**			**100.0%**	**1.32 [0.93, 1.86]**
Total events	69		60					
Heterogeneity: Chi² = 0.37, df = 1 (P = 0.55); I² = 0%								
Test for overall effect: Z = 1.54 (P = 0.12)								
1.4.2 Low risk patients								
Yoshii 2014	1	60	1	104	0.185	0.45	100.0%	1.51 [0.08, 28.02]
Subtotal (95% CI)		**60**		**104**			**100.0%**	**1.51 [0.08, 28.02]**
Total events	1		1					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.28 (P = 0.78)								
1.4.3 High risk patients								
Yoshii 2014	3	36	3	76	0.99	0.58	100.0%	5.51 [0.42, 72.27]
Subtotal (95% CI)		**36**		**76**			**100.0%**	**5.51 [0.42, 72.27]**
Total events	3		3					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								

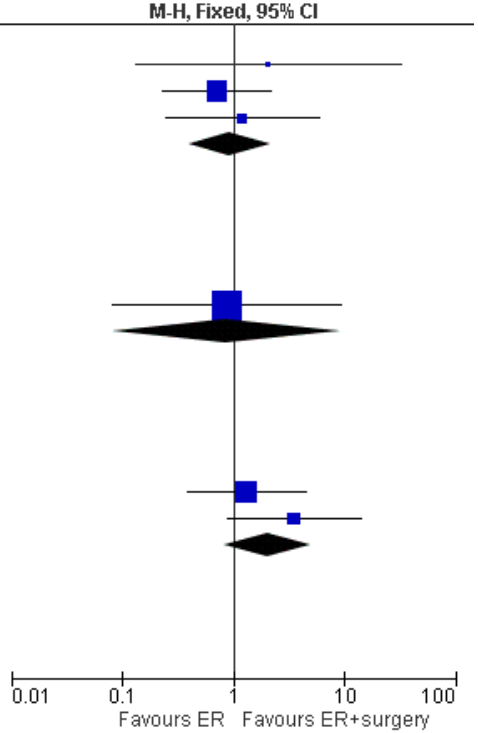


Footnotes
(1) Follow-up (months, mean): 52.3 ± 37.2. Effect of colon/rectum primary accounted for in analysis.
(2) Mean follow-up: 7.5 years (3-188 months). Effect of colon/rectum primary accounted for in analysis.

CI: confidence interval; ER: endoscopic resection; O-E: observed minus expected; V: variance

Figure 6: Comparison 1: endoscopic resection only versus endoscopic resection + surgery - distant metastasis

Study or Subgroup	Endoscopic resection Events	Total	Endo. resection + surgery Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 All patients						
Kouyama 2018 (1)	1	248	1	513	6.3%	2.07 [0.13, 32.93]
Levic 2018	5	152	7	152	67.5%	0.71 [0.23, 2.20]
Yoshii 2014 (2)	3	151	3	183	26.2%	1.21 [0.25, 5.92]
Subtotal (95% CI)		**551**		**848**	**100.0%**	**0.93 [0.39, 2.19]**
Total events	9		11			
Heterogeneity: Chi² = 0.64, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.87)						
1.3.2 Low risk patients						
Yoshii 2014 (3)	1	60	2	104	100.0%	0.87 [0.08, 9.36]
Subtotal (95% CI)		**60**		**104**	**100.0%**	**0.87 [0.08, 9.36]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.91)						
1.3.3 High risk patients						
Tamaru 2017 (4)	4	92	6	182	67.6%	1.32 [0.38, 4.56]
Yoshii 2014 (5)	5	36	3	76	32.4%	3.52 [0.89, 13.92]
Subtotal (95% CI)		**128**		**258**	**100.0%**	**2.03 [0.83, 4.97]**
Total events	9		9			
Heterogeneity: Chi² = 1.08, df = 1 (P = 0.30); I² = 7%						
Test for overall effect: Z = 1.55 (P = 0.12)						



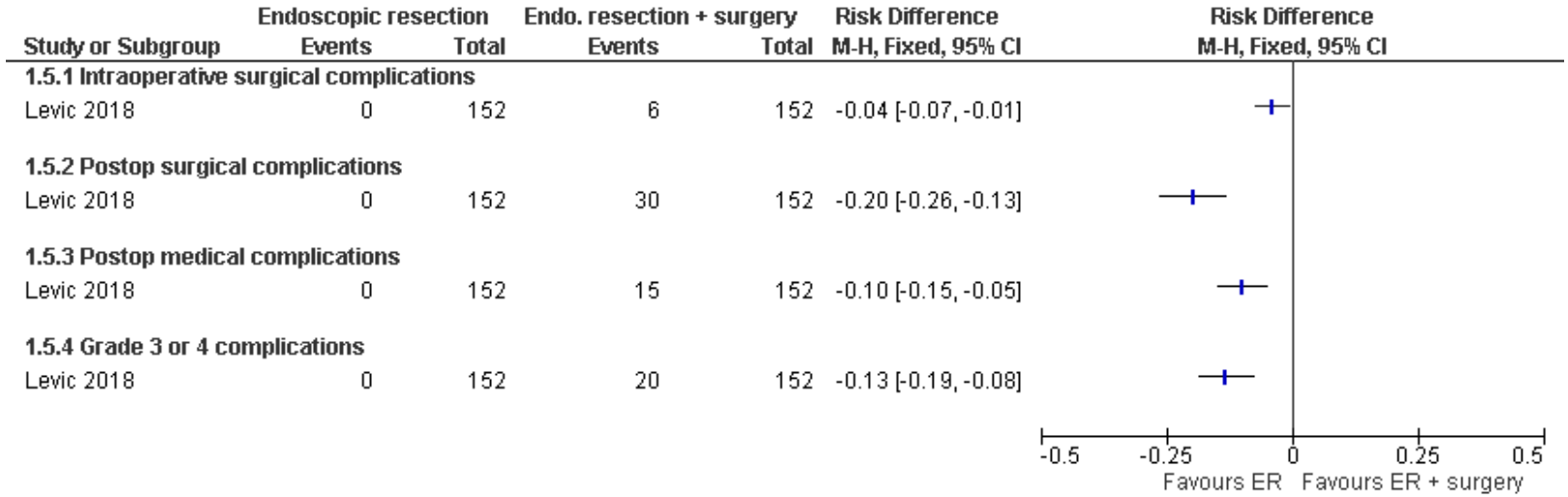
Test for subgroup differences: Chi² = 1.65, df = 2 (P = 0.44), I² = 0%

Footnotes

(1) Follow-up (months, mean): 52.3 ± 37.2
(2) Follow-up 0 to 85 months. Colon cancer patients only.
(3) Follow-up: 0-84 months
(4) Follow-up: Mean 100.8 months; ± 46.8. Colon cancer only.
(5) Follow-up: 0-84 months

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

Figure 7: Comparison 1: endoscopic resection only versus endoscopic resection + surgery- treatment-related morbidity



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

1 Appendix F – GRADE tables

2 GRADE tables for review question: Which people with early colon cancer can be treated with endoscopic resection alone?

3 Table 5: Clinical evidence profile for comparison 1: endoscopic resection alone versus endoscopic resection + surgery

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ER alone**	**ER + surgery**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
1	Observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	60/152 (39.5%)	52/152 (34.2%)	HR 1.20 (0.82 to 1.73)	42 more per 1,000 (from 43 fewer to 131 more)	VERY LOW	CRITICAL
Local recurrence – all patients												
3	observational studies	serious[1]	serious[7]	very serious[2]	serious[2]	none	16/551 (2.9%)	3/848 (0.4%)	RD 0.03 (-0.05 to 0.10)	30 more per 1,000 (from 50 fewer to 100 more)	VERY LOW	CRITICAL
Local recurrence – low risk patients												
1	Observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	2/60 (3.3%)	0/104 (0.0%)	RD 0.03 (-0.02 to 0.08)	30 more per 1,000 (from 20 fewer to 80 more)	VERY LOW	CRITICAL
Local recurrence – high risk patients												
2	observational studies	serious[1]	serious[8]	serious[1]	serious[2]	none	13/128 (10.2 %)	7/258 (2.7%)	RR 3.42 (0.75 to 15.66)	66 more per 1,000 (from 7 fewer to 398 more)	VERY LOW	CRITICAL
Disease free survival – all patients												

2	observational studies	serious[2]	no serious inconsistency	very serious[4]	serious[2]	none	69/450 (15.3%)	60/784 (7.7%)	HR 1.32 (0.93 to 1.86)	22 more per 1,000 (from 5 fewer to 57 more)	VERY LOW	CRITICAL
Disease free survival – low risk patients												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	1/60 (1.7%)	1/104 (1.0%)	HR 1.51 (0.08 to 28.02)	5 more per 1,000 (from 9 fewer to 199 more)	VERY LOW	CRITICAL
Disease free survival – high risk patients												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	3/36 (8.3%)	3/76 (3.9%)	HR 5.51 (0.42 to 72.27)	145 more per 1,000 (from 23 fewer to 709 more)	VERY LOW	CRITICAL
Quality of life												
-	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Distant metastasis – all patients												
3	observational studies	serious[2]	no serious inconsistency	very serious[4]	serious[2]	none	9/551 (1.6%)	11/848 (1.3%)	RR 0.93 (0.39 to 2.19)	1 fewer per 1,000 (from 8 fewer to 15 more)	VERY LOW	IMPORTANT
Distant metastasis – low risk patients												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	1/60 (1.7%)	2/104 (1.9%)	RR 0.87 (0.08 to 9.36)	3 fewer per 1,000 (from 18 fewer to 161 more)	VERY LOW	IMPORTANT
Distant metastasis – high risk patients												
3	observational studies	serious[3]	no serious inconsistency	serious[1]	serious[2]	none	9/128 (7.0%)	9/258 (3.8%)	RR 2.03 (0.83 to 4.97)	36 more per 1,000 (from 6 fewer to 138 more)	VERY LOW	IMPORTANT
Morbidity – interoperative surgical complications												
1	observational studies	very serious[4]	no serious inconsistency	serious[1]	serious[2]	none	0/152 (0.0%)	6/152 (3.9%)	Risk difference -0.04 (-0.07 to -0.01)	40 more per 1,000 with surgery	VERY LOW	IMPORTANT

										(from 10 more to 70 more)		
Morbidity – postoperative surgical complications												
1	observational studies	very serious[4]	not serious	serious[1]	serious[2]	none	0/152 (0.0%)	30/152 (19.7%)	Risk difference -0.20 (-0.26 to -0.13	200 more per 1,000 with surgery (from 130 more to 260 more)	VERY LOW	IMPORTANT
Morbidity – postoperative medical complications												
1	observational studies	very serious[4]	no serious inconsistency	serious[1]	serious[2]	none	0/152 (0.0%)	15/152 (9.9%)	Risk difference -0.10 (-0.15 to -0.05)	100 more per 1,000 with surgery (from 50 more to 150 more)	VERY LOW	IMPORTANT
Morbidity – grade 3 or 4 complications												
1	observational studies	very serious[4]	no serious inconsistency	serious[1]	serious[2]	none	0/152 (0.0%)	20/152 (13.2%)	Risk difference -0.13 (-0.19 to -0.08)	130 more per 1,000 with surgery (from 80 more to 190 more)	VERY LOW	IMPORTANT

CI: confidence interval; ER: endoscopic resection; HR: hazard ratio; OR: odds ratio; RR: relative risk

1 Quality of evidence downgraded by 1 because patients with rectal cancer were included.

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

3 Quality of evidence downgraded by 1 because of potential bias due to confounding not controlled for in Kouyama and Levic and due to post-treatment deviations from intended interventions (Levic).

4 Quality of evidence downgraded by 2 because patients with rectal cancer were included and the comparison group included patients who had surgery rather than ER as their initial treatment.

5 Quality of evidence downgraded by 1 because of potential bias due to confounding not controlled for in Tamaru.

6 Quality of evidence downgraded by 2 because of potential for bias due to confounding not controlled for and post-treatment deviations from intended interventions (Levic)

7 Quality of evidence downgraded by 1 - 1 study shows no difference but the other 2 show significant benefit with surgery

8 Quality of evidence downgraded by 1 due to considerable heterogeneity not explained by subgroup analysis.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: Which people with early colon cancer can be treated with endoscopic resection alone?

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: Which people with early colon cancer can be treated with endoscopic resection alone?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: Which people with early colon cancer can be treated with endoscopic resection alone?

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

Appendix J – Economic analysis

Economic evidence analysis for review question: Which people with early colon cancer can be treated with endoscopic resection alone?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: Which people with early colon 3 cancer can be treated with endoscopic resection alone?

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

Study	Reason for exclusion
Andreoni B, Camellini L, Sonzogni A, et al. (2011) Multicentric GISCoR Study "intensive clinical follow-up versus surgical radicalization after complete endoscopic polypectomy of a malignant adenoma" (SEC-GISCoR). Updates in Surgery 63: 171-177	0% event rates.
Asayama N, Oka S, Tanaka S, et al. (2016) Long-term outcomes after treatment for pedunculated-type T1 colorectal carcinoma: a multicenter retrospective cohort study. Journal of Gastroenterology 51: 702-710	Poor quality reporting/uncertainty regarding data that are reported.
Asayama, N, Oka, S, Tanaka S, et al. (2016) Long-term outcomes after treatment for T1 colorectal carcinoma. International Journal of Colorectal Disease 31: 571-578	Data reported in Tamaru paper.
Backes Y, De Vos T, Van Bergeijk J, et al. (2017) Risk for Incomplete Resection after Macroscopic Radical Endoscopic Resection of T1 Colorectal Cancer: A Multicenter Cohort Study. American Journal of Gastroenterology 112: 785-796	Does not report multivariate analyses.
Belderbos T, van Erning F, de Hingh I, et al. (2017) Long-term Recurrence-free Survival After Standard Endoscopic Resection Versus Surgical Resection of Submucosal Invasive Colorectal Cancer: A Population-based Study. Clinical Gastroenterology and Hepatology 15: 403-411.e1	Does not report multivariate analyses.
Benizri E, Bereder J, Rahili A, et al. (2012) Additional colectomy after colonoscopic polypectomy for T1 colon cancer: A fine balance between oncologic benefit and operative risk, International Journal of Colorectal Disease, 27, 1473-1478	All patients underwent colectomy.
Borschitz T, Heintz A, Junginger T (2006) The influence of histopathologic criteria on the long-term prognosis of locally excised pT1 rectal carcinomas: Results of local excision (transanal endoscopic microsurgery) and immediate reoperation, Diseases of the Colon and Rectum, 49, 1492-1500.	Does not report multivariate analyses.
Buchner A, Guarner-Argente C, Ginsberg G (2012) Outcomes of EMR of defiant colorectal lesions directed to an endoscopy referral center, Gastrointestinal Endoscopy, 76, 255-63	Does not compare post endoscopic resection treatment (deferral of surgery vs surgery) in a sample who have all had endoscopic resection.
Chen T, Zhang Y, Chen W, et al. (2017) Efficacy and safety of additional surgery after non-curative endoscopic submucosal dissection for early colorectal cancer, BMC Gastroenterology, 17, 134	Not comparative
Choi J, Jung S, Shim K, et al. (2015) Meta-analysis of predictive clinicopathologic factors for lymph node metastasis in patients with early colorectal carcinoma, Journal of Korean medical science, 30, 398-406, 2015	Measures risk of lymph node metastasis rather than outcomes specified in our protocol
Coleman H, Loughrey M, Murray L, et al. (2015) Colorectal cancer risk following adenoma removal: A large prospective population-based cohort study, Cancer Epidemiology Biomarkers and Prevention, 24, 1373-1380, 2015	Does not compare post endoscopic resection treatment (deferral of surgery vs surgery) in a sample who have all had endoscopic resection.

Cooper G, Xu F, Barnholtz S, et al. (2012) Management of malignant colonic polyps: a population-based analysis of colonoscopic polypectomy versus surgery, Cancer, 118, 651-9	The study compares surgical resection to colonoscopic polypectomy. Not all patients were treated with endoscopic resection to begin with.
Desgrippes R, Beauchamp C, Henno S, et al. (2013) Prevalence and predictive factors of the need for surgery for advanced colorectal adenoma, Colorectal Disease, 15, 683-688	Does not compare post endoscopic resection treatment (deferral of surgery vs surgery) in a sample who have all had endoscopic resection. Measures predictive factors for surgery in a sample in which some of the patients have had endocsopic resection.
Gill M, Rutter M, Holtham S (2013) Management and short-term outcome of malignant colorectal polyps in the north of England. Colorectal Disease, 15, 169-176	Does not report multivariate analysis.
Goncalves B, Fontainhas V, Caetano A, et al. (2013) Oncological outcomes after endoscopic removal of malignant colorectal polyps. Revista Espanola de Enfermedades Digestivas, 105, 454-61	Does not present multivariate analysis of outcomes of interest.
Hahnloser D, Wolff B, Larson D, et al. (2005) Immediate radical resection after local excision of rectal cancer: an oncologic compromise? Diseases of the Colon and Rectum, 48, 429-437	All patients had rectal cancer.
Hassan C, Pickhardt P, Di Giulio E, et al. (2010) Value-of-information analysis to guide future research in the management of the colorectal malignant polyp, Diseases of the Colon and Rectum, 53, 135-142	Does not report on outcomes specified in protocol.
Hassan C, Repici A, Sharma P, et al. (2016) Efficacy and safety of endoscopic resection of large colorectal polyps: A systematic review and meta-analysis, Gut, 65, 806-820	Comparisons do not match those specified in protocol.
Issa N, Fenig Y, Khatib M, et al. (2017) Transanal Endoscopic Microsurgery Combined with Laparoscopic Colectomy for Synchronous Colorectal Tumors: A Word of Caution. Journal of Laparoendoscopic and Advanced Surgical Techniques 27, 605-610	Study evaluates transanal endoscopic microsurgery laparoscopic colectomy. Does not compare post endoscopic resection treatment (deferral of surgery vs surgery) in a sample who have all had endoscopic resection.
Kidane B, Chadi S, Kanters S, et al. (2015) Local resection compared with radical resection in the treatment of T1N0M0 rectal adenocarcinoma: A systematic review and meta-analysis, Diseases of the Colon and Rectum, 58, 122-140	Comparisons not relevant to protocol.
Kobayashi H, Higuchi T, Uetake H, et al. (2012) Resection with en bloc removal of regional lymph node after endoscopic resection for T1 colorectal cancer, Annals of Surgical Oncology, 19, 4161-4167	Comparison does not include deferral of surgery.
Kogler P, Kafka-Ritsch R, Ofner D, et al. (2013) Is limited surgery justified in the treatment of T1 colorectal cancer? Surgical Endoscopy and Other Interventional Techniques. 27: 817-825	Descriptive. Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Kozak V, Kalady M, Gamaleldin M, et al. (2017) Colorectal surveillance after segmental resection for young-onset colorectal cancer: is there evidence for extended resection? Colorectal Disease, 19, O386-O392	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.

Lebedyev A, Tulchinsky H, Rabau M, et al. (2009) Long-term results of local excision for T1 rectal carcinoma: The experience of two colorectal units. Techniques in Coloproctology 13 231-236	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Lee T, Rees C, Nickerson C, et al. (2013) Management of complex colonic polyps in the English Bowel Cancer Screening Programme, British Journal of Surgery, 100, 1633-1639	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Levic K, Kjaer M, Bulut O, et al. (2015) Watchful waiting versus colorectal resection after polypectomy for malignant colorectal polyps, Danish Medical Journal, 62, A4996	Does not present multivariate analysis of outcomes of interest.
Lim D, Robinson R, Wurm P, et al. (2017) Outcome of an endoscopic mucosal resection service for large sessile colonic polyps (>= 20 mm) over A 9-Year period: A single centre experience and analysis of change over time in a university teaching hospital. Journal of Gastroenterology and Hepatology Research, 6, 2318-2323	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Meining A, von Delius S, Eames T et al. (2011) Risk Factors for Unfavorable Outcomes After Endoscopic Removal of Submucosal Invasive Colorectal Tumors, Clinical Gastroenterology and Hepatology, 9, 590-594	Does not present multivariate analysis of outcomes of interest.
Mitchell R, Zhang C, Galorport C et al. (2018) Characteristics of Patients with Colonic Polyps Requiring Segmental Resection, Canadian journal of gastroenterology & hepatology, 2018, 7046385	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Nozawa H, Ishihara S, Fujishiro M, et al. (2016) Outcome of salvage surgery for colorectal cancer initially treated by upfront endoscopic therapy, Surgery (United States), 159, 713-720	Does not present multivariate analysis of outcomes of interest.
Overwater A, Kessels K, Elias S, et al. (2018) Endoscopic resection of high-risk T1 colorectal carcinoma prior to surgical resection has no adverse effect on long-term outcomes. Gut 67: 284-290	Primary surgery (only) vs surgery after endoscopic resection. Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Park J, Cheon J, Kwon J, et al. (2011) Clinical outcomes and factors related to resectability and curability of EMR for early colorectal cancer. Gastrointestinal Endoscopy, 74 1337-1346	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Quaresima S, Balla A, D'Ambrosio G, et al. (2016) Endoluminal loco-regional resection by TEM after R1 endoscopic removal or recurrence of rectal tumors, Minimally Invasive Therapy & Allied Technologies: Mitat, 25, 134-40	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Rickert A, Aliyev R, Belle S, et al. (2014) Oncologic colorectal resection after endoscopic treatment of malignant polyps: Does endoscopy have an adverse effect on oncologic and surgical outcomes?, Gastrointestinal Endoscopy, 79, 951-960	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection. Impact of prior ER on outcomes after surgical resection.
Shin J, Han K, Hyun J, et al. (2018) Risk of recurrence after endoscopic resection of early colorectal cancer with positive margins, Endoscopy, 50, 241-247	Not comparative.
Silva G, de Moura E, Bernardo W, et al. (2016) Endoscopic versus surgical resection for early colorectal cancer-a systematic review and meta-analysis, Journal of Gastrointestinal Oncology, 7, 326-335	Comparisons do not match those specified in protocol.
Stipa F, Giaccaglia V, Burza A (2012) Management and outcome of local recurrence following transanal endoscopic	Does not present multivariate analysis of outcomes of interest.

microsurgery for rectal cancer, Diseases of the Colon and Rectum, 55, 262-269	
Su M, Ho Y, Hsu C, et al. (2005) How can colorectal neoplasms be treated during colonoscopy?, World Journal of Gastroenterology, 11, 2806-2810	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Voloyiannis T, Snyder M, Bailey R, et al. (2008) Management of the difficult colon polyp referred for resection: Resect or rescope?, Diseases of the Colon and Rectum, 51, 292-295	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Watanabe D, Toyonaga T, Ooi M, et al. (2018) Clinical outcomes of deep invasive submucosal colorectal cancer after ESD, Surgical Endoscopy, 32, 2123-2130	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.
Wu X, Liang J, Church J (2015) Management of sessile malignant polyps: is colonoscopic polypectomy enough? Surgical Endoscopy, 29, 2947-52	Descriptive.
Yoshida D, Kono S, Moore M et al. (2007) Colorectal polypectomy and risk of colorectal cancer by subsite: The Fukuoka colorectal cancer study. Japanese Journal of Clinical Oncology, 37, 597-602	Does not compare deferral of surgery vs surgery in patients who have previously received endoscopic resection.

CRC: colorectal cancer; CT: chemotherapy; RCT: randomised control trial

Appendix L – Research recommendations

Research recommendations for review question: Which people with early colon cancer can be treated with endoscopic resection alone?

No research recommendations were made for this review question.