Evidence Tables

Citation: Benson AB, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, Krzyzanowska MK, Maroun J, McAllister P, Van Cutsem E, Brouwers M, Charette M, Haller DG (2004) American Society of Clinical Oncology Recommendations on adjuvant chemotherapy for stage II colon cancer (review) *Journal of Clinical Oncology* 22;16:3408-3419

Design: Literature based meta-analysis

Country: USA

Aim: to address whether all medically fit patients with curatively resected stage II colon cancer should be offered adjuvant chemotherapy as part of routine clinical practice, to identify patients with poor prognosis characteristics and to describe strategies for oncologists to use to discuss adjuvant chemotherapy in practice.

Inclusion criteria
Randomised Controlled Trials with appropriate control groups
Meta-analyses of RCTs comparing adjuvant therapy with observation in patients with stage II colon cancer who had undergone surgery with curative intent.

Exclusion criteria

Population

Interventions

Outcomes

Results
Should patients with Curatively Resected Stage II Colon Cancer and with Identifiable Characteristics that Predict for a Poor Prognosis (i.e. high-risk patients) be Offered Adjuvant Chemotherapy?

The evidence base considered included final reports of early stage II and III adjuvant chemotherapy trials that include risk factor data, large scale National Caner Data Base (NCDB) analyses of nodal status and prognosis, a secondary analysis of data from a large intergroup randomised trial to demonstrate the association between number of nodes recovered and overall survival, a recent pooled analysis of prognostic and predictive factors in colorectal cancer, a College of American Pathologists consensus statement on prognostic factors in colorectal cancer and selected studies on emerging molecular markers.

Patients with a small number of sampled lymph nodes can be considered inadequately staged and at greater risk of having microscopic residual disease and could therefore be offered adjuvant chemotherapy.

Patients with any of a number of poor prognostic features (T4 lesion, perforation or poorly differentiated histology) might be considered suitable candidates for adjuvant chemotherapy. It should be made clear however, that these tumour characteristics may be prognostic but there is no data to suggest that they are predictive of response to adjuvant chemotherapy. It should also be noted that the magnitude of risk conferred by these characteristics, relative to nodal status, cannot be estimated from the currently available data.

There is no direct evidence to demonstrate a survival benefit of adjuvant chemotherapy in high-risk patients. As the small numbers of such patients evaluated in trials; the potential benefits have not been tested and there are toxic effects associated with adjuvant chemotherapy it is therefore reasonable to recommend against the use of adjuvant treatment.

Patients and Oncologists who are prepared to accept results from stage III diseases as indirect evidence of the benefits of adjuvant chemotherapy are justified in considering the use of such therapy in stage II patients provided they appreciate that the magnitude of benefit as measured in absolute improvement in survival, is small.

The optimal approach is to encourage patients with high-risk stage II disease to participate in randomised trials.

General comments
This guideline document used an updated version (Figueredo, 2004) of an earlier published review from the Cancer Care Ontario Program (Figueredo, 1997).

The guideline has been assessed using the AGREE Tool for the appraisal of guidelines. The completed assessment is available for review if required.

Only the information for the section on high-risk patients has been presented here as it is all that is relevant to the topic.

Some of the evidence has been drawn from studies which have used Levamisole as part of the treatment regimen and therefore recommendations should be considered with caution as they may draw on evidence that is not relevant to current clinical practice in the UK.

References of Included Studies (For systematic reviews):

Moertel CG, Fleming TR, MacDonald JS, et al (1995) Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/Dukes B2 colon cancer *Journal of Clinical Oncology* 13:2936-2943

Moertel CG, Fleming TR, MacDonald JS, et al (1995) Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: A final report *Annals of International Medicine* 122:321-326

Swanson RS, Compton CC, Stewart AK et al (2003) The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined *Annals of Surgical Oncology* 10:65-71

Greene FL, Stewart AK, Norton HJ (2002) A new TNM staging strategy for node-positive (stage III) colon cancer: An analysis of 50,042 patients *Annals of Surgery* 236:416-421

Le Voyer TE, Sigurdson ER, Hanlon AL et al (2003) Colon Cancer survival is associated with increasing number of lymph nodes analyzed: A secondary survey of intergroup trial INT-0089 *Journal of Clinical Oncology* 21:2912-2919

Gill S, Loprinzi C, Sargent D et al (2004) Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: Who benefits and by how much? *Journal of Clinical Oncology* 22:1797-1806

Compton CC, Fielding LP, Burgart LJ et al (2000) Prognostic Factors in Colorectal Cancer College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med* 124;979-994

Graziano F, Cascinu S, Staccioli MP et al. Potential Role and Chronology of abnormal expression of the deleted in colon cancer (DCC) and the p53 proteins in the development of gastric caner http://www.biomedcentral.com/content/pdf/1471-2407-1-9.pdf

Ribic CM, Sargent DJ, Moore MJ et al (2003) Tumour micro-satellite instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer *New England Journal of Medicine* 349;247-257

Figuerdo A, Germond C, Maroun J (1997) Adjuvant therapy for stage II colon cancer after complete resection. Provincial Gastrointestinal Disease Site Group *Cancer Prevention and Control* 1;5:379-392

Figuerdo A, Charette ML, Maroun J (2004) Adjuvant therapy for stage II colon caner: a systematic review from the Cancer Care Ontario Program in evidence-based care's gastrointestinal cancer disease site group (Review) *Journal of Clinical Oncology* 22;16:3395-3407

Citation: Des Guetz G, Schischmanoff O, Nicola P, Perret GY, Morere JF, Uzzan B (2009) Does microsatellite instability predict the efficacy of adjuvant chemotherapy in colorectal cancer? A systematic review with meta-analysis *European Journal of Cancer* 45;10:1890-1896

Design: Systematic Review/Meta-analysis

Country: France

Aim: to assess the predictive values of MSI-H status among patients receiving or not receiving adjuvant chemotherapy for colorectal cancer.

Inclusion criteria
Studies dealing with colon or rectum assessing the relationship between MSI status, chemotherapy and recurrence free survival or overall survival for localised disease.

Exclusion criteria
Studies where survival data were not available

Population
7 studies representing a population of 3690 patients
1345 men and 1198 women (1147 missing data)
1777 colon cancer and 213 rectum (1700 missing data)
810 Stage II and 2444 stage III (436 missing data)

Interventions
Adjuvant chemotherapy

Outcomes
Not clearly defined

Results
7 studies assessed two cohorts; one receiving adjuvant chemotherapy and one not receiving adjuvant chemotherapy; two of the studies included samples from RCTs evaluating the potential benefit of adjuvant chemotherapy.

Most patients were treated with 5Fu-based chemotherapy with or without folinic acid or levamisole.

MSI-high was found in 454 patients and microsatellite stable (MSS) was found in 2871 patients (365 missing data). The number of microsatellite markers analysed differed greatly across studies (range 1-17).

There was no significant heterogeneity between the studies (pHet=0.3 for overall survival and pHet=0.4 for recurrence free survival, I^2=16% and 4% respectively)

No benefit of chemotherapy was observed among MSI-H patients. From 6 studies, global HR for overall survival was 0.7 (95% CI: 0.44-1.09) and from 5 studies, global HR for relapse free survival was 0.96 (95% CI: 0.62-1.49)

Subgroup analysis could not be performed for stage II and stage III patients as the majority of included studies did not separate the stages for analysis.

Evaluation of whether MSI-H and MSS patients benefit similarly from adjuvant chemotherapy found statistically significant interaction meaning that chemotherapy had no effect among MSI-H patients compared with a beneficial effect in MSS patients (HR for relapse free survival 0.77; 95% CI 0.68-0.87, p<0.001).

General comments
Although this topic was not to include papers looking at levamisole, this study is a meta-analysis of studies with mixed treatments (including levamisole) for an area of particular interest (MSI) and so is included here.

Searches were conducted on PubMed, EMBASE, Cochrane Database, there was no start date given for the searches, but searches ran up to February 2008.

Determination of MSI status was always done retrospectively

A pooled random HR estimate and 95% CI was calculated using a fixed effects model due to the absence of

heterogeneity between the studies.

Citation: Erlichman, C. (1999) Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer *Journal of Clinical Oncology* 17;5:1356-1363

Design: Pooled Analysis

Country: Various

Aim: To determine whether fluorouracil (FU) and folinic acid (leucovorin) is an effective adjuvant therapy for patients after potentially curative resection of colon cancer in patients with B2 tumours.

Inclusion criteria

- Adenocarcinoma of the colon
- T3 or T4, N0 M0 colon cancer
- Chemo therapy to start between 21 and 56 days after surgery

Exclusion criteria

Patients for whom adequate staging data were not available or that were incorrectly staged (N=9)

Population

N=1016 patients from 5 trials

Interventions

Fluorouracil (FU) combined with Folinic Acid (Leucovorin, LV); all trials used a regimen of FU 370-425 mg/m^2 plus LV 20-200 mg/m^2 daily for 5 days every 28-35 days. 4/5 trials administered treatment for six cycles and 1/5 for 12 cycles (Francini, 1994).

Outcomes

Event free survival (EFS), defined as time from randomisation to first event (first recurrence, second tumour or death from any cause).

The number of events required for this analysis was estimated from the data in a previous publication (Labianca, 1995) in which a 3-year EFS was reported to be 76% for the control population, 5-year EFS (assuming exponential lifetime) was estimated to be 63%. It was determined that 168 events were required in order to have an 80% chance of detecting a 10% improvement in EFS at 5-years for the FU+LV arm.

Results

Median follow-up time was 5.75 years (range 5.17-8.54 years)

Follow up times for the individual studies were: 5.17, 5.29, 5.89, 6.41 and 8.54 years

Median FU dose for the whole population was 11.1g/m^2 (range 9.5-24g/m^2)

- There were 110 relapses in the control arm (22%) and 101 in the FU+LV arm (20%); there was no statistically significant difference between the control arm and treatment arms (HR 0.83, 90% CI 0.68-1.01, p=0.061, one-sided).
- Kaplan-Meier OS curves showed no statistically significant difference in survival between the two arms (HR 0.81,90% CI; 0.64-1.01, p=0.057, one-sided).
- Multivariate Cox analysis revealed age and tumour grade to be independent predictors for both overall survival (OS) (overall adjusted HR 0.86, 90% CI; 0.68-1.07, p=0.13, one-sided) and event free survival (EFS) (overall adjusted HR 0.88, 90% CI; 0.72-1.07, p=0.137, one-sided).
- When EFS and OS were analysed according to treatment arm and corrected for age and tumour grade, no difference was observed between the treatment arms.
- There was a statistically significant difference in EFS (p<0.001, two-sided) and OS (p<0.01, two-sided) between patients with well/moderately differentiated tumours and patients with poorly differentiated tumours.

	Hazards Ratio	
	Control	**FU+LV**
5-year EFS	0.73	0.76
SE	0.02	0.02
5-year OS	0.80	0.82
SE	0.02	0.02

Table: Differences in Event Free Survival and Overall Survival between control and treatment arms

- The commonest adverse events were gastrointestinal. Grade 3 and 4 nausea occurred in 4% of patients, stomatitis in 11% and diarrhoea in 8%.
- Leukopenia and thrombocytopenia grade 3 or 4 occurred in 2% of patients.

General comments
There were no details provided as to the methodology employed for the pooling of the data from different trials; a protocol outlining the criteria for the pooling of study patients into one common data set, standard definitions and coding for events and patient characteristics, minimum clinical difference to be tested, required statistical power, duration of follow-up and appropriate timing for the main comparison and the analytical approach were outlined in other papers.

None of the individual trials were designed to address *a priori* the question of whether FU+LV was effective in the individual subsets of B2 and C.

Author Conclusions
Individual studies have not clearly demonstrated a statistically significant benefit from adjuvant chemotherapy in patients with B2 colon cancer, neither has the pooled analysis of over 1,000 patients from 5 separate trials shown a statistically significant benefit to FU+LV in patients with B2 colon cancer. It is unlikely that the lack of effect was due to an imbalance of events other than colon cancer favouring the control arm as the two arms in the data set were equally balanced for relapse rate, second malignancy and deaths from any cause.

Some of the trials are not referenced therefore it is difficult to tell which publication in the reference list relates to which trial in the analysis.

The first row of table 4 is titled 5-year EFS; it is assumed that this is a typo and the table should read 5-year OS as table 4 relates to overall survival rather than event free survival.

References of Included Studies (For systematic reviews):
Labianca R (1995) Efficacy of adjuvant fluorouracil and folinic acid in colon cancer *Lancet* 345;8955:939-944

Francini G, Petrioli R, Lorenzini L, Mancini S, Armenio S, Tanzini G, Marsili S, Aquino A, Marzocca G, Civitelli S, Mariani L, deSando D, Bovenga S, Lorenzi M (1994) Folinic Acid and 5-fluorouracil as adjuvant chemotherapy in colon cancer *Gastroenterology* 106;4:899-906

O'Connell MJ, Mailliard JA, Kahn MJ et al. (1997) Controlled trial of fluorouacil and low-dose Leucovorin given for six months as postoperative adjuvant therapy for colon cancer *Journal of Clinical Oncology* 15:246-250

Citation: Figeuredo A, Charette, ML, Maroun J, Brouwers MC, Zuraw L (2004) Adjuvant Therapy for Stage II Colon Cancer: A Systematic Review from the Cancer Care Ontario Program in Evidence-Based Care's Gastrointestinal Cancer Disease Site Group *Journal of Clinical Oncology* 22;16:3395-3407

Design: Systematic Review

Country: USA

Aim: To address the question of whether stage II colon cancer patients should receive adjuvant chemotherapy

Inclusion criteria
Randomised Controlled trials or meta-analyses of RCTs involving patients with stage II colon cancer who had undergone surgery with curative intent that compared adjuvant therapy with observation

Exclusion criteria
Trials published before 1987 as a previous study summarised the results of randomised trials up to that point (Buyse et al, 1988). The current meta-analysis provides a summary of this previous study.

Population
Data on Stage II colon cancer patients were available for pooling from 18 studies using survival curves to estimate the number of events.
Data on specific subgroups (high-risk vs. low risk) were not available

Interventions
Adjuvant Chemotherapy following surgery with curative intent versus surgery alone/observation

Outcomes
Survival
Disease Free Survival

Results
Buyse et al, 1988

- 17 English (British?) trials comparing adjuvant therapy in patients with all stages of colorectal cancer with a total of 6791 patients.
- The pooled results showed no statistically significant difference in the odds of death between treatment and observation groups (OR, 0.96; 95% CI 0.87 – 1.06).
- There was a significant decrease in the odds of death for patients treated with 5FU compared with patients in the observation group (OR, 0.83; 95% CI 0.7 – 0.98; p=0.03) (Subgroup analysis).

Trials after 1987

- Patients with stage II colon cancer had undergone surgery with curative intent and were randomised to receive adjuvant therapy or observation in all trials reviewed.
- In most trials, adjuvant therapy started within 5 to 6 weeks postoperatively, though in studies where portal vein infusion (PVI) was the treatment under investigation, treatment began immediately after surgery.
- Patients were eligible for entry into the individual trials if they had good performance status or general health, no active comorbidity or previous malignancy apart from skin cancer and good haematological, renal and hepatic functions.
- Median age for participants was in the mid-60's.

Results of adjuvant treatment for stage II colon cancer are derived mainly from clinical trials that also included patients with stage III and in some cases, stage I as well as patients with rectal cancer. The results are therefore based primarily on subgroup analysis and should thus the generalisability of the results may be open to interpretation.

Systemic Adjuvant Chemotherapy: FU combined with Semustine
From one trial, no significant difference was reported for either overall survival or disease free survival for whole population or for the subgroup of Stage II patients (Panettiere et al, 1988).
A second trial did not provide separate results for stage II patients, however the results stated that there was no significant interaction between treatment effect and stage although there was a significant improvement in both disease free and overall survival favouring adjuvant chemotherapy for the whole patient group (Wolmark et al, 1988).

Systemic Adjuvant Chemotherapy: FU and folinic Acid (Leucovorin)
Five trials, three of which have published individually, tested the combination of FU modulated by folinic acid (Leucovorin).
The best data were available from one pooled analysis; using individual patient data for stage II patients, no significant difference was observed in 5-year event free survival (HR 0.83, 90% CI 0.72-1.07 (these results differ from the actual publication – it appears that the HR for the unadjusted model has been paired with the confidence interval for the adjusted model) or overall survival (HR 0.86; 90% CI 0.68 – 1.07) (IMPACT).

Regional Chemotherapy: PVI
Although 14 randomised trials and two meta-analyses were found, only 6 papers reported data specific to stage II patients (Taylor et al, 1985; Fielding et al, 1992; Beart et al, 1990, Gray et al, 1987; SAKK, 1995 and Schlag et al, 1990).
Taylor et al reported a significant improvement in 5-year overall survival for PVI of FU compared with observation in the subgroup of patients with stage II colon cancer (95% vs. 65%, p=0.002) and for all subgroups combined (78% vs. 58%, p=0.002).
A 7-day PVI of FU and heparin was tested in eight subsequent trials, with data on stage II patients presented separately in 3 (Fielding et al, 1992; Beart et al, 1990 and Gray et al 1987) none of which reported significant differences in overall or disease free survival.
From two trials (Ryan et al, 1988 and SAKK) the addition of mitomycin C to the standard PVI reported no significant difference in disease free or overall survival.
From one trial (Schlag et al, 1990) no significant difference between adjuvant floxuridine delivered by PVI and observation was observed in the subgroup of stage II patients or in the whole population.

Regional Chemotherapy: IP chemotherapy
From one trial (Vaillant et al, 2000) reported improved 5-year disease-free survival in the treatment group in patients with stage II cancer (89% vs. 73%, p=0.05) for patients receiving a full dose of intraperitoneal FU (n=58) compared to patients receiving surgery alone (n=77). When all stage II patients were considered, the difference was not significant.
From one trial (Scheithauer et al, 1995), no significant difference in disease free or overall survival in stage II patients was observed.

Regional Chemotherapy: hepatic arterial infusion
From one trial (Sadahiro et al, 2001), three year disease-free survival (86% vs. 76%; p=0.002) and overall survival (91% vs. 83%; p=0.03) were significantly improved in patients receiving chemotherapy though this result was for stage II and stage III colon cancer patients.

Oral FU or analogs
Data specific to stage II patients were available from a single trial (CCCSGJ) comparing a combination of mitomycin and FU to observation. No significant differences in disease free or overall survival were reported for the subgroup of stage II patients.
From a meta-analysis using individual patient data from three trials of oral FU and its prodrugs (tegafur, carmofur) (Sakamoto J, 1999) there was no significant difference in overall survival (p=0.721) or disease free-survival (p=0.296) for adjuvant chemotherapy compared with surgery after a median follow-up of almost 5 years. An update which included 9,819 patients from six trials subgroup analysis found a significant difference for disease-free (RR 0.78, 95% CI 0.68 to 0.88, p<0.001) and overall survival (RR 0.84, 95% CI 0.72 – 0.97, p=0.017) for oral agents versus surgery alone in Stage II patients (Sakamoto, 2001).

General comments
Quality of Life data and data on treatment toxicities were excluded from the analysis due to the inconsistencies in reporting methods.

References of Included Studies (For systematic reviews):
Buyse M, Zeleniuch-Jacquotte A, Chalmers TC (1988) Adjuvant therapy of colorectal cancer: Why we still don't know *JAMA* 259:3571-3578.

Panettiere FJ, Goodman PJ, Costanzi JJ et al (1988) Adjuvant therapy in large bowel adenocarcinoma: Long term results of a Southwest Oncology Group Study *Journal of Clinical Oncology* 6:947-954

Wolmark N, Fisher B, Rockette H et al (1988) Postoperative adjuvant chemotherapy of BCG for colon caner: results from NSABP protocol C-01. *Journal of National Cancer Institute* 80;30-36

IMPACT: International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators (1999) Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer *Journal of Clinical Oncology* 17:1356-1363

Taylor I, Machin D, Mullee M et al (1985) A randomised controlled trial of adjuvant portal vein cytotoxic perfusion after curative resection for colorectal adenocarcinoma British Journal of Surgery 72:359-363

Fielding LP, Hittinger R, Grace RH et al (1992) Randomised controlled trial of adjuvant chemotherapy by portal vein perfusion after curative resection for colorectal adenocarcinoma *Lancet* 340:502-506

Beart RW, Moertel CG, Wieand HS et al (1990) Adjuvant therapy for resectable colorectal carcinoma with fluorouracil administered by portal vein infusion: A study of the Mayo Clinic and the North Central Cancer Treatment Group *Archives of Surgery* 125:897-901

Gray BN, deZwart J, Fisher R et al (1987) The Australia and New Zealand Trial of adjuvant chemotherapy in colon cancer, in, Salmon SE (ed): Adjuvant Therapy of Cancer. New York, NY, Grune-Stratton pp537-554

Swiss Group for Clinical Cancer Research (SAKK) (1995) Long term results of single course of adjuvant intraportal chemotherapy for colorectal cancer *Lancet* 345;349-353

Schlag P, Saeger HD, Friedl P et al (1990) Adjuvant intraportal FUDR-chemotherapy in colon cancer patients, in, Salmon SE (ed) (1990) Adjuvant Therapy of Cancer. New York, NY, Grune-Stratton pp439-445

Ryan J, Weiden P, Crowley J et al (1988) Adjuvant portal vein infusion for colorectal cancer; a 3-arm randomised trial. *Proc Am Soc Clin Oncol* 7;95 abstract 361

The Colorectal Cancer Chemotherapy Study Group of Japan (1995) Five-year results of a randomised controlled trial of adjuvant chemotherapy for curatively resected colorectal canrcinoma *Japanese Journal of Clinical Oncology* 25:91-103

Sakamoto J, Hamada C, Kodaira S et al (1999) adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: Individual patient data meta-analysis of randomised trials *Japanese Journal of Clinical Oncology* 29;78-86

Sakamoto J, Hamada C, Yasutomi M et al (2001) Adjuvant therapy with oral fluorinated pyrimidines after curative resection for colorectal cancer: Individual patient data meta-analysis of randomised trials *Proc Am Soc Clin Oncol* 20;147a:abstract 583

Citation: Labianca R (1995) Efficacy of adjuvant fluorouracil and Folinic acid in colon cancer *Lancet* 345;8955:939-944

Note: The three trials pooled here are included in the Erlichman pooled analysis but the numbers of patients included in this analysis (3 trials) is smaller than that included in the Erlichman pooled analysis (5 trials).

Design: Pooled Analysis

Country: Multiple

Aim: To determine the efficacy of fluorouracil and high-dose folinic acid after surgery for Dukes B and C stage colon cancer.

Inclusion criteria
Each trial included in the analysis had their own inclusion/eligibility criteria which included such factors as Duke's Stage, Age, Tumour Site, Performance Status and Chemotherapy start following surgery (days).

Exclusion criteria
Of the initial patients randomised, 33 were excluded before analysis for the following reasons:
Incorrect histology (3)
Wrong stage (25)
Other (not specified) (5)

Population
N=1526 randomised
N=1493 eligible for analysis (756 in the treatment arm and 757 in the control arm)

Interventions
All three trials used a regimen of fluorouracil 370-400 mg/m^2 plus folinic acid 200 mg/m^2 daily for 5 days every 28 days for 6 cycles. In one trial the racemic form of Folinic acid was used initially but about 150 patients were treated with pure L-form at a dose of 100 mg/m^2 due to the racemic mixture not being available.

Outcomes
3-year Event free survival
3-year Overall Survival

Results
Median follow-up time for the treatment group was 40 months and for the control group was 37 months (inter quartile range was 29-48 for both groups).

Survival
Fluorouracil plus folinic acid significantly increased survival and event free survival and results were consistent with and without stratification. The global test for interaction of treatment effect with stage and country was not significant for either EFS (p=0.176) or OS (p=0.254).

	Stage B	Stage C	Total	P
3-year EFS				
Control	0.76 (0.04)	0.44 (0.06)	0.62 (0.03)	
FU/FA	0.79 (0.03)	0.62 (0.04)	0.71 (0.03)	
HR for EFS (95% CI)				
Unstratified	0.84 (0.62-1.12)	0.55 (0.44-0.70)	0.67 (0.56-0.80)	P<0.0001
Stratified by country	0.84 (0.62-1.13)	0.55 (0.43-0.70)	0.67 (0.56-0.81)	P<0.0001
Stratified by stage and country			0.65 (0.54-0.78)	P<0.0001
3-year OS				
Control	0.90 (0.02)	0.64 (0.04)	0.78 (0.02)	
FU/FA	0.88 (0.02)	0.76 (0.03)	0.83 (0.02)	
HR for OS (95% CI)				
Unstratified	0.91 (0.63-1.34)	0.70 (0.53-0.92)	0.77 (0.62-0.96)	P=0.018
Stratified by country	0.93 (0.63-1.37)	0.71 (0.54-0.94)	0.79 (0.63-0.98)	P=0.034
Stratified by stage and country			0.78 (0.62-0.97)	0.029

Table: Event free survival (EFS) and overall survival (OS)

Multivariate Cox analyses revealed nodal status to be an independent predictor for EFS and OS, and age was significantly associated with OS.

	Event Free Survival		Overall Survival	
	Hazard Ratio (95% CI)	**P**	**Hazard Ratio (95% CI)**	**P**
Treatment Group				
Control	Reference Category, not retained in the final model (p>0.05)			
FU/FA	0.65 (0.54-0.78)	P<0.0001	0.76 (0.61-0.96)	P=0.018
Age				
≤65	NR			
>65			1.27 (1.01-1.59)	P=0.039
Stage				
B, 0 positive nodes	Reference Category, not retained in the final model (p>0.05)			
C 1-4 positive nodes	2.01 (1.63-2.47)		2.17 (1.67-2.80)	
C >4 positive nodes	4.05 (3.13-5.23)	P<0.0001	5.40 (4.01-7.27)	p<0.0001

Table: Cox analysis of prognostic factors

First Events

There were 394 relapses overall, with the pattern of relapse differing slightly between treatment groups (X^2 for heterogeneity=6.997, p=0.072).

The crude relapse rate for hepatic recurrence as a first event was twice as high in the control group as in the treatment group.

Deaths unrelated to the tumour were equally distributed in the two groups.

Toxic Effects

The most common adverse effect of treatment was gastrointestinal with substantial variation among the three trials (p<0.001 for the association of side-effects with trial site).

General comments

It seems that the folinic acid used in the included trials was Leucovorin.

Event free survival was defined as time from randomisation to the first event; events being first recurrence, second tumour, death with no relapse or date of last observation.

Survival was defined as time from randomisation to death from any cause

Citation: Lin CC, Lin JK, Chang SC, Wang HS, Yang SH, Jiang JK, Chen WS, Lin TC (2009) Is adjuvant chemotherapy beneficial to high risk stage II colon cancer? Analysis at a single institute *International Journal of Colorectal Disease* 24;6:665-676

Design: Prospective Case Series

Country: Taiwan

Aim: To identify the risk factors of tumour recurrence in stage II colon cancer and to investigate the benefit of adjuvant chemotherapy for high-risk stage II.

Inclusion criteria
None Given – appears to be all stage II colon cancer patients that underwent surgery with curative intent

Exclusion criteria
None Given

Population
N=375 patients with stage II colon cancer

Interventions
Adjuvant chemotherapy following surgery with curative intent

Outcomes
Survival

Results
375 patients underwent surgery with curative intent of which 66 patients received 5FU based adjuvant chemotherapy either oral or IV form.
66 patients were lost to follow-up in 3-years and the follow-up rate was 83.7%. Median follow-up time was 48.5 months (0.7-96.6 months).

Recurrence occurred in 35 patients (9.3%), 8 of whom had received adjuvant chemotherapy (22.9%). The most frequent site of recurrence was the liver (62.9%) followed by lung and peritoneum.

Univariate analysis showed that T4 lesion (p=0.024), lymphovascular invasion (p=0.022), obstruction at presentation (p=0.008) and mucinous component more than 50% (p=0.032) were significantly associated with decreased disease free survival.
Multivariate analysis showed that lymphovascular invasion and obstruction were independent factors predicting disease free survival.

Patients with at least one risk factor (T4 lesion, lymphovascular invasion, obstruction at presentation or mucinous component more than 50%) were considered as high-risk group.
There was a significant difference in disease free survival between patients with high-risk factor and patients without (3-year disease free survival 84.7% and 95% respectively, p=0.001)
There was a significant difference in disease free survival for patients with no high risk factor, patients with one high risk factor and patients with more than one risk factor (p=0.003).

There was no significant difference in survival for stage II patients receiving adjuvant chemotherapy compared with patients that did not receive adjuvant chemotherapy, however in the subgroup of patients with high risk factors, there was a significant 3-year disease free survival benefit (96.4% vs. 84.7%, p=0.045) and 5-year overall survival benefit (100% vs. 86.4%, p=0.015) in favour of adjuvant chemotherapy.

Citation: Mamounas E, Wieand S, Wolmark N, Bear HD, Atkins JN, Song K, Jones J, Rockette H (1999) Comparative Efficacy of Adjuvant Chemotherapy in Patients with Dukes B versus Dukes C colon Cancer: Results from Four National Surgical Adjuvant Breast and Bowel Project Adjuvant Studies (C-01, C-02, C-03 and C-04) *Journal of Clinical Oncology* 17:5;1349-1355

Note: This study presents results from four trials, however only two of the trials (C-01 and C-02) included are of potential relevance to the PICO (adjuvant chemotherapy versus surgery alone) and as such the results of those two studies are presented here.

Design: Pooled Analysis

Country: USA

Aim: To determine whether patients with Dukes' B disease benefit from adjuvant chemotherapy and to evaluate the magnitude of benefit compared with that observed in Dukes' C patients.

Inclusion criteria
Eligible patients in C-01, C-03 and C-04 included:

- Patients with adenocarcinoma of the colon resected with curative intent with no evidence of gross residual or metastatic disease at the time of laparotomy.
- Patients with pathologically confirmed tumour extension into adjacent organs, provided all tumour was removed en bloc with negative resection margins

Eligible patients in C-02 included:

- Patients were required to have a potentially curable adenocarcinoma – documented by barium enema or endoscopic biopsy

Eligible patients in all trials included :

- Patients presenting with obstruction of contained perforation
- Patients with adequate hepatic or renal function and adequate WBC counts and platelet counts
- Patients with ECOC performance status of 0, 1 or 2

Exclusion criteria
Patients presenting with free perforation

Population

- 4,006 patients recruited in the four studies
- N=3,820 patients eligible for analysis; 1,565 Dukes' B and 2,255 Dukes' C
- C-01: N=726; 316 Dukes' B and 410 Dukes' C
- C-02: N=683; 389 Dukes' B and 294 Dukes' C

Interventions
C-01: Adjuvant semustine, vincristine and 5-FU (MOF) regimen versus surgery alone
C-02: Peri-operative administration of a portal venous infusion (PVI) of 5-FU versus surgery alone

Outcomes
5-Year Overall Survival

Results
C-01
The administration of the MOF regimen resulted in a 7% absolute improvement in survival over surgery alone (p=0.07).
For Dukes' B patients and Dukes' C patients, the administration of MOF resulted in an absolute improvement in survival of 3% (p=0.73) and 9% (p=0.05) respectively over surgery alone.
Similar results were observed for disease-free and recurrence free survival but these results were not shown.
The administration of the MOF regimen resulted in a 7% reduction in mortality for Dukes' B patients compared with a 26% reduction for Dukes' C patients.

C-02*
The administration of peri-operative PVI of 5-FU resulted in a 7% absolute improvement in survival over surgery alone (p=0.08).
There was a 12% improvement in survival for Dukes' B patients (p=0.005) and a 2% improvement for Dukes' C patients (p=0.81) with peri-operative PVI compared with surgery alone.
The administration of 7-days perioperative PVI of 5-FU resulted in a 51% reduction in mortality for Dukes' B patients compared with a 4% reduction for Dukes' C patients.

The individual trial data were presented to demonstrate that all four trials showed similar treatment effects between Dukes' B and Dukes' C patients but due to limited numbers in each trial any one individual could not rule out a substantial difference in treatment effect according to Dukes' stage so the authors combined the data from the four trials into two treatment groups. Treatment 1 consisted of the treatment groups from each trial with the inferior overall, disease free and recurrence free survival for all patients and treatment 2 consisted of the treatment groups with the superior overall, disease free and recurrence free survival for all patients.

Treatment 1	Treatment 2
Operation (C-01)	MOF (C-01)
Operation (C-02)	5-FU PVI (C-02)
MOF (C-03)	5-FU + LV (C-03)
5-FU + Levamisole (C-04)	5-FU + LV C-04)

Table: Treatment Groups

In the total population, 26% of Dukes' B and 28% of Dukes' C patients had high-risk characteristics defined as the presence of obstruction, bowel perforation (contained), or extension of tumour into adjacent organs. It could not be elucidated from the paper what percentage of patients from each of the individual trials had high risk characteristics so the results for the high risk group represent the whole population, including from the trials that were not relevant; results should therefore be interpreted with caution.
In Dukes' B patients without high-risk characteristics there was a 32% reduction in mortality (cumulative OR 0.68; 95% CI 0.5-0.92; p=0.01) compared with a 20% reduction in mortality (cumulative OR 0.8; 95% CI 0.55-1.17; p=0.26) for patients with high-risk characteristics. This reduction in mortality translated into an absolute improvement in survival of 5% in each risk category (treatment 2, 87% vs. treatment 1, 82% in the low risk group and treatment 2, 75% vs. treatment 1, 70% in the high risk category).

*The protocol for C-02 was designed to use a one-sided test for the final conclusions and to maintain consistency across protocols, a two-sided test for p-values was used in this study.

General comments
Patients were classified as Dukes' B if the tumour demonstrated full-thickness penetration of the bowel wall (through the serosa or into the pericolic fat) with no regional lymph node involvement on pathological examination. Patients were classified as Dukes' C if there was evidence of involvement of the regional lymph nodes on pathological examination.

The follow-up requirements for all trials were similar:

- First 2 years - Investigators were required to submit patient follow-up forms every three months which reported results of a physical exam, complete blood cell count and chemistry profile, including liver function test. A chest x-ray and carcinoembryonic antigen levels were required every six months and a barium enema and/or colonoscopy was required yearly.
- Years to 5 – A physical exam, including weight and performance status, complete blood cell count, chemistry profile including liver function tests, chest x-ray and carcinoembryonic antigen levels required every six months. A barium enema and/or colonoscopy were required yearly.
- After year 5 – status of the disease to be reported on a yearly basis

Citation: O'Connell MJ, Mailliard JA, Kahn MJ, Macdonald JS, Haller DG, Mayer RJ, Wieand HS (1997) Controlled Trial of Fluorouracil and Low Dose Leucovorin Given for 6 Months as Postoperative Adjuvant Therapy for Colon Cancer *Journal of Clinical Oncology* 15;1:246-250

Design: Randomised Trial

Country: USA

Aim: To determine the efficacy of intensive course fluorouracil (5FU) plus low dose Leucovorin given for 6 months following potentially curative resection of colon cancer

Inclusion criteria

- Histological proof of adenocarcinoma of the colon
- Undergone complete resection of the primary tumour without gross or microscopic evidence of residual disease
- Patients at high risk of relapse as indicated by one or more of the following features:
    - Regional Lymph Node Metastases
    - Transmural Penetration of the muscular wall of the bowel with evidence of bowel obstruction, perforation, adherence, or invasion of adjacent organs
    - Regional peritonela or mesenteric implants resected en bloc.
- The inferior margin had to be above the peritoneal reflection
- Patients had to be ambulatory and maintaining adequate oral nutrition

Exclusion criteria

- White blood cell count less than 3,500/µL
- Platelet count less than 100,000/µL
- Prior or concurrent radiation or chemotherapy for colon cancer
- Concurrent or previous second malignant disease within the preceding three years
- Pregnancy or lactation

Population
N=317

N=309 included in the statistical analysis

Interventions
5FU given by rapid intravenous infusion at a dose of 425 mg/m^2/d for 5 consecutive days with Leucovorin at a dose of 20mg/m^2 immediately preceding each dose of 5FU.
Courses were repeated at 4 weeks, 8 weeks and then every 5 weeks for a total of six cycles

Outcomes

Results
Median follow-up duration was 72 months
195/205 patients still alive at the time of the study had at least 4 years of follow-up evaluation

Tumour Relapse
41% (62/151) of patients in the control group and 27% (43/158) of patients in the chemotherapy group relapsed. The proportion of patients that were relapse-free at 5-years was 0.74 in the chemotherapy group and 0.58 in the control group. The difference in time to relapse between the two groups was significant (p=0.004 before adjusting for covariates and p=0.001 after adjusting for covariates).
When stratification factors, age and sex were combined with treatment in a multivariate proportional hazards model, older age, increased nodal involvement and the presence of regional implants resected en bloc were significantly associated with increased risk of tumour relapse. There was no significant interaction between treatment and any of the prognostic variables.
The 95% confidence intervals for the relative risk of relapse for control patients versus chemotherapy patients was 1.19 – 2.60 for the unadjusted model and 1.29 – 2.82 for the adjusted model.

Survival
40% of patients in the control group and 28% of patients in the treatment group had died at the time of analysis. The proportion of patients alive at 5-years was 0.74 for patients in the chemotherapy group and 0.63 for patients in

the control group. The difference in survival between the two groups was significant (p=0.02 before adjusting for covariates and p=0.01 after adjusting for covariates).
When stratification factors plus age and sex were combined with treatment in a multivariate proportional hazards model, extent of nodal involvement and presence of regional implants were significantly associated with an increased risk of death.
The 95% confidence interval for the relative risk of death for patients in the control group versus the treatment group was 1.06 – 2.31 with no covariate and 1.12 – 2.45 after covariate adjustment.

Toxicity
There were no deaths associated with chemotherapy.
Toxicities were generally tolerable and manageable by reducing the dosage of 5-FU on subsequent cycles.

General comments
Patients were stratified according to the extent of primary tumour invasion, presence/absence of intestinal obstruction, presence/absence of regional peritoneal metastases resected en bloc and extent of regional lymph node metastases
Details of Randomisation Method is not provided
Statistical analysis details note that proportional hazards models were use for all multivariate analysis and therefore the results should refer to Hazards Ratios (HR), however the results refer to Relative Risks (RR) and it is not clear whether they are using RR in place of HR as there is a tendency in literature to use two terms interchangeably although they are not the same thing. The actual relative risk values have not been included in the results, just the 95% CI.

Citation: Yoshimatsu K, Umehara A, Ishibashi K, Yokomizo H, Yoshida K, Fujimoto T, Watanabe K, Ogawa K (2006) Indication and Efficacy of Adjuvant Chemotherapy with Oral Fluorouropyrimidines for Dukes B Colorectal Cancer *Anticancer Research* 26;3089-3094

Design: Retrospective Case Series

Country: Japan

Aim: to examine retrospectively the prognostic value of routinely assessable clinicopathological factors to identify subgroups of Dukes B colorectal cancer patients at high risk of recurrence and death and to assess adjuvant chemotherapy with oral fluoropyrimidines for the high-risk subgroup.

Inclusion criteria
Patients with Dukes B colorectal cancer who had undergone curative resection between 1991 and 2000

Exclusion criteria
None Given

Population
N=229

Interventions
Oral fluorouropyrimidines versus surgery alone

Outcomes
Survival

Results

- The average age of patients was 64.8 and ranged from 29-93 years.
- There were 127 males and 102 females
- The 5-year cancer related survival rate was 83.5% and recurrence rate was 20.1%.
- CEA, CA19-9, histological type, lymphatic invasion, venous invasion, depth of invasion, number of dissected nodes and adjuvant chemotherapy were found to be significantly correlated with cancer-related survival on univariate analysis.
- On multivariate analysis depth of invasion, number of dissected nodes and adjuvant chemotherapy were prognostic factors in Dukes B and as depth of invasion was the most significant prognostic factor (p=0.0186), patients with tumour exposed at the serosa or invasion of other organ were identified as high-risk (n=64) while patients with tumour invasion under the subserosa were considered low risk (n=161).

- 44 patients in the high risk group had chemotherapy with oral fluoropyrimidines compared with 114 in the low risk group. The 5-year survival rates in the low risk group were 91.8% for patients receiving adjuvant chemotherapy and 87.9% for patients without chemotherapy. In the high risk group there was a significant difference in 5-year survival for patients receiving adjuvant chemotherapy (75.8%) and patients not receiving chemotherapy (44%); p=0.0008.
- In patients treated with adjuvant chemotherapy there was a significant decrease in recurrence rate, especially in the liver and lung; 4.5% for patients with chemotherapy compared to 25% for patients without chemotherapy, p=0.0346).

General comments
Retrospective study which does not represent very high quality evidence, one of the key factors here is that the study does not compare survival between the high-risk and low-risk groups.