Chemotherapy in colorectal cancer: new options and new challenges

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Colorectal cancer is the second most common cause of cancer-related mortality in Europe and North America. Studies conducted in the last two decades have established the role of adjuvant therapy in stage III colon cancer. However, there is currently no international consensus with the role of adjuvant treatment in stage II disease. The introduction of irinotecan, oxaliplatin, oral fluoropyrimidines and raltitrexed has broadened the treatment options available for patients with advanced colorectal cancer. The integration of these drugs with the new molecular targeted therapies such as epidermal growth factor receptor, cyclooxygenase, angiogenesis and matrix metalloproteinase inhibition will form the basis of clinical research in the next few years and may, in the future, impact on the survival of patients with colorectal cancer. This review will focus on the place of chemotherapy in colorectal cancer, but not its role in combination with radiotherapy in rectal cancer.

Every year, about 1 million new cases of colorectal cancers (CRCs) are diagnosed world-wide with 500,000 patients dying from the disease¹. About 75–80% of patients with colon cancer present with localised diseases. However, despite curative surgery, patients still have a significant probability of disease relapse and cancer-related death. Much interest has been generated in the last few decades in adjuvant treatment that would eliminate microscopic disease, thus preventing recurrent diseases. Whereas radiotherapy is often considered as part of the adjuvant treatment in rectal cancer, it has not been shown to improve outcome in colon cancer². In patients with advanced CRC, 5-year survival is only 8.3% in the US³. 5-Fluorouracil (5-FU) has been the mainstay treatment for the last few decades. However, the recent introduction of drugs such as irinotecan, oxaliplatin, oral fluoropyrimidines and raltitrexed have increased the treatment options available for these patients.

Adjuvant chemotherapy in colon cancer

Stage III colon cancer
A series of large randomised studies performed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and National Cancer
<table>
<thead>
<tr>
<th>Study &amp; Country/Year of main publication</th>
<th>Author &amp; Year of publication</th>
<th>Stage</th>
<th>Treatment</th>
<th>Treatment duration</th>
<th>No. of eligible patients (total)</th>
<th>3–5-yr overall survival</th>
<th>P 3–5-yr disease/relapse-free survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intergroup-0035 USA, [1984–1987]</td>
<td>Moertel et al.</td>
<td>III</td>
<td>(A) Observation</td>
<td>315</td>
<td>55%</td>
<td>0.007</td>
<td>47% &lt; 0.0001</td>
<td>0.40% decrease in recurrence and 33% decrease in mortality with 5-FU/LV compared with observation. LEV alone had no detectable survival advantage (P = 0.57)</td>
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<td>Intergroup-0085 USA, [1988–1989]</td>
<td>O'Connell et al.</td>
<td>II &amp;  III</td>
<td>(A) Observation</td>
<td>151</td>
<td>63%</td>
<td>0.01</td>
<td>58% 0.004</td>
<td>5-FU/low dose LV for 6 months produced survival advantage over observation alone</td>
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<td>Intergroup-0089 USA, [1988]</td>
<td>Haller et al.</td>
<td>II &amp;  III</td>
<td>(A) 5-FU (450 mg/m²)/LEV days 1–5 then weekly from day 29</td>
<td>6 mth</td>
<td>63%</td>
<td>0.09</td>
<td>56% 0.09</td>
<td>5-FU/low dose LV/LEV has statistically better disease-free survival and overall survival than 5-FU/LEV. Otherwise pair-wise comparisons between treatment arms showed no differences in overall survival disease-free and survival. 6 months of adjuvant therapy with 5-FU + LV at either high or low dose represent standard adjuvant treatment for patients</td>
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<tr>
<td>Intergroup-0089-46-51 USA, [not stated]</td>
<td>O'Connell et al.</td>
<td>III or high</td>
<td>(A) 5-FU (450 mg/m²)/LEV days 1–5 then weekly from day 29</td>
<td>6 mth</td>
<td>60%</td>
<td>0.05</td>
<td>58% 0.25</td>
<td>No significant difference is detected between 6 and 12 months' treatment with same regimen. If only 6 months of treatment were given, 5-FU/LEV was significantly worse than 5-FU/LV/LEV.</td>
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(Continued on next page)
Table 1 (continued from opposite page)

| NSABP C-01 | Wolmark et al<sup>59</sup> III | (A) Observation – | 383 | 59% (5 yr) | 0.05 | 51% (5 yr) | 0.02 | First randomised study showing survival advantage with adjuvant chemotherapy in Dukes’ B and C cancers. BCG resulted in the same disease-free survival but prolonged overall survival compared to observation due to decrease in cardiovascular deaths – an effect not seen when surgery was compared with chemotherapy.
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<tbody>
<tr>
<td>USA</td>
<td>1988</td>
<td>(B) 5-FU (325–375 mg/m² days 1–5, days 36–40)/Semustine (150 mg/m² day 1)/vincristine (1 mg/m² days 1,3,6) [MOF regimen]. Cycle repeated every 10 weeks (C) BCG (6×10⁶ viable organisms weekly)</td>
<td>358</td>
<td>67% (5 yr)</td>
<td>0.02</td>
<td>58% (5 yr)</td>
<td>0.02</td>
<td></td>
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</tbody>
</table>

| NSABP C-02 | Wolmark et al<sup>60</sup> III | (A) Observation – | 459 | 70% (5 yr) | 0.07 | 60% (5 yr) | 0.02 | Although portal venous infusion showed an improvement in disease-free survival and overall survival, i.v. chemotherapy was preferred by NSABP as control in future studies.
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<tbody>
<tr>
<td>USA, et al&lt;sup&gt;63&lt;/sup&gt; A, B</td>
<td>Dukes’ III (5 yr) (A vs B) (5 yr) (A vs C)</td>
<td>(B) 5-FU (600 mg/m²) portal vein infusion</td>
<td>442</td>
<td>78% (5 yr)</td>
<td>0.09</td>
<td>69% (5 yr)</td>
<td>0.09</td>
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</table>

| NSABP C-03 | Wolmark et al<sup>64</sup> III | (A) 5-FU (325–375 mg/m² days 1–5, days 36–40)/Semustine (130 mg/m² day 1)/vincristine (1 mg/m² days 1,3,6) [MOF regimen]. Cycle repeated every 10 weeks (B) 5-FU (500 mg/m²)/LV (500 mg/m²) weekly 6 times every 8 weeks | 524 | 66% (5 yr) | 0.003 | 54% (5 yr) | 0.0004 | 5-FU/high dose LV was superior to MOF.
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<tr>
<td>USA, et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>[1987–1989] 1993</td>
<td>(B) 5-FU (500 mg/m²)/LV (500 mg/m²)/IFN (5 _ 10⁶ U/m²) days 1–5 then weekly from day 29</td>
<td>521</td>
<td>76% (5 yr)</td>
<td>0.67</td>
<td>66% (5 yr)</td>
<td>0.67</td>
<td></td>
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</table>

| NSABP C-04 | Wolmark et al<sup>67</sup> III | (A) 5-FU (500 mg/m²)/LV (500 mg/m²)/IFN (5 _ 10⁶ U/m²) days 1–5 then weekly from day 29 (B) 5-FU (450 mg/m²)/LEV days 1–5 weekly 6 times every 8 weeks | 691 | 74% (5 yr) | 0.13 | 65% (5 yr) | 0.13 | 5-FU/high dose LV resulted in small prolongation of OS and disease-free survival compared with 5-FU/LEV. The addition of LEV to 5-FU/LV conferred no additional benefit.
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<tbody>
<tr>
<td>USA, et al&lt;sup&gt;70&lt;/sup&gt;</td>
<td>[1989–1990] 1999</td>
<td>(B) 5-FU (450 mg/m²)/LEV days 1–5 then weekly from day 29</td>
<td>696</td>
<td>70% (5 yr)</td>
<td>0.67</td>
<td>60% (5 yr)</td>
<td>0.67</td>
<td></td>
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</tbody>
</table>

| NSABP C-05 | Wolmark et al<sup>72</sup> III | (A) 5-FU (370 mg/m²)/LV (500 mg/m²) days 1–5 every 4 weeks (B) 5-FU (370 mg/m²)/LV (500 mg/m²)/IFN (5 _ 10⁶ U/m²) days 1–5 every 4 weeks | 1069 | 76% (5 yr) | 0.34 | 65% (5 yr) | 0.34 | No survival advantage of adding IFN to 5-FU/LV with significantly increased toxicity due to IFN.
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</thead>
<tbody>
<tr>
<td>USA, et al&lt;sup&gt;74&lt;/sup&gt;</td>
<td>[1991–1994] 1998</td>
<td>(C) BCG (6×10⁶ viable organisms weekly)</td>
<td>1060</td>
<td>77% (5 yr)</td>
<td>0.64</td>
<td>68% (5 yr)</td>
<td>0.64</td>
<td></td>
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</tbody>
</table>

(Continued on next page)
Table 1 (continued) Studies of adjuvant therapy for colon cancer conducted by Intergroup, NSABP and IMPACT

<table>
<thead>
<tr>
<th>Study &amp; Country/Year of main publication</th>
<th>Author &amp; Stage of disease</th>
<th>Treatment arms</th>
<th>Treatment duration</th>
<th>Treatment No. of eligible patients (total)</th>
<th>3–5-yr overall survival</th>
<th>P 3–5-yr disease/freedom of relapse</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT-1, IMPACT-4 &amp; IMPACT-600</td>
<td>International (Italy, France and Canada), 1995–1997</td>
<td>(A) Observation</td>
<td>–</td>
<td>757</td>
<td>68%</td>
<td>0.018</td>
<td>62% &lt; 0.0001</td>
</tr>
<tr>
<td>NACCP, Taal et al (46%) III (90%)</td>
<td>The Netherlands, 2001 &amp; III (54%)</td>
<td>(A) Observation</td>
<td>–</td>
<td>515</td>
<td>58%</td>
<td>0.007 Not reported</td>
<td>NR Both colorectal cancers are included</td>
</tr>
<tr>
<td>AGO, Porschen et al (47%) III</td>
<td>Germany, 1991–1994</td>
<td>(A) Observation</td>
<td>–</td>
<td>331</td>
<td>65.3%</td>
<td>0.0089 49 mth 0.037</td>
<td></td>
</tr>
<tr>
<td>QUASAR, QUASAR-15 &amp; QUASAR-730</td>
<td>UK, 1994–1997</td>
<td>(A) 5-FU (370 mg/m²)/LV (175 mg fixed dose) weekly or 4-weekly versus</td>
<td>6 mth</td>
<td>2464</td>
<td>70.1%</td>
<td>0.43 A vs B 36%</td>
<td>0.94</td>
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<tr>
<td></td>
<td></td>
<td>(B) 5-FU (370 mg/m²)/LV (25 mg fixed dose) weekly or 4-weekly</td>
<td>6 mth</td>
<td>2463</td>
<td>71.0%</td>
<td>0.38 A vs B</td>
<td></td>
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<td>(C) 5-FU (370 mg/m²)/high or low dose LV/LEV weekly or 4-weekly versus</td>
<td>6 mth</td>
<td>2429</td>
<td>69.4%</td>
<td>0.06 C vs D 37.0%</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(D) 5-FU (370 mg/m²)/high or low dose LV/placebo weekly or 4-weekly</td>
<td>6 mth</td>
<td>2434</td>
<td>71.5%</td>
<td>34.9%</td>
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</tr>
</tbody>
</table>

NSABP, National Surgical Adjuvant Breast and Bowel Project; IMPACT, International Multicenter Pooled Analysis of Colon Cancer Trials; LEV, lewamisole given 50 mg 8-hourly for 3 days every 2 weeks; LV, leucovorin; IFN, interferon α-2a; NR, Not reported in the publication; wk, weeks; yr, years; mth, months; vs, versus
Institute sponsored co-operative groups has defined the role of adjuvant chemotherapy in patients with stage III (Dukes’ C) colon cancer. Table 1 shows the details of these studies. Encouraged by the initial results from the NCCTG (North Central Cancer Treatment Group), 5-FU/levamisole was shown to increase disease-free survival and overall survival in the confirmatory US Intergroup-0035 study with mature results showing 40% reduction in recurrence and 33% reduction in mortality. This led to the recommendations from the National Institutes of Health consensus conference for this drug combination to be given as adjuvant therapy in patients with stage III colon cancer. 5-FU/levamisole became the standard of care in the US and formed the control arm in many studies conducted in the 1990s.

5-FU and leucovorin (LV) has been used in various doses and schedules in advanced colorectal cancer and it is, therefore, logical to test this combination as adjuvant therapy. Its efficacy is confirmed in Intergroup-0085, NSABP C-03 and IMPACT-1 studies. In addition, this combination has also been tested against 5-FU/levamisole as well as the addition of levamisole or interferon-α-2a (IFN) to 5-FU/LV. Evidence emerging from these studies shows that: (i) 5-FU/low dose LV (20 mg/m²) is equivalent to 5-FU/high dose LV (200–500 mg/m²); (ii) 5-FU/LV given for 6 months is as good as given for 12 months; (iii) there is no significant difference between the two most commonly used bolus 5-FU/LV dose schedules – 5-FU 425 mg/m² and LV 20 mg/m² days 1–5 every 4 weeks for 6 cycles (Mayo Clinic regimen) and 5-FU 500 mg/m² and LV 500 mg/m² weekly 6 times every 8 weeks for 3–4 cycles (Roswell Park regimen); (iv) 5-FU/levamisole given for 6 months is inferior to the same treatment given for 12 months; and (v) interferon produced no additional survival benefit at the expense of excessive toxicities.

Although the use of adjuvant therapy was widely disseminated between 1989 and 1990 in the US, there remained some uncertainties in Europe. Several studies that were reported in the last two years were originally initiated in the 1990s and were mainly conducted in Europe – some of which were aimed to replicate the results achieved in the US. In The Netherlands Adjuvant Colon Cancer Project (NACCP) study, patients were randomised to receive 12 months of adjuvant 5-FU/levamisole or observation. This study confirmed the survival benefit of adjuvant therapy with a 27% reduction in odds-of-death in stage III disease. Apart from overall survival, adjuvant chemotherapy also resulted in significantly better recurrence-free survival.

Another study in Germany randomised 702 patients with stage III disease to receive either 5-FU/levamisole or 5-FU/LV (100 mg/m²). 5-FU/LV given for 12 months showed a better overall and disease-free survival albeit a higher incidence of gastrointestinal toxicity. In another 3-arm German study, patients were compared between 5-FU/levamisole
with the addition of either LV (200 mg/m²) or interferon⁰⁴. The addition of LV to 5-FU/levamisole resulted in a better 4-year survival whereas the addition of interferon did not influence survival but resulted in much greater grade 3 and 4 toxicities than either 5-FU/levamisole or 5-FU/levamisole/LV.

The QUASAR (Quick And Simple And Reliable) study was the largest adjuvant study conducted to date⁰⁵. A total of 4927 patients were recruited with 95% of patients entered from the UK. In a two by two factorial design, patients were randomised to receive 5-FU with either high-dose (175 mg fixed dose) or low dose (25 mg fixed dose) LV and with either levamisole or placebo. No differences in survival or recurrence were observed between high or low dose LV. However, more recurrences and borderline worse survival occurred in the levamisole arm compared to placebo. Therefore, results from QUASAR, Intergroup-0089 and the previously mentioned German study⁰⁴ suggested that although 5-FU/levamisole/LV may be superior to 5-FU/levamisole, it does not confer any benefits over 5-FU/LV. Toxicities between high and low dose LV were similar in the QUASAR trial although treatment with levamisole resulted in more dermatological toxicities than placebo arm. Treatment-related mortality occurred in 0.1% of patients confirming these adjuvant chemotherapy regimens are safe in large-scale phase III studies.

Stage II colon cancer

Adjuvant therapy in patients with stage II (Dukes’ B) colon cancer remains controversial with no international consensus. Two large analyses have addressed this issue⁰⁴,⁰⁵. NSABP used results from C-01, C-02, C-03 and C-04 to compare the relative efficacy of adjuvant chemotherapy in patients with stage II and stage III colon cancer⁰⁵. When these 4 trials were examined independently, a similar benefit from treatment was seen in stage II and stage III, but the number of patients with stage II cancer was too limited to rule out a difference in treatment effect according to staging. In addition, NSABP also examined the trials collectively by creating two comparison groups: the first group consisted of all patients with the superior treatment in each of the 4 trials and the second consisted of patients on the inferior treatment. Using this methodology, the results were pooled in 1565 stage II patients and reductions in mortality and recurrence were seen with adjuvant chemotherapy. However, not all NSABP studies had an observation arm and pooling results in this way represented an unconventional approach given that the treatment received in these four trials varied widely. In contrast, the IMPACT B2 study pooled results from 5 trials including 1006 patients with Dukes’ B2 colon cancer and the results did not
support the use of 5-FU/LV as a standard adjuvant treatment for such patients\textsuperscript{20}. This study showed no differences in 5-year overall survival rate (80\% in control group \textit{versus} 82\% in 5-FU/LV group; hazard ratio [HR], 0.86; 90\% confidence interval [CI], 0.68–1.07, \(P = 0.130\)) and event-free survival (73\% in control group \textit{versus} 76\% in 5-FU/LV group; HR, 0.88; 90\% CI, 0.72–1.07, \(P = 0.137\)).

However, the previously mentioned Dutch NACCP study has reported a beneficial effect of adjuvant chemotherapy in stage II patients\textsuperscript{16}. In addition to the expected benefit in stage III, this study also showed a 19\% reduction in death from 468 patients with stage II disease. Although the prognosis is significantly different for stage II and stage III, the size of reduction in odds-of-death by treatment was similar.

Taken together, the value of adjuvant chemotherapy for Dukes’ B/stage II disease is not yet proven, but relatively few patients have been randomised. Small treatment difference can only be detected reliably with many more patients. To detect an absolute risk reduction of 4\% at 5 years, 4700 patients will be required\textsuperscript{22}. In individual stage II patients without other medical contra-indications, adjuvant treatment with 6 months of 5-FU/leucovorin could be offered after a careful discussion with the patient who should understand that such adjuvant treatment is not definitely proven and that any benefit is likely to be small. However, in patients with high-risk characteristics such as intestinal obstruction, perforation, T4 tumours, poorly differentiated tumours, extramural venous or lymphatic invasion or perineural invasion and no other medical contra-indications, adjuvant therapy can reasonably be offered to them.

\textbf{Infused 5-FU as adjuvant therapy}

Prolonged infusion of 5-FU results in less haematological toxicity and a small, but statistically significant, survival advantage over bolus regimens in advanced colorectal cancer\textsuperscript{23}, thus providing the rationale to investigate infused 5-FU as adjuvant therapy. Three months of protracted venous infusion (PVI) 5-FU produced similar overall and relapse-free survival compared with 6 months of bolus 5-FU/LV in a recent UK study\textsuperscript{24}. Significantly less diarrhoea, stomatitis, neutropenia, anaemia and alopecia occurred with PVI 5-FU. A French study co-ordinated by GERCOR (Group d’Etude et de Recherche Clinique en Oncologie Radiotherapies) compared 2-weekly continuous infusion of 5-FU/LV with 4-weekly bolus 5-FU/LV with a second randomisation to either 24 or 36 weeks of treatment. A total of 905 patients recruited from 1996 to 1999 showed that 2-weekly treatment was less toxic than monthly treatment with lower incidences of neutropenia, diarrhoea and mucositis. No differences in disease-free survival was seen between the
treatment arms (HR, 1.042; 95% CI, 0.814–1.335) or between different
duration of treatment (HR, 0.942; 95% CI, 0.735–1.21)\textsuperscript{25}. In the
Intergroup-0153 study, continuous infusion of 5-FU with levamisole
was compared to bolus 5-FU/LV and levamisole\textsuperscript{26}. The study was closed
prematurely after 1078 patients had been recruited when an interim
analysis showed no survival advantage in the continuous infusion arm
and this was unlikely to happen even if the accrual goal of 1800 patients
was reached.

Given that the current studies do not support a dramatic survival
benefit of bolus 5-FU/LV over infused 5-FU or \textit{vice versa} and these dose
schedules show different toxicity profiles, it is reasonable to consider
infused 5-FU to be used in place of bolus 5-FU/leucovorin depending on
treating clinicians’ and patients’ preference. Two-weekly infused 5-
FU/LV has been adopted as the control arm when comparing with the
addition of irinotecan or oxaliplatin to 2-weekly 5-FU/LV in two large
European studies.

\textbf{Active new drugs in adjuvant therapy}

Capecitabine has been shown to have equivalent survival to bolus 5-
FU/LV in advanced colorectal cancer\textsuperscript{27,28}. Oral tegafur (UFT) and uracil
plus LV have also been shown to have similar survival to bolus 5-FU/LV
in advanced colorectal cancer\textsuperscript{29,30}. In the adjuvant setting, capecitabine
is being tested against bolus intravenous 5-FU/LV in 1956 stage III
patients with colon cancer. NSABP C-06 was designed to compare
treatment using UFT/LV against bolus 5-FU/LV and recruited 1608
patients. Accrual has finished in both studies and efficacy results are
expected in the next couple of years.

Irinotecan has been shown to improve survival in both first and second
line settings in advanced colorectal cancer\textsuperscript{31–34}. Its role in adjuvant
treatment was tested in 2 large studies – CALGB (Cancer and Leukemia
Group B) C89803 and PETACC-3. However, in April 2001, an unexpected
number of deaths occurred within the first 60 days of study entry in
N9741, an Intergroup randomised study using irinotecan and bolus 5-
FU/LV in recurrent and metastatic colorectal cancer, and a review of early
death rate in C89803 concurred with the result. Some 2.2% of patients in
study C89803 receiving irinotecan and bolus 5-FU/LV experienced early
deaths as opposed to a treatment-related mortality of 0–0.8% in recently
reported colon cancer adjuvant studies. In relation to other arms of the
studies, irinotecan and bolus 5-FU/LV had a 3-fold increased rate of
treatment induced or treatment exacerbated deaths\textsuperscript{35}. The majority of
deaths are attributable to either multiple gastrointestinal toxicities or
sudden unexpected thrombo-embolic events or both. In the PETACC-3
Chemotherapy in colorectal cancer

Oxaliplatin is a third generation platinum compound that has shown promise in advanced colorectal cancer and is used widely in Europe. A European study (MOSAIC) recruited 2248 stage II and III colon cancer patients and preliminary data confirm the safety of oxaliplatin/infused 5-FU/LV as adjuvant treatment. NSABP C-07 is still on-going, testing the adjuvant role of oxaliplatin/bolus 5-FU/LV and aims to recruit 2472 patients.

Edrecolomab is a monoclonal antibody against human tumour associated antigen Ep-CAM (also known as 17-1A). In a German study comparing edrecolomab monotherapy with observation in 189 stage III colorectal cancer patients, edrecolomab monotherapy resulted in a significantly better overall and disease-free survival. Two large phase III studies have been reported. The first 3-arm randomised study of 2761 stage III colon cancer patients showed that edrecolomab monotherapy was inferior to either 5-FU/LV or 5-FU/LV/edrecolomab whilst there were no differences in overall survival and disease-free survival between 5-FU/LV and 5-FU/LV/edrecolomab. A second study randomised 1839 patients to receive 5-FU-based chemotherapy with or without edrecolomab. A significant survival benefit favoured the addition of edrecolomab, but an absolute survival benefit of only 2.7% in 3-year overall survival was seen. Combining edrecolomab with 5-FU-based treatment did not alter the incidences of 5-FU related toxicities.

Chemotherapy in metastatic colorectal cancer

5-Fluorouracil (5-FU)

Single agent 5-FU given as an intravenous bolus injection produces a response rate of approximately 10%. Two strategies have been pursued to improve on this – prolonged infusion schedules and biochemical modulation. Prolonged infusions of 5-FU have been shown in a meta-analysis to have a higher response rate and longer duration of response compared with bolus schedules. A small improvement in overall survival was also demonstrated. However, the pattern of toxicity is different with more haematological toxicity occurred with bolus schedules and more hand-foot syndrome with the infused schedules. No significant differences in diarrhoea, nausea/vomiting and mucositis were seen. Biomodulation of 5-FU with leucovorin, methotrexate, trimethrexate, interferon, dipyridamole, N-phosphonacetyl-L-aspartic acid (PALA) have been investigated. Among these, biomodulation with LV has been used most extensively. Although highly significant improved tumour response rates were noted compared with 5-FU alone, no discernible survival advantage was seen.
Table 2  Pivotal studies in the treatment of advanced colorectal cancer

<table>
<thead>
<tr>
<th>Drugs/study</th>
<th>Treatment arms</th>
<th>Patients (n)</th>
<th>Response rates (%)</th>
<th>Median overall survival (months)</th>
<th>Median progression free survival (months)</th>
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<tbody>
<tr>
<td><strong>Oral fluoropyrimidines</strong></td>
<td></td>
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<tr>
<td>Capecitabine</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hoff et al(^{p2})</td>
<td>Capecitabine</td>
<td>302</td>
<td>25.8*</td>
<td>12.5</td>
<td>4.3#</td>
</tr>
<tr>
<td></td>
<td>Bolus S-FU/LV</td>
<td>303</td>
<td>11.6</td>
<td>13.3</td>
<td>4.7#</td>
</tr>
<tr>
<td>Van Cutsem et al(^{p3})</td>
<td>Capecitabine</td>
<td>301</td>
<td>18.9</td>
<td>13.2</td>
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<td>Van Cutsem et al(^{p7})</td>
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<td>Irinotecan and bolus S-FU/LV</td>
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<td>28</td>
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\(^*\) P < 0.05; #time to disease progression; NR, Not reported.
Oral fluoropyrimidines

Oral fluoropyrimidines may represent an alternative to continuous intravenous infusion of 5-FU, which is cumbersome to use and compromises patients’ independence. Moreover, the elimination of ports and pumps required for intravenous infusion and the avoidance of the associated complications with intravenous catheters may translate into cost-saving measures. Several oral fluoropyrimidines have completed phase III clinical studies as first-line treatment for advanced CRC. In all these trials, bolus 5-FU/LV (Mayo Clinic regimen) was used as the control arm (Table 2).

Capecitabine

Capecitabine is an oral, tumour-selective fluoropyrimidine carbamate. It was designed to be sequentially converted to 5-FU by 3 enzymes located in the liver and in tumours. The final step is the conversion of 5′-deoxy-5-fluorouridine (5′-DUFR) to 5-FU by thymidine phosphorylase (dThdPase) in tumours. Tumour selectivity has been studied in patients receiving capecitabine twice daily for 5–7 days before surgical resection of primary colorectal tumours, liver metastases or both. 5-FU concentrations were found to be 3.2 times greater in primary tumours than surrounding healthy tissue, 1.17 times greater in liver metastases than non-cancerous liver tissue and 20 times greater in primary tumour than in the plasma. These results demonstrated the preferential activation of capecitabine to 5-FU in colorectal tumour after oral administration to patients.

Two phase III randomised trials have been conducted evaluating capecitabine in advanced colorectal cancers involving 1207 patients. These two studies had identical study design to demonstrate equivalence in overall response rates between oral capecitabine (1.25 g/m² twice daily for 14 days, every 3 weeks) with intravenous bolus 5-FU/LV (Mayo Clinic regimen). When data from these two studies were pooled, a significantly superior overall response rate was seen in the capecitabine arm compared with 5-FU/LV (25.7% versus 16.7%, \( P < 0.0002 \)). Equivalent median time to disease progression and overall survival were seen in both arms. When toxicities were compared, a significantly lower incidence of diarrhoea, stomatitis, nausea and alopecia was seen with capecitabine. Hand-foot syndrome was, however, seen more frequently with capecitabine. Grade 3/4 neutropenia was significantly more common in the 5-FU/LV group compared with capecitabine (21.1% versus 2.2%) resulting in significantly higher incidence of neutropenic fever and sepsis.

UFT

UFT, another oral fluoropyrimidine formulation, combines uracil and tegafur in a fixed molar ratio of 4:1. Tegafur is a prodrug of 5-FU and is
completely and rapidly absorbed after oral administration. After absorption, it is converted to 5-FU by the hepatic microsomal system. Uracil inhibits the dihydropyrimidine dehydrogenase (DPD), the main catabolic enzyme of 5-FU, resulting in elevated and sustained concentrations of 5-FU in the body. Two phase III studies in advanced colorectal cancer have been reported comparing oral UFT plus LV (UFT 300 mg/m²/day, LV 75–90 mg/m²/day for 4 weeks every 5 weeks) to intravenous bolus 5-FU/LV (Mayo regimen). In the first study where 816 patients were randomised, overall survival was similar in both arms with a median survival of 12.4 months (UFT/LV) and 13.4 months (5-FU/LV)\textsuperscript{29}. However, this study was designed to demonstrate equivalence in survival for UFT/LV and bolus 5-FU/LV and the statistical equivalence was based on the lower boundary of 95.6\% CI of the hazard ratio exceeding 0.8. At the final planned analysis, the lower bound of HR for this study was 0.794 and only in an updated survival analysis a HR of 0.96 (95.6\% CI, 0.83–1.13) was seen. Time to progression was significantly worse in the UFT/LV arm (3.5 months versus 3.8 months, \(P = 0.011\)). In addition, there is a disparity in survival effect between US and non-US patients with UFT/LV performing poorly with US patients. In a second study of 380 patients which was designed to show superiority of UFT/LV over a less dose intensive bolus 5-FU/LV regimen (given every 5 weeks instead of every 4 weeks), similar survival was demonstrated (HR, 1.144; 95\% CI, 0.920–1.424) and the survival of the patients receiving this bolus 5-FU/LV regimen fared badly in comparison to other contemporary trials\textsuperscript{30}. As such, UFT/LV has not gained approval for US use yet.

Aside from efficacy, UFT/LV resulted in significantly less grade 3/4 stomatitis, neutropenia, febrile neutropenia (\(P < 0.001\)) and infections (\(P < 0.05\)) compared with bolus 5-FU/LV. In contrast to capecitabine, the incidence of hand-foot syndrome was very low with only 2\% of patients developing grade 1/2 toxicities\textsuperscript{29,30}. Since the reporting of these two studies, a randomised cross over trial, conducted by the European Organisation for Research and Treatment of Cancer (EORTC), assessed the patients’ preference for oral UFT/LV to intravenous 5-FU/LV chemotherapy\textsuperscript{45}. A total of 37 previously untreated patients were randomised with 84\% of the patients preferring oral UFT/LV over intravenous 5-FU/LV. The most frequently reported factor for patient preference was the ability of the medication to be taken at home.

Eniuracil

Eniuracil is a potent and highly effective inactivator of DPD. Administration of eniuracil with 5-FU significantly increases the oral bioavailability, decreases the clearance and reduces the pharmacokinetic variability of 5-FU. Two randomised phase III studies have been reported. In the first study designed to show equivalence in survival, 981
North American patients were randomised. Statistical criteria for equivalence was not met although eniluracil/5-FU was not statistically inferior in survival to bolus 5-FU/LV. However, in a second study performed predominantly in Europe and Australasia randomising 531 patients, an inferior overall survival was shown in patients treated with eniluracil/5-FU. In view of these results, the clinical development of eniluracil/5-FU has been halted in colorectal cancer.

**Irinotecan (CPT-11)**

Irinotecan is a semi-synthetic derivative of the natural alkaloid camptothecin. It interacts with topoisomerase-I, which is a ubiquitous nuclear enzyme with key roles in DNA replication, transcription and possibly DNA recombination, and repair by relaxing torsionally strained supercoiled duplex DNA. *In vitro* and *in vivo* evidence suggested schedule-dependent cytotoxic interactions for the combination of thymidylate synthase inhibitors and irinotecan or its active metabolite SN-38. *In vitro* cytotoxic synergism was also noted with oxaliplatin, a third generation platinum compound.

During its clinical development, several doses and schedules of single agent irinotecan have been evaluated. In patients with advanced colorectal cancers with prior exposure to a fluorouracil-based regimen, overall response rates ranging from 11–17% were reported and these response rates were similar with different dose schedules.

Irinotecan has been evaluated in two studies in patients resistant to fluorouracil-based chemotherapy (Table 2). The first study compared irinotecan to best supportive care whereas the second one compared with infused fluorouracil. In the first study, overall survival was significantly better in the irinotecan group with 1-year survival of 36.2% compared with 13.8% in the best supportive care group (*P* = 0.0001). Pain-free survival and quality-of-life analysis were both in favour of the irinotecan group. In the second study, 1-year survival was also significantly improved with irinotecan (45%) compared with infused fluorouracil (32%). These results led to the acceptance of irinotecan as a standard second-line treatment in advanced colorectal cancer.

On the basis of promising efficacy for the combination of irinotecan with 5-FU/LV in phase I and II studies, two phase III randomised studies were conducted. In the first study of 683 patients conducted in the US, Canada, Australia and New Zealand, three treatment arms were compared: arm A consisted of irinotecan 125 mg/m², LV 20 mg/m² followed by 5-FU bolus 500 mg/m² weekly 4 times every 6 weeks (IFL/Saltz regimen); arm B consisted of bolus 5-FU/LV (Mayo regimen); and arm C consisted of irinotecan 125 mg/m² weekly 4 times every 6
weeks. IFL regimen resulted in a longer overall survival ($P = 0.04$) compared with 5-FU/LV whereas irinotecan monotherapy resulted in similar survival to 5-FU/LV in first-line treatment.$^{34}$

In the second study conducted in 13 European countries, Israel and South Africa, 387 patients were randomly assigned to irinotecan combined with infused 5-FU/LV or same schedule of infused 5-FU/LV. Depending on the treating clinicians, infusion schedules of 5-FU/LV were given either once weekly or every 2 weeks. Survival was again superior in the irinotecan group ($P = 0.031$)$^{32}$. These two studies demonstrated that irinotecan in combination with 5-FU/LV improved tumour control irrespective of the schedules of 5-FU/LV administration.

The main toxicities encountered with irinotecan are delayed onset diarrhoea, neutropenia, nausea, vomiting, asthenia, acute cholinergic-like syndrome and alopecia. Delayed onset diarrhoea occurs 24 h after irinotecan infusion, with the peak incidence at days 5 or 6. Diarrhoea, especially when accompanied with neutropenia and dehydration, can be potentially life-threatening. However, with appropriate supportive measures, these side-effects can be manageable. If a first liquid stool occurs, patients must take anti-diarrhoeal drugs such as loperamide 4 mg immediately followed by 2 mg every 2 h for at least 12 h and for 12 h after the last liquid stool. Patients should be informed that they must drink large volumes of beverages containing electrolytes during the diarrhoeal episode. Loperamide should be provided when they leave clinic/hospital. Patients who experience concomitant vomiting or fever should be hospitalised quickly for intravenous rehydration. If diarrhoea persists for more than 24 h despite the recommended loperamide treatment, patients should be treated with a prophylactic oral broad-spectrum antibiotic (e.g. ciprofloxacin 250 mg twice a day, orally), which should be supplied to patients when they leave hospital. If diarrhoea persists for more than 48 h despite loperamide and ciprofloxacin treatment, the patient should be considered for hospitalisation for parenteral support and treatment with another anti-diarrhoeal agent. Acute cholinergic-like syndrome is characterised by sweating, lacrimation, salivation, early diarrhoea, abdominal cramps and bradycardia. Symptoms are usually short-lasting and will respond within minutes to administration of atropine (0.25–1 mg subcutaneously).

**Oxaliplatin**

Oxaliplatin is a third-generation platinum compound with a 1,2-diaminocyclohexane (DACH) carrier ligand. This important difference in the molecule, and hence in the DNA adducts formed, confers a different spectrum of activity compared with that of cisplatin. As a single agent,
oxaliplatin has been evaluated in untreated patients with metastatic colorectal cancer with response rates of 12–24.3%\(^\text{49}\). However, \textit{in vitro} synergy with 5-FU/LV has led most studies to evaluate oxaliplatin in combination with 5-FU/LV either as flat-rate or chronomodulated infusions. In a phase III study, the addition of oxaliplatin to chronomodulated 5-FU/LV in the first-line treatment of metastatic CRC resulted in an improved response rate and median progression free survival, but no difference in overall survival was detected (Table 2)\(^\text{37}\). In another phase III study, the addition of oxaliplatin to flat-rate infusion of 5-FU/LV again resulted in an improved response rate and median progression free survival, but no difference in overall survival\(^\text{36}\). However, a significant proportion of patients in the 5-FU/LV-alone arm received oxaliplatin on disease progression, therefore potentially diminishing the survival advantage with oxaliplatin given in the first line setting. A further international randomised study comparing flat-rate infusions of 5-FU/LV with or without oxaliplatin has recently finished recruitment. In this study, all patients were mandated to receive irinotecan as second-line treatment, therefore eliminating the cross-over effect of the use of second-line oxaliplatin.

The US Intergroup study N9741 has recently reported an overall survival advantage with an oxaliplatin-containing regimen. This study was originally designed as a 6-arm study. Two of the arms were closed early due to poor tolerability (irinotecan/bolus 5-FU/LV and oxaliplatin/bolus 5-FU/LV) and one arm was closed due to inferior efficacy from emerging evidence (bolus 5-FU/LV; Mayo regimen). The three remaining arm were irinotecan/bolus 5-FU/LV (IFL regimen), oxaliplatin/infused 5-FU/LV (FOLFOX regimen) and oxaliplatin/irinotecan. The FOLFOX regimen was found to have a better overall survival, time to progression, response rate and safety profile compared with IFL\(^\text{50}\). Currently, it is unclear whether these results from the N9741 trial could be attributed to the differences in the efficacy and toxicity profiles between bolus and infused 5-FU/LV schedules. Notably, about half of the patients randomised to FOLFOX arm in this trial received irinotecan on disease progression whereas few patients in the IFL arm received oxaliplatin as second-line treatment since oxaliplatin is currently not licensed in the US.

The adverse events most often cited with oxaliplatin are haematological, nausea, vomiting, diarrhoea, mucositis, early onset cold-induced dysaesthesia and a cumulative peripheral sensory neuropathy. Nephrotoxicity and ototoxicity were not reported in clinical trials unlike cisplatin. Moreover, there is a very low incidence of alopecia. Acute onset dysaesthesia is common, appears within hours of infusion and is usually short-lived. Cold contact provokes or exacerbates the characteristic acral and pharyngolaryngeal dysaesthesias that are occasionally accompanied by muscular and laryngeal spasms. Prolonging the infusion
time reduces its recurrence and no oxaliplatin dose reduction is required. Cumulative dose limiting peripheral sensory neuropathy occurs in 10–15% of patients after a total cumulative dose of 780–850 mg/m². Persistent paraesthesia occurs after multiple cycles of treatment. It is recommended that the oxaliplatin dose should decrease by 25% when paraesthesia becomes persistent between treatments. Oxaliplatin should be omitted in cases of functional impairment.

Irinotecan/oxaliplatin

In the first-line setting, combinations of both irinotecan/5-FU/LV and oxaliplatin/5-FU/LV appear to be of benefit especially in younger patients with good clinical conditions. However, the sequence of use or the efficacy of irinotecan/oxaliplatin combination has not been defined. A French randomised study of 220 patients addressed the issue of sequence. Patients were assigned to irinotecan/5-FU/LV (FOLFIRI) followed by oxaliplatin/5-FU/LV (FOLFOX) on disease progression (sequence A) or the inverse sequence (FOLFOX followed by FOLFIRI, sequence B). Although response rates in first-line setting were similar between FOLFIRI and FOLFOX (56% versus 53%, respectively), response rate was lower in FOLFIRI compared with FOLFOX in second line setting (4% versus 15%). However, time to progression after 2 lines of treatment, which was the primary objective of the trial, was similar between sequence A and sequence B (14.5 months and 11.9 months, respectively)\textsuperscript{51}.

Experimental data have shown synergistic effects between SN38 (active metabolite of irinotecan) and oxaliplatin. Combination regimens of irinotecan/oxaliplatin given weekly, every 2 weeks and every 3 weeks have been evaluated. Two randomised phase II studies have been conducted to test this combination against 5-FU/LV/alternating irinotecan (FOLFIRI) and oxaliplatin (FOLFOX)\textsuperscript{52} or raltitrexed\textsuperscript{53}. The first study compared 3-weekly irinotecan/oxaliplatin in the second-line setting with alternating FOLFIRI and FOLFOX. Irinotecan/oxaliplatin resulted in a more favourable response rate (23% versus 6%) and 1-year survival (54% versus 40%)\textsuperscript{52}. The second study evaluated 2-weekly irinotecan/oxaliplatin with raltitrexed in previously untreated patients with metastatic CRC. Upon disease progression, second-line treatment with the opposite arm was used. Patients allocated to irinotecan/oxaliplatin had a better response rate (43.5% versus 19.6%, P = 0.0025) and longer progression-free survival (median 7.1 versus 5.0 months, P = 0.0033), but no difference in overall survival (16.0 months versus 16.5 months, P = 0.3943). Similar numbers of patients crossed over to the opposite arm on disease progression\textsuperscript{53}.
In the US Intergroup N9741 study, 3-weekly irinotecan/oxaliplatin was compared with IFL and FOLFOX in a first-line setting. However, the data reported were still immature to define the true efficacy of irinotecan/oxaliplatin. Another on-going randomised study is comparing irinotecan/oxaliplatin with irinotecan in a second-line setting.

Most common grade 3/4 toxicities encountered with irinotecan/oxaliplatin combination are neutropenia, nausea and vomiting, diarrhoea, alopecia and asthenia. These toxicities are generally manageable, but an excessive number of serious adverse events did prompt a protocol specified adjustment of chemotherapeutic drug doses in one of the phase II studies.

Safety issues with irinotecan and oxaliplatin when combined with bolus schedules of 5-FU/LV

Recently, concerns have been raised over the safety of irinotecan when given in combination to bolus 5-FU/LV (IFL regimen). Higher than expected 60-day all-cause mortality rates were noted in two US randomised trials in adjuvant and metastatic colorectal cancer – CALGB C89803 and Intergroup N9741. This has been attributed to a gastrointestinal syndrome characterised by diarrhoea, nausea and vomiting, dehydration coupled with febrile neutropenia and electrolyte imbalances and a vascular syndrome characterised by acute, fatal myocardial infarction, cerebrovascular accident and pulmonary embolism. Arterial and venous thrombotic events were not in general associated with irinotecan when tested in advanced disease setting. However, when the data in the European advanced colorectal cancer study were reviewed, a higher than expected thromboembolic events were evident. In the US Intergroup N9741 trial, the treatment arm consisting of oxaliplatin/bolus 5-FU/LV was also associated with excessive treatment related deaths and was closed due to safety.

However, infused schedules of 5-FU/LV with irinotecan or oxaliplatin have not been shown to cause excessive treatment-related mortality. The evolution of combining irinotecan or oxaliplatin with 5-FU/LV appeared to have followed different avenues in the US and in Europe. Whereas a bolus schedule of 5-FU/LV given weekly is favoured in the US, a continuous infusion schedule given weekly or every 2 weeks is more in vogue in Europe. Treatment-related death with irinotecan and bolus 5-FU/LV is of concern and is even more unacceptable in adjuvant settings. It is possible that the bolus schedule is not the optimum partner with irinotecan and oxaliplatin, both of which can cause considerable side-effects if supportive measures are not instituted immediately at the onset of toxicity. Oral fluoropyrimidines such as capecitabine and UFT have been shown to have a more favourable toxicity profile than bolus 5-FU/LV although no direct comparisons with continuous infusion.
have been made. The efficacy of oral fluoropyrimidines with irinotecan or oxaliplatin has been demonstrated in phase II studies in metastatic colorectal cancer\textsuperscript{53,56}. These agents may prove in the future to bridge the gap between bolus and continuous infusion schedules when combining with irinotecan and oxaliplatin.

**Raltitrexed**

Raltitrexed is an inhibitor of thymidylate synthase although it inhibits this enzyme via different mechanisms from 5-FU. Prolonged thymidylate synthase inhibition is achieved by rapid polyglutamylation of folates and its subsequent retention within cells. Four large phase III studies have been conducted comparing raltitrexed with the Mayo regimen or the Machover regimen (5-FU 400 mg/m\textsuperscript{2}, LV 200 mg/m\textsuperscript{2}) and infused schedules. Median survival with raltitrexed was similar to 5-FU/LV regimens (bolus or infusion) in three of the four studies, but was inferior in the remaining study\textsuperscript{57}.

The major side-effects from raltitrexed are gastrointestinal, haematological and asthenia. However, treatment related deaths occurred in 2.3–6.0% of patients. Fatal adverse events were often due to a combination of diarrhoea complicated by neutropenia especially within the context of impaired renal function. As approximately 50% of the dose of raltitrexed is excreted unchanged in the urine, patients are required to have evaluation of their renal function prior to and during their treatment with raltitrexed and the dose of raltitrexed modified accordingly.

**Conclusions**

The current evidence confirms the role of adjuvant chemotherapy in patients with stage III colon cancer and 5-FU/LV should be the reference regimen to which new drugs test against in the adjuvant setting. In stage II colon cancer, because the risk of recurrence is lower, any absolute benefit of chemotherapy is likely to be less than stage III disease. The studies performed so far have been generally underpowered to detect what might be a clinically significant effect in survival. Although the recent results from the Dutch trial are supportive of adjuvant therapy in stage II disease, the relatively small group of stage II patients in this study is unlikely to convince all of the oncological community of the benefit of adjuvant chemotherapy, but will re-inforce consideration of this treatment in patients with adverse risk factors.

Irinotecan, oxaliplatin and oral fluoropyrimidines have been shown to be effective in advanced colorectal cancer and increase the treatment
options for patients with this disease. However, the optimal integration and the sequence of use of these drugs still need to be defined. In addition, with the improved understanding of colorectal cancer biology, novel molecular targets such as epidermal growth factor receptor, cyclooxygenase, angiogenic factors and matrix metalloproteinases have been identified. In combination with cytotoxic drugs, the inhibition of these new targets may impact on the survival of these patients in the future.

**Key points for clinical practice**

- Adjuvant chemotherapy should be routinely offered to medically fit patients with stage III colon cancer
- The role of adjuvant chemotherapy in stage II colon cancer is still controversial
- The introduction of irinotecan and oxaliplatin has broadened the treatment options for patients with advanced colorectal cancer
- Oral fluoropyrimidines has been shown to have better toxicity profiles and equivalent survival compared to bolus intravenous fluorouracil/leucovorin and may represent a more optimal partner when combined with irinotecan and oxaliplatin

**References**


Taal BG, Van Tinteren H, Zoetmulder FA. Adjuvant SFU plus levamisole in colon or rectal cancer: improved survival in stage II and III. Br J Cancer 2001; 85: 1437–43


Staub L, Link KH, Beger HG. Toxicity and effects of adjuvant therapy in colon cancer: results of the German prospective, controlled randomized multicenter trial FOGT-1. J Gastrointest Surg 2001; 5: 275–81

QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, high-dose folic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. Lancet 2000; 355: 1588–96


Saini A, Cunningham D, Norman A et al. Multicentre randomized trial of protracted venous infusion (PVI) 5FU compared to 5FU/folinic Acid (SFU/FA) as adjuvant therapy for colorectal cancer. Proc Am Soc Clin Oncol 2000; 19: 240a


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51 Achille E, Tourngand C, Andre T et al. FOLFIRI then FOLFOX or FOLFOX then FOLFIRI in metastatic colorectal cancer: results of a phase III trial. Eur J Cancer 2001; 37 (Suppl. 6): S289