National Institute for Health and Care Excellence

Final

Colorectal cancer (update)

[C7] Preoperative chemotherapy for non-metastatic 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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Which people with non-metastatic colon cancer would benefit from preoperative chemotherapy?

This evidence review supports recommendation 1.3.13.

Review question

Which people with non-metastatic colon cancer would benefit from preoperative chemotherapy?

Introduction

Localised and resectable non-metastatic colon cancer has traditionally required an aggressive therapeutic approach through complete oncologic resection with post-operative chemotherapy, with extensive surgical resection needed to achieve negative margins. While preoperative chemotherapy is commonly used for localised oesophageal, gastric and rectal cancers, its use is not well-established for colon cancer as of yet. Preoperative chemotherapy has the potential to provide earlier and more effective eradication of occult micrometastatic disease, minimise the extent of surgery and debulk tumours to reduce the frequency of tumour cell shedding during surgery. Therefore, the aim of this review was to determine which people with non-metastatic colon cancer would benefit from preoperative chemotherapy.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	Adults with localised, resectable, non-metastatic colon cancer
	
	Non-metastatic cancer defined as:
	• Tany N1-2
	• T3
	• T4
	• M0
	
	Subgroups by:
	• Disease characteristics:
	  ○ Radiological T stage
	  ○ Radiological N stage
	• Tumour location
	• Colonic obstruction status (no/complete/partly)

Intervention	Preoperative chemotherapy
Comparison	No preoperative chemotherapy
Outcomes	**Critical** • Disease-free survival

	• Overall survival • Resection margins **Important** • Any grade 3 or 4 adverse events • Overall quality of life • Treatment-related mortality • Local recurrence

For further details see the review protocol in appendix A.

Methods and process

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

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

Clinical evidence

Included studies

Two studies were included in this review (FOxTROT trial [Agbamu 2012]; Dehal 2017).

The clinical studies included in this evidence review are summarised in Table 2.

One pilot RCT (FOxTROT 2012 [Agbamu 2012]) compared preoperative chemotherapy + surgery + postoperative chemotherapy to surgery + postoperative chemotherapy and 1 retrospective cohort study (Dehal 2017) compared preoperative chemotherapy + surgery to surgery + postoperative chemotherapy.

Expert evidence

The published evidence base is weak and relies on one retrospective study and the pilot phase of the FOxTROT trial. The FOxTROT trial is an international, mainly UK-based, phase III randomised trial that investigates the efficacy of neoadjuvant chemotherapy in colon cancer and is the only trial in the topic to date. The results from FOxTROT were presented to the guideline committee as academic in confidence data by one of the FOxTROT trialists as expert witness evidence. Where outcomes were reported in both the pilot trial and expert evidence presentation, data from the expert evidence presentation were used as these data were most recent and more mature (longer follow-up). Since the expert witness presentation, the results of the trial have been presented in a conference making them publicly available, although not peer-reviewed.

See the summary of expert evidence in appendix M.

Excluded studies

Studies not included in this review and their reasons for exclusion are listed in appendix K.

Summary of clinical studies included in the evidence review

Table 2: Summary of included studies

Study	Population	Intervention/Comparison	Outcomes
FOxTROT trial [Agbamu 2012] Pilot RCT UK	N=150 patients with locally advanced (T4 or T3 with extramural depth ≥ 5mm) adenocarcinoma of the colon with staging determined preoperatively by either spiral or multidetector CT	Preoperative chemotherapy + surgery + postoperative chemotherapy versus surgery + postoperative chemotherapy	• Grade 3 or 4 adverse events
Dehal 2017 Retrospective cohort study US	N=27,575 patients with clinically staged T3 or T4, non-metastatic primary colon cancer who had both surgery and chemotherapy and a tumour with a mucinous, signet ring cell, or adenocarcinoma	Preoperative chemotherapy + surgery versus surgery + postoperative chemotherapy	• Overall survival • Positive resection margins

CT: computed tomography; N: number; RCT: randomised controlled trial; 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: Preoperative chemotherapy versus no preoperative chemotherapy

Critical outcomes

Disease-free survival

No evidence was identified to inform this outcome.

Overall survival

T3 patients

- Very low quality evidence from 1 retrospective cohort study (N=27,575) showed no clinically important difference in 3-year overall survival between those receiving preoperative chemotherapy + surgery compared to surgery + postoperative chemotherapy.

T4a patients

- Very low quality evidence from 1 retrospective cohort study (N=27,575) showed no clinically important difference in 3-year overall survival between those receiving preoperative chemotherapy + surgery compared to surgery + postoperative chemotherapy.

T4b patients

- Very low quality evidence from 1 retrospective cohort study (N=27,575) showed a clinically important increase in 3-year overall survival between those receiving preoperative chemotherapy + surgery compared to surgery + postoperative chemotherapy.

Resection margins

T4b patients

- Very low quality evidence from 1 retrospective cohort study (N=27,575) showed a clinically important decrease in resection margins between those receiving preoperative chemotherapy + surgery compared to surgery + postoperative chemotherapy.

Important outcomes

Any Grade 3 or 4 adverse events

Grade ≥3 adverse events

- Very low quality evidence from 1 RCT (N=150) showed no clinically important difference in Grade ≥3 adverse events within 6, 12, 18, or 24 weeks between those receiving preoperative chemotherapy + surgery + postoperative chemotherapy compared to surgery + postoperative chemotherapy.

Anastomotic leak

- More recent data for this outcome were available in the expert evidence summary.

Wound infection with or without intra-abdominal abscess

- Very low quality evidence from 1 RCT (N=150) showed no clinically important difference in wound infection with or without intra-abdominal abscess between those receiving preoperative chemotherapy + surgery + postoperative chemotherapy compared to surgery + postoperative chemotherapy.

Bronchopneumonia

- Very low quality evidence from 1 RCT (N=150) showed no clinically important difference in bronchopneumonia between those receiving preoperative chemotherapy + surgery + postoperative chemotherapy compared to surgery + postoperative chemotherapy.

Deep vein thrombosis

- Very low quality evidence from 1 RCT (N=150) showed no clinically important difference in deep vein thrombosis between those receiving preoperative chemotherapy + surgery + postoperative chemotherapy compared to surgery + postoperative chemotherapy.

Neutropenia

- Very low quality evidence from 1 RCT (N=150) showed no clinically important difference in neutropenia between those receiving preoperative chemotherapy + surgery + postoperative chemotherapy compared to surgery + postoperative chemotherapy.

Overall quality of life

No evidence was identified to inform this outcome.

Treatment-related mortality

- More recent data for this outcome were available in the expert evidence summary.

Local recurrence

No evidence was identified to inform this outcome.

Expert evidence statements

Comparison 1: Preoperative chemotherapy versus no preoperative chemotherapy

Critical outcomes

Disease-free survival

- Moderate quality evidence from 1 RCT (N=1052) showed a clinically important decrease in recurrence between those receiving preoperative chemotherapy + surgery + postoperative chemotherapy compared to surgery + postoperative chemotherapy.

Overall survival

No evidence was identified to inform this outcome.

Resection margins

No evidence was identified to inform this outcome.

Important outcomes

Any Grade 3 or 4 adverse events

Anastomotic leak

- Moderate quality evidence from 1 RCT (N=1052) showed a clinically important decrease in anastomotic leak between those receiving preoperative chemotherapy + surgery + postoperative chemotherapy compared to surgery + postoperative chemotherapy.

Wound infection with or without intra-abdominal abscess

- No evidence was identified to inform this outcome.

Bronchopneumonia

- No evidence was identified to inform this outcome.

Pulmonary embolism ± deep vein thrombosis

- No evidence was identified to inform this outcome.

Overall quality of life

No evidence was identified to inform this outcome.

Treatment-related mortality

- Moderate quality evidence from 1 RCT (N=1052) showed no clinically important difference in treatment-related mortality (postoperative mortality) between those receiving preoperative chemotherapy + surgery + postoperative chemotherapy compared to surgery + postoperative chemotherapy.

Local recurrence

No evidence was identified to inform this outcome.

Economic evidence statements

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

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Disease-free survival and overall survival were considered critical outcomes for decision making because disease progression suggests ineffective control of the localised colon cancer, potentially requiring further treatment and affecting overall survival. Resection margins were also critical as they are indicative of whether further treatment, likely surgical, is needed.

Quality of life was an important outcome because of the impact that different treatment options can have on patients' functioning and the potential long term adverse effects. Any grade 3 or 4 adverse events and treatment-related mortality were also important outcomes, as they are indicative of the complications of treatments. Additionally, local recurrence was an important outcome because lesions that extend into surrounding structures and organs indicate the need for further surgical resection.

The quality of the evidence

Evidence was available from 1 pilot RCT comparing preoperative chemotherapy + surgery + postoperative chemotherapy to surgery + postoperative chemotherapy and 1 retrospective cohort study comparing preoperative chemotherapy + surgery to surgery + postoperative chemotherapy.

Evidence was available for overall survival, resection margins, any grade 3 or 4 adverse events and treatment-related mortality. There was no evidence for quality of life or local recurrence. The quality of the 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 around the risk estimate.

Methodological limitations leading to risk of bias were due to confounding from differences in baseline characteristics, lack of blinding and allocation concealment.

Indirectness in the study interventions was attributable to numerous protocol violations in both arms of the RCT that potentially diluted the effectiveness of the interventions.

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

An expert witness presented academic in confidence results of the FoXTROT trial which provided expert evidence for the comparison of preoperative chemotherapy + surgery + postoperative chemotherapy versus surgery + postoperative surgery. Evidence was available for disease-free survival, any grade 3 or 4 adverse events and treatment-related mortality. This evidence was assessed using GRADE as moderate quality.

The range in quality of the evidence and lack of evidence for many comparisons and outcomes impacted the decision-making and the strength of the recommendation as there was insufficient evidence to make a strong recommendation or to make recommendations for all subgroups within the population.

Benefits and harms

The evidence indicated that there were benefits for disease-free survival, overall survival and clear resection margins for patients with more advanced (T4b) colonic tumours who received preoperative chemotherapy. No benefit on overall survival was found for patients with T3 or T4a colonic tumours. However, the committee agreed that differentiating between T4a and T4b tumours would be difficult in preoperative clinical staging (imaging), therefore, based on their clinical experience and knowledge they agreed that the recommendation to consider preoperative therapy should cover patients with T4 tumours.

While the expert evidence showed that there was a clinically important decrease in anastomotic leak, otherwise the clinical evidence did not show any clinically important difference between treatment groups in terms of adverse events or treatment-related mortality. From their clinical experience, the committee noted that there is a potential for harm from increased surgical morbidity. The committee was not aware of any evidence regarding treatment decision-making pertaining to the extent of surgical resection (that is, whether decisions should be based on pre- or post-chemotherapy imaging). However, they noted that most clinicians would base their decisions on the extent of surgery on pre-chemotherapy imaging.

Cost effectiveness and resource use

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

The committee considered that the addition of preoperative chemotherapy would not increase costs for patients with T4 colon cancer as postoperative chemotherapy is current standard of care and costs between pre and post would be similar given the almost identical regimens. The committee acknowledged that preoperative chemotherapy was already being done in some centres and that it would only represent a change for some centres. There would also be increases in overall survival and quality of life through reduced surgical morbidity.

Other factors the committee took into account

The committee acknowledged the FOxTROT trial, which compares preoperative plus post-operative chemotherapy (+/- panitumumab) with standard post-operative chemotherapy. Results from the earlier feasibility trial (FOxTROT trial [Agbamu 2012]) were included in this review. Primary outcomes include 2-year recurrence-free survival and pathological down-staging and secondary outcomes include disease-specific survival and overall survival at 2 years and quality of life by EORTC QLQ C-30 and EuroQol EQ-5D before surgery, before the first post-operative chemotherapy and 1 year post-randomisation. The committee considered expert evidence about the unpublished results of the FOxTROT trial from the primary randomisation (preoperative-and-postoperative chemotherapy versus standard postoperative chemotherapy) to neoadjuvant treatment as data analysis for the substudy (patients with *KRAS*-wild type tumours randomised 1:1 to preoperative-and-postoperative chemotherapy +/- panitumumab) was not complete. Moderate quality evidence from the primary randomisation phase showed that complete clinical response and tumour downstaging are more likely in those who receive preoperative chemotherapy, although follow-up is not yet long enough to assess long-term outcomes. The results presented to the committee as academic in confidence were since presented at an international conference. See more details in appendix M.

References

FOxTROT trial [Agbamu 2012]

Agbamu D, Day N, Walsh C, et al. (2012) Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: The pilot phase of a randomised controlled trial. Lancet Oncology 13(11): 1152-1160

Dehal 2017

Dehal A, Vuong B, Graff-Baker A, et al. (2017) Neoadjuvant chemotherapy improves survival in patients with clinical T4B colon cancer. Gastroenterology 152 (5): S1209

1 Appendices

2 Appendix A – Review protocol

3 Review protocol for review question: Which people with non-metastatic co-
4 lon cancer would benefit from preoperative chemotherapy?

5 **Table 3: Review protocol for pre-operative chemotherapy for people with non-**
6 **metastatic colon cancer**

Field (based on PRISMA)	Content
Review question in guideline	Which people with non-metastatic colon cancer would benefit from preoperative chemotherapy?
Type of review question	Intervention
Objective of the review	To determine which people with non-metastatic colon cancer would benefit from preoperative chemotherapy.

Eligibility criteria – population/disease/condition/issue/domain	Adults with localised, resectable, non-metastatic colon cancer
	
	Non-metastatic cancer defined as:
	• Tany N1-2
	• T3
	• T4
	• M0
	
	Subgroups according to (analysed separately):
	• Disease characteristics:
	  ○ Radiological T stage
	  ○ Radiological N stage
	• Tumour location
	• Colonic obstruction status (no/complete/partly)

Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Preoperative chemotherapy
Eligibility criteria – comparator(s)/control or reference (gold) standard	No preoperative chemotherapy
Outcomes and prioritisation	**Critical outcomes:** • Disease-free survival (minimally important difference [MID]: statistical significance) • Overall survival (MID: statistical significance) • Resection margins (MID: statistical significance) **Important outcomes:** • Any Grade 3 or 4 adverse events (MID: statistical significance)

Field (based on PRISMA)	Content
	• Overall quality of life measured using validated scales (MID: published MIDs from literature, see below) • Treatment-related mortality (MID: statistical significance) • Local recurrence (MID: statistical significance) Quality of Life MIDs from the literature: • EORTC QLQ-C30: 5 points • EORTC QLQ-CR29: 5 points • EORTC QLQ-CR38: 5 points • EQ-5D: 0.09 using FACT-G quintiles • FACT-C: 5 points • FACT-G: 5 points • SF-12: > 3.77 for the mental component summary (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 PCS
Eligibility criteria – study design	• Systematic reviews • Randomised controlled trials • Prospective or retrospective comparative cohort studies will only be considered if eligible RCTs are not available
Other inclusion exclusion criteria	Inclusion: • English-language • All settings will be considered that consider medications and treatments available in the UK • Studies published post-2005 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 no longer be relevant.

Proposed sensitivity/sub-group analysis, or meta-regression	Cohort studies should include multivariate analysis controlling for the following confounding factors:
	• Patient characteristics (i.e. age [life expectancy], comorbidities)
	• Type of chemotherapy
	• Tumour characteristics
	  ○ T stage
	  ○ Tumour location

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

Field (based on PRISMA)	Content
	systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Potential sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): • Apply standard animal/non-English language exclusion • Limit to RCTs and systematic reviews in first instance, but download all results • Dates: from 2005
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060Developer: 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.

Field (based on PRISMA)	Content
	The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	**Synthesis of data:** Pairwise meta-analysis of randomised trials will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled if baselines are comparable. If any studies report both, the method used in the majority of studies will be analysed. **Minimally important differences:** The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except quality of life for which published MIDs from literature will be used (see outcomes section for more information).
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan 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 NGA 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

Field (based on PRISMA)	Content
Roles of sponsor	NICE funds the NGA to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; 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: no distant metastasis; MCS: mental component summary; MID: minimally important difference; N: nodal stage; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PCS: physical component summary; RCT: randomised controlled trial; RevMan5: Review Manager version 5; RoB: risk of bias; ROBINS-I: Risk Of Bias In Non-randomised Studies - of Interventions; ROBIS: risk of bias in systematic reviews; SD: standard deviation; SF-12: 12-Item Short Form Survey; SF-36: 36-Item Short Form Survey; T: tumour stage

1 Appendix B – Literature search strategies

2 Literature search strategies for review question: Which people with non-meta-
3 static colon cancer would benefit from preoperative chemotherapy?

4 Databases: Embase/Medline

5 Last searched on: 31/10/2018

#	Search
1	exp colonic neoplasms/ use ppez
2	exp colon tumor/ use emez
3	((colon or colonic) adj3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)).tw.
4	or/1-3
5	(local* advanc* or locali?ed or non-metasta* or non metasta* or operable or operative or resectable).tw.
6	(t3 or t4 or m0 or N1 or N2).tw.
7	or/5-6
8	preoperative chemotherapy/ use emez
9	neoadjuvant chemotherapy/ use emez
10	Neoadjuvant Therapy/ use ppez
11	((preop* or pre?op* or neoadjuvant) adj3 (chemotherap* or therap* or treat*)).tw.
12	or/8-11
13	4 and 7 and 12
14	Letter/ use ppez
15	letter.pt. or letter/ use emez
16	note.pt.
17	editorial.pt.
18	Editorial/ use ppez
19	News/ use ppez
20	exp Historical Article/ use ppez
21	Anecdotes as Topic/ use ppez
22	Comment/ use ppez
23	Case Report/ use ppez
24	case report/ or case study/ use emez
25	(letter or comment*).ti.
26	or/14-25
27	randomized controlled trial/ use ppez
28	randomized controlled trial/ use emez
29	random*.ti,ab.
30	or/27-29
31	26 not 30
32	animals/ not humans/ use ppez
33	animal/ not human/ use emez
34	nonhuman/ use emez
35	exp Animals, Laboratory/ use ppez
36	exp Animal Experimentation/ use ppez
37	exp Animal Experiment/ use emez
38	exp Experimental Animal/ use emez
39	exp Models, Animal/ use ppez
40	animal model/ use emez
41	exp Rodentia/ use ppez
42	exp Rodent/ use emez
43	(rat or rats or mouse or mice).ti.

#	Search
44	or/31-43
45	13 not 44
46	limit 45 to (yr="2005 - current" and english language)
47	remove duplicates from 46

1 **Database: Cochrane Library**

2 Last searched on: 31/10/2018

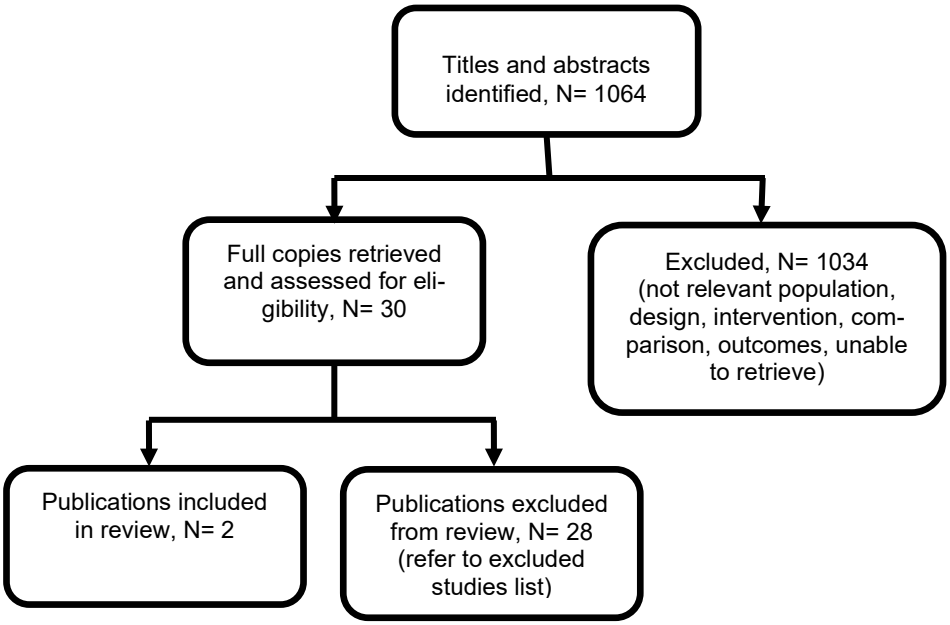
#	Search
1	MeSH descriptor: [Colonic Neoplasms] explode all trees
2	((colon or colonic) near/3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)):kw,ti,ab
3	#1 or #2
4	(local* advanc* or locali?ed or non-metasta* or non metasta* or operable or operative or resectable):kw,ti,ab
5	(t3 or t4 or m0 or N1 or N2):kw,ti,ab
6	#4 or #5
7	MeSH descriptor: [Neoadjuvant Therapy] this term only
8	((preop* or pre?op* or neoadjuvant) near/3 (chemotherap* or therap* or treat*)):kw,ti,ab
9	#7 or #8
10	#3 and #6 and #9 with Cochrane Library publication date Between Jan 2005 and Dec 2018

3

Appendix C – Clinical evidence study selection

Clinical study selection for review question: Which people with non-metastatic colon cancer would benefit from preoperative chemotherapy?

Figure 1: Study selection flow chart



1 Appendix D – Clinical evidence tables

2 Clinical evidence tables for review question: Which people with non-metastatic colon cancer would benefit from preoperative 3 chemotherapy?

4 **Table 4: Clinical evidence tables**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Agbamu D, Day N, Walsh C, et al. (2012) Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: The pilot phase of a randomised controlled trial. Lancet Oncology 13: 1152-1160 **Ref Id** 745295 **Country/ies where the study was carried out** UK **Study type** Pilot RCT **Aim of the study** The aim of the study was to assess patient selection and recruitment, safety, and tumour response to	**Sample size** n= 150 Preoperative + postoperative chemotherapy (CT), n=99 Standard postoperative chemotherapy alone, n=51 **Characteristics** Preoperative + postoperative CT, n=99 Age, years, median (IQR)= 64 (59-68) Sex, male, n=65 Colonic obstruction, n=3 Radiological T-stage, n T3=69 T4=30 Radiological N-stage, n Nx=3 N0=23 N1=44 N2=29 Extramural vascular invasion, n= 57/98 (one radiology form had missing data)	**Interventions** "Chemotherapy was the standard UK modified de Gramont (OxMdG) regimen, consisting of cycles of oxaliplatin at 85 mg/m2 combined with l-folinic acid 175 mg/m2 plus fluorouracil 400 mg/m2 by intravenous bolus, followed by a 46 h infusion of 2400 mg/m2 through an indwelling line, repeated at 2-weekly intervals. Capecitabine could not be substituted for fluorouracil and folinic acid in this pilot study because of higher toxicity when combined with panitumumab. Dose reductions and delays of up to 4 weeks were allowed for reversible toxicity." Preoperative + postoperative CT= "Preoperative chemotherapy duration was only 6 weeks (three cycles of OxMdG) to minimise the risk of progression of chemoresistant tumours (15–20% of advanced metastatic colon	**Details** Randomisation: "Eligible patients were randomly assigned, in a 2:1 ratio, between preoperative plus postoperative and postoperative chemotherapy. Patients were also randomly assigned, in a 1:1 ratio, to receive panitumumab with the first 6 weeks of chemotherapy or not. Patients were allocated to a treatment group by a telephone or web-based central randomisation service at the University of Birmingham Clinical Trials Unit. A computerised minimised randomisation procedure was used to ensure a good balance between groups for age, radiological T-stage, radiological	**Results** <u>Grade ≥3 adverse events within 6 weeks, n/N</u> Preoperative + postoperative CT= 32/94 Postoperative CT= 12/39 <u>Grade ≥3 adverse events within 12 weeks, n/N:</u> Preoperative + postoperative CT= 14/81 Postoperative CT= 9/38 <u>Grade ≥3 adverse events within 18 weeks, n/N:</u> Preoperative + postoperative CT= 18/75 Postoperative CT= 8/34	**Limitations** Quality assessment performed with the Cochrane risk of bias tool Selection bias Random sequence generation: low risk (computer generated randomisation was used) Allocation concealment: unclear risk (study was not blinded) Performance bias Blinding of participants and personnel: unclear risk (study was not blinded) Detection bias Blinding of outcome assessment: low risk (study was not blinded, but lack of blinding unlikely to affect outcome assessment)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
preoperative treatment as part of a feasibility phase to the wider FOxTROT (Fluoropyrimidine Oxaliplatin and Targeted Receptor Pre-Operative Therapy) trial. **Study dates** May 15, 2008 to September 21, 2010 **Source of funding** Cancer Research UK	Postoperative CT only, n=51 Age, years, median (IQR)=65 (56-69) Sex, male, n=32 Colonic obstruction, n=1 Radiological T-stage, n T3=35 T4=16 Radiological N-stage, n Nx=1 N0=12 N1=22 N2=16 Extramural vascular invasion, n=31 **Inclusion criteria** "18 years or older with locally advanced (T4 or T3 with extramural depth ≥5 mm) adenocarcinoma of the colon, with staging determined preoperatively by either spiral or multidetector computed tomography and for whom a 24-week course of oxaliplatin and fluoropyrimidine-based adjuvant chemotherapy would be judged appropriate. Patients were required to have adequate blood counts-haemoglobin greater than 100 g/L after transfusion and before surgery and chemotherapy, greater than 3・0×10^9 white blood cells per L, and	cancers progress during 12 weeks of similar combination chemotherapy). Surgery with curative intent was undertaken at least 3 weeks after completing preoperative therapy, to reduce perioperative morbidity, followed by a further 18 weeks (nine cycles) of OxMdG. CT scans were repeated before surgery in the pre-operative group." Postoperative CT only= "For the patients who were not assigned to receive preoperative chemotherapy, postoperative chemotherapy duration was 24 weeks (12 cycles) of OxMdG. If allocated, panitumumab (6 mg/kg) was given by intravenous infusion at 2-weekly intervals during the first 6 weeks of chemotherapy (preoperative or postoperative)."	nodal status, site of primary tumour, and defunctioning colostomy." Allocation concealment: Allocation not concealed Blinding: Not blinded Follow up: Not reported **Outcomes:** Feasibility, safety, tolerance of preoperative therapy, and the accuracy of radiological staging. Other key outcomes were completion of planned surgery, perioperative morbidity, timely completion of preoperative KRAS testing, and downstaging of the resected tumour as measured by histopathological tumour diameter and stage. Statistical analysis: "Comparisons of preoperative versus postoperative chemotherapy were by intention to treat including all patients randomly assigned to treatment groups, ignoring panitumumab	<u>Grade ≥3 adverse events within 24 weeks, n/N:</u> Preoperative + postoperative CT= 47/95 Postoperative CT= 20/39 <u>Anastomotic leak, n/N:</u> Data extracted from expert evidence provided , refer to appendix M <u>Wound infection with or without intra-abdominal abscess, n/N:</u> Preoperative + postoperative CT= 13/99 Postoperative CT= 4/51 <u>Bronchopneumonia, n/N:</u> Preoperative + postoperative CT= 2/99 Postoperative CT= 0/51	Attrition bias Incomplete outcome data: low risk (intention-to-treat analysis used) Reporting bias Selective reporting: low risk (primary outcome points were reported) Other bias Other sources of bias: No other sources of bias **Other information** "The FOxTROT study aims to randomly assign at least 1050 patients to detect a 25% proportional reduction (roughly 8% absolute difference) in recurrence at 2 years (eg, 32% reduced to 24%) with 80% power at p<0.05. The prespecified sample size of 150 for the pilot phase was chosen pragmatically as a sufficient number to assess the potential rate of recruitment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	greater than 100×10^9 platelets per L; adequate renal biochemistry with a glomerular filtration rate of greater than 50 mL per minute as calculated by the Wright or Cockroft formula or EDTA clearance of greater than 70 mL per minute; adequate hepatobiliary function with bilirubin less than 25 µmol per L; and serum magnesium levels within the normal range at trial entry." **Exclusion criteria** Not reported		allocation, and using t tests to compare continuous variables, Mantel-Haenszel tests of association for ordinal variables."	<u>Deep vein thrombosis, n/N:</u> Preoperative + postoperative CT= 2/99 Postoperative CT= 0/51 <u>Neutropenia, n/N:</u> Preoperative + postoperative CT= 1/99 Postoperative CT= 0/51 <u>Treatment-related mortality, n/N:</u> Data extracted from expert evidence provided , refer to appendix M	and any large differences in other primary outcomes." Preoperative + postoperative CT: "15 patients had no postoperative CT; five patients (including three who had no preoperative chemotherapy) did not have postoperative chemotherapy because of low-risk pathology, five because of previous adverse events (four because of toxicity of preoperative CT, one because of surgical morbidity), three refused, one had metastatic disease, and one died in the postoperative period. Additionally, two had off-protocol treatment (one patient had a different chemotherapy regimen, and one was treated with bevacizumab)." Postoperative CT alone: "Of 51 patients allocated postoperative CT, 94% (48 of 51) had resectional surgery with

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					one dying beforehand and two who were not resected because of inoperable peritoneal spread detected at surgery. 78% (40 of 51) started postoperative chemotherapy with 11 not having postoperative chemotherapy because of low risk pathology (seven) or dying beforehand (four). 95% (38 of 40) of those starting completed the first 6 weeks and 72% (29 of 40) completed all 24 weeks of CT. Toxicity caused six patients to discontinue chemotherapy." Thus, a higher proportion of patients started preoperative than postoperative chemotherapy (96% [95 of 99] vs 78% [40 of 51]; p=0.001), and CT completion rates were also higher in the preoperative therapy group with 68% (67 of 99) of those allocated pre plus postoperative

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					CT completing 24 weeks of treatment compared with 57% (29 of 51) of postoperative CT patients (p=0.19)."
Full citation Dehal A, Vuong B, Graff-Baker A, et al. (2017) Neoadjuvant chemotherapy improves survival in patients with clinical T4B colon cancer. Gastroenterology 152 (5 Supplement 1), S1209 **Ref Id** 919057 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** The aim of the study was to assess the effect of neoadjuvant chemotherapy for locally advanced colon cancer on survival.	**Sample size** n= 27,575 Preoperative CT + surgery= 921 Surgery + postoperative CT= 26,654 **Characteristics** Preoperative CT + surgery, n= 921 Age, years, mean (SD)=58.4 (12.1) Sex, male, n=533 Histology, n Adenocarcinoma=786 Mucinous=121 Signet cell=14 T stage, n T3=479 T4a=69 T4b=350 N stage, n N0=450 N1=291 N2=106 Nx=74 Grade, n Low=636	**Interventions** Preoperative CT + surgery Surgery + postoperative CT Surgery: segmental resection, subtotal colectomy/hemicolectomy, total colectomy, en bloc resection	**Details** Data collection: Patient records were retrieved from the National Cancer Data Base from 2006-2014 using ICD-9-O coding schema. Follow up: 3 years Outcomes: 3-year overall survival, en bloc resection, resection margins Factors controlled for: "Characteristics with statistically significant p values ($p < 0.001$) as well as clinically relevant variables obtained from univariate Cox proportional-hazards regression analysis were used to match the two treatment groups. This included age, gender, race, insurance status, comorbidity score, hospital type, histology, N stage, grade,	**Results** 3-year overall survival, hazard ratio (95% CI), p-value (propensity score matched for age, gender, race, insurance status, comorbidity score, hospital type, tumour histology, grade, N stage, tumour location, number of nodes examined, margin, and extent of surgery): *T3 patients* Preoperative CT + surgery= 1.15 (0.92-1.43), 0.24 Surgery + postoperative CT= reference *T4a patients* Preoperative CT + surgery= 1.43 (0.85-2.40), 0.18 Surgery + postoperative CT= reference	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: High risk of bias due to confounding ("There were significant differences in patient demographics, tumour features, and treatment between the two groups...and though propensity score matching was used to minimize confounding, there remained a small number of unmatched patients") Bias in selection of participants into the study: Unclear risk of bias ("The data does not include the small groups of patients who underwent surgical resection but

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 2006 to 2014 **Source of funding** Not reported	High=184 Unknown=101 Nodes retrieved, n 1-11=168 ≥12=745 Unknown=8 Margin, n Negative=776 Positive=126 Unknown=19 Surgery + postoperative CT, n= 26,654 Age, years, mean (SD)=61.5 Sex, male, n=13,270 Histology, n Adenocarcinoma=22,834 Mucinous=3243 Signet cell=577 T stage, n T3=19,999 T4a=3201 T4b=2987 N stage, n N0=11,106 N1=8985 N2=5343 Nx=1220 Grade, n Low=18,843 High=7086 Unknown=725 Nodes retrieved, n 1-11=2844		tumour location, nodes examined, margin, and extent of surgery. The matching rate for T3, T4a, and T4b was 80, 70, and 78%, respectively. The standard mean difference between the two groups after propensity score matching was < 0.1, indicating negligible difference." Statistical analysis: "To examine the association between the two treatment groups and 3-year overall survival (OS), univariate Cox proportional-hazards regression analysis was performed, followed by propensity score matching to minimize the confounding effects due to nonrandomised assignment within clinical tumour stages (T3, T4a, and T4b). Survival curves were also plotted using the Kaplan-Meier method and compared with the log-rank test for each tumour stage	*T4b patients* Preoperative CT + surgery= 0.77 (0.60-0.98), 0.04 Surgery + postoperative CT= reference <u>Positive margins for T4b patients, odds ratio (CI), p-value (adjusted for age, gender, race, insurance status, comorbidity score, hospital type, tumour histology, grade, N stage, extent of surgery, and tumour location):</u> Preoperative CT + surgery= 0.95 (0.90-0.98), p=0.04* Surgery + postoperative CT= reference (* Note that calculated values appearing in the forest plot and corresponding table are different 0.95 [0.91, 0.99] due to rounding)	did not receive AC due to morbidity and mortality nor patients that had neoadjuvant chemotherapy but never had surgery due to disease progression.") At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Unclear risk of bias (Some data missing from patient characteristics) Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias **Other information** None

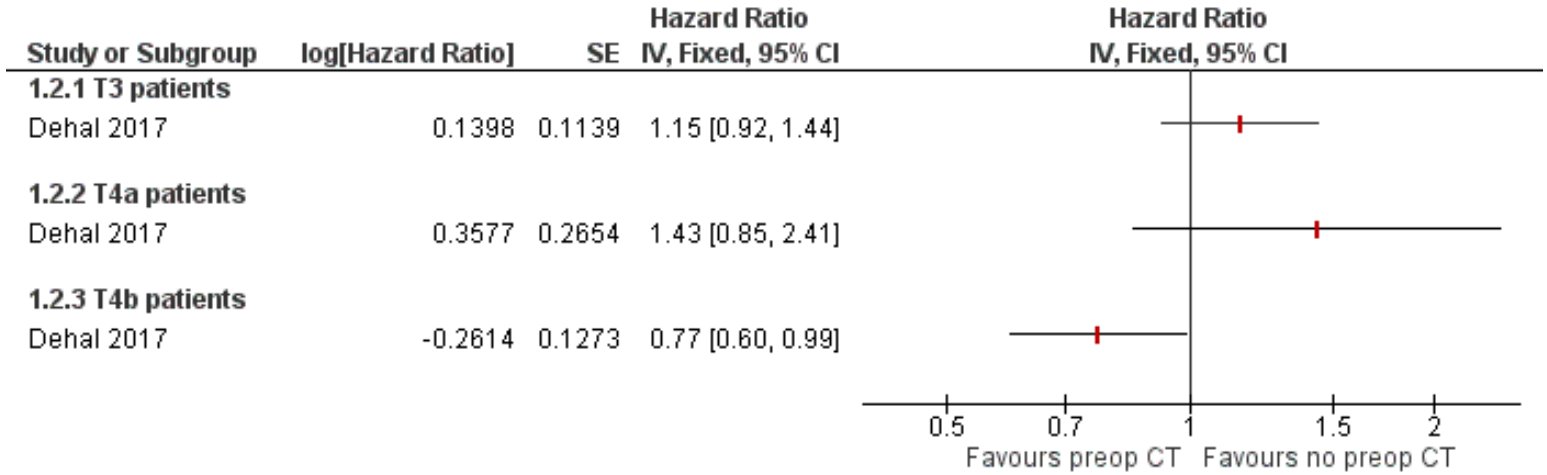
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	≥12=23,602 Unknown=208 Margin, n Negative=23,619 Positive=2669 Unknown=208 **Inclusion criteria** All patients aged ≥18 years with clinically staged T3 and T4, non-metastatic, primary colon cancer, had both surgery and chemotherapy and a tumour with a mucinous, signet ring cell, or adenocarcinoma. **Exclusion criteria** Not reported		(T3, T4a, and T4b)... Multivariate analysis, adjusted for the same variables, was performed to predict the likelihood of having an en bloc resection or positive margin between the treatment groups for patients with T4b colon cancer. Survival data was calculated from time of diagnosis until last contact or death."		

CI: confidence interval; CT: chemotherapy; EDTA: 51 Cr-ethylenediaminetetraacetic acid; FOxTROT: Fluoropyrimidine, Oxaliplatin and Targeted-Receptor pre-Operative Therapy for patients with high-risk, operable colon cancer; ICD: International Classification of Disease; KRAS: Kirsten rat sarcoma; N: nodal status; OxMdG: oxaliplatin/modified de Gramont chemotherapy; IQR: interquartile range; ROBINS-I: Risk Of Bias In Non-Randomized Studies - of Interventions; SD: standard deviation; T: tumour grade

Appendix E – Forest plots

Forest plots for review question: Which people with non-metastatic colon cancer would benefit from preoperative chemotherapy?

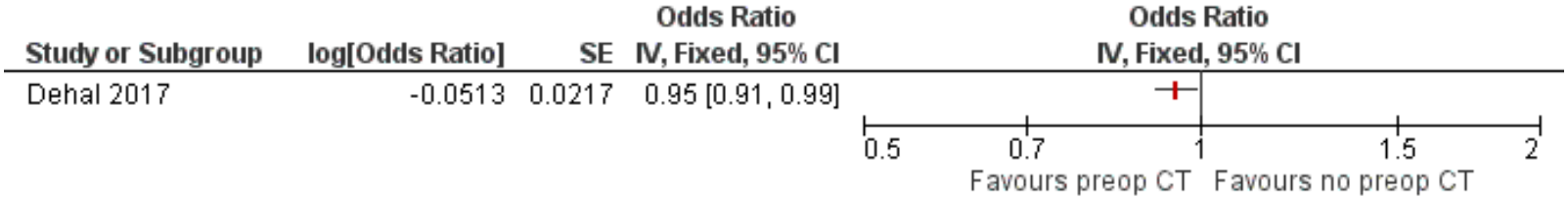
Figure 2: Preoperative chemotherapy versus no preoperative chemotherapy - 3-year overall survival*; event is death from any cause



CI: confidence interval; CT: chemotherapy; IV: inverse variance; SE: standard error; T: tumour stage

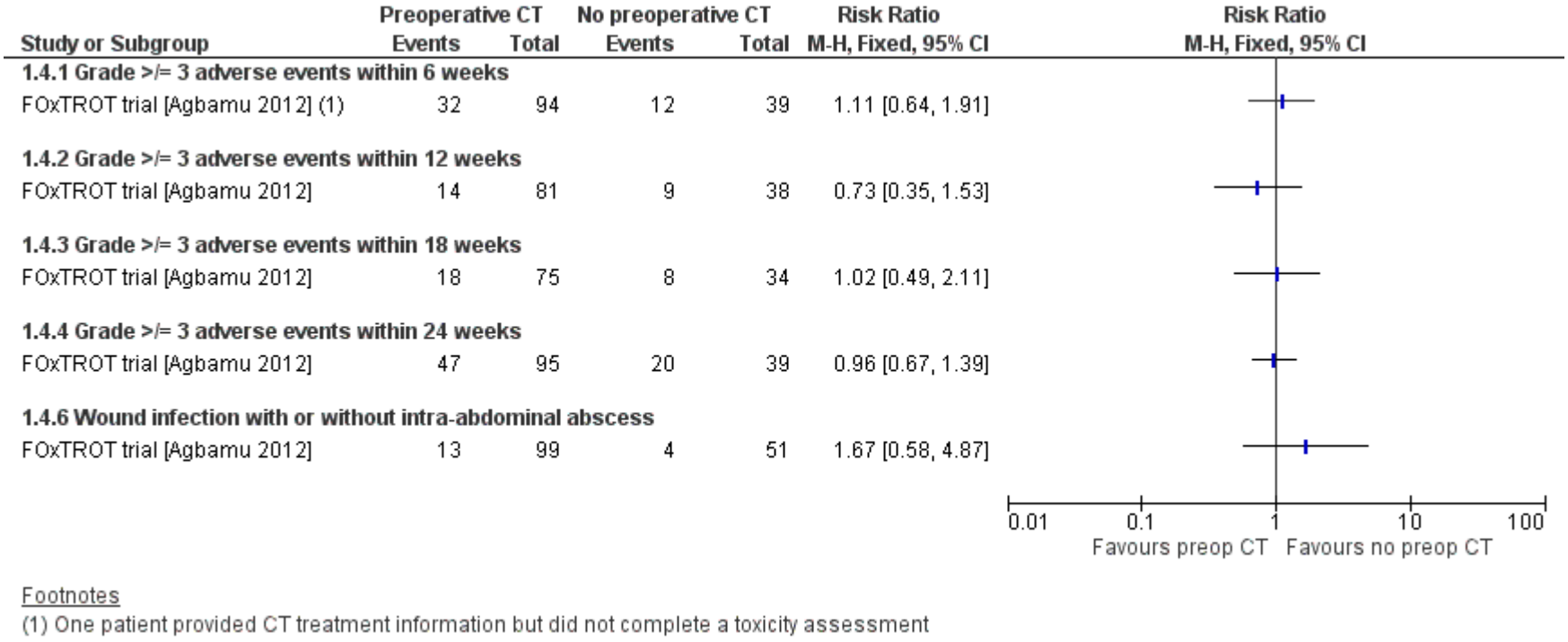
**propensity score matched for age, gender, race, insurance status, comorbidity score, hospital type, tumour histology, grade, N stage, tumour location, number of nodes examined, margin, and extent of surgery*

Figure 3: Preoperative chemotherapy versus no preoperative chemotherapy - Positive resection margins*, T4b patients



CI: confidence interval; CT: chemotherapy; IV: inverse variance; SE: standard error; T: tumour stage
**adjusted for age, gender, race, insurance status, comorbidity score, hospital type, tumour histology, grade, N stage, extent of surgery, and tumour location*

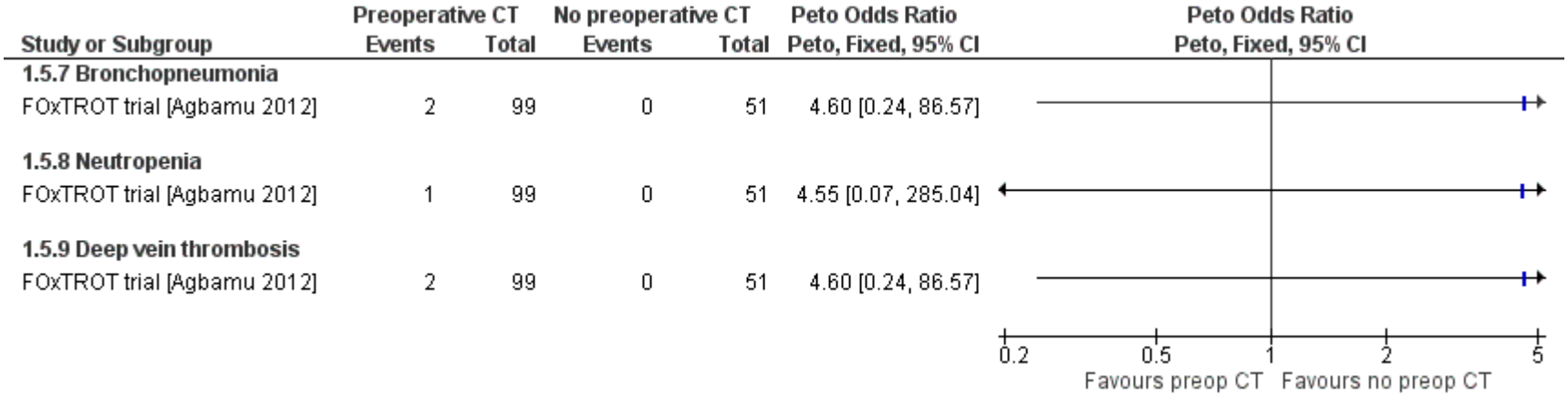
Figure 4: Preoperative chemotherapy versus no preoperative chemotherapy – Any Grade 3 or 4 events and wound infection with or without intra-abdominal abscess



Footnotes
(1) One patient provided CT treatment information but did not complete a toxicity assessment

CI: confidence interval; CT: chemotherapy; FOxTROT: Fluoropyrimidine, Oxaliplatin and Targeted-Receptor pre-Operative Therapy for patients with high-risk, operable colon cancer; M-H: Mantel Haenszel

Figure 5: Preoperative chemotherapy versus no preoperative chemotherapy – Grade 3 or 4 events; bronchopneumonia, neutropenia, deep vein thrombosis



CI: confidence interval; CT: chemotherapy; FOxTROT: Fluoropyrimidine, Oxaliplatin and Targeted-Receptor pre-Operative Therapy for patients with high-risk, operable colon cancer; M-H: Mantel Haenszel

Appendix F – GRADE tables

GRADE tables for review question: Which people with non-metastatic colon cancer would benefit from preoperative chemotherapy?

Table 5: Clinical evidence profile for comparison preoperative chemotherapy versus no preoperative chemotherapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preop CT	No preop CT	Relative (95% CI)	Absolute	Quality	Importance
Disease-free survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
3-year overall survival, event is death from any cause (propensity score matched for age, gender, race, insurance status, comorbidity score, hospital type, tumour histology, grade, N stage, tumour location, number of nodes examined, margin, and extent of surgery) - T3 patients												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15,999	383	HR 1.15 (0.92 to 1.44)	At 3 years no preop CT[a] 84.5%, preop CT 82.4% (78.5% to 85.6%)	VERY LOW	CRITICAL
3-year overall survival, event is death from any cause (propensity score matched for age, gender, race, insurance status, comorbidity score, hospital type, tumour histology, grade, N stage, tumour location, number of nodes examined, margin, and extent of surgery) – T4a patients												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2,241	48	HR 1.43 (0.85 to 2.41)	At 3 years no preop CT[a] 73.2%, preop CT 64.0% (47.1% to 76.7%	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Preop CT**	**No preop CT**	**Relative (95% CI)**	**Absolute**		
3-year overall survival, event is death from any cause (propensity score matched for age, gender, race, insurance status, comorbidity score, hospital type, tumour histology, grade, N stage, tumour location, number of nodes examined, margin, and extent of surgery) - T4b patients												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2,330	273	HR 0.77 (0.60 to 0.99)	At 3 years no preop CT[a] 69.1%, preop CT 75.2% (69.4% to 80.1%)	VERY LOW	CRITICAL
Positive resection margins, T4b patients (adjusted for age, gender, race, insurance status, comorbidity score, hospital type, tumour histology, grade, N stage, extent of surgery, and tumour location)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2,987	350	OR 0.95 (0.91 to 0.99)	12 fewer per 1000 (from 24 fewer to 4 fewer)	VERY LOW	CRITICAL
Any Grade 3 or 4 adverse events - Grade ≥ 3 toxicity within 6 weeks												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	32/94 (34%)	12/39 (30.8%)	RR 1.11 (0.64 to 1.91)	34 more per 1000 (from 111 fewer to 280 more)	VERY LOW	IMPORTANT
Any Grade 3 or 4 adverse events - Grade ≥ 3 adverse events within 12 weeks												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	14/81 (17.3%)	9/38 (23.7%)	RR 0.73 (0.35 to 1.53)	64 fewer per 1000 (from 154 fewer to 126 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Preop CT**	**No preop CT**	**Relative (95% CI)**	**Absolute**		
Any Grade 3 or 4 adverse events - Grade ≥ 3 adverse events within 18 weeks												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	18/75 (24%)	8/34 (23.5%)	RR 1.02 (0.49 to 2.11)	5 more per 1000 (from 120 fewer to 261 more)	VERY LOW	IMPORTANT
Any Grade 3 or 4 adverse events - Grade ≥ 3 adverse events within 24 weeks												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	47/95 (49.5%)	20/39 (51.3%)	RR 0.96 (0.67 to 1.39)	21 fewer per 1000 (from 169 fewer to 200 more)	VERY LOW	IMPORTANT
Any Grade 3 or 4 adverse events - Wound infection with or without intra-abdominal abscess												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	13/99 (13.1%)	4/51 (7.8%)	RR 1.67 (0.58 to 4.87)	53 more per 1000 (from 33 fewer to 304 more)	VERY LOW	IMPORTANT
Any Grade 3 or 4 adverse events - Bronchopneumonia												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	2/99 (2%)	0/51 (0%)	Peto OR 4.60 (0.24, 86.57)	20 more per 1000 (from 60 fewer to 20 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Preop CT**	**No preop CT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Any Grade 3 or 4 adverse events - Neutropenia												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	1/99 (1%)	0/51 (0%)	Peto OR 4.55 (0.07, 285.04)	10 more per 1000 (from 30 fewer to 50 more)	VERY LOW	IMPORTANT
Any Grade 3 or 4 adverse events – Deep vein thrombosis												
1	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	2/99 (2%)	0/51 (0%)	Peto OR 4.60 (0.24, 86.57)	20 more per 1000 (from 60 fewer to 20 more)	VERY LOW	IMPORTANT
Overall quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Local recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; CT: chemotherapy; HR: hazard ratio; OR: odds ratio; RR: risk ratio

1 Subgroups based on propensity score match at a rate of 80, 70 and 78% respectively for T3, T4a, and T4b patients were used in the analysis (Dehal 2017)

2 Quality of evidence downgraded by 1 because high risk of confounding despite use of propensity score matching and bias in the selection of participants (Dehal 2017)

3 Quality of evidence downgraded by 2 due to lack of allocation concealment and blinding (FOxTROT trial [Agbamu 2012])

4 Quality of evidence downgraded by 1 due to numerous protocol violations in both arms (FOxTROT trial [Agbamu 2012])

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

a The absolute risk at 3 years in the control group taken from Dehal 2017

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: Which people with non-metastatic colon cancer would benefit from preoperative chemotherapy

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 non-metastatic colon cancer would benefit from preoperative chemotherapy

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

1 Appendix I – Economic evidence profiles

2 Economic evidence profiles for review question: Which people with non-meta-
3 static colon cancer would benefit from preoperative chemotherapy?

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

Appendix J – Economic analysis

Economic analysis for review question: Which people with non-metastatic colon cancer would benefit from preoperative chemotherapy?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: Which people with non-metastatic 3 colon cancer would benefit from preoperative chemotherapy?

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

Study	Reason for exclusion
Anonymous, FOxTROT: safety and feasibility of neoadjuvant chemotherapy in locally advanced, resectable colon cancer based on the phase III of a randomised controlled trial, Colorectal disease. Conference: 12th scientific and annual meeting of the european society of coloproctology. Germany, 19, 3, 2017	Waiting for full text of paper to be published in 2019; results from pilot study reported in Agbamu 2012
Arredondo, J., Gonzalez, I., Baixauli, J., Martinez, P., Rodriguez, J., Pastor, C., Ribelles, M. J., Sola, J. J., Hernandez-Lizoain, J. L., Tumor response assessment in locally advanced colon cancer after neoadjuvant chemotherapy, Journal of Gastrointestinal Oncology, 5, 104-111, 2014	Not comparative
Arredondo, J., Martinez, P., Baixauli, J., Pastor, C., Rodriguez, J., Pardo, F., Rotellar, F., Chopitea, A., Hernandez-Lizoain, J. L., Analysis of surgical complications of primary tumor resection after neoadjuvant treatment in stage IV colon cancer, Journal of Gastrointestinal Oncology, 5, 148-153, 2014	Not comparative; population not relevant - all had liver metastases
Arredondo, J., Pastor, C., Baixauli, J., Rodriguez, J., Gonzalez, I., Vigil, C., Chopitea, A., Hernandez-Lizoain, J. L., Preliminary outcome of a treatment strategy based on perioperative chemotherapy and surgery in patients with locally advanced colon cancer, Colorectal Disease, 15, 552-557, 2013	Not comparative
Artac, M., Turhal, N. S., Kocer, M., Karabulut, B., Bozcuk, H., Yalcin, S., Karaagac, M., Gunduz, S., Isik, N., Uygun, K., Do high-risk features support the use of adjuvant chemotherapy in stage II colon cancer? A Turkish Oncology Group study, Tumori, 100, 143-8, 2014	Intervention not relevant - adjuvant chemotherapy vs no adjuvant chemotherapy
Blencowe, N. S., Chana, P., Whistance, R. N., Stevens, D., Wong, N. A. C. S., Falk, S. J., Blazeby, J. M., Outcome reporting in neoadjuvant surgical trials: A systematic review of the literature and proposals for new standards, Journal of the National Cancer InstituteJ Natl Cancer Inst, 106 (9) (no pagination), 2014	Systematic review - studies assessed individually
Chaves, J. A., Neoadjuvant chemotherapy in locally advanced colon cancer -ELECLA trial, Colorectal disease. Conference: 11th scientific and annual meeting of the european society of coloproctology. Italy, 18, 126, 2016	Abstract - trial still in progress
Cukier, M., Smith, A. J., Milot, L., Chu, W., Chung, H., Fenech, D., Herschorn, S., Ko, Y., Rowsell, C., Soliman, H., Ung, Y. C., Wong, C. S., Neoadjuvant chemoradiotherapy and multivisceral resection for primary locally advanced adherent colon cancer: A single institution experience, European Journal of Surgical Oncology, 38, 677-682, 2012	Not comparative

Study	Reason for exclusion
Dehal, A., Graff-Baker, A. N., Vuong, B., Fischer, T., Klempner, S. J., Chang, S. C., Grunkemeier, G. L., Bilchik, A. J., Goldfarb, M., Neoadjuvant Chemotherapy Improves Survival in Patients with Clinical T4b Colon Cancer, Journal of Gastrointestinal Surgery, 22, 242-249, 2018	Conference abstract, full text not available
Deng, Y., Zhang, J., Cai, Y., Hu, H., Ling, J., Xiao, J., Huang, M., Kang, L., Wang, L., Lan, P., Wang, J., Neoadjuvant chemotherapy alone with mFOLFOXIRI in locally advanced rectal cancer: A single-arm phase II study, Journal of Clinical Oncology. Conference, 34, 2016	Abstract - trial still in progress
Engstrom, P. F., Arnoletti, J. P., Benson, Iii A. B., Chen, Y. J., Choti, M. A., Cooper, H. S., Covey, A., Dilawari, R. A., Early, D. S., Enzinger, P. C., Fakih, M. G., Fleshman Jr, J., Fuchs, C., Grem, J. L., Kiel, K., Knol, J. A., Leong, L. A., Lin, E., Mulcahy, M. F., Rao, S., Ryan, D. P., Saltz, L., Shibata, D., Skibber, J. M., Sofocleous, C., Thomas, J., Venook, A. P., Willett, C., Colon cancer, JNCCN Journal of the National Comprehensive Cancer Network, 7, 778-831, 2009	Clinical practice guideline
Gray, R. G., Morton, D., Brown, G., Ferry, D. R., Magill, L., Quirke, P., Seymour, M. T., Warren, B., FOxTROT: Randomized phase II study of neoadjuvant chemotherapy with or without an anti-EGFR monoclonal antibody for locally advanced, operable colon cancer, Journal of Clinical Oncology. Conference, 28, 2010	Abstract
Hansen, T. F., Kjaer-Frifeldt, S., Lindebjerg, J., Rafaelsen, S. R., Jensen, L. H., Jakobsen, A., Sorensen, F. B., Tumor-stroma ratio predicts recurrence in patients with colon cancer treated with neoadjuvant chemotherapy, Acta Oncologica, 57, 528-533, 2018	Not comparative
Jakobsen, A., Andersen, F., Fischer, A., Jensen, L. H., Jorgensen, J. C. R., Larsen, O., Lindebjerg, J., Ploen, J., Rafaelsen, S. R., Vilandt, J., Neoadjuvant chemotherapy in locally advanced colon cancer. A phase II trial, Acta Oncologica, 54, 1747-1753, 2015	Not comparative
Karoui, M., Rullier, A., Luciani, A., Bonnetain, F., Auriault, M. L., Sarran, A., Monges, G., Trillaud, H., Le Malicot, K., Leroy, K., et al.,, Neoadjuvant FOLFOX 4 versus FOLFOX 4 with Cetuximab versus immediate surgery for high-risk stage II and III colon cancers: a multicentre randomised controlled phase II trial - the PRODIGE 22 - ECKINOXE trial, BMC Cancer, 15, 2015	Abstract - expected study completion date February 2021
Karoui, M., Rullier, A., Luciani, A., Bonnetain, F., Auriault, M. L., Sarran, A., Monges, G., Trillaud, H., Le Malicot, K., Leroy, K., Sobhani, I., Bardier, A., Moreau, M., Brindel, I., Seitz, J. F., Taieb, J., Neoadjuvant FOLFOX 4 versus FOLFOX 4 with Cetuximab versus immediate surgery for high-risk stage II and III colon cancers: a multicentre randomised controlled phase II trial--the PRODIGE 22--ECKINOXE trial, BMC Cancer, 15, 511, 2015	Abstract - expected study completion date February 2021

Study	Reason for exclusion
Karoui, M., Rullier, A., Mariette, C., Maillard, E., Bardier, A., Poizat, F., Luciani, A., Sarran, A., Legoux, J. L., De Chaisemartin, C., et al.,, Neoadjuvant FOLFOX 4 versus FOLFOX 4 plus cetuximab versus immediate surgery for high-risk stage II and III colon cancers: a phase II multicentre randomised controlled trial (PRODIGE 22), Annals of oncology. Conference: 42nd ESMO congress, ESMO 2017. Spain, 28, v159, 2017	Abstract - estimated study completion date February 2021
Nct,, Neoadjuvant Chemotherapy Verse Surgery Alone After Stent Placement for Obstructive Colonic Cancer, Https://clinicaltrials.gov/show/nct02972541, 2016	Clinical trial entry
Nct,, Neoadjuvant FOLFOX Chemotherapy for Patients With Locally Advanced Colon Cancer, Https://clinicaltrials.gov/show/nct03426904, 2018	Clinical trial entry
Nct,, Fluorouracil and Oxaliplatin With or Without Panitumumab In Treating Patients With High-Risk Colon Cancer That Can Be Removed by Surgery, Https://clinicaltrials.gov/show/nct00647530, 2008	Clinical trial entry
Nct,, Perioperative Versus Postoperative CapOX Chemotherapy for Locally Advanced Colon Cancer, Https://clinicaltrials.gov/show/nct03125980, 2017	Clinical trial entry
Nct,, Neoadjuvant Chemotherapy for the Treatment of Resectable Locally Advanced Colon Cancer, Https://clinicaltrials.gov/show/nct02882269, 2016	Clinical trial entry
Nct,, Neoadjuvant Chemotherapy Versus Standard Treatment in Patients With Locally Advanced Colon Cancer, Https://clinicaltrials.gov/show/nct01918527, 2013	Clinical trial entry
Park, S., Park, J., Kim, H., Choi, G., Pilot study of neoadjuvant chemotherapy with three cycles of capox for treatment of locally advanced colon cancer, Diseases of the colon and rectum. Conference: 2018 american society of colon and rectal surgeons annual meeting, ASCRS 2018. United states, 61, e279, 2018	Abstract - full text unavailable
Sekiya, S., Imamura, K., Takeuchi, S., Teramura, K., Watanabe, Y., Tamoto, E., Takada, M., Kinoshita, Y., Anbo, Y., Nakamura, F., Kashimura, N., Noguchi, H., Miura, K., Hirano, S., Pathological complete response of locally advanced colon cancer after preoperative radiotherapy: a case report and narrative review of the literature, Surgical Case Reports, 4, 58, 2018	Case study and narrative review
Tresallet, C., Benoist, S., Nordlinger, B., Adjuvant and neoadjuvant treatment in resectable and non-resectable metastatic colon cancer, European Journal of Cancer, Supplement, 3, 275-281, 2005	Patients had metastatic disease
Trojan, J., Lubomierski, N., Lehnert, T., Engels, K., Zeuzem, S., Bechstein, W. O., Neoadjuvant treatment with cetuximab, 5-Fluorouracil, folinic Acid and oxaliplatin in unresectable retroperitoneal recurrent colon cancer, Zeitschrift fur Gastroenterologie, 46, 776-9, 2008	Full text in German; case report

Study	Reason for exclusion
Zhou, Z., Nimeiri, H. S., Benson, A. B., 3rd, Pre-operative chemotherapy for locally advanced re-sectable colon cancer - a new treatment paradigm in colon cancer?, Annals of Translational Medicine, 1, 11, 2013	Narrative review

1

Appendix L – Research recommendations

Research recommendations for review question: Which people with non-metastatic colon cancer would benefit from preoperative chemotherapy?

No research recommendations were made for this review question.

1 Appendix M – Expert evidence

2 Expert evidence for review question: Which people with non-metastatic colon 3 cancer would benefit from preoperative chemotherapy?

4 **Table 7: Expert evidence: Preliminary findings from the FOxTROT trial**

Section A: Developer to complete	
Name:	Dion Morton
Role:	Principal Investigator (FOxTROT trial)/Consultant Colorectal Surgeon
Institution/Organisation (where applicable):	University of Birmingham
Contact information:	dion.morton@uhb.nhs.uk
Personal assistant:	Martha Holmes M.Holmes@bham.ac.uk
Guideline title:	Colorectal cancer
Guideline Committee:	Colorectal cancer
Subject of expert testimony:	Preliminary findings from the FOxTROT trial (Fluoropyrimidine, Oxaliplatin and Targeted-Receptor pre-Operative Therapy for patients with high-risk, operable colon cancer)
Evidence gaps or uncertainties:	The guideline committee is reviewing the evidence for the review question "Which people with non-metastatic colon cancer would benefit from preoperative chemotherapy?" The published evidence base is weak and relies on one retrospective study and the pilot phase of the FOxTROT trial. The FOxTROT trial is an international, mainly UK-based phase III randomised trial that investigates the efficacy of neoadjuvant chemotherapy in colon cancer and is the only trial in the topic to date. However, the findings of the trial have not yet been published and the timeline of the guideline does not allow us to wait for the results to be published later this year. Therefore, the guideline committee has invited Professor Dion Morton, the principal investigator of the FOxTROT trial, to present the preliminary findings of the trial to the guideline committee and to answer questions the committee may have.

Section B: Expert to complete

Summary testimony:

This is a summary of the FOxTROT data after completion of the trial and cleaning of the data. The final figures are however being checked and so may be subject to minor changes.

A total of 1052 patients with radiologically-staged T3-4 N0-2 M0 colon cancer, from 88 hospitals in 3 countries, were randomised 2:1 between preoperative-and-postoperative (neoadjuvant), or standard postoperative (control) adjuvant oxaliplatin and fluoropyrimidine (OxFp) combination chemotherapy. Total planned chemotherapy duration was the same in both arms, but patients allocated to pre-and-postop received the first 6 weeks ahead of surgery. In an optional substudy, patients with *RAS*-wild type tumours could also be randomised 1:1 to preoperative-and-postoperative chemotherapy +/- panitumumab, 6 mg/kg 2-weekly for 3 doses alongside preoperative FOLFOX chemotherapy. In patients not being randomised for panitumumab, a 'dealer's choice' alternative of 3-weekly CAPOX was permitted. Treatment allocation was minimised by age, T and N-stage, primary tumour location, chemotherapy regimen and need for defunctioning stoma. The primary endpoint was persistent disease or recurrence within 2 years. Prespecified secondary endpoints included safety, toxicity, and pathological stage at surgery. Comparisons were by intention-to-treat. This trial is registered with the International Clinical Trial Registry (ISRCTN 87163246).

This summary will only deal with the primary randomisation to neoadjuvant treatment as data analysis for the panitumumab is not yet completed.

Findings: Of 698 patients allocated preoperative chemotherapy, 673 (97%) started and 605 (90%) completed 6 weeks of preoperative chemotherapy; most non-compliance was due to patients electing for surgery first.

98.0% (684/698) of those allocated preoperative-and-postoperative chemotherapy and 99.2% (351/354) of those allocated postoperative chemotherapy had tumour resections. 12 withdrew from the trial before surgery (11 from the preoperative-and-postoperative, 1 from the control arm) and 4 died prior to surgery (3 allocated preoperative-and-postoperative and 1 control.

Twenty of 698 (3%) preoperative-and-postoperative and 3/354 (1%) control patients developed abdominal pain/obstructive symptoms requiring expedited surgery (p=0.03). Perioperative morbidity was generally lower in those allocated preoperative-and-postoperative chemotherapy compared with control: anastomotic leak/intra-abdominal abscess [4.7% (32/682) versus 7.1% (26/350), p=0.07], need for reoperation [4.3% (29) versus 6.7% (25), p=0.05] and complications prolonging hospital stay [12% (79) vs 14% (50), p=0.21]; 30-day postoperative mortality was similar 0.4% (3) vs 0.3% (1). The stoma formation rate was 12% (79/673) vs 9% (31/244), p=0.18.

The pathological stage of resected tumours was significantly lower in patients receiving neoadjuvant therapy, both for T-stage (p<0.0001) and N-stage (p<0.0001). In intention-to-treat (ITT) analysis, 3.5% (24/682) preoperative (and no postoperative) patients had pCR, a further 28 (4.1%) had near-complete (Mandard TRG2), and 12.3% (84) moderate histological regression. Among resected patients, the R1/R2 resection rate was reduced [4.6% (31/682) vs 10.1% (35/347), p<0.001], and fewer patients had Dukes' stage C2/D: 5.0% (34) versus 8.1% (28), p<0.05.

26% (90/352) of patients allocated postoperative chemotherapy did not receive any chemotherapy. Although 16% (56) had low-risk pathology, 34 (10%) declined or were unfit for postoperative chemotherapy, a substantially higher non-compliance rate than the 4% rate of non-compliance with preoperative chemotherapy group.

Disease recurrence at 2 years – the primary outcome - was less frequent after pre-operative-and-postoperative chemotherapy (95/698 versus 61/354: hazard ratio (HR) =0.74 (95% CI 0.53 to 1.04); 2p=0.08), although this difference was of only borderline statistical significance.

In an exploratory blinded subgroup analysis, preoperative-and-postoperative chemo-therapy appeared substantially less effective for most mismatch-repair deficient (dMMR) tumours. Although 5 complete responses were seen in 106 dMMR tumours, 74% (78/106) of dMMR compared to just 27% (154/462) of MMR-proficient tumours were classified as no tumour regression. In the subgroup of patients with pMMR tu-mours the reduction in the 2-year recurrence rate was somewhat larger than in the overall population [HR 0.69 [0.47-1.00), p=0.05, which may be a chance subgroup finding. Nonetheless, the low response rate in dMMR tumours suggests that OxFp chemotherapy (whether neoadjuvant or adjuvant) is not indicated for such tumours, which comprise 17% of this population.

Interpretation:

Six weeks of preoperative OxFp chemotherapy for radiologically-staged, locally ad-vanced operable primary colon cancer:

1. Can be safely and effectively delivered to an appropriate high risk population
2. Has acceptable toxicity and does not increase perioperative morbidity.
    a. This is associated with evidence of improved surgical outcomes, with a significant reduction in incomplete tumour resection.
3. Is associated with a substantial down-staging and tumour regression (in a blinded histological analysis), demonstrable in both the primary tumour and in lymph node metastases.
4. Fewer patients had persistent disease or recurrence within 2 years [HR 0.74 (95% CI 0.53-1.04), p=0.08] but this did not reach statistical significance.
    a. An exploratory analysis suggested this benefit may be somewhat larger in MMR proficient than MMR deficient tumours, which appear not to benefit from chemotherapy.

Recommendations:
These results show that this treatment regimen (6 weeks of combination OxFP chem-otherapy) can be considered in the treatment of patients with radiological evidence of locally advanced disease and should be considered for any patients in whom the re-section margin may be compromised.

The trial has also shown that some 50% of patients have no apparent response to 3 cycles of combination chemotherapy. The clinical assumption is that these are less (not) chemo-responsive (survival analysis will follow). The benefits of neoadjuvant therapy could potentially be enhanced by identifying a more responsive subpopulation (and enabling alternative therapies for the unresponsive population).

Molecular stratification for DNA mismatch repair (MMR) deficiency (an exploratory analysis) has shown no tumour regression following preoperative chemotherapy in 74% of dMMR patients, whereas only 27% of MMR proficient tumours had no re-sponse. This finding indicates that dMMR tumours should not receive preoperative oxaliplatin and 5FU as only ~1 in 28 (as compared to ~1 in 4 MMR-proficient tumours) will show substantial tumour regression. dMMR tumours made up 17% of this colon cancer population.

Future studies should explore the use of neoadjuvant therapy in the older or frail population, many of whom are currently excluded from treatment. The escalation of neoadjuvant therapy should also be explored, ideally in combination with predictive (molecular) biomarkers such as tumour MMR status.
References to other work or publications to support your testimony' (if applicable):
Agbamu D, Day N, Walsh C, et al. (2012) Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: The pilot phase of a randomised controlled trial. Lancet Oncology 13(11): 1152-1160 Seymour M, Dion Morton D, and on behalf of the International FOxTROT Trial Investigators. FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer. Journal of Clinical Oncology 2019 37:15_suppl, 3504-3504

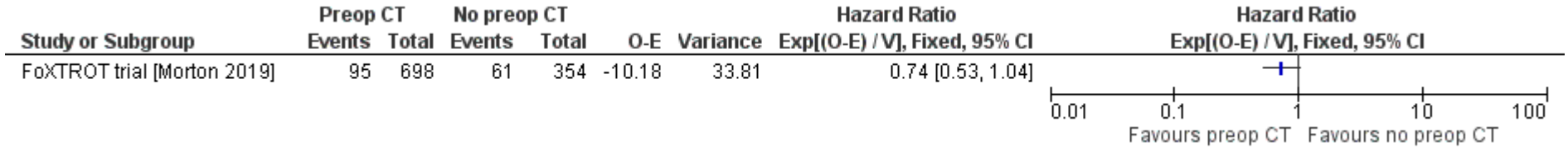
CI: confidence interval; dMMR: mismatch-repair deficient; DNA: deoxyribosenucleic acid; FOxTROT: Fluoropyrimidine, Oxaliplatin and Targeted-Receptor pre-Operative Therapy for patients with high-risk, operable colon cancer; HR: hazard ratio; ISCTRN: International Standard Randomised Controlled Trial Number; ITT: intention-to-treat; KRAS: Kirsten rat sarcoma; MMR –ve/+ve: mismatch repair negative/positive; N: nodal status; OxFP: oxaliplatin and fluoropyrimidine; pCR: pathologic complete response; R1: cancer cells present microscopically at the resection margin (microscopic positive margin); R2: gross examination by the naked eye shows tumour tissue present at the resection margin (macroscopic positive margin); T: tumour grade; TRG: tumour regression grading

Table 8: Gaps addressed and recommendations supported by expert evidence

Expert testimony	Gaps addressed	Recommendations supported
• Preliminary findings from the FOxTROT trial	• The published evidence base is weak and relies on one retrospective study and the pilot phase of the FOxTROT trial. The FOxTROT trial is a UK Phase III randomised trial that investigates the efficacy of neoadjuvant chemotherapy in colon cancer and is the only trial in the topic to date. However, the timeline of the guideline does not allow us to wait for the full results to be published later this year.	• 1.3.13

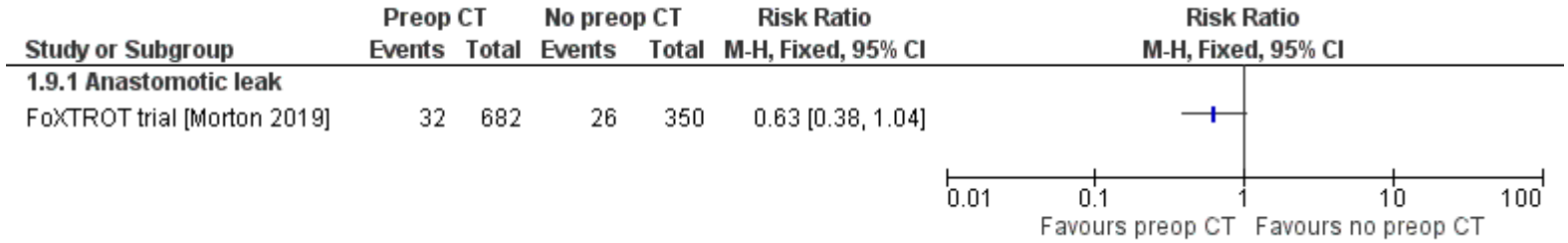
FOxTROT: Fluoropyrimidine, Oxaliplatin and Targeted-Receptor pre-Operative Therapy for patients with high-risk, operable colon cancer

Figure 6: Forest plot: Preoperative chemotherapy versus no preoperative chemotherapy - Disease-free survival



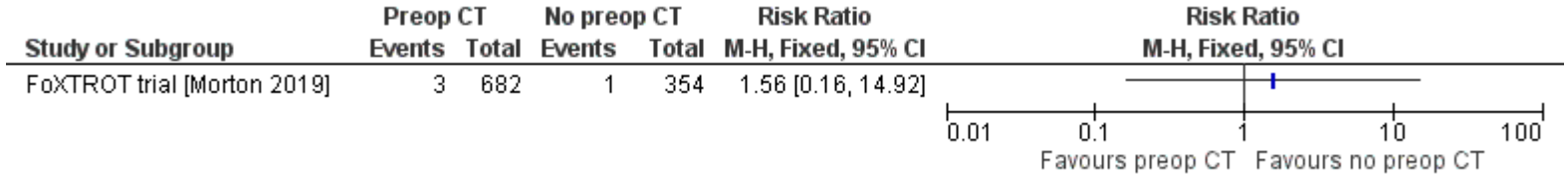
CI: confidence interval; CT: chemotherapy; E: expected; M-H: Mantel-Haenszel; O: observed; Preop: preoperative; V: variance

Figure 7: Forest plot: Preoperative chemotherapy versus no preoperative chemotherapy - Grade 3 or 4 adverse events: anastomotic leak



CI: confidence interval; CT: chemotherapy; DVT: deep vein thrombosis; M-H: Mantel-Haenszel; Preop: preoperative

Figure 8: Forest plot: Preoperative chemotherapy versus no preoperative chemotherapy - Treatment-related mortality



CI: confidence interval; CT: chemotherapy; M-H: Mantel-Haenszel; Preop: preoperative;

Table 9: Quality assessment of expert evidence

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preop CT	No preop CT	Relative (95% CI)	Absolute	Quality	Importance
Disease-free survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	95/698 (13.6%)	61/354 (17.2%)	HR 0.74 (0.53, 1.04)	42 fewer per 1000 (from 77 fewer to 6 more)	MODERATE	CRITICAL
Overall survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Positive resection margins, T4b patients												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Any Grade 3 or 4 adverse events												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Any Grade 3 or 4 adverse events - Anastomotic leak												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32/682 (4.7%)	26/350 (7.4%)	RR 0.63 (0.38, 1.04)	27 fewer pre 1000 (from 68 fewer to 136 more)	MODERATE	IMPORTANT
Any Grade 3 or 4 adverse events - Wound infection												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Any Grade 3 or 4 adverse events – Bronchopneumonia												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Any Grade 3 or 4 adverse events – Pulmonary embolism ± deep vein thrombosis												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Preop CT**	**No preop CT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Treatment-related mortality (postoperative death rate)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	3/682 (0.4%)	1/350 (0.3%)	RR 1.52 [0.16, 14.57]	1 more per 1000 (from 2 fewer to 387 more)	MODERATE	IMPORTANT
Local recurrence												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; CT: chemotherapy; HR: hazard ratio; OR: odds ratio; RR: risk ratio
1 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (< 300 events for dichotomous outcomes or < 400 patients for continuous outcomes).