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A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Use of Leucovorin in Colorectal Cancer

J.J. Biagi, N. Coakley, C. Earle, C. Erlichman, and A. Fields

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Report Date: February 8, 2016

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Evidence Summary #12-17

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The Use of Leucovorin in Colorectal Cancer

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OBJECTIVES AND RESEARCH QUESTIONS

The objective of this evidence summary was to examine evidence regarding outcomes associated with different doses of leucovorin (LV) for the treatment of colorectal cancer (CRC) patients.

This expert panel considered the following research question:

- What is the effect of altering the dose of LV for patients with CRC in terms of overall survival, progression-free survival (PFS), disease-free survival, response rate, and adverse events/toxicity, given a constant dose of 5-fluorouracil (5-FU)?

TARGET POPULATION

Patients with CRC, any stage, and treatment in the adjuvant or advanced setting, as part of a trial that compares different doses of LV in combination with 5-FU chemotherapy.

INTENDED USERS

1. Clinicians and pharmacists involved in the prescription and preparation of LV with 5-FU chemotherapy.
2. Cancer Care Ontario (CCO) Systemic Treatment Program

INTRODUCTION

In June 2015, CCO convened an expert panel to determine whether there is an optimum LV dose in 5-FU/LV dosing combinations for the treatment of CRC. This request arose out of recognition that there was variation in LV dosages across some cancer centres within the province. In Canada, it is estimated that there will be 27,000 new cases of CRC in 2015 (1). In Ontario, it is estimated that in 2015 there will be 9200 cases with 3350 deaths (2).

LV calcium (also known as folinic acid) is a reduced form of folic acid. As an adjunct in CRC regimens combining LV and 5-FU, it enhances the activity of 5-FU by binding to and stabilizing the 5-FU-thymidylate synthase enzyme complex. The active moiety is the levo-stereoisomer, but it is commercially available in Canada as a racemic mixture of D/L enantiomers. Reference to doses of LV in this Evidence Summary relates to the racemic mixture, which is double the dose of l-LV.

There are two approaches to 5-FU/LV delivery, commonly termed bolus and infusional. The development research of LV was in the context of bolus 5-FU delivery. Bolus regimens

include Mayo and Roswell Park, while the infusional regimen is based on the de Gramont backbone, which has largely replaced bolus regimens for both the adjuvant and advanced settings. The modern infusional regimens include a bolus component; preceded by LV infusion; the role of a LV dose without the bolus component is unknown.

The CCO formulary (3) recommends the following dose of LV combined with 5-FU:

- Every four weeks (bolus regimen: 20 mg/m^2 intravenous (IV) × five days (bolus)
- Every two weeks (as infusional): 400 mg/m^2 on day 1 (as infusional)

When this expert panel was first convened, a preliminary guideline search of the national and international guideline developers was undertaken. The results of this search can be seen in Appendix A. Only the National Comprehensive Cancer Network (NCCN), the Spanish consensus guideline, the National Health and Medical Research Council of Australia and BC Cancer Agency recommended dosages with the recommendations in their guidelines.

- The NCCN guidelines for rectal and colon cancer recommended 400 mg/m^2 of LV as part of the infusional FOLFIRI[8] and FOLFOX[6] regimens (4, 5).
- The Medical Research Council of Australia recommends the bolus Mayo regimen of 5-FU 425 mg/m^2 plus LV 20 mg/m^2 and the bolus Roswell Park regimen of 5-FU 500 to 600 mg/m^2 plus LV 500 mg/m^2 (6).
- The BC Cancer Agency recommends the following doses of LV: If the cycle is one to four weeks, the bolus regimen is 20 mg/m^2 IV for one dose on days 1 to 5 (total dose per cycle [range 20 to 100 mg/m^2]). If the cycle is two weeks, i.e, the infusional, then: 400 mg/m^2 IV for one dose on day 1 (total dose per cycle 400 mg/m^2) (7).
- The Spanish consensus guidelines recommended the Roswell Park or National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Mayo or North Central Cancer Treatment Group (NCCTG) regimen (8).

The National Institute for Health and Care Excellence (NICE) guideline did not recommend any dosages in their recommendations. However, the economic analysis included the dosages of the regimens. The list of trials that were part of the guideline and their included dosages are included as part of the table (9).

The guidelines from NCCN comment on the recent LV shortage in the United States. They state that one of the possible options to address a shortage is to lower the dose of LV, although it is not an empiric recommendation. They note that three studies have shown that lowering the dose of LV does not influence survival and recurrence (4, 5, 10-12), but all three studies used bolus regimens.

The National Health and Medical Research Council (NHMRC) guidelines from Australia state that the optimal dose of LV is unclear. Randomized studies have looked at low- versus high-dose LV with the Mayo regimen of 5-FU and are the subject of this current review (6).

METHODS

This evidence summary was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews are identified that address the research questions and are of reasonable quality, then those systematic reviews would form the core of the evidence review.

2. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

The Program in Evidence-Based Care (PEBC) is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC and any associated Programs is editorially independent from the Ministry.

Search for Systematic Reviews

A search was conducted for existing systematic reviews. Systematic reviews published as a component of practice guidelines were also considered eligible for inclusion. The methods for locating and evaluation existing systematic reviews are described below:

- Databases searched (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews)
- 1980–June 30, 2015
- LV and CRC
- Any systematic reviews examining different doses of LV and a fixed dose of 5-FU were suitable for inclusion

Identified systematic reviews were further evaluated based on their clinical content and the similarity of the questions they addressed to the questions and objectives of this guideline. Systematic reviews that were found to be directly relevant to this guideline and, therefore, potential foundations for this evidence review, were assessed using the AMSTAR tool (13). The results of the assessments were used to determine whether an existing systematic review could be incorporated.

Any identified reviews that did not meet the criteria above, whose AMSTAR assessments indicated important deficiencies in quality, or that were otherwise not incorporated as part of the evidence base were reported in the reference list, but not further described or discussed.

Search for Primary Literature

If no systematic reviews are found for inclusion, the methods for locating and evaluating primary literature are listed below.

Literature Search Strategy

A search was conducted of the primary literature. The methods for locating and evaluation existing primary literature are described below:

- Databases searched (MEDLINE, Embase, Cochrane Database of Systematic Reviews)
- 1980–June 30, 2015
- LV and CRC
- Any comparative studies examining different doses of LV and a fixed dose of 5-FU were suitable for inclusion

See Appendix B for the full search strategies.

Study Selection Criteria and Protocol

Inclusion Criteria

- Patients with CRC
- Comparative studies

- A fixed dose of 5-FU and varying doses of LV

Exclusion Criteria

- Studies with <30 participants
- Single-arm studies

A review of the titles and abstracts that resulted from the search was performed by four reviewers collaboratively (NC, RC, EK, and HM). For those items that warranted full-text review, one reviewer (NC) reviewed each item independently.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was performed independently by NC. Ratios, including hazard ratios (HRs), were expressed with a ratio <1.0 indicating that the events in the intervention group are significantly less frequent than in the control group. All extracted data and information were audited by an independent auditor. Important quality features, such as type of study, phase, concealment, stratification, funding, and power reported for each study were extracted by NC.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis would be conducted using the Review Manager (RevMan) software (14), available from the Cochrane Collaboration. For time-to-event outcomes, HRs, rather than the number of events at a certain time point, would be the preferred statistic for meta-analysis, and would be used as reported. If the HR and/or its standard error were not reported, they would be derived from other information reported in the study, if possible, using the methods described by Parmar et al (15). For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in RevMan would be used. Statistical heterogeneity would be calculated using the x^2 test for heterogeneity and the I^2 percentage. A probability level for the x^2 statistic ≤10% ($p \leq 0.10$) and/or an I^2 >50% would be considered indicative of statistical heterogeneity.

RESULTS

Search for Existing Systematic Reviews

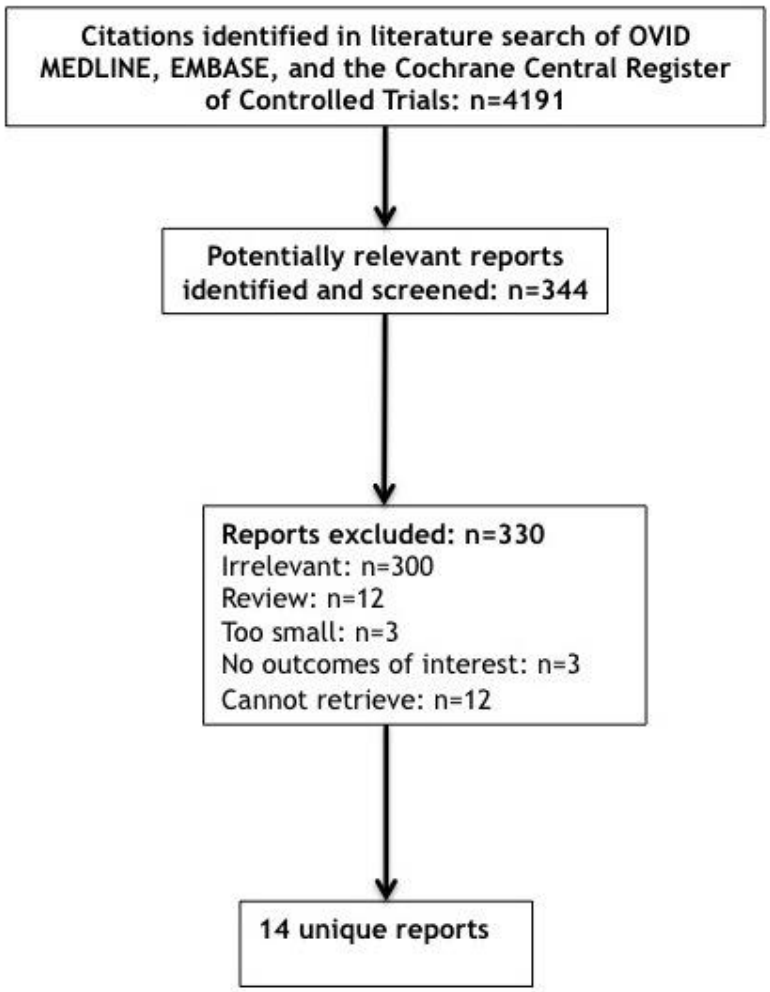
No systematic reviews were found that met our inclusion criteria.

Primary Literature Systematic Review

Literature Search Results

Articles were selected for consideration in this evidence review if they were published reports of randomized controlled trials (RCTs). A total of 4191 English and foreign-language studies were identified. The literature flow diagram can be seen in Figure 1.

Figure1: Literature search flow diagram.



Three hundred forty-four reports were identified for full-text review; of those, 331 were excluded. Fourteen reports met the inclusion criteria. However, two of those reports were published in Japanese and since we do not have translation capabilities they were excluded in the report (16, 17), resulting in a total of 12 reports. The final reports are listed in Table 1 below.

Table 1. Studies selected for inclusion.

Reference	Study type	Inclusion criteria	Treatment
Quasar collaborative group (10) – Lancet 2000	2×2 factorial design double-blind RCT	Complete resection with no evidence of distant metastases	All patients received 370 mg/m^2 FU, either high- (175 mg) or low-dose (25 mg) L-folinic acid AND either levamisole or placebo N=4927 patients 2464 to high-dose LV 2463 to low-dose LV

Reference	Study type	Inclusion criteria	Treatment
			2429 to levamisole 2434 to placebo L-Folinic acid Order of doses or type was not mentioned.
Jäger (11) 1996	RCT	CRC with progressive disease No radiotherapy or chemotherapy within 8 weeks before treatment onset Minimal Karnofsky PS status 50%	FU 500 mg/m^2 as weekly bolus + LV 500 mg/m^2, N=148 FU 500 mg/m^2 as weekly bolus + LV 20 mg/m^2, N=143 FU was administered as bolus injection 1 hour after LV
Labianca (18) 1997 A GISCAD phase 3 study	RCT	Advanced CRC No previous chemotherapy for advanced disease ECOG PS 0-2	6S-LV 100 mg/m^2 IV (n=216) or 10 mg/m^2 (n=206) 370 mg/m^2 5-FU given as 15 min infusion for both. Drugs given for 5 consecutive days, every 4 weeks
O'Connell (12) 1989	RCT	Metastatic CRC	5-FU alone rapid IV bolus 500 mg/m^2 for 5 consecutive days × 5 weeks, N=70 LV 200 mg/m^2 followed by 5-FU 370 mg/m^2 by rapid IV injection daily for 5 days repeated at 4 and 8 weeks and every 5 weeks after that, N=68 LV 20 mg/m^2 followed by 5-FU 370 mg/m^2 by rapid IV injection daily for 5 days repeated at 4 and 8 weeks and every 5 weeks after that, N=70 After the first 100 patients, the dose of 5-FU was increased to 425 mg/m^2 in the low-dose LV group after the toxicity was analyzed.
Petrelli (19) 1989	RCT (responses were blinded)	Metastatic or recurrent CRC ECOG 0-2 No previous chemotherapy or radiotherapy	5-FU alone with initial bolus of 500 mg/m^2, N=113 5-FU IV bolus of 600 mg/m^2 1 hour after initiation of 2-hour infusion of 500 mg/m^2 of LV diluted in 250 mL of saline. 6 weekly treatments followed by 2 weeks or rest, N=115 5-FU IV bolus of 600 mg/m^2 1 hour after initiation of 10 min infusion of 25 mg/m^2 of LV, N=115
Poon (20) 1989	RCT	Unresectable or metastatic CRC ECOG 0-3 Only results for high versus low dose of LV will be discussed and presented.	LV 200 mg/m^2 immediately followed by 370 mg/m^2. Both drugs given by rapid injection for 5 consecutive days, repeated at 4, 8 and every 5 weeks, N=69 LV 20 mg/m^2 immediately followed by 370 mg/m^2. Both drugs given by rapid injection for 5 consecutive days, repeated at 4, 8 and every 5 weeks, N=73

Reference	Study type	Inclusion criteria	Treatment
			5-FU alone, N=70 5 FU plus cisplatin, N=73 5-FU + high-dose methotrexate with LV rescue, N=72 5-FU + low-dose methotrexate with LV rescue, N=72
Tsavaris 2002 (21)	RCT	Measurable disease Karnofsky PS of ≥60 Life expectancy of >2 months	50 mg/m^2 as 2-hour IV infusion + 5-FU 500 mg/m^2 as an IV bolus at mid-time of LV infusion. Repeated weekly, N=50 100 mg/m^2 as 2-hour IV infusion + 5-FU 500 mg/m^2 as an IV bolus at mid-time of LV infusion. Repeated weekly, N=50 Type of LV not mentioned but study from Greece.
Ychou (22) 1998	RCT	Unresectable metastatic CRC No prior chemotherapy ECOG PS 0-2	LV 200mg/m^2 was give in a 15 min infusion before 400 mg/m^2 of 5-FU in a 1 hour infusion for 5 days, with courses repeated every 4 weeks N=41 LV 20mg/m^2 was give in a 15 min infusion before 400 mg/m^2 of 5-FU in a 1 hour infusion for 5 days, with courses repeated every 4 weeks N= 42
Budai (23) 2013	Retrospective observational study	CRC with 1 radiologically measurable lesion ECOG PS 0-2	mFOLFIRI Irinotecan 180 mg/m^2, d,l-LV 400 mg/m^2, then 5-FU 400 mg/m^2 bolus then 2400 mg/m^2 5-FU over 46 hours, N=128 Same as above but with 200 mg/m^2 LV, N=104 Bevacizumab 5 mg/kg + above regimen with d,l-LV 400 mg/m^2, N=89 Bevacizumab 5 mg/kg + above regimen with d,l-LV 200 mg/m^2, N=129
Reynolds (24) 2014 ASCO abstract	Retrospective	Metastatic CRC Consecutive patients that received one cycle of FOLFOX 6 with or without bevacizumab	Modified FOLFOX6 (with or without bevacizumab) + LV 400 mg/m^2, N=71 Modified FOLFOX6 (with or without bevacizumab) + LV 20 mg/m^2, N=58
Carlsson (25) 1990	No mention of how patients were allocated	Symptomatic non-curable CRC	50 mg/m^2 LV, 500 mg/m^2 5-FU, N=41 200 mg/m^2 LV and 500 mg/m^2 5-FU, N=9 Dose of 5-FU was 600 mg/m^2 to start and then reduced to 500 mg/m^2 because of toxicities Patients were treated either once weekly or 2

Reference	Study type	Inclusion criteria	Treatment
			consecutive days, every other week. IV bolus of 5-FU followed 30-40 min later by LV IV bolus injection
Poorter (26) 1995	Study type not stated N=20 metastatic CRC N=10 other gastrointestinal cancer	Progressive measurable disease No previous chemotherapy	Continuous dose of 300 mg/m^2 a day of 5-FU for 14 days LV was administered at a dose of 5 mg/day in the first 6 patients and then escalated by 5 mg/day in every subsequent group of 6 patients until toxicity
Abbreviations: ASCO = American Society of Clinical Oncology; CRC = colorectal cancer; ECOG = Eastern Cooperative Oncology Group; FU = fluorouracil; IV = intravenous; LV = Leucovorin; PS = performance status; RCT = randomized controlled trial			

Study Design and Quality

Eight randomized trials were found that met the inclusion criteria for this review (10-12, 18-22). Two retrospective studies and two other comparative studies were included as well. The study by the Quasar group was double blind (10) and the study by Petrelli (19) had blinded outcome assessors. The studies selected for inclusion can be seen in Table 1. A quality table for the studies can be seen in Appendix C. Many of the studies are older and the reporting or results was not as standard as it is today. Therefore, study methods are often missing and many p values are missing in the tables.

Outcomes

Outcomes of interest were: response rate, PFS, overall survival, and toxicities. A meta-analysis was not appropriate for any of the outcomes since the studies were too heterogeneous.

Response Rate

The response rate was assessed in 10 studies (11, 12, 18-23, 25, 26) and can be seen in Table 2. The overall response rate (complete response plus partial response) was described in nine of the 10 studies. None of the studies showed statistical significance between the two – lower dose and higher dose – arms, although four studies showed a higher not significant response rate with the higher dose of LV (11, 20, 22, 23).

The retrospective study by Budai et al. had four arms. Patients were given (mFOLFIRI) irinotecan, 5-FU, and either 200 mg or 400 mg of LV and the same was repeated with the addition of bevacizumab. The response rate was significant in patients who received bevacizumab plus mFOLFIRI and had the higher dose of LV (p=0.00015). The response rate in the low-dose LV group in patients who did not receive any bevacizumab did not reach significance (p=0.41) (23). The study by Poorter was difficult to interpret because it did not provide results by dose but by type of cancer instead (26). The RCT by Petrelli measured response by a reduction in 50% in sums of the cross-products of the maximum perpendicular tumour measurement. The results were not significant between doses (p=0.46) (19). Overall, the response rate was very similar between the high- and low-dose groups.

Table 2: Response rate.

Reference	Interventions	Response rate		
Jäger (11) 1996 RCT	FU 500 mg/m^2 + LV 500 mg/m^2, N=148 FU 500 mg/m^2 + LV 20 mg/m^2, N=143		500 mg/m^2 of LV (%)	20 mg/m^2 of LV (%)
		CR+ PR	32	25 (18)

Reference	Interventions	Response rate
		(22) | | No change | 64 (43) | 63 (44) PD | 52 (35) | 55 (39) Median duration of objective response was 24.8 weeks in the 500 mg/m^2 group and 23.1 in 20 mg/m^2 group
Labianca (18) 1997 A GISCAD phase 3 study RCT	6S-LV 100 mg/m^2 IV, N=216 or 10 mg/m^2, N=206 + 370 mg/m^2, 5-FU	100 mg/m^2 of 6S-LV | 10 mg/m^2 of 6S-LV CR | 2 | 3 PR | 18 | 19 No change | 71 | 74 PD | 115 | 103 No chemo | 10 | 7 CR + PR | 9.3% | 10.7% 95% CI | 5.4-13.1 | 6.5-14.9 p=0.78
O'Connell (12) 1989 RCT	5-FU alone 500 mg/m^2, N=70 LV 200 mg/m^2 followed by 5-FU 370 mg/m^2, N=68 LV 20 mg/m^2 followed by 5-FU 370 mg/m^2, N=70 After the first 100 pts, the dose of 5-FU was increased to 425 mg/m^2 in the low-dose LV group after the toxicity was analyzed.	**Objective response rate** N=39, 10% N=35, 26%; p=0.04 N=37, 43%; p=0.001 Only pts with measureable disease were included
Petrelli (19) 1989 RCT	5-FU alone 500 mg/m^2, N=113 5-FU 600 mg/m^2 and 500 mg/m^2 of LV, N=115 5-FU 600 mg/m^2 and 25 mg/m^2 of LV, N=115	13 of 107, 12.1% 33 or 109, 30.3% 21 of 112, 18.8% High vs low dose; p=0.46 Response required a reduction in 50% in sums of the cross-products of the maximum perpendicular tumour measurement.
Poon (20) 1989 RCT	LV 200 mg/m^2 and 5-FU 370 mg/m^2 LV 20 mg/m^2 and 5-FU 370 mg/m^2	Objective tumour response rate N=35, 26% N=37, 43%
Tsavaris (21) 2002	LV 50 mg/m^2 and 5-FU 500 mg/m^2, N=50 LV 100 mg/m^2 and 5-FU 500 mg/m^2, N=50 Type of LV not mentioned but study from Greece.	No difference in response rates between the two arms, p=0.7 High dose (%) | Low dose (%) CR | 1 (2) | 2 (4) PR | 9 (18) | 10 (20) SD | 19 (38) | 16 (32) PD | 21 (42) | 22 (44)
Ychou (22) 1998	LV 200 mg/m^2 and 400 mg/m^2 of 5-FU, N=41 LV 20 mg/m^2 and 400 mg/m^2 of 5-FU, N=42	ORR 8.3% (95% CI, 2.3-22.5%)

Reference	Interventions	Response rate
		16.2% (95% CI, 7.6-31%) p=0.48
Budai (23) 2013 RCT	mFOLFIRI Irinotecan 180 mg/m^2, d,l-LV 200 mg or 400 mg, then 5-FU 400 mg/m^2 bolus then 2400 mg/m^2 5-FU over 46 hours Bevacizumab 5 mg/kg + above regimen	CR+PR (%) [95% CI] **Bevacizumab + mFOLFIRI** LV 200 mg, N=104 39 (38) [29-47] 400 mg, N=128 80 (63) [54-70] p=0.00015 **mFOLFIRI** LV 200 mg, N=129 55 (43) [34-51] 400 mg, N=89 33 (37) [28-48] p=0.41
Carlsson (25) 1990	50 mg LV, 500 mg/m^2 5-FU, N=41 200 mg LV and 500 mg/m^2 5-FU, N=9 Dose of 5-FU was 600 mg/m^2 to start and then reduced to 500 mg/m^2 because of toxicities Patients were treated either once weekly or 2 consecutive days. Every other week. IV bolus of 5-FU followed 30-40 by LV IV bolus injection	50 mg LV, N=34 (%) CR - 0 PR - 10 (29) SD - 10 (29) PD - 14 (41) 200 mg LV, N=6 (%) CR - 0 PR - 1 (17) SD - 2 (33) PD - 3 (50)
Poorter (26) 1995	Continuous dose of 300 mg/m^2 a day of 5-FU for 14 days LV was administered at a dose of 5 mg/day in the first 6 patients and then escalated by 5 mg/day in every subsequent group of 6 patients until toxicity	Gastrointestinal cancer, N=27 CR - 1 PR - 3 SD - 16 PD - 7 ORR - 15% (95% CI 4-34%) Colorectal cancer, N=17 CR - 1 PR - 3 SD - 10 PD - 3 ORR - 24% (95% CI 7-50%)

Abbreviations: CI = confidence interval; CR = complete response; FU = fluorouracil; IV = intravenous; LV = leucovorin; ORR = overall response rate; PD = progressive disease; PR = partial response; pts = patients; RCT = randomized controlled trial; SD = stable disease; vs = versus.

Progression-Free Survival or Recurrence

PFS was reported in five studies (11, 12, 18, 20, 23). They can be seen in Table 3. Recurrence was reported in the Quasar collaborative trial (10). PFS was very similar between arms. The only study where it differed was in the four-arm retrospective study by Budai et al. Patients were given (mFOLFIRI) irinotecan, 5-FU, and either 200 mg or 400 mg of LV and the same was repeated with the addition of bevacizumab. PFS was longest in the high-dose LV

group with bevacizumab 13 months compared with nine months for the low-dose LV and bevacizumab arm (p=0.000005). PFS was not significant for the high- and low-dose LV groups who did not have bevacizumab added to mFOLFIRI (23).

Recurrence was reported in the Quasar collaborative trial which was the only trial that addressed treatment in the adjuvant setting. Patients were randomized in the double-blind, 2×2 factorial trial to 370 mg/m^2 FU, either high-dose (175 mg) or low-dose (25 mg) L-folinic acid AND either levamisole or placebo. The trial saw no difference in recurrence between the high- and low-dose LV groups; there were the same number of recurrences in each arm (888 of 2464 versus 888 of 2463) (10). In addition, there was no difference in PFS in patients who has had the addition of levamisole to either high- or low-dose LV. The three-year risk of recurrence was 36.0% with the high-dose and 35.8% with the low-dose LV. The odds ratio of recurrence in the high-dose group versus the low-dose group was 1.00 (95% confidence interval [CI], 0.91 to 1.09) (10).

The median time to progression was examined in the Tsavaris trial. Patients received either 50 mg/m^2 or 100 mg/m^2 of LV and 500 mg/m^2 of 5-FU. The type of LV was not discussed, but the trial took place in Greece. Time to progression between groups was not statistically significant. It was 6.9 months in the high-dose group and 7.2 months in the low-dose group (p=0.12) (21).

Table 3: Progression-free survival and recurrence.

Reference	Treatment	PFS
Jäger (11) 1996 RCT	FU 500 mg/m^2 + LV 500 mg/m^2, N=148 FU 500 mg/m^2 + LV 20 mg/m^2, N=143	Median time to progression was 29.2 weeks (95% CI, 24-34) in HD group and 30 weeks (95% CI, 25-32.2) in LD group
Labianca (18) 1997 RCT	6S-LV 100 mg/m^2 IV, N=216 or 10 mg/m^2, N=206 and 370 mg/m^2 5-FU given as 15 min infusion	Median time to progression HD 8 months, LD 8 months
O'Connell (12) 1989 RCT	5-FU 500 mg/m^2, N=70 LV 200 mg/m^2 and 5-FU 370 mg/m^2, N=68 LV 20 mg/m^2 and 5-FU 370 mg/m^2, N=70	Median time to progression among responding patients was 10 months; p=NS
Poon (20) 1989 RCT	LV 200 mg/m^2 and 370 mg/m^2, N=69 LV 20 mg/m^2 and 370 mg/m^2, N=73 After the first 100 pts, the dose of 5-FU was increased to 425 mg/m^2 in the LD LV group after the toxicity was analyzed.	HR, 1.46 (95% CI, 1.03-2.07) HR 1.53 (95% CI, 1.09-2.16) P for between arms NR
Budai (23) 2013 Retrospective observational	mFOLFIRI Irinotecan 180 mg/m^2, d,l-LV 200 mg or 400 mg, then 5-FU 400 mg/m^2 bolus then	Median PFS after median of 21 months follow-up Bevacizumab + mFOLFIRI LD 9 months

Reference	Treatment	PFS
study	2400 mg/m^2 5-FU Bevacizumab 5 mg/kg + above regimen	HD 13 months p=0.000005 mFOLFIRI after median follow-up of 50 months LD 7 months HD 8 months p=0.51
Quasar collaborative group (10) – Lancet 2000 2×2 factorial design double blind RCT	370 mg/m^2 FU, either HD (175 mg) or LD (25 mg) L-folinic acid AND either levamisole or placebo 4927 pts 2464 to HD LV 2463 to LD LV 2429 to levamisole 2434 to placebo	No difference in recurrence between HD and LD group (888/2464 vs 888/2463) No difference between levamisole and placebo for risk of recurrence Levamisole / HD LV / LD LV Yes (%) / 37.8 / 36.6 No (%) / 34.3 / 35.6 3-year risk of recurrence 36.0% with HD and 35.8 with LD. Odds ratio of recurrence in HD vs LD was 1.00 (95% CI, 0.91-1.09)
Tsavaris (21) 2002	LV 50 mg/m^2 and 5-FU 500 mg/m^2, N=50 LV 100 mg/m^2 and 5-FU 500 mg/m^2, N=50 Type of LV not mentioned but study from Greece.	Time to progression between groups was not statistically significant HD 6.9 months, LD 7.2 months; p=0.12
Abbreviations: CI = confidence interval; FU = fluorouracil; HD = high dose; HR = hazard ratio; IV = intravenous; LD = low dose; LV = leucovorin; NR = not reported; NS = not significant; PFS = progression-free survival; pts = patients; RCT = randomized controlled trial; vs = versus.		

Overall Survival

Overall survival was addressed in 10 studies (10-12, 18-20, 22-24, 26). The results can be seen in Table 4. There was no difference in overall survival in seven of the studies (10-12, 18, 20, 22, 23). In contrast, in the RCT by Petrelli (19) and the retrospective study by Reynolds (24), survival was longer with the higher dose of LV (55 versus 45 months and 23 versus 20 months, respectively) (HR, 1.020; 95% CI, 0.677 to 1.536; p not reported). In the four-arm retrospective study by Budai et al., patients who were given (mFOLFIRI) with 400 mg of LV and bevacizumab had a longer overall survival than patients who received the lower dose of LV (26 months versus 21 months, p=0.0058). In the patients who did not receive bevacizumab, there was no difference in survival between the high and low doses of LV (23). The dose escalation study by Poorter showed survival to be nine months for the whole group. The results were not broken down by doses (26).

Table 4: Overall survival.

Reference	Treatment	Overall survival
Quasar collaborative group (10) – Lancet 2000 2×2 factorial design double-blind RCT	370 mg/m^2 FU, either HD (175 mg) or LD (25 mg) L-folinic acid AND either levamisole or placebo 4927 patients 2464 to HD LV 2463 to LD LV	801 deaths in the HD group and 775 in LD group 3-year survival was 70.1% with HD and 71.0% with LD Odds ratio of death in high group compared with low group was 1.04 (95%

Reference	Treatment	Overall survival
	2429 to levamisole 2434 to placebo	CI, 0.94-1.15)
Jäger (11) 1996 RCT	FU 500 mg/m^2 + LV 500 mg/m^2, N=148 FU 500 mg/m^2 + LV 20 mg/m^2, N=143	Median survival time was 55.1 weeks (95% CI, 41.2-72.4) in HD group and 54.1 weeks (95% CI, 46.4-65.5) in LD group P=NS
Labianca (18) 1997 A GISCAD phase 3 study RCT	6S-LV 100 mg/m^2 IV, N=216 or 10 mg/m^2, N=206 and 370 mg/m^2 5-FU given as 15 min infusion	11 months for both groups P=NR
O'Connell (12) 1989 RCT	5-FU 500 mg/m^2, N=70 LV 200 mg/m^2 and 5-FU 370 mg/m^2, N=68 LV 20 mg/m^2 and 5-FU 370 mg/m^2, N=70	Median follow-up time 11 months No significant survival difference between high and low doses and 5-FU P=NR
Petrelli (19) 1989 RCT (responses were blinded)	5-FU 600 mg/m^2 after 500 mg/m^2 of LV, N=115 5-FU 600 mg/m^2 after 25 mg/m^2 of LV, N=115	Minimum survival follow-up 10 months 55 weeks 45 weeks P=NS
Poon (20) 1989 RCT	LV 200 mg/m^2 and 370 mg/m^2, N=69 LV 20 mg/m^2 and 370 mg/m^2, N=73 After the first 100 pts, the dose of 5-FU was increased to 425 mg/m^2 in the LD LV group after the toxicity was analyzed.	HD 12.2 months HR, 1.39 (95% CI, 0.97-2.00) LD 12.0 months HR, 1.35 (95% CI, 0.94-1.93) P for between arms NR
Ychou (22) 1998 RCT	LV 200 mg/m^2 before 400 mg/m^2 of 5-FU, N=41 LV 20 mg/m^2 before 400 mg/m^2 of 5-FU, N=42	323 days 346 days – no significant difference between arms, p=NR
Budai (23) 2013 Retrospective observational study	mFOLFIRI Irinotecan 180 mg/m^2, d,l-LV 200 mg or 400 mg, then 5-FU 400 mg/m^2 bolus then 2400 mg/m^2 5-FU Bevacizumab 5 mg/kg + above regimen	Bevacizumab + mFOLFIRI + LD LV 21 months (95% CI, 17-22 months) Bevacizumab + mFOLFIRI + HD LV 26 months (95% CI, 23-32 months) p=0.0058 mFOLFIRI + LD LV 22 months (95% CI, 20-24 months) mFOLFIRI + HD LV 21 months (95% CI, 17-23 months)

Reference	Treatment	Overall survival
		p=0.38
Poorter (26) 1995 N=20 Metastatic CRC N=10 other gastrointestinal cancer To determine maximum tolerated dose of oral LV -10 mg was the established dose	300 mg/m^2 5-FU and LV was administered at a dose of 5 mg/day in the first 6 pts and then escalated by 5 mg/day in every subsequent group of 6 pts until toxicity	CRC median survival 10 months (range 1-22 months) For responders 17 months (range 13-22 months) For the whole group, median overall survival 9 months (range 1-22 months)
Reynolds (24) 2014 ASCO abstract retrospective	Modified FOLFOX6 (with or without bevacizumab) + LV 400 mg/m^2, N=71 Modified FOLFOX6 (with or without bevacizumab) + LV 20 mg/m^2, N=58	23 months 20 months (HR, 1.020; 95% CI, 0.677-1.536) P=NR
Abbreviations: ASCO = American Society of Clinical Oncology; CI = confidence interval; CRC = colorectal cancer; FU = fluorouracil; HD = high dose; HR = hazard ratio; LD = low dose; LV = leucovorin; NR = not reported; NS = not significant; pts = patients; RCT = randomized controlled trial		

Toxicity

Toxicity and adverse events were examined in 11 studies (10-12, 18-23, 25, 26). These can be seen in Table 5. Overall toxicity did not differ much between arms, but with the higher dose of LV having slightly greater toxicity in some studies. The study by the Quasar group reported that occurrence of stomatitis was statistically significant in the group that received 175 mg of L-folinic acid compared with 25 mg (p=0.002) (10). Although not accessed for significance, this was also seen in two other studies (12, 20). It should be noted that only four studies assessed stomatitis as part of their results. In the study by Ychou there was no stomatitis in either group (22). The higher dosage of LV also showed more diarrhea in nine studies (10-12, 18, 19, 21, 23, 25, 26).

Table 5: Toxicity

Reference	Treatment	Toxicity		
Quasar collaborative group (10) – Lancet 2000 2×2 factorial design double-blind RCT	370 mg/m^2 FU, either HD (175 mg) or LD (25 mg) L-folinic acid AND either levamisole or placebo 4927 patients N=2464 to HD LV N=2463 to LD LV N=2429 to levamisole N=2434 to placebo	All events Diarrhea Stomatitis p=0.002 Vomiting/nausea Any hematological Dermatological Cardiovascular L-folinic acid dose reduction	HD 362 216 169 111 95 42 33%	LD 338 158 150 116 79 37 30%
Jäger (11) 1996 RCT	FU 500 mg/m^2 + LV 500 mg/m^2, N=184 FU 500 mg/m^2 + LV 20 mg/m^2, N=143	Grade 3 and 4 (%) Anemia Leukopenia Thrombocytopenia Nausea Mucositis Diarrhea	HD 2 (1.4) 1 (0.7) 0 8 (5.4) 1 (0.7) 40 (27)	LD 0 2 (1.4) 1 (0.7) 8 (5.6) 0 23 (16.1)
Labianca (18) 1997	6S-LV 100 mg/m^2 IV, N=216	Grade 3 and 4	HD	LD

Reference	Treatment	Toxicity		
A GISCAD phase 3 study RCT	or 10 mg/m^2, N=206 and 370 mg/m^2 5-FU	Nausea/vomiting Diarrhea Mucositis Leukopenia Thrombocytopenia	3% 10% 7% 3% 0%	2% 5% 5% 1% 1%
O'Connell(12) 1989 RCT	5-FU 500 mg/m^2, N=70 LV 200 mg/m^2 and 5-FU 370 mg/m^2, N=68 LV 20 mg/m^2 and 5-FU 370 mg/m^2 , N=70	Severe Nausea Vomiting Diarrhea Stomatitis	HD 8 6 9 30	LD 10 9 14 26
Petrelli (19) 1989 RCT (responses were blinded)	5-FU 600 mg/m^2 after 500 mg/m^2 of LV, N=115 5-FU 600 mg/m^2 after 25 mg/m^2 of LV, N=115	Severe Nausea/vomiting Diarrhea Skin Mucostitis Anemia Leukopenia Thrombocytopenia	HD 10 25 4 4 2 8 3	LD 6 13 4 0 3 4 1
Poon (20) 1989 RCT	LV 200 mg/m^2 and 370 mg/m^2, N=69 LV 20 mg/m^2 and 370 mg/m^2, N=73 After the first 100 pts, the dose of 5-FU was increased to 425mg/m^2 in the LD LV group after the toxicity was analyzed.	Severe Nausea Vomiting Diarrhea Stomatitis	HD 8 6 9 30	LD 10 9 14 26
Tsavaris (21) 2002	LV 50 mg/m^2 and 5-FU 500 mg/m^2, N=50 LV 100 mg/m^2 and 5-FU 500 mg/m^2, N=50 Type of LV not mentioned but study from Greece.	Grade 3 (%) Anemia Neutropenia Nausea/ vomiting Diarrhea Mucositis Fatigue	HD 22 (2) 32 (4) 1 32 (4) 10 (1) 1	LD 12 (1) 21 (3) 0 13 (1) 10 (1) 0
Ychou (22) 1998 RCT	LV 200 mg/m^2 before 400 mg/m^2 of 5-FU, N=41 LV 20 mg/m^2 400 mg/m^2 of 5-FU, N=42	Grade 3 and 4 Diarrhea Nausea/vomiting Stomatitis	HD (%) 2.8 0 0	LD (%) 2.8 0 0
Budai (23) 2013 Retrospective observational study	mFOLFIRI Irinotecan 180 mg/m^2, d,l-LV 200 mg or 400 mg, then 5-FU 400 mg/m^2 bolus then 2400 mg/m^2 5-FU Bevacizumab 5 mg/kg + above regimen	Grade 3 and 4 (%) **Bevacizumab + mFOLFIRI** Hypertension Neutropenia Diarrhea Vomiting Nausea Bleeding Fatigue mucositis	HD, N=128 18 (14) 12 (9) 5 (4) 15 (12) 6 (5) 0 3 (2) 4 (3)	LD, N=104 16 (15) 12 (12) 6 (6) 8 (8) 4 (4) 0 0 5 (5)

Reference	Treatment	Toxicity		
		Grade 3 and 4 (%)	HD, N=89	LD, N=129
		mFOLFIRI		
		Hypertension	0	0
		Neutropenia	12 (13)	11 (10)
		Diarrhea	10 (12)	8 (6)
		Vomiting	9 (10)	9 (7)
		Nausea	1 (1)	3 (2)
		Bleeding	0	0
		Fatigue	3 (3)	1 (1)
		mucositis	4 (4)	5 (4)
Carlsson (25) 1990	41 pts got 50 mg LV and 500 mg/m^2 5-FU 9 pts got 200 mg LV and 500 mg/m^2 5-FU -Dose of 5-FU was 600 mg/m^2 to start and then reduced to 500 mg/m^2 because of toxicities	Grade 3 and 4 (%)	LV 200, N=9	LV 50, N=17
		Diarrhea	4 (44)	0
		Stomatitis	1 (11)	0
		Vomiting/nausea	1 (11)	0
		Conjunctivitis	0	0
		Granulocytopenia	0	0
		10 other patients with advanced cancer included in toxicity assessment (breast pancreatic and liver)		
Poorter (26) 1995 N=20 Metastatic CRC N=10 other gastrointestinal cancer To determine maximum tolerated dose of oral LV - 10 mg was the established dose	300 mg/m^2 5-FU and LV was administered at a dose of 5 mg/day in the first 6 patients and then escalated by 5 mg/day in every subsequent group of 6 patients until toxicity		10 mg N=18	5 mg N=18
		Muscositis	3	4
		Diarrhea	5	3
		Nausea	3	1
		Hand-foot syndrome	1	1
		(Includes some excluded patients in 5 mg, used to toxicity only)		
Abbreviations: CRC = colorectal cancer; FU = fluorouracil; HD = high dose; IV = intravenous; LD = low dose; LV = leucovorin; RCT = randomized controlled trial				

Ongoing, Unpublished, or Incomplete Studies

One ongoing study was found searching through www.clinicaltrials.gov and it can be seen in Table 6.

Table 6: Ongoing studies

Number	Title	Purpose	Dose
NCT00155558	A Phase I Trial of HDFL48 (Weekly 48-Hour Infusion of High-Dose 5-Fluorouracil and Leucovorin) in Recurrent or Metastatic Colorectal Cancer	To determine the maximum tolerated dose and dose limiting toxicity of 5-FU and leucovorin with novel 48-hour infusion schedule, and to collect toxicity profile at different dose level of 5-FU/LV 48-hour infusion.	Dosages not provided

DISCUSSION

There is no convincing evidence to identify the optimum dose of LV to be used in 5-FU/LV combinations. However, while the studies included in this review did not consistently show a survival difference with different LV doses, among all studies that did show a numerical survival difference, the trend was for improved survival in favour of the higher dose. Similarly, differences in toxicities when identified were consistently greater with the higher dose.

The expert panel concludes that the existing literature describing LV dose provides insufficient data to suggest that protocols should deviate from recommended doses. Since the doses of LV in modern bolus and infusional protocols are based on large randomized trials, the panel recommends that doses of leucovorin lower than those in the relevant trials not be used in routine clinical practice. It is not possible from the available evidence to be confident that equivalent survival outcomes would be achieved with lower LV dose than those defined in established protocols.

INTERNAL REVIEW

Almost all PEBC documents undergo internal review. With evidence summaries, this review is conducted by the Director of the PEBC. The Working Group is responsible for considering the changes, and if those changes could be made without substantially altering the conclusions, the altered draft would not need to be resubmitted for approval again.

Report Review by the Director of the PEBC

The purpose of the review by the Director of the PEBC is to ensure the methodological rigour and quality of PEBC evidence summaries. The Working Group is responsible for ensuring the necessary changes are made. If those changes could be made without substantially altering the conclusions, the altered draft would not need to be resubmitted for approval again.

The Director of the PEBC reviewed the document after the Working Group was satisfied with the draft. During this review the Director provided the following key feedback.

In response to this feedback, the Working Group made the following changes.
Only minor stylistic changes were needed for clarity

Report Approval

After internal review, the report is presented to the Gastrointestinal Disease Site Group (GI DSG).

The GI DSG reviewed the document through an email distribution. During this review the GI DSG provided the following key feedback.

-There is no discussion regarding data on LV in the setting of deleting the bolus.

In response to this feedback, the Working Group made the following changes.
A statement was added to provide clarification.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Three authors declared they had no conflicts. One author (AF) declared conflicts and reported having had managerial responsibility for Cancer Care, Alberta Health Services (AHS) as Vice-President. This organization had received multiple research and education grants from

different pharmaceutical companies. AF also disclosed that he was involved in discussions in a similar review a few years ago in Alberta, but was not an author on the report.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca

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Updating

All PEBC documents are maintained and updated
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Appendix A

Guideline table.

Developer	Title	Recommended dose of leucovorin
NCCN (National Comprehensive Cancer Network) 2015 (4, 5)	Colon Cancer Version 3.2015 Rectal Cancer Version 3.2015 http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (2 separate guidelines, but recommendation of leucovorin is the same)	400 mg/m^2 of leucovorin as part of the FOLFIRI[8] (Irinotecan 180 mg/m^2 IV over 30–90 minutes, day 1 Leucovorin 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2 /day × 2 days (total 2400 mg/m^2 over 46–48 hrs) continuous infusion. Repeat every 2 weeks) and FOLFOX[6] regimens (Oxaliplatin 85 mg/m^2 IV over 2 hrs, day 1 Leucovorin 400 mg/m^2 IV over 2 hrs, day 1 5-FU 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46-48 hrs) IV continuous infusion. Repeat every 2 weeks) In addition, both guidelines state: A leucovorin shortage recently existed in the United States. No specific data guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levo-leucovorin is equivalent to 400 mg/m^2 of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer (10). Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high-dose (500 mg/m^2) or low-dose (20 mg/m^2) leucovorin (11). Also, the Mayo Clinic and NCCTG determined that there was no therapeutic difference between the use of high-dose (200 mg/m^2) or low-dose (20 mg/m^2) leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms (12).
CCO	**2-29 Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection (27) 2008** Dose not stated, but the following trials and	Francini: Treatment initiated within 3 weeks of surgery. 5-FU, IV, 400 mg/m^2 days 1-5. Folinic acid 200 mg/m^2 days 1-5. Cycle repeated every 4 weeks, for 12 cycles O'Connell: 5-FU, bolus, 425 mg/m^2 per day for 5 consecutive days. Leucovorin, bolus, 20 mg/m^2 immediately preceding each dose of 5-FU. Courses repeated at 4 weeks, 8 weeks, then every 5 weeks for a total of 6 cycles. Zaniboni: Chemotherapy initiated within 5 weeks of surgery. 5-FU, 370 mg/m^2 daily for 5 days every 4 weeks for 6 cycles. Folinic acid, 200 mg/m^2 daily for 5 days every 4 weeks for 6 cycles.

Developer	Title	Recommended dose of leucovorin	
	regimens were cited in the report	McDermott	Folinic acid, 2-hr infusion, 200 mg/m^2, followed by 5-FU, IV bolus, 400 mg/m^2 and 5-FU, 22-hr infusion, 400 mg/m^2 for 2 consecutive days, cycle repeated every 2 weeks for 8 cycles.
		Gray	5-FU, IV, 370 mg/m^2, either six 5-day, 4-weekly, or 30 once-weekly courses. L-folinic acid, either high dose (175 mg) or low dose (25 mg) Levamisole or placebo.
		Twelves	5-FU/LV arm: Leucovorin, IV bolus, 20 mg/m^2, followed immediately by 5-FU, IV bolus, 425 mg/m^2 days 1-5, cycle repeated every 28 days, 6 cycles.
			Capecitabine arm: Capecitabine, oral, 1250 mg/m^2, twice daily, days 1-14, cycle repeated every 21 days, 8 cycles.
		Lembersky	5-FU/ LV arm: Leucovorin, 2-hr infusion, 500 mg/m^2 and 5-FU, IV bolus, 1 hr after leucovorin infusion, weekly for six weeks, cycle repeated after 2 weeks rest, 3 cycles.
			UFT + LV arm: UFT, oral, 300 mg/m^2 per day and LV, oral, 90 mg per day, daily doses divided in 3 and taken every 8 hrs, for 4 weeks, cycle repeated after 1 week rest, 5 cycles.
		Ychou	LV5-FU2 arm: Leucovorin, 2-hr infusion, 200 mg/m^2 and 5-FU 400 mg/m^2, bolus, 40 0mg/m^2 and 5-FU, 22-hr continuous infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles.
			LV5-FU2 + irinotecan arm: Irinotecan, 90-min infusion, 180 mg/m^2 day 1, plus leucovorin, 2-hr infusion, 200 mg/m^2 and 5-FU 400 mg/m^2, bolus, 400 mg/m^2 and 5-FU, 22-hr continuous infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles.
		Van Cutsem	5-FU/LV arm: Leucovorin, 2-hr infusion, 200 mg/m^2 and 5-FU 400 mg/m^2, bolus, 400 mg/m^2 and 5-FU, 22-hr continuous infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles. or AIO regimen, weekly
			5-FU/LV + irinotecan arm: Irinotecan, IV, 180 mg/m^2 day 1, plus leucovorin, 2-hr infusion, 200 mg/m^2 and 5-FU 400 mg/m^2, bolus, 400 mg/m^2 and 5-FU, 22-hr continuous infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles. or AIO regimen plus irinotecan, 80 mg/m^2, weekly.
		Saltz	5-FU/LV arm: Roswell park regimen Leucovorin, 2-hr infusion, 500 mg/m^2, then 5-FU, 500 mg/m^2, 1 hr after start of leucovorin, for 6 weeks, cycle repeated every 8 weeks, 4 cycles.
			IFL arm: Irinotecan, 90-min infusion, 125 mg/m^2, followed by leucovorin, IV bolus, 20 mg/m^2, then 5-FU, IV bolus, 500 mg/m^2, for 4 weeks, cycle repeated every 6 weeks, 5 cycles.
			5-FU/LV arm:

Developer	Title	Recommended dose of leucovorin	
		Andre	Leucovorin, 2-hr infusion, 200 mg/m^2, then 5-FU, IV bolus, 400 mg/m^2 and 5-FU, 22-hr infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles.
			5-FU/LV + oxaliplatin arm: Leucovorin, 2-hr infusion, 200 mg/m^2, then 5-FU, IV bolus, 400 mg/m^2 and 5-FU, 22-hr infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles. Oxaliplatin, 2-hr infusion, 85 mg/m^2 day 1, given simultaneously with leucovorin.
		Wolmark	5-FU/LV arm: 5-FU, IV bolus, 500 mg/m^2, and leucovorin, IV, 500 mg/m^2, weekly for 6 weeks, cycle repeated every 8 weeks, 3 cycles.
			5-FU/LV + oxaliplatin (FLOX) arm: 5-FU, IV bolus, 500 mg/m^2, and leucovorin, IV, 500 mg/m^2, weekly for 6 weeks, cycle repeated every 8 weeks, 3 cycles. Oxaliplatin, IV, 85 mg/m^2, weeks 1, 3, and 5 of each 8-week cycle, 3 cycles.
CCO	**2-16b Use of Irinotecan (Camptosar®, CPT-11) Combined with 5-Fluorouracil and Leucovorin (5FU/LV) as First-line Therapy for Metastatic Colorectal Cancer (28) (ARCHIVED)** Dose not stated, but the following trials and regimens were cited in the report	Comella et al.	Irinotecan 200 mg/m^2 (90 min IV inf.) d1 + 5-FU 850 mg/m^2 (bolus IV inf.) d2 + LV 250 mg/m^2 (2hr IV inf.) d2, q2week. Methotrexate 750 mg/m^2 (2hr IV inf.) d1 + 5-FU 800 mg/m^2 (IV bolus) d2 + LV 250 mg/m^2 (2hr IV inf.).
		Comella et al.	Irinotecan 200 mg/m^2 d1 + 5-FU 850 mg/m^2 IV bolus inf. d2 + LV 250 mg/m^2 d2, q2weeks. Oxaliplatin 100mg/m^2 d1 + 5-FU 1050 mg/m^2 IV bolus inf. d2 + LV 250 mg/m^2 d2, q2weeks.
		Köhne et al.	Irinotecan 80 mg/m^2 + 5-FU 2300* mg/m^2 (24 hr inf.) + LV 500 mg/m^2 weekly, q6week, q50d. (AIO 2.3 + IRI) 5-FU 2600 mg/m^2 (24hr inf.) + LV 500 mg/m^2, weekly, q6week, q50d. (AIO) * after three toxic deaths, AIO 2.3 was reduced to AIO 2.0
		Pozzo et al.	Irinotecan 350 mg/m^2 d1 + 5-FU 425 mg/m^2 (bolus IV) + LV 20mg/m2 d21-25, q6weeks (IRI + MAYO) 5-FU 425 mg/m^2 (bolus IV) + LV 20mg/m2 d21-25, q4weeks (MAYO)
CCO	**2-22 The Role of Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in the First and Second-Line Treatment of Advanced Colorectal Cancer (29) (ARCHIVED)** Dose not stated, but the following trials and	Lévi et al 1994 IOCC trial	5-FU 600, FA 300, oxaliplatin 20 d1-5 q21d (16d intermission) via programmable pump. Arm A: constant infusion Arm B: CM infusion (max delivery of 5-FU/FA: 0400 hrs, oxaliplatin 1600 hrs).
		Lévi et al, 1997 IOCC trial	5-FU 600, FA 300, oxaliplatin 20 d1-5 q21d (16d intermission). Arm A: constant infusion Arm B: CM infusion
		Buechele et al, 2000 Germany	Oxaliplatin 50 2h inf + FA 500 2 hr inf + 5-FU 2000 24 hr inf d1,8,15,22 q36d *versus* Bolus 5-FU/FA (Mayo Clinic regimen)

Developer	Title	Recommended dose of leucovorin	
	regimens were cited in the report	de Gramont et al, 2000	Oxaliplatin 85 2h inf d1 + 5-FU 400 B then 600 CI d1,2 + FA 200 CI d1,2 q2wk *versus* 5-FU 400 B then 600 CI d1,2 + FA 200 CI d1,2 q2wk (LV5-FU2 regimen)
		Giacchetti et al, 2000	Oxaliplatin 125 6h inf d1 + 5-FU 700 + FA 300 CM d1-5 q3wk *versus* 5-FU 700 + FA 300 CM d1-5 q3wk
		Giacchetti et al, 2002 EORTC trial	CM oxaliplatin 25 [peak@16:00], CM 5-FU 750 [peak@4:00], CM FA 300 [peak@4:00]. All three drugs are given every d for 4d, repeat q2wk *versus* Oxaliplatin 100 2hr inf d1, 5-FU 1500 22hr inf (every day for 2 days), FA 600 2hr inf (every day for 2 days), repeat q2wk [FOLFOX 2]
		Grothey et al, 2002 Germany	Oxaliplatin 50 2hr inf + 5-FU 2000 24hr inf + FA 500 24hr inf d1,8,15,22 q5wk (FUFOX) *versus* 5-FU 425 B + FA 20 d1-5 q29d (Mayo)
		Colucci et al, 2003 GOIM trial	Oxaliplatin 85 d1, FA 100 2hr inf d1,2, 5-FU 400 B inf followed by 5-FU 600 22 hr inf d1,2 q2wk *versus* Irinotecan 180 d1, FA 100 2hr inf d1,2 5-FU 400 B inf followed by 5-FU 600 22hr inf d1,2 q2wk.
		Goldberg et al, 2004 Intergroup N9741 trial	Oxaliplatin 85 d1 followed by 5-FU 400 B + 600 22hr inf d1,2, FA 200 d1,2 q2wk [de Gramont FOLFOX 4] *versus* Irinotecan 125 + 5-FU 500 + FA 20 d1,8,15,22 q6wk [Saltz IFL] *versus* Oxaliplatin 85 d1 + irinotecan 200 d1, q3wk [Wasserman IROX]
		Tournigand et al, 2004 GERCOR trial	1st line FOLFIRI: irinotecan 180 2h inf d1, FA 200 2h inf d1, 5-FU 400 B inf d1, followed by 5-FU 2400-3000 48h inf d2, q2wk until progression → followed by 2nd line FOLFOX (as below) *versus* 1st line FOLFOX6: oxaliplatin 100 2h inf d1, FA 200 2h inf d1, 5-FU 400 B inf d1, followed by 5-FU 2400-3000 48h inf d2, q2wk until progression → followed by 2nd line FOLFIRI (as above)
		Comella P et al, SICOG	IRIFAFU: Irinotecan 200 mg/m^2 d1 IV, FA 250 mg/m^2 IV, followed by 5-FU 850 mg/m^2 d2 *versus* OXAFAFU hd: Oxaliplatin 100 mg/m^2 d1, followed by FA 250 mg/m^2 and 5-FU 1050 mg/m^2 d2 *versus* OXAFAFU ld: Oxaliplatin 85 mg/m^2 d1, FA 250 mg/m^2 and 5-FU 850 mg/m^2 d1
		Colucci G et al) GOIM	FOLFIRI: Irinotecan 180 mg/m^2 d1, FA 100 mg/m^2 2-hr infusion, 5-FU 400 mg/m^2 IV bolus injection, followed by 5-FU 600 mg/m^2 22-hr infusion d1,2. *versus* FOLFOX4: Oxaliplatin 85 mg/m^2 d1, irinotecan 180 mg/m^2 d1, FA 100 mg/m^2 2-hr infusion, 5-FU 400 mg/m^2 IV bolus injection, followed by 5-FU 600 mg/m^2 22-hr infusion d1,2.
		Falcone A et al	FOLFOXIRI: oxaliplatin 85, day 1; irinotecan 165, day 1; 5-FU 3200 48-hr infusion starting on day 1; l-FA 200, day 1; every 2 weeks.

Developer	Title	Recommended dose of leucovorin	
		GONO	*versus* FOLFIRI: irinotecan 180, day 1; l-leucovorin 100, days 1 and 2; 5-FU 400 bolus, days 1 and 2; followed by 5-FU 600 22-hr infusion, days 1 and 2; every 2 weeks. At progression on FOLFIRI, a FOLFOX regimen was recommended.
		Hospers GAP et al	OXAFAFU: Oxaliplatin 85 mg/m^2, 2 hr infusion, FA 200 mg/m^2, 1 hr infusion, 5-U 2600 mg/m^2, 24 hr infusion d1, q2week. *versus* FAFU: 5-FU 425 mg/m^2 d1-5, FA 20 mg/m^2 d1-5, q4week.
		Souglakos J et al HORG	FOLFOXIRI: oxaliplatin 65, day 2; irinotecan 150, day 1; FA 200, days 2 and 3; 5-FU 400 bolus, followed by 5-FU 600 22-hr infusion, days 2 and 3. *versus* FOLFIRI: irinotecan 180, day 1; FA 200, days 2 and 3; 5-FU 400 bolus, followed by 5-FU 600 22-hr infusion, days 2 and 3.
		Stanculeanu DL et al	FOLFOX4: Oxaliplatin 85 mg/m^2 d1, FA 200 mg/m^2 d1,2, 5-FU 400 mg/m^2 bolus injection d1,2, followed by 5-FU 600 mg/m^2 22 hr infusion d1,2 q15d. *versus* FOLFIRI: Irinotecan 180 mg/m^2, FA 400 mg/m^2, 5-FU 400 mg/m^2 bolus injection, followed by 5-FU 2400 mg/m^2 46 hr infusion q15d. *versus* IROX: Irinotecan 300 mg/m^2 d1, oxaliplatin 85 mg/m^2 d2, q3week.
		Tournigand C et al GERCOR	FOLFOX4: Oxaliplatin 85 mg/m^2 2 hr injection d1, FA 2 hr infusion (either 100 mg/m^2 l-LV or 200 mg/m^2 of dl-LV), 5-FU 400 mg/m^2 bolus injection, followed by 5-FU 600 mg/m^2 22 hr infusion d1,2 q2weeks *versus* FOLFOX7(6 cycles)→LV5-FU2(12 cycles)→FOLFOX7(6 cycles): FOLFOX7: Oxaliplatin 130 mg/m^2 2 hr injection, d1, FA 2 hr injection (either 200 mg/m^2 l-LV or 400 mg/m^2 dl-LV), followed by 5-FU 2400 mg/m^2 46 hr infusion, q2weeks. LV5-FU2: FA 2 hr injection (either l-LV 200 mg/m^2 or dl-LV 400 mg/m^2), 5-FU 400 mg/m^2 bolus injection, followed by 5-FU 3000 mg/m^2 46 hr infusion q2weeks
		Rothenberg et al, 2003 EFC 4584 trial	*Treatment given as second-line to IFL* Oxaliplatin 85 2hr inf d1, 5-FU 400 B inf, followed by 5-FU 600 22 hr inf d1,2, q2wk (FOLFOX4) *versus* 5-FU 400 B inf, followed by 5-FU 600 22hr inf d1,2, FA 200 q2wk (LV5-FU2)
		Garay et al, 2003 Sanofi/ Memorial Sloan Ketttering Cancer Centre trial	*Treatment given as second-line to 5-FU + irinotecan ± FA* Oxaliplatin 85 2hr inf d1, 5-FU 400 B inf, followed by 5-FU 600 22hr inf d1,2, q2wk (FOLFOX4) *versus* 5-FU 400 B inf, followed by 5-FU 600 22hr inf d1,2, FA 200 q2wk (LV5-FU2) Crossover trial

Developer	Title	Recommended dose of leucovorin
		Giantonio BJ et al ECOG: FOLFOX4+Be: Bevacizumab 10 mg/kg IV biweekly, oxaliplatin 85 mg/m^2 d1, FA 200 mg/m^2 IV 2 hrs, 5-FU 400 mg/m^2 bolus injection, followed by 5-FU 600 mg/m^2 22 hr infusion d1,2 *versus* FOLFOX4: Oxaliplatin 85 mg/m^2 d1, FA 200 mg/m^2 IV 2 hrs, 5-FU 400 mg/m^2 bolus injection, followed by 5-FU 600 mg/m^2 22 hr infusion d1,2. *versus* Be: Bevacizumab 10 mg/kg IV biweekly.
		Pitot HC et al N9841: Irinotecan→FOLFOX4 *versus* FOLFOX4→Irinotecan: Irinotecan: 350 mg/m^2 d1, q3week (reduced to 300 mg/m^2 for ECOG PS =2, age ≥70, or prior pelvic radiation). FOLFOX4: Oxaliplatin 85 mg/m^2, FA 200 mg/m^2, 5-FU 400 mg/m^2 bolus injection, followed by 600 mg/m^2 22 hr infusion d1,2 q2week.
NHMRC (National Health and Medical Research Council) Australia (6) 2005	Clinical Practice Guidelines for the prevention, early detection and management of Colorectal Cancer	Two standard regimens that combine 5-FU and leucovorin have been developed. The Mayo regimen of 5-FU 425 mg/m^2 plus leucovorin 20 mg/m^2 as an IV push is administered day 1–5 every four weeks. The Roswell Park regimen of 5-FU 500–600 mg/m^2 plus leucovorin 500 mg/m^2 over two hrs is given weekly for 6 weeks, with courses repeated every eight weeks. A randomised study that compared these two regimens in 362 patients found similar response rates, palliative effects and survival outcomes (30). The Mayo regimen was associated with significantly more leukopenia and stomatitis, but less diarrhea and fewer hospital admissions. The optimal dose of leucovorin is unclear. Randomized studies looking at low- versus high-dose leucovorin with the Mayo regimen of 5-FU found no significant difference in response rates or survival outcome (18, 20). Two similar studies, where the 5-FU was given according to a weekly schedule (11, 19), reported increased response rates in the high-dose leucovorin arms, but survival end points were again unaltered, and toxicity and expense were increased.
BC Cancer Agency (7) 2013	BC Cancer Agency Drug Manual	If Cycle is 1-4 weeks: 20 mg/m^2 IV for one dose on days 1-5 (total dose per cycle [range 20-100 mg/m^2]) If Cycle is 2 weeks: 400 mg/m^2 IV for one dose on day 1. (total dose per cycle 400 mg/m^2) FU is usually given after, or at the midpoint of, a leucovorin infusion. Doses of leucovorin are not adjusted for toxicity but would be delayed or omitted if fluorouracil is delayed or omitted
BC Cancer Agency (31)	BCCA Protocol Summary for Palliative Therapy of	leucovorin 20 mg/m^2/day x 5 days (d1-5) IV push prior to fluorouracil

Developer	Title	Recommended dose of leucovorin
2015	Advanced Colorectal Cancer using Leucovorin and Fluorouracil	fluorouracil (5-FU)400 mg/m^2/day x 5 days (d1-5) IV push
BC Cancer Agency (31) 2015	BCCA Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil, Leucovorin, and Bevacizumab	Irinotecan 180 mg/m^2 IV in 500 mL of D5W over 1 hr 30 min Leucovorin 400 mg/m^2 IV in 250 mL D5W over 1 hr 30 min FU 400 mg/m^2 IV bolus, after leucovorin, THEN bevacizumab 5 mg/Kg IV in 100 mL NS over 10 minutes FU 2400 mg/m^2 IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via appropriate infusor device Repeat every 14 days for a maximum of 12 cycles.
BC Cancer Agency (32) 2015	BCCA Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, Fluorouracil, Leucovorin, and Bevacizumab	Oxaliplatin 85 mg/m^2 IV in 500 mL of D5W over 2 hrs Leucovorin 400 mg/m^2 IV in 250 mL D5W over 2 hrs FU 400 mg/m^2 IV bolus, after leucovorin THEN bevacizumab 5 mg/Kg IV in 100 mL NS over 10 minutes FU 2400 mg/m^2 IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via appropriate infuser device Repeat every 14 days for a maximum of 12 cycles
BC Cancer Agency (33) 2015	BCCA Protocol Summary for Adjuvant Combination Chemotherapy for Stage III and Stage IIB Colon Cancer Using Oxaliplatin, Fluorouracil, and Leucovorin	Oxaliplatin 85 mg/m^2 IV in 500 mL of D5W over 2 hrs Leucovorin 400 mg/m^2 IV in 250 mL D5W over 2 hrs FU 400 mg/m^2 IV bolus, after leucovorin, THEN fluorouracil 2400 mg/m^2 IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via appropriate infuser device Repeat every 14 days for 12 cycles.
BC Cancer Agency(34) 2015	BCCA Protocol Summary for Adjuvant Therapy of Colon Cancer using Fluorouracil Injection and Infusion and Leucovorin Infusion	Leucovorin 400 mg/m^2 IV in 250 mL D5W over 2 hrs FU 400 mg/m^2 IV bolus, after FA, THEN FU 2400 mg/m^2 IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via appropriate infuser device Repeat every 14 days for 12 cycles
BC Cancer Agency (35) 2015	BCCA Protocol Summary for Palliative Combination Chemotherapy for	Oxaliplatin 85 mg/m^2 IV in 500 mL of D5W over 2 hrs Leucovorin 400 mg/m^2 IV in 250 mL D5W over 2 hrs

Developer	Title	Recommended dose of leucovorin
	Metastatic Colorectal Cancer Using Oxaliplatin, Fluorouracil, and Leucovorin	FU 400 mg/m^2 IV bolus, after leucovorin, THEN fluorouracil 2400 mg/m^2 IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via appropriate infuser device Repeat every 14 days for a maximum of 24 cycles
Spain (8) 2011 – consensus meeting	Recommendations and expert opinion on the adjuvant treatment of colon cancer in Spain	Roswell Park or NSABP Bolus 5-FU (500 mg/m^2) + LV 500 mg/m^2) weekly MAYO or NCCTG Bolus 5-FU (450 mg/m^2) and leucovorin 20 mg/m^2) daily for 5 days every 28 days
NICE 2011 (9)	The diagnosis and management of colorectal cancer	Drugs doses and administration schedule taken from economic analysis section FOLFIRI 5-FU 400 mg/m^2 IV bolus day 1, 2400 mg/m^2 ci, 46 hrs, FA 200 mg/m^2 IV, 2 hrs, day 1 Irinotecan 180 mg/m^2, IV 30 mins, day 1 2 week cycle FOLFOX 5-FU 400 mg/m^2 IV bolus day 1, 2400 mg/m^2 ci, 46 hrs FA 200 mg/m^2 IV, 2 hrs, day 1 Oxaliplatin 85 mg/m^2 IV, 2 hrs, day 1 2 week cycle
ASCO (36, 37) endorsed the Cancer Care Ontario guidelines and the dose was not stated for ESMO (38, 39) and the New Zealand (40) Guidelines Groups		

Abbreviations: ASCO = American Society of Clinical Oncology; AIO = Association of Medical Oncology of the German Cancer Society regimen; D5W = 5% dextrose in water; FA = folinic acid; FU = fluorouracil; IFL = 5-FU/FA/irinotecan; NCCTG = North Central Cancer Treatment Group; NS = normal saline; NSABP = National Surgical Adjuvant Breast and Bowel Project

Appendix B
Literature Search Strategy

1. (dose or dosage or dosing).mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
2. d,l-leucovorin.mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
3. levoleucovorin.mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
4. (Elvorine or Isovorin or Levofolene or Levorin).mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
5. folinic acid.mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
6. 2 or 3 or 4 or 5
7. fluorouracil.mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
8. irinotecan.mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
9. folfox.mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
10. folfiri.mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
11. 7 or 8 or 9 or 10
12. colorectal cancer.mp. or Colorectal Neoplasms/
13. leucovorin.mp. or Leucovorin/
14. colon carcinoma.mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
15. colon tumor.mp. or exp colon tumor/
16. (colon cancer or cancer of the colon).mp.
17. colonic neoplasm.mp.
18. colorectal cancer.mp. or exp colorectal cancer/
19. exp colorectal tumor/ or exp colorectal cancer/ or exp colorectal carcinoma/ or colorectal cancer of colorectal neoplasms.mp.
20. colon tumour.mp.
21. colorectal tumour.mp.
22. colorectal neoplasm.mp. or exp Colorectal Neoplasms/
23. colonic neoplasms.mp. or exp Colonic Neoplasms
24. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 1 and 6
26. 25 and 11
27. 26 and 24
28. remove duplicates from 27

Appendix C
Quality table.

Reference	Phase	Type	Random allocation	Blinding	Stratification	Power reported	ITT	Funding
Quasar collaborative group (10) – Lancet 2000	NR	RCT	Yes	Double Blind	Age, site, portal vein infusion, preoperative radiotherapy, planned postoperative radiotherapy, chemotherapy schedule-weekly or not	Yes	NR	Principally by government grants and some industry
Jäger (11) 1996	NR	RCT	Yes	No	Age, sex, Karnosfsky PS, primary tumour or local recurrence and CEA level	Yes	NR	NR
Labianca (18) 1997 A GISCAD phase 3 study	3	RCT	Yes	No	NR	Yes	NR	Government grant
O'Connell (12) 1989	3	RCT	NR	No	ECOG PS, site of metastatic disease and institution	NR	NR	Grants and leucovorin supplied by manufacture
Petrelli (19) 1989	3	RCT	Yes	No	Site, and ECOG PS	Yes	NR	Government and industry
Poon (20) 1989	NR	RCT	NR		ECOG PS, presence or absence of measurable malignant disease, site of principal lesion and institution	Yes	NR	Leucovorin provided by manufacturer
Tsavaris (21) 2002	NR	RCT	Yes	No	Age, sex, Karnofsky PS, and site of metastases	NR	Yes	NR
Ychou (22) 1998	NR	RCT	NR	No	NR	NR	NR	NR
Budai (23) 2013	NA	Retrospective	NA	NA	NA	Yes	NA	NR
Reynolds	NA	Retrospective	NA	NR	NA	NR	NA	NR

(24) 2014 ASCO abstract								
Carlsson (25) 1990	NR	Comparative	NA	No	NR	No	NR	Government grants
Poorter (26) 1995	NA	Dose escalation	No	No	NA	NR	NR	NR

Abbreviations: ASCO = American Society of Clinical Oncology; CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; ITT = intention-to-treat; NA = not applicable; NR = not reported; PS = performance status; RCT = randomized controlled trial