5. Adjuvant systemic treatment for colon cancer

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Abstract. The prognosis associated with colon cancer remains poor, as less than 60% of patients are potentially curable with radical resection of the primary tumour [1]. For this reason, adjuvant therapy has been combined with surgery, and this has made a significant impact on cure rates for this disease. The benefits of adjuvant therapy in colon cancer will be outlined in the following chapter.

Introduction

Bolus of fluorouracil and leucovorin has been accepted as the standard adjuvant therapy in stage III colon cancer for many years. New drugs such as irinotecan, oxaliplatin and oral fluoropyrimidines have all completed phase III randomised evaluation in colon cancer and several of these studies have been reported recently.

As a result of these studies, oxaliplatin-based chemotherapy has emerged as the new standard of care in adjuvant treatment of stage III colon cancer.

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The advent of monoclonal antibodies such as cetuximab and bevacizumab has further broadened the treatment horizon for CRC and they were the focus of the recent randomised studies in adjuvant therapy of this disease.

In stage II colon cancer, adjuvant treatment remains controversial, but it is recommended in several subsets including poorly differentiated histology, T4 lesions, bowel perforation presentation and inadequately sampled lymph nodes (<13).

This chapter will review deeply all these treatments, thereby assisting clinicians in deciding the optimal adjuvant treatment for patients in routine clinical practice.

1. The history of adjuvant therapy in colon cancer

After many years of belief that adjuvant chemotherapy was of no benefit to patients with resectable adenocarcinoma of the colon, studies published in the 1980s evoked a great change in the surgical and medical approaches to this disease.

Chemotherapy in colon cancer began in the 1950s with use of the drugs, thiotepa, floxuridine and the fluoropyrimidines in patients with or without curative resections. A major therapeutic impact was not observed with these drugs, probably because knowledge concerning their pharmacological effects and mechanism of action was limited, the dose intensity offered was insufficient, and the patient groups studied were too small. Although the benefits noted were minimal, they were enough to stimulate research into finding better agents and combinations, leading to an improvement in adjuvant chemotherapy. The 1970s saw the introduction of the concept of biomodulation of 5-fluorouracil (5FU) by several different agents (levamisole (LEVA), leucovorin (LV), methotrexate, interferon, and N-(phosphonacetyl)-L-aspartate (PALA)), as well as immunotherapy, represented at first by the well-known Bacillus Calmette-Guérin (BCG) vaccine. The studies using methotrexate, interferon, or PALA with 5FU concluded that those modulators conferred no statistically significant benefit, and at the same time, increased toxicity. In addition, at around the same time, in the American National Surgical Adjuvant Breast and Bowel Project (NSABP) CO-1 study [2], conducted between 1977 and 1983, 1116 patients were randomly assigned to observation, chemotherapy with MOF (MeCCNU or semustine, plus vincristine and 5FU), or immunotherapy with BCG. This was the first large-scale trial that found a small increase in disease-free survival (DFS) and overall survival (OS) in patients receiving chemotherapy, especially in those with right-sided colonic tumours, while BCG did not influence any of the parameters studied. Despite this benefit, it was noted that meCCNU and other
alkylating agents could be leukemogenic and have renal toxicity, and so in subsequent studies these kinds of drugs were abandoned.

1.1. 5FU plus levamisole

Two American trials published in 1989 and 1990 showed significant benefits in using adjuvant chemotherapy, and subsequently changed the standard of care for patients with resectable colon cancer. The first, a study designed by the North Central Cancer Treatment Group (NCCTG) [3], assigned 408 patients (35% stage II and 65% stage III) to observation or to receive 1 year of the immunomodulatory agent LEVA with or without 5FU (table 1). When given with 5FU, patients treated with LEVA (5FU/LEVA), showed a small improvement in DFS and OS and with only mild toxicity. Results from this study stimulated the design of the next, the Intergroup (INT)-0035 trial, with 1,247 patients (25% stage II and 75% stage III) who were randomised to observation or to LEVA with or without 5FU (using the same regimens as in the NCCTG study). 5FU/LEVA reduced the recurrence rate by 33% compared with surgery alone (95% confidence interval (CI): 16–47%; hazard ratio (HR): 0.67, p= 0.0007) and reduced the risk of cancer recurrence by 40% (p<0.0001) [4,5]. The most common toxicities reported with this combination were mild and included myelosuppression, mild elevation of hepatic transaminases, dysgeusia, arthralgia, neurotoxicity and depression. In 1990, the magnitude of the benefit associated with the combination of 5FU/LEVA demonstrated in both of these studies resulted in FDA (Food and Drugs Administration) approval of the regimen for stage III CRC, and in recommendation by the USA National Cancer Institute consensus conference for its use as standard adjuvant therapy for stage III colon cancer [6].

1.2. 5FU-based regimens

Once 5FU/LEVA had become the acknowledged standard adjuvant therapy in CRC, it was used in studies conducted in the 1990s as the reference for new protocols. Between 1990 and 1999, results of large clinical trials defined the relative efficacy of 5FU-based regimens in a variety of doses and schedules in advanced disease. The next step was testing them as adjuvant therapies; this is presented in the six relevant studies below.

The first, the International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) study [7], involving 1,526 patients, enrolled three independent trials in Italy, Canada and France, measuring the efficacy of 5FU and high-dose LV (5FU/LV) after surgery for stage II (56%) and stage III
Table 1. Chemotherapy regimens.

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>CHEMOTHERAPY</th>
<th>SCHEDULE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLUOROPYRIMIDINES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5FU + LEVA NCCTG</td>
<td>LEVA 150 mg/d 3 d + 5FU 450 mg/m²/d bolus 5 d and next Q1w starting on d28</td>
<td>LEVA: Q2w 5FU: Q1w, 1 year</td>
</tr>
<tr>
<td>Mayo Clinic: FULV NCCTG 89-4651</td>
<td>LV 20 mg/m²/d bolus d1-5 + 5FU 425 mg/m²/d iv bolus d1-5</td>
<td>Q4-5w, 6 cycles</td>
</tr>
<tr>
<td>High-dose LV regimen: mFULV IMPACT</td>
<td>LV 200 mg/m²/d iv d1-5 + 5FU 400 mg/m²/d iv 15' d1-5</td>
<td>Q4w, 6 cycles</td>
</tr>
<tr>
<td>Roswell Park: FL NSABP C-04</td>
<td>LV 500 mg/m² iv over 2 h + 5FU 500 mg/m² bolus 1 h after the start of LV</td>
<td>Q1w for 6 of 8 weeks, 3-4 cycles</td>
</tr>
<tr>
<td>De Gramont: LV5FU2 GERCOR C96.1</td>
<td>LV 200 mg/m² over 2 h + 5FU 400 mg/m² bolus followed by a 600 mg/m² IVCI 22 h</td>
<td>D1 and 2, Q2w, 12 cycles</td>
</tr>
<tr>
<td>Raltitrexed PETTAC1</td>
<td>3 mg/m² d1</td>
<td>Q3w, 8 cycles</td>
</tr>
<tr>
<td>Capcitabine X-ACT</td>
<td>1250 mg/m² po bid</td>
<td>14 d</td>
</tr>
<tr>
<td>UFT + LV NSABP C-06</td>
<td>UFT 100 mg/m² po every 8 h + LV 30 mg po every 8 h</td>
<td>4 weeks Q5w, 5 cycles</td>
</tr>
<tr>
<td><strong>OXALIPLATIN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX4 MOSAIC</td>
<td>LV 200 mg/m² iv over 2 h + 5FU 400 mg/m² bolus and then 600 mg/m² IVCI 22 h + Oxaliplatin 85 mg/m² iv over 2 h only d1</td>
<td>D1 and 2, Q2w, 12 cycles</td>
</tr>
<tr>
<td>FOLFOX6</td>
<td>LV 400 mg/m² iv over 2 h d1 + 5FU 400 mg/m² bolus d1 followed by 2400 mg/m² IVCI 46 h + Oxaliplatin 100 mg/m² iv over 2 h d1</td>
<td>Q2w, 12 cycles</td>
</tr>
<tr>
<td>mFOLFOX6 NSABP C-06</td>
<td>LV 400 mg/m² iv over 2 h d1 + 5FU 400 mg/m² bolus d1 followed by 2400 mg/m² IVCI 46 h + Oxaliplatin 85 mg/m² iv over 2 h d1</td>
<td>Q2w, 12 cycles</td>
</tr>
<tr>
<td>FOLFOX7</td>
<td>LV 400 mg/m² iv over 2 h d1 + followed by 5FU 2400 mg/m² IVCI 46 h + Oxaliplatin 130 mg/m² iv over 2 h d1</td>
<td>Q2w, 12 cycles</td>
</tr>
<tr>
<td>mFOLFOX7</td>
<td>LV 400 mg/m² iv over 2 h d1 + followed by 5FU 2400-3000 mg/m² IVCI 46 h + Oxaliplatin 100 mg/m² iv over 2 h d1</td>
<td>Q2w, 12 cycles</td>
</tr>
<tr>
<td>FLEX NSABP C-07</td>
<td>LV 500 mg/m² iv over 2 h + 5FU 500 mg/m² bolus + Oxaliplatin 85 mg/m² iv 2 h before 5FU</td>
<td>5FU and LV, Qw Oxaliplatin week 1, 3, 5 Q8w, 3 cycles</td>
</tr>
<tr>
<td>XELOX NO16968</td>
<td>Capcitabine 1000 mg/m² po bid x 14 d + Oxaliplatin 130 mg/m² iv d1</td>
<td>Q3w, 8 cycles</td>
</tr>
<tr>
<td>IRINOTECAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFL CALGB-89803</td>
<td>LV 20 mg/m² bolus + 5FU 500 mg/m² bolus + Irinotecan 125 mg/m² iv</td>
<td>Qw for 4 of 6 weeks, 3-4 cycles</td>
</tr>
<tr>
<td>FOLFIRI PETACC3-EORTC</td>
<td>LV 400 mg/m² iv over 2 h d1 + 5FU 400 mg/m² bolus d1 followed by 2400 mg/m² IVCI 46 h + Irinotecan 180 mg/m² iv over 90' d1</td>
<td>Q2w, 12 cycles</td>
</tr>
<tr>
<td>BEVACIZUMAB NSABP CO-8</td>
<td>5-10 mg/kg iv over 30-90 d1</td>
<td>Q2w, 24 cycles</td>
</tr>
<tr>
<td>CETUXIMAB NSCTG-N0147</td>
<td>400 mg/m² iv over 2 h d1, and then 250 mg/m² iv over 1 h</td>
<td>Q1w, 6 months</td>
</tr>
</tbody>
</table>

Qw= weekly, Q2w= every 2 weeks, Q3w= every 3 weeks, ’= minute, h=hour, d=day, bid= twice a day, po=oral, iv=intravenous, IVCI=intravenous continuous infusion
(44%) colon cancer. The three trials used the same regimen (table 1) and compared it with surgery alone. 5FU/LV was associated with a significant increase in 3-year event-free survival (EFS) (from 62% to 71%, HR: 0.67, p<0.0001) and OS (from 78% to 83%; HR 0.77, p=0.03), as well as with a significant reduction in both mortality by 22% (95% CI: 3–38%; p=0.029) and in events by 35% (95% CI 22–46%; p<0.0001) (table 2). Grade 4 toxicities, the most common of which being of the gastrointestinal (GI) tract, were reported in less than 3% of the patients, and more than 80% of patients completed the planned treatment. These analyses concluded that 5FU plus high-dose LV was an effective, well-tolerated 6-month adjuvant therapy for colon cancer.

The second, the American NSABP CO-4 study [8], compared the Roswell Park regimen (FL) (table 1), with or without LEVA, with the standard regimen of 5FU/LEVA for a period of 12 months in 2,151 patients (41% stage II and 58% stage III). Results showed that 5FU/LV was superior to 5FU/LEVA in DFS (64% versus 60%; p=0.04) and 5-year OS (74% versus 69%; p=0.07). The three-drug regimen, 5FU/LV/LEVA, was intermediate in efficacy (table 2). This study suggested that 5FU plus high-dose LV for six cycles was superior to the standard 12 months of 5FU/LEVA. Grade 3 toxicity was reported in 36% of patients who received 5FU/LV, 38% of those who received 5FU/LV/LEVA and 28% of those who received 5FU/LEVA.

The third, the German adjCCA-01 study [9], randomised 680 patients with stage III colon cancer to 12 months of 5FU/LV (5FU 450 mg/m² plus LV 100 mg/m², 5 days every 4 weeks) or LEVA, and demonstrated that 5FU/LV improved both DFS and OS (p=0.04 and 0.01, respectively).

The fourth study, the American NCCTG 894651 trial [10], involved 915 patients with stage II and III CRC and compared the standard regimen of 5FU/LEVA, with the Mayo Clinic regimen of 5FU plus low-dose LV (FULV) (table 1), with or without LEVA, both regimens administered for 12 or 6 months. The study demonstrated that 12 months of 5FU/LEVA was equally as effective as 6 months of the three-drug regimen, 5FU/LEVA/LV, and more effective than 6 months of 5FU/LEVA (table 2). The toxicity of the triple-drug regimen was greater in terms of diarrhea and stomatitis.

In the fifth, the American INT-0089 study [11], which involved 3,794 patients with stage II (20%) and stage III (80%) colon cancer, the standard regimen of 5FU/LEVA for 12 months was compared with both the 24-week (6 months) regimen of 5FU plus low-dose LV (Mayo Clinic regimen, table 1), with or without LEVA, and the 32-week (8-months) regimen of 5FU plus high-dose LV (table 1). The results demonstrated that the 5-year DFS (60% to 59%) and OS (65% to 63%) rates for patients with high-risk stage II (obstructing and/or perforated, node-negative lesions) and stage III colon
cancers were no different when using 5FU plus high- or low-dose LV, and no benefit was registered with the addition of LEVA (table 2). These results contrasted somewhat with those of the NSABP CO-4 study [8], which showed that 5FU plus high-dose LV was superior to 5FU/LEVA. It is important to mention that, in the NSABP CO-4 trial [8], 5FU/LV therapy was administered over six cycles (12 months), whereas in the INT-0089 trial [11] the same regimen was administered only for four cycles (8 months). This trial also revealed clinically important differences in toxicity profiles among the various treatments according to age and gender. 5FU plus low-dose LV regimens, with or without LEVA, were associated with a significantly higher incidence of mucositis than 5FU/LEVA or 5FU plus high-dose LV regimens. On the other hand, diarrhea was almost three times more common with 5FU plus high-dose LV than with 5FU/LEVA. Patients older than 70 years (unpublished data) and females had significantly higher rates of mucositis and neutropenia; therefore, clinicians should pay more attention when using 5FU/LV regimens in these groups of patients, and should only consider 5FU/LEVA as an alternative once severe toxicity occurs.

The sixth, the INK Colon Trial Group study [12], randomised 500 patients with stage III colon cancer to 5FU/LEVA or to LV (20 mg/m² i.v.), 5FU and LEVA for 1 year. The addition of low-dose LV increased toxicity (especially mucositis and conjunctivitis) without a significant increase in 5-year DFS (without LV: 49%, LV-group: 46%; log-rank test, p=0.86) or in OS (55% versus 59%; log-rank test, p=0.96) (table 2). Therefore, the study concluded that LV, 5FU and LEVA were not recommended in a 12-month adjuvant regimen of stage III colon cancer.

In summary, available data in 1999 indicated that 5FU/LV given for 6 months was at least as effective as 5FU/LEVA for 12 months. Only the NSABP CO-4 study [8] showed that 5FU/LV was better than 5FU/LEVA. Thus, use of the 24-week (6 months) NCCTG schedule [10], the Mayo Clinic regimen (“FULV”: table 1), the 32-week (8 months) NSABP schedule [8] or the Roswell Park regimen (“FL”: table 1) were then considered the preferred adjuvant treatments in patients with resected stage III colon cancer, leading to a 5% to 10% improvement in OS.

Subsequent studies performed between 1996 and 2004 were designed to clarify the optimal duration of therapy, the advantage of high- or low-dose LV and the effectiveness of bolus compared with infusional treatment. The five most relevant are described below.

The first was a German trial [13], which analysed bolus or infusional 5FU, with or without LV, in stage III colon cancer using three different regimens: 1) 5FU 450 mg/m² and LV 100 mg/m², 5 days every 4 weeks; six cycles; 2) 24 h infusion of high-dose 5FU 2600 mg/m² and LV 500 mg/m²,
weekly for 6 of 8 weeks, two cycles (16 weeks, 4 months); and 3) 24 h infusion of high-dose 5FU 2600 mg/m², weekly for 6 of 8 weeks, two cycles (16 weeks, 4 months). The study enrolled only 145 patients (although 325 patients per treatment arm were programmed) between 1997 and 2001, and it was stopped in 2001 due to the slow recruitment. No statistically significant difference in efficacy and the percentage of patients with severe toxicity was found between the three treatment arms (table 2). There was, however, a significant difference in the type of toxicity as we will describe below.

The second was the French Groupe d’Etude et de Recherche Clinique en Oncologie Radiotherapies (GERCOR) C96.1 study [14,15], which enrolled 905 patients with stage II (43%) and III (57%) colon cancer over 3 years (1996–1999). The 2 × 2 factorial study compared a semimonthly De Gramont’s infusion regimen (LV5FU2: table 1) with a monthly regimen (mFULV with high-dose LV European regimen: table 1), while also comparing the 24 week (6 months) versus 36 week (9 months) duration of each regimen. This mFULV reference regimen differs from the monthly Mayo Clinic regimen by a higher dose of LV (200 versus 20 mg/m²), a different period of administration (15 minutes versus bolus), and a slightly lower dose per day of 5FU (400 versus 425 mg/m²). At 3 years, the DFS and OS had not been influenced by the duration of the therapy (6 or 9 months), by the type of administration (bolus or infusional) or by the frequency of administration (semi-monthly or monthly) (table 2). Although patients in the LV5FU2 group received twice the dose of 5FU compared with those in the mFULV group (930 versus 463 mg/m²/week), the incidence of grade 3–4 neutropenia, diarrhea and mucositis was higher with mFULV (p=0.001), whereas grade 3–4 nausea and vomiting were lower in the LVFU2 group, although not significantly (p=0.093). In later studies using De Gramont’s schedule, an increase in hand-foot syndrome and toxicity related to the implantable port was noticed; however, the study detailed here did not report any of these adverse events. The overall rate of toxicity is lower with continuous infusion of 5FU than with bolus, and the toxicity patterns of these two means of administration are completely different. The present trial does not offer any evidence of a difference in efficacy between the semimonthly LVFU2 and monthly FULV regimens. However, the small size of the study precludes any definitive conclusion about relative survival benefit. We cannot conclude that these two treatment regimens are equivalent, firstly because the upper boundary of the CI falls outside 0.8 to 1.25, often regarded as an acceptable region of equivalence, and also because the sample size is insufficient to confirm small benefits in DFS and OS (within this interval, the relative difference in the HR does not exceed 20%).
The third, a British study [16] conducted between 1993 and 2003, randomised 801 patients with stage II (44%) and III (54%) colon cancer to the 6-month Mayo Clinic regimen or to a 12-week protracted venous infusion (PVI) of 5FU alone (300 mg/m² daily). The trial showed that reducing treatment duration to 12 weeks did not influence the efficacy of infused 5FU (table 2), although it did reduce the probability of neutropenia, diarrhea and mucositis (p<0.0001), as well as nausea and vomiting (p=0.46), but with a higher incidence of hand-foot syndrome, albeit not significantly (p=0.09). The major side effects due to the implantable port in the PVI FU regimen were pneumothorax (0.6%), septicemia (1.2%) and thromboses (7%).

In the fourth, the American Southwest Oncology Group (SWOG) 9415/INT-0153 study [17], 1,135 patients with stage II (16%) and III (84%) colon cancer were enrolled between 1994 and 1999, and received the 6-month Mayo Clinic regimen plus LEVA or the PVI low-dose 5FU (250 mg/m² day for 56 days every 9 weeks, three cycles) plus LEVA (50 mg three times a day (tid) 3 days every other week). There were no differences in the 5-year DFS and OS between the two regimens. This trial showed that neither LEVA nor continuous infusion of 5FU added any benefit to the treatment (table 2), which, as mentioned by the authors themselves, could also have been compromised by hand-foot syndrome and thromboses related to catheters. The estimated 5-year DFS was 78%, 67% and 47%, while the 5-year OS was 83%, 74% and 55% for stages N0, N1 and N2–3, respectively, based on the 4th TNM edition [18]. The authors of this trial suggest that the poor survival of patients with four or more positive nodes (N2-3) could have been the consequence of including some with undetected metastases in the study. At the same time, they recommend a more rigorous imaging staging to identify the presence of distant metastases, in which case the treatment would be different, and more intensive chemotherapy might be considered.

The fifth, the Pan European Trials in Adjuvant Colon Cancer 2 (PETACC-2) study [19] between 1997 and 2004, randomised 1,624 patients with stage III colon cancer to receive the Mayo Clinic FULV regimen, PVI 5FU, the weekly high-dose German Arbeitsgemeinschaft Internische Onkologie (AIO) regimen, the De Gramont LV5FU2 regimen, or the Spanish weekly high-dose TTD regimen. There was no difference among them, either in the 5-year DFS (p=0.9) or in the 5-year OS (p=0.44) (table 2). Grade 3–4 neutropenia, mucositis and diarrhea were more frequent in the bolus arm, while hand-foot syndrome was more frequent in the infusion arm. This trial showed no increased benefit for continuous infusion, although this delivery was associated with less toxicity.
### Table 2. Randomised trials with 5FU.

<table>
<thead>
<tr>
<th>Study</th>
<th>patient no.</th>
<th>Stage</th>
<th>Arms</th>
<th>5-year DFS</th>
<th>p</th>
<th>5-year OS</th>
<th>p</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT</td>
<td>1526</td>
<td>II (56%), III</td>
<td>Observation 5FU+LV 6 m</td>
<td>62%</td>
<td>&lt;0.000 1</td>
<td>78%</td>
<td>0.03</td>
<td>Chemo benefit</td>
</tr>
<tr>
<td>NSABP C-04</td>
<td>2151</td>
<td>II (41%), III</td>
<td>5FU+LEVA 12 m</td>
<td>60%</td>
<td>0.04</td>
<td>70%</td>
<td>0.07</td>
<td>LEVA no benefit</td>
</tr>
<tr>
<td>adjCCA-O1</td>
<td>680</td>
<td>II (0%), III</td>
<td>5FU+ LEVA 12 m</td>
<td>49%</td>
<td>0.04</td>
<td>65%</td>
<td>0.01</td>
<td>Better: 5FU+LV</td>
</tr>
<tr>
<td>AGO</td>
<td>915</td>
<td>II and III</td>
<td>5FU+ LEVA 12 m</td>
<td>58%</td>
<td>60%</td>
<td>68%</td>
<td>&lt;0.01</td>
<td>6 m=12 m</td>
</tr>
<tr>
<td>NCCTG 8946S1</td>
<td>3704</td>
<td>II (20%), III</td>
<td>5FU+ LEVA 12 m</td>
<td>56%</td>
<td>63%</td>
<td>68%</td>
<td>0.18</td>
<td>3-year DFS &amp; OS</td>
</tr>
<tr>
<td>INT 0089</td>
<td>500</td>
<td>II (0%), III</td>
<td>5FU+ LEVA 12 m</td>
<td>59%</td>
<td>60%</td>
<td>67%</td>
<td>0.96</td>
<td>LEVA no benefit</td>
</tr>
<tr>
<td>IKN</td>
<td>145</td>
<td>II (0%), III</td>
<td>FULV 6 m</td>
<td>72.2%</td>
<td>82%</td>
<td>0.45</td>
<td>3-year DFS &amp; OS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>905</td>
<td>II (43%), III</td>
<td>LV5FU2 6 or 9 m</td>
<td>72%</td>
<td>88%</td>
<td>0.18</td>
<td>3-year DFS &amp; OS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>801</td>
<td>II (44%), III</td>
<td>FULV 6 m</td>
<td>66.7%</td>
<td>71.5%</td>
<td>0.08</td>
<td>Na</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1135</td>
<td>II (14%), III</td>
<td>FULV+ LEVA 6 m</td>
<td>61%</td>
<td>70%</td>
<td>0.18</td>
<td>Na</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1624</td>
<td>II (0%), III</td>
<td>FULV 6 m</td>
<td>63%</td>
<td>60%</td>
<td>0.44</td>
<td>Na</td>
<td></td>
</tr>
</tbody>
</table>

**Adjuvant Chemotherapy: 5FU bolus +/- LEVA +/- LV. Regimens: Mayo Clinic (FULV), Roswell Park (FL).**

**Adjuvant Chemotherapy: 5FU IVCL. Regimens: De Gramont (LV5FU2), monthly European FULV (mFULV).**

**German trial**

- 145 | II (0%), III | FULV 6 m | 72.2% | 0.45 | 3-year DFS & OS     |
- 905 | II (43%), III | LV5FU2 6 or 9 m | 72% | 0.18 | 3-year DFS & OS     |
- 801 | II (44%), III | FULV 6 m | 66.7% | 0.08 | Na                |
- 1135 | II (14%), III | FULV+ LEVA 6 m | 61% | 0.18 | Na                |
- 1624 | II (0%), III | FULV 6 m | 63% | 0.44 | Na                |

Ns= no statistical significance
1.3. Portal vein and peritoneal chemotherapy

It is well known that colon carcinoma dissemination frequently involves the liver via the portal vein system; a fact that led to the hypothesis that cytotoxic therapy delivered into the portal vein could destroy microscopic metastases and, therefore, increase the OS. The first study of interest regarding portal vein infusion was published by Taylor et al in 1977 [20] and updated in 1985. It randomised 243 patients to 5FU and heparin via the portal vein or to surgery alone. Patients receiving intraportal therapy experienced a significantly increased 5-year survival rate (p=0.002), although this was limited to patients with stage II colon cancer. Between 1984 and 1988, NSABP CO-2, an interesting study [21] involving 1,158 patients, demonstrated not only an increase in DFS but also in OS, even though it did not have a significant impact on liver metastases. It was suggested that the benefit of intraportal therapy was probably due to the timing of administration (intraportally when given immediately after surgery, whereas 30 to 40 days postoperatively it was given as intravenous chemotherapy) rather than to the way it was administered.

The concept of “immediate postoperative delivery of chemotherapy” was being tested in INT-0136, a phase III study in which 7 days of 5FU administered by intravenous infusion was initiated within 24 h of surgery and compared with a standard 5FU/LEVA program started within 35 days of the colon resection. The Swiss Group for Clinical Cancer Research (SAKK) study [22], involved 533 patients who were randomised to a single course of intraportal mitomycin (10 mg/m², one dose) and 5FU (500 mg/m² 24-h continuous infusion for 7 days) starting immediately after surgery, or to surgery alone. The differences in OS and DFS were attributed to a consistent reduction of recurrences (local and distant metastases) in the treated group, rather than to a reduction of the liver metastases only, concluding that part of the benefit was due to the systemic effects of the intraportal chemotherapy. A meta-analysis published in 1997 [23] of 4,000 patients belonging to 10 studies suggested that despite showing a statistically significant 4.7% improvement in 5-year OS (p=0.006), intraportal infusion was too toxic, too complicated to administer and clinically irrelevant. Randomised studies involving more patients are needed to confirm the results of this meta-analysis before considering intraportal infusion as a standard treatment. A phase III Gastrointestinal Tract Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer (GITCCG-EORTC 1983-1987) trial [24] included 199 patients from different European countries who were randomised to intraportal heparin alone (5000 IU daily × 7 days), to intraportal heparin (5000 IU daily × 7 days) and intraportal 5FU (500 mg/m²).
daily \times 7\) days), or to surgery (the control group). There were no differences in the postoperative complications and toxicity between those that received heparin or those receiving heparin and 5FU. Although intraportal 5FU infusion was safe and had a tolerable toxicity, there was no statistically significant improvement in the 5-year OS and DFS. A more recent multicentre European study [25] randomised about 1,500 patients to the same heparin and intraportal 5FU schedule or to surgery alone, obtaining no significant differences between survival rates and liver dissemination. An Italian ACOI/GIVIO/GISCAD group study [26] demonstrated that while 5FU-based adjuvant chemotherapy after surgical resection of colon cancer was the standard treatment, the best route of administration, either systemic or regional, remained controversial. In this trial, 1,084 eligible patients were randomised to the intraportal regimen (i.e., intraportal heparin and 5FU mentioned previously), to systemic (SY) (bolus 5FU 370 mg/m\(^2\) and LV 100 mg/m\(^2\), both daily for 5 days every month for six cycles, with treatment initiated 15–35 days after surgery), or to intraportal and SY. The OS and EFS rates were similar in all regimens and the combined regimen was no better than the single regimen alone.

In conclusion, the difficulties related to finding eligible patients, accomplishing the protocol and achieving homogeneity among different centres, makes it difficult to attribute small benefits to intraportal adjuvant therapy, at this point, it should, therefore, only be considered as an investigational approach rather than a standard one [27].

The treatment of peritoneal carcinomatosis is based on cytoreduction followed by hyperthermic intraperitoneal chemotherapy (HIPEC) and is combined with adjuvant chemotherapy. In 2003, a randomised trial [28], comparing systemic chemotherapy alone with cytoreduction followed by HIPEC and systemic chemotherapy, showed that the latter significantly increased the survival of patients affected by peritoneal carcinomatosis from CRC. However, it is still not known if intraperitoneal chemotherapy could prevent peritoneal dissemination in patients with stage II or III colon cancer.

The administration of chemotherapy through the hepatic artery has been examined using arterial injection of Tc99 [29]. This study demonstrated that the concentration of drugs reaching liver metastases was higher when cytotoxic agents were delivered by this route than through the portal vein. This is because the main blood supply of the normal liver is provided by the portal vein, while metastases are mainly irrigated by the hepatic artery. However, despite this benefit, only a small number of studies of drug delivery via the hepatic artery have been completed because of the difficulty of the procedure.

Despite enthusiasm for evaluating monoclonal antibodies as adjuvant therapy for colon cancer, as demonstrated, for example, by the German phase III trial of 17-1A monoclonal antibody (edrecolomab), which reported a survival benefit resulting from the prevention of distant metastatic disease, such findings have not been confirmed by two large, international studies. These studies, which recruited 4,600 patients, investigated edrecolomab in combination with 5FU [31,32]. Some authors have suggested that the lack of antibody activity could be explained by the fact that chemotherapy has the potential to alter the immune response which could mask any benefit from an immunotherapeutic agent in CRC.

1.5. Vaccines

A randomised Eastern Cooperative Oncology Group Study E5283 phase III trial of adjuvant immunotherapy with an autologous tumour cell- BCG vaccine (412 patients) showed no significant clinical benefit [33].

Targeting CEA epitopes as a vaccine in colon cancer also failed to show benefit in phase I studies and its use therefore remains limited to an investigational setting [34].

1.6. Other antimetabolites

At the beginning of the 21st century, the inconvenience and cost of a central venous line and ambulatory infusion pump prompted research into other antimetabolites, such as raltitrexed and oral fluoropyrimidines (capecitabine and UFT).

A) Raltitrexed

The European PETACC-1 trial [35] was closed prematurely when 17 (1.9%) raltitrexed-related deaths, while using the standard approved drug dose in metastatic disease, were reported. Moreover, this study failed to demonstrate non-inferiority of raltitrexed compared to 5FU and LV for relapse-free survival and OS in stage III colon cancer (table 3). Despite this, another study showed that raltitrexed adjuvant therapy could be administered safely and effectively in patients for whom further 5FU was contraindicated, such as those with heart or vascular disease [36].
B) Oral fluoropyrimidines

Two strategies were developed to avoid the erratic intestinal absorption of 5FU after oral administration: the coadministration of an inhibitor of dihydropyrimidine dehydrogenase (DPD)-uracil with oral 5FU (tegafur), together known as UFT (uracil/tegafur, ratio 1:4), and the administration of a 5FU prodrug that is not catabolised by DPD (capecitabine).

**UFT**

Between 1997 and 1999, the NSABP C-06 trial [37] compared UFT and LV (table 1) with the Roswell Park regimen in 1,608 patients with stage II (47%) and III (53%) colon cancer and demonstrated similar rates of DFS and OS between the two treatment arms, with a comparable toxicity profile (table 3). Although UFT was used in Europe and Asia because it was convenient to administer, it was withdrawn by the manufacturer in the United States. Nowadays, it has been replaced by capecitabine in most European centres.

**Capecitabine**

Between 1998 and 2001, the International X-ACT phase III trial [38], involving 1,987 patients with stage III colon cancer, compared capecitabine with the Mayo Clinic regimen (table 1). Despite their equivalence in DFS, which led to its approval by the EMEA (European Medicines Agency), it is still uncertain as to whether the results would have been equivalent if capecitabine had been compared with a more tolerable schedule of intravenous continuous 5FU infusion (table 3).

**Table 3.** Randomised trials with other antimetabolites, raltitrexed and oral fluoropyrimidines.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Arms</th>
<th>5-year DFS p</th>
<th>5-year OS p</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETACC1</td>
<td>1921</td>
<td>FULV 6 m Raltitrexed 6 m</td>
<td>-</td>
<td>Ns</td>
<td>DFS and OS: Ns at 4 years</td>
</tr>
<tr>
<td>Raltitrexed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP C-06</td>
<td>1608</td>
<td>FL 6 m UFT+LV 6 m</td>
<td>68.2% 67%</td>
<td>78.7% 78.5%</td>
<td>Equivalent efficacy and toxicity</td>
</tr>
<tr>
<td>UFT-LV</td>
<td>II (47%), III</td>
<td></td>
<td>0.96</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>X-ACT</td>
<td>1987</td>
<td>FULV 6 m Capecitabine 6 m</td>
<td>60.6% 64.2%</td>
<td>77.6% 81.3%</td>
<td>3-year DFS, OS: equivalent</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>II (0%), III</td>
<td></td>
<td>0.12</td>
<td>0.051</td>
<td>Lower toxicity: Capecitabine</td>
</tr>
</tbody>
</table>
Nowadays, for patients who are candidates only for monotherapy without oxaliplatin, oral fluoropyrimidines might be used instead of the more toxic, less cost-effective intravenous 5FU/LV, which is also less favoured by patients.

1.7. New drugs associated with fluoropyrimidines (Oxaliplatin and Irinotecan)

A) Oxaliplatin

Oxaliplatin (L-OHP) is active as a single agent and is synergistic when combined with 5FU, possibly due to oxaliplatin-induced downregulation of thymidylate synthetase (TS).

Three phase III clinical trials evaluated oxaliplatin and a fluoropyrimidine in the adjuvant treatment of colon cancer.

In Europe, the Multicenter International Study of Oxaliplatin and 5-FU and LV (FOLFOX4) in the Adjuvant Treatment of Colon Cancer (MOSAIC) study [39], randomised 2,246 patients, with stage II (40%) and stage III (60%) colon cancer to receive 6 months of De Gramont’s LV5FU2 regimen with or without oxaliplatin 85 mg/m$^2$ on day 1 (table 1) between 1998 and 2001. The 5-year follow-up confirmed an increase in the DFS for patients who received oxaliplatin (73.3% versus 67.4%, HR 0.80, p=0.003). After a longer follow-up, there was a trend for improvement in the 6-year OS for the whole population, which was significant for stage III (73.3% versus 67.4%; HR 0.80; 95% CI: 0.65–0.97; p=0.023) (table 4).

In the USA, Canada, Australia and New Zealand, the NSABP C-07 trial [40] randomised 2,492 patients with resected stage II (29%) or stage III (71%) colon cancer to receive 6 months of the Roswell Park FL regimen with or without oxaliplatin (85 mg/m$^2$ weekly over 6 weeks, followed by a 2-week rest period) (table 1) between 2000 and 2002. There was a benefit in the 3-year DFS rate (76.1% versus 71.8%; HR 0.80; 95% CI: 0.69–0.93; p=0.0034) for patients who received oxaliplatin (FLOX regimen), except for those older than 65 or those without pathological adenopathies; however, there was still no statistically significant difference in the 6-year OS (table 4).

Comparing the toxicity profile of all patients treated in both studies with 5FU and oxaliplatin, the incidence of neuropathy was significantly lower in the NSABP C-07 trial than in the MOSAIC trial (6.9% versus 12%, p<0.0001), as a result of the lower accumulative dose of oxaliplatin given (676 mg/m$^2$ in C07 versus 894 mg/m$^2$ in Mosaic) than that planned (1020 mg/m$^2$ versus 900 mg/m$^2$ respectively). Although grade 1 neurotoxicity persisted for more than 2 years in at least 10% patients in the oxaliplatin arm
in both studies, grade 2–3 neuropathy decreased to 1.3% at 6 months after FOLFOX4 and to 0.5% at 6 months after FLOX [41].

Despite this, the benefit in the DFS was similar between both oxaliplatin regimens; therefore, FLOX may offer an advantage to patients who are at risk of neuropathy. However, grade 3–4 diarrhea was more frequent with FLOX than with FOLFOX (38% versus 10.8%). Moreover, of all the patients with severe GI toxicity who required hospitalisation, 64.6% belonged to the FLOX and 35.4% to the FOLFOX4 regimen (p<0.01). From a practical point of view, FOLFOX therapy is more difficult to manage because it requires the placement of a central venous catheter, a procedure which may involve complications (infections, port malfunction, or clot formation in the subclavian vein), as well as the necessity of carrying a pump for the 5FU infusion. On the other hand, FLOX therapy requires more time in the clinic and more frequent visits to the hospital (18 visits rather than 12 visits for FOLFOX4 during the course of the therapy). Despite the advantages and inconveniences of each of them, FOLFOX was the most used therapy for resectable stage III colon cancer, but FLOX was also an effective alternative.

A third international study conducted between 2003 and 2004, known as the XELOXA trial (NO16968) [42], randomised 1,886 patients with resected stage III colon cancer to receive either XELOX (capecitabine and oxaliplatin, 8 cycles) (table 1) or bolus 5FU and LV (Mayo Clinic or Roswell Park regimen) at the discretion of each centre. Five-year DFS was significantly superior with XELOX than with 5FU/LV (66.1% versus 59.8%, respectively; p=0.0045) but there were no statistically significant differences in the 5-year OS (77.6% versus 74.2%, respectively; p=0.14) (table 4). XELOX was associated with fewer cases of diarrhea, hematological toxicity, mucositis and alopecia, but more cases of neurotoxicity, vomiting, and hand-foot syndrome when compared to the Mayo Clinic regimen. In addition, it was associated with fewer GI but more hematological events when compared to the Roswell Park regimen [43].

To prevent neurotoxicity, different neuromodulators have been studied such as calcium and magnesium (CaMg), xaliproden, glutathione, gabapentin, carbamazepine and venlafaxine, giving controversial results. Although the NCCTG N04C7 trial demonstrated the reduction of neurotoxicity by intravenous CaMg, another study, as yet unpublished (presented at ASCO 2009 by Grothey et al), found a decrease in the efficacy of FOLFOX in the group that received CaMg [44]. Another study from the same group, confirmed that CaMg reduced accumulative but not acute neurotoxicity [45]. In a phase III trial, xaliproden was shown to be efficient in reducing oxaliplatin-induced acute or accumulative neurotoxicity without influencing FOLFOX4 antitumour activity in metastatic disease [46].
B) Irinotecan

At least four randomised trials of adjuvant irinotecan with either bolus or infusional 5FU and LV have been reported.

In the USA between 1999 and 2001, the Cancer and Leukemia Group B (CALGB)-89803 trial [47] randomised 1,264 patients with resected stage III colon cancer to receive either the Roswell Park regimen for 8 months, or the Saltz regimen of irinotecan for 7.5 months (IFL) (table 1). Surprisingly, although IFL had proven superior to 5FU and LV in patients with metastatic disease, it did not improve either the DFS or OS when administered as an adjuvant therapy (table 4). A higher early all-cause mortality rate was found with IFL (2.8%; p=0.008) and was attributable to GI syndrome or thromboembolic events, but how irinotecan was implicated was not clear. The incidence of neutropenia was greater in the IFL than in the FULV arm (43% versus 5%, respectively; p<0.00001), while other common adverse events such as diarrhea and vomiting were similar in both arms.

In Europe, the phase III multicentre PETACC-3-EORTC trial [48] randomised 3,333 patients with resected stage II (29%) or III (71%) colon cancer to receive infusional 5FU and LV (De Gramont LV5FU2 or the German AIO regimen) with or without irinotecan (180 mg/m² every 2 weeks in LV5FU2 (FOLFIRI) and 80 mg/m² weekly in AIO, respectively) (table 1) for 6 months. The addition of irinotecan did not significantly improve the 5-year DFS (56.7% with irinotecan/LV5FU2 and 54.3% with LV5FU2 alone; p=0.106), nor the 5-year OS (73.6% versus 71.3%, respectively; p=0.094) (table 4), but it did increase the incidence of grade 3–4 GI events and neutropenia without changing the early mortality rate (1%), suggesting that irinotecan might be better tolerated with infusional 5FU and LV.

A smaller European trial published in 2006, the ACCORD 02 trial [49], randomised 400 patients with resected high-risk stage III colon cancer (N2, or N1 with colonic obstruction or perforation) to receive adjuvant therapy with LV5FU2 alone or with irinotecan (FOLFIRI) (table 1). After a median follow-up of 36 months, the rate of 3-year DFS was actually poorer in patients who had received irinotecan (table 4). This finding was also demonstrated in another European trial, the Aventis V307 trial.

In summary, the addition of irinotecan to 5FU and LV in each of these four clinical trials resulted in increased toxicity without a meaningful improvement in outcome. The overall negative results of PETACC-3 [48] might be explained by the increased incidence of death in the early follow-up of the experimental arm and the inclusion of more T4 patients, without the benefit from the addition of irinotecan that was reported in the ACCORD2 trial [49].
Table 4. Randomised trials with Oxaliplatin- or Irinotecan-based regimens.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Arms</th>
<th>5-year DFS</th>
<th>p</th>
<th>5-year OS</th>
<th>p</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOSAIC FOLFOX</td>
<td>2246</td>
<td>FUSLV2 6 m, FOLFOX 6 m</td>
<td>67.4%</td>
<td>0.003</td>
<td>76%</td>
<td>0.046</td>
<td>DFS: HR:0.80 Better: Oxaliplatin</td>
</tr>
<tr>
<td></td>
<td>II (40%), III</td>
<td></td>
<td>73.3%</td>
<td></td>
<td>78.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP C-07 FLOX</td>
<td>2492</td>
<td>FL 6 m, FLOX 6 m</td>
<td>64%</td>
<td>0.002</td>
<td>73.5%</td>
<td>0.06</td>
<td>DFS: HR:0.80 Better: Oxaliplatin</td>
</tr>
<tr>
<td></td>
<td>II (28%), III</td>
<td></td>
<td>69%</td>
<td></td>
<td>77.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO16968 XELOXA</td>
<td>1886</td>
<td>5FU bolus 6 m, XELOXA 6 m</td>
<td>59.8%</td>
<td>0.0045</td>
<td>74.2%</td>
<td>0.14</td>
<td>DFS: HR:0.80 XELOXA: no inferior</td>
</tr>
<tr>
<td></td>
<td>II (0%), III</td>
<td></td>
<td>66.1%</td>
<td></td>
<td>77.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB89803 IFL</td>
<td>1264</td>
<td>FL 6 m, IFL 6 m</td>
<td>-</td>
<td>0.8</td>
<td>-</td>
<td>0.81</td>
<td>Irinotecan: high early mortality rate, p&lt;0.008</td>
</tr>
<tr>
<td></td>
<td>II (0%), III</td>
<td></td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PETACC3 FOLFIRI</td>
<td>3333</td>
<td>LVSFU2 6 m, FOLFIRI 6 m</td>
<td>54.3%</td>
<td>0.11</td>
<td>71.3%</td>
<td>0.094</td>
<td>Irinotecan: no benefit</td>
</tr>
<tr>
<td></td>
<td>II(28%), III</td>
<td></td>
<td>56.7%</td>
<td></td>
<td>73.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD02 FOLFIRI</td>
<td>400</td>
<td>LVSFU2 6 m, FOLFIRI 6 m</td>
<td>60%</td>
<td>0.22</td>
<td>67%</td>
<td>0.26</td>
<td>3-year DFS Irinotecan: no benefit</td>
</tr>
<tr>
<td></td>
<td>II (0%), III</td>
<td></td>
<td>51%</td>
<td></td>
<td>61%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
When combined with infusional 5FU in patients with metastatic disease, unlike the adjuvant therapy setting, the benefit of irinotecan is similar to that observed with oxaliplatin. There are several cell biology-related theories that could explain this discrepancy, one of them being that irinotecan acts on a phase of cell cycle that is rarer in micrometastases, while oxaliplatin activity is independent of the cell cycle. At the same time, irinotecan target protein, topoisomerase I is found at lower levels in micrometastases, while oxaliplatin has less specific targeting. Moreover, irinotecan sensitivity may change during the various stages of tumour progression while oxaliplatin is more stable [50].

1.8. Targeted agents

A) Bevacizumab

Bevacizumab is a humanised monoclonal antibody directed against vascular endothelial growth factor (VEGF), the addition of which to a variety of cytotoxic agents results in enhanced therapeutic outcomes in patients with advanced CRC. The next step was to test the potential benefit and safety of bevacizumab in the adjuvant setting, and to do this, four large studies were developed as we will describe below.

The NSABP C-08 phase III study [51] randomised 2,672 patients with resected stage II (25%) or III (75%) colon cancer to modified FOLFOX6 (mFOLFOX6) (table 1) or to mFOLFOX6 for 6 months plus bevacizumab 5 mg/kg every 2 weeks for 12 months. Addition of bevacizumab did not result in an overall statistically significant prolongation in the 3-year DFS (HR: 0.87; p=0.089); however, there was a transient benefit in DFS during the first 1-year interval that bevacizumab was administered (HR: 0.6; p=0.0004). Futures studies should, therefore, consider a longer duration of bevacizumab administration. At the same time, more clinical trials in the adjuvant setting that address the possibility of angiogenesis inhibition as well as its influence on metastatic behaviour and subsequent course of the disease could be necessary. The studies also showed a lower dose-intensity effect and more grade 3 toxicity in patients ≥70 years (81% versus 73% in younger people; p<0.001), leading to caution in the use of complex regimens in elderly people [52].

Between December, 2004 and June, 2007, the international AVANT trial [53] compared 6 months of XELOX or FOLFOX4, either alone or with bevacizumab, for 1 year in 3,451 patients with stage III (83%) or high-risk stage II (17%) colon cancer; however, the DFS and OS results are still not available. Toxicity in this trial was comparable to the safety profile in metastatic CRC and in the NSABP C-08 trial. The arms with bevacizumab
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reported more cases of grade 3–4 hypertension, but similar venous or arterial thromboses, bleeding, wound healing complications, abscess/fistula and GI perforations. There were no differences in adverse events due to bevacizumab between the capecitabine and 5FU-based regimens. All-cause mortality within 60 days of treatment start was less than 1% in all arms.

Other studies currently using bevacizumab in an adjuvant setting include the ECOG5202 trial, which has randomised patients to no adjuvant treatment if chromosome 18q loss of heterozygosity (18q-LOH) was absent and microsatellite instability (MSI) was present, or to FOLFOX6 with or without bevacizumab if 18q-LOH and microsatellite stability (MSS) were present. Also being conducted is the English Quick And Simple And Reliable (QUASAR)2 trial, which has randomized patients to capecitabine alone or with bevacizumab. The results of these studies, to be communicated in the near future, will likely help to determine the convenience of bevacizumab in the adjuvant setting.

B) Cetuximab

Cetuximab is a human-murine chimeric monoclonal antibody that targets the epidermal growth factor receptor (EGFR). Autophosphorylation of the intracellular tyrosine kinase domain of the EGFR activates downstream signalling pathways, including the Ras/Raf/mitogen-activated protein kinase pathway. KRAS mutation status is an independent prognosis factor in advance CRC and KRAS wild-type is predictive for cetuximab responsiveness in this setting. On the other hand, KRAS mutation predicts resistance to cetuximab, and thus its status can be included in the treatment decision algorithm in advanced CRC [54].

The benefit from cetuximab in the adjuvant setting was addressed in the NCCTG-N0147 trial [55], in which 1,760 patients with resected, KRAS wild-type stage III colon cancer were randomly assigned to mFOLFOX6 with or without cetuximab (250 mg/m²/weekly with 400 mg/m² as first dose). Results did not show an increase in survival, instead showing an impaired DFS and a trend towards impaired OS. Another trial with FOLFOX4 alone or with cetuximab is PETTAC-8, the interim analysis of which is expected in 2011.

1.9. Summary

As previously emphasised, only a handful out of 100 stage II patients will benefit from adjuvant chemotherapy. Most of them will receive undue treatment and will have to face toxicity. Similarly, in stage III, over approximately 50% are cured by surgery and might not need adjuvant
2. Controversies

As mentioned above, there are no clear recommendations for adjuvant treatment in certain groups (in stage II colon cancer, in elderly patients, or in some clinical practice contexts).

2.1. Adjuvant in stage II colon cancer

The vast majority of patients with stage II colon cancer has a good prognosis after surgery alone and never develops recurrence. With a 5-year survival rate of approximately 80%, physicians question whether the small potential gain with adjuvant treatment justifies subjecting the entire population to the risks, toxicities and costs of the therapy. However, considering that adjuvant chemotherapy is indicated in patients with stage III colon cancer, and that stage IIB (T4No) has a 5-year survival rate inferior to stage IIIA (T3N1), we might speculate that a subset of patients with stage II could benefit, even if the biological similarity of a tumour confined to the bowel wall and one that presents as nodal metastasis is still a debated issue [57]. Moreover, it is difficult to gather 4,700 patients per group, the sample size that is required to detect a 4% survival difference between the treatment and control arm (90% power with a significance level of 0.05); therefore, physicians need to identify prognostic markers capable of reducing the number needed to treat (NNT) [58,59].
Nowadays, high-risk stage II disease is defined as the presence of T4 tumour, tumour perforation, poorly differentiated histology, extramural venous or lymphatic invasion, an elevated pre-surgical CEA value, residual tumour after surgery or fewer than 10 sampled lymph nodes. There are other factors: size of tumour, left-sided tumour, mucinous histology, perineural invasion, high proliferation index, peritoneal disease, absence of MSI, 18q-LOH, bax expression, loss of p27 expression, increased mitotic index, low bcl2 or p53 expression, as well as other more recently identified molecular markers (such as indicators of angiogenesis (vascular count, VEGF)) and markers of invasion/metastasis (plasminogen-related molecules, matrix metalloproteinases) which should be confirmed on a prospective basis [60].

Although the first high-risk factors mentioned above are unquestionably associated with a poor prognosis, whether adjuvant therapy could improve outcome in this group is still not clear [60].

To discover whether an adjuvant treatment is necessary, there are three groups of clinical trials to which we can refer: those with the control arm of surgery or of fluoropyrimidines, and meta-analyses. Meta-analysis is used to increase statistical power to reveal small benefits from studies with small sample sizes such as those of stage II CRC.

A) Clinical trials

There is a lack of well-designed trials specifically conducted to investigate the efficacy of adjuvant therapy in stage II colon cancer.

Despite the fact that the INT-0035 trial (5FU/LEVA) [4,5] was one of the first studies to demonstrate the benefit of chemotherapy in resected colon cancer, it could not confirm its utility in patients with stage II disease (table 5).

The INT-0089 trial [11] demonstrated the same 5-year DFS and OS rates for patients with high-risk stage II (obstructing and/or perforating node-negative lesions) as those with stage III using 5FU plus high or low-dose LV and at the same time, showed no benefit and more toxicity with LEVA (table 5).

A study from the Austrian Breast and CRC Study Group, published by Schippinger et al [61] investigated the use of adjuvant 5FU/LV only in patients with stage II colon cancer (500 patients). The results demonstrated a trend towards a lower risk of relapse in patients treated with chemotherapy but it failed to detect small improvements in the DFS or OS because of the limited number of patients enrolled (table 5).

The Netherlands Adjuvant CRC Project (NACCP) conducted a prospective trial [62], in which 1,029 patients with stage II (45%) and III colon cancer were randomised to receive 1 year of 5-FU/LEVA or surgery
alone; the results support the hypothesis that adjuvant therapy might be equally effective in stage II colon cancer (p=0.007).

The translational studies of the PETACC3/EORTC40993/SAKK 60-00 trial [63] (5FU/LV or 5FU/LV/irinotecan adjuvant therapy) showed that there was a higher incidence of MSI in stage II (22%) versus stage III (12%) and that MSI was a significant prognostic factor for DFS (HR: 0.265; p=0.0044) and OS (HR: 0.159; p=0.011) in stage II colon cancer.

Although a statistically significant benefit was not observed in those patients with stage II disease in the MOSAIC study, a 5.4% absolute improvement in DFS was noted in patients with high-risk stage II disease, defined as the presence of T4 tumour, bowel obstruction, tumour perforation, poorly differentiated histology, venous invasion, or fewer than 10 examined lymph nodes (table 5).

The QUASAR study [64] enrolled 3,239 patients (91% with stage II disease) between 1994 and 2003 who were randomised to 5FU/LV with or without LEVA (63% received 5FU 370 mg/m² with low-dose LV 25 mg 5 days per month for 6 months) or to surgery alone. The study concluded that patients with stage II CRC treated with chemotherapy had a small but statistically significant absolute improvement in survival of 3.6% (95% CI: 1.0-6.0; p=0.001). In comparison with other studies, such as those carried out by Moertel et al [4,5], QUASAR did not find an increased mortality rate due to non-tumoural causes in the arm treated with chemotherapy (table 5).

Another study, NSABP C-06 [37] involving 1,608 patients (47% stage II), compared 5FU with an oral fluoropyrimidine, UFT, and found that UFT was comparable to 5FU in patients with stage II and stage III colon cancer.

B) Meta-analyses

The IMPACT B2 meta-analysis [65], which included 5 separate trials (1,016 patients with B2 colon cancer who were randomised to 5FU/LV or observation), did not detect a significant DFS or an OS difference among treated versus untreated patients (table 4).

Although, none of the four individual NSABP (C-01, C-02, C-03 (MOF vs 5FU) and C-04) trials [66] were designed to evaluate a treatment benefit in the subpopulation of patients with stage II colon cancer, a meta-analysis of all of them concluded that adjuvant chemotherapy benefited this subset of patients. Moreover, the reduction in mortality was superior in stage II compared to that in stage III (30% versus 18%) independent of the presence of risk factors (T4, obstruction or perforation) (table 4). However, it is important to mention that this analysis could have been influenced by both the heterogeneity of the statistical method used and the heterogeneity in
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chemotherapy regimens (intraportal administration, the use of alkylating agents).

The Mayo Clinic group conducted a meta-analysis [67] of 3,302 patients with stage II (44%) and III colon cancer from seven randomised trials comparing 5FU/LV or 5FU/LEVA to surgery alone and tested the value of treatment, age, sex, tumour location, T stage, nodal status and grade as both prognostic and predictive factors. The results showed that the only factors which influenced the DFS and OS were nodal status, T stage, and grade. An increase in DFS (p=0.049) with adjuvant chemotherapy in stage II colon cancer but not in OS (table 5) was also observed.

A meta-analysis performed by The American Society of Clinical Oncology in collaboration with the Cancer Care Ontario Practice Guideline Initiative (CCOPGI) [68] included 37 trials and 11 meta-analyses (20,317 patients) comparing adjuvant therapy to surgery alone. They found that adjuvant therapy was associated with a benefit in DFS, but not in OS, for patients with stage II colon cancer (table 5). However, there is concern that the inclusion of rectal cancer patients and immunotherapy trials could have caused confusion.

### Table 5. Chemotherapy in stage II CRC.

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage II patients (n)</th>
<th>Arms</th>
<th>OS (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT 0035</td>
<td>318</td>
<td>5FU+Leva</td>
<td>0.10</td>
</tr>
<tr>
<td>Schipinger et al</td>
<td>500</td>
<td>5FU+LV</td>
<td>0.49</td>
</tr>
<tr>
<td>QUASAR</td>
<td>3239</td>
<td>5FU+LV</td>
<td>0.001</td>
</tr>
<tr>
<td>INT 0089</td>
<td>752</td>
<td>5FU+Leva</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>NSABP C-06</td>
<td>746</td>
<td>FL vs. UFT+LV</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MOSAIC</td>
<td>899</td>
<td>FOLFOX vs. FU5LV2</td>
<td>0.986</td>
</tr>
<tr>
<td>NSABP C-07</td>
<td>718</td>
<td>FLOX vs. FL</td>
<td>NA</td>
</tr>
<tr>
<td>Meta-analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMPACT</td>
<td>1016</td>
<td>5FU+LV</td>
<td>0.057</td>
</tr>
<tr>
<td>NSABP</td>
<td>1565</td>
<td>SFU-based regimens</td>
<td>0.01 (with risk factors) 0.26 (without risk factors)</td>
</tr>
<tr>
<td>CCOPGI</td>
<td>20317</td>
<td>SFU-based regimens immunotherapy</td>
<td>0.07</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>1440</td>
<td>5FU+LV or 5FU+Leva</td>
<td>0.112</td>
</tr>
</tbody>
</table>
C) Microsatellite instability (MSI) as a predictive or prognostic factor

One of the risk factors that plays an important part in locally advanced colon cancer is MSI. It reflects a defective DNA mismatch repair mechanism (MMR), which results in somatic alterations in the size of simple repeat nucleotide sequences (microsatellites); MLH1 and MSH2 are the most frequently altered genes [69]. Tumours may be characterised based on: high-frequency MSI (MSI-H) if two or more of the five markers show instability, low-frequency MSI (MSI-L) if only one of the five markers shows instability and MSS if none of the markers shows instability. The existence of MSI is related to certain clinical characteristics, such as: female gender, mucinous tumours, proximal localisation of the neoplasm, poorly differentiated histology and small number of lymph nodes invaded [70]. Moreover, Teipja et al. [71] found that its presence differed from stage to stage: 22% in stage II, 12 % in stage III and 3.5% in stage IV. After corroboration with the results of other studies [72], it was suggested that MSI-H could be a protective factor against metastases (including node metastases) since functionally active lymphocytes infiltrate the MSI-positive colon cancer, which explains why this alteration was seen more frequently in non-advanced tumours. Moreover, the MSI-H colorectal tumours seem to share a less aggressive clinical course than stage-matched MSI-L or MSS, which is also associated with a better prognosis independent of tumour stage [73,74].

However, the studies of Hemminki et al and Elsaleh et al found that patients with MSI-H have a poor response to 5FU therapy [75,76]. This finding was confirmed in the study by Ribic et al, which included 570 patients from five clinical trials with previous colon surgery, whose aim was to detect the benefit of adjuvant chemotherapy (three of these trials were using 5FU/LV and the other two 5FU/LEVA) [77]. When all 570 patients were considered, it was found that chemotherapy did not make a significant difference (p=0.11), but when the group of patients with MSS were analysed it was found to benefit from the chemotherapy (p=0.02). For the reciprocal group that presented with MSI-H, adjuvant treatment had negative effects, although these were not statistically significant (p=0.1). Furthermore, there was a trend towards better survival in MSH-L patients from the control arm (p=0.004).

Kim et al [78] reported contradictory results. From 542 cases in the NSABP studies (C-01, C-02, C-03, C-04) they found a favourable DFS for the 103 patients with MSI, but this was not reflected in the OS or in multivariate analyses with both parameters. They did, however, find concordance with the relationship between MSI-H and patient characteristics, such as gender, age, stage and tumour localisation. The difference in results among these trials
could be explained by differences in the techniques used, or by the fact that only two of the studies had surgery as the control arm.

Labianca et al at the European Society of Medical Oncology (ESMO) congress 2009 [79], extending the work of Ribic et al [77], presented data from 1,027 patients with MSI-positive stage II colon cancer and showed that adjuvant treatment was associated with a decrease in survival (p=0.04).

A meta-analysis of 32 studies (14 with patients with localised and metastatic disease, 15 with stages I–III and three with stage IV) [80] carried out in 16 countries and with a total of 7,742 patients looked for a correlation between survival and MSI which was detected in 16% of the patients. In 13 of the 32 trials statistically significant differences were found and the authors concluded that survival was increased in the group with MSI. Moreover, even though the results concerning the effect of the chemotherapy were limited, they did report a lack of benefit from adjuvant therapy for the MSI group (HR 1.24; 95% CI: 0.72–2.14). We should add that the meta-analyses included patients whose MSI status was defined only by genetic study and not by immunohistochemical analysis (IHC).

It is possible that the relationship between TS overexpression and MSI could explain both the lack of benefit of 5FU-based adjuvant treatment and the efficacy of other agents that use molecular mechanisms not involving TS [81]. Oxaliplatin acts by binding to DNA in a way that cannot be detected by the MMR system, and thus its activity might not be modified in MSI-positive tumours. Zaanan et al [82] presented a retrospective study of 233 stage III patients, 39 of who were part of the MOSAIC study. It compared the patients treated before October, 2003 (5FU/LV regimen) and those treated after this date (FOLFOX regimen). They found, not only in patients with p53 mutations but also in those with MSI, that the DFS in the FOLFOX group was superior to that in the 5FU group. We should analyse these data carefully, however, because not only was the study retrospective, but the number of patients included in it was also very small: 123 patients with a p53 mutation and 32 with MSI.

There are three retrospective studies of patients treated with FOLFOX in which MSI does not correlate with treatment efficacy but they were non-randomised, two of them included patients in stage IV and the third enrolled a heterogeneous group (9.6%, 80%, and 10.4% in stages II, III, and IV, respectively) [83,84,85].

Surprisingly, a similar result was found in a retrospective analysis of Cancer and Leukemia Group B 89803 trial [86], which randomised patients with stage III CRC to 5FU/LV or IFL. Although the results were negative, a slight increase in DFS in MSI patients treated with IFL (p=0.07) was observed.
When completed, the ECOG 5202 study may clarify the indication of chemotherapy for stage II. The patients at high risk (MSS, 18q-LOH) were randomised to FOLFOX with or without bevacizumab, while those with good prognosis were treated exclusively with surgery.

Starting a study of patients with MSI randomised to FOLFOX or to a regimen without fluoropyrimidines being used for stage IV, such as an irinotecan and oxaliplatin combination (IROX), has nevertheless been suggested [87].

Finally, we should find out how this knowledge is going to help us in everyday medical practice [88]. Knowing that FOLFOX in patients younger than 65 years and with stage III colon cancer may be a standard treatment, the determination of MSI seems unlikely to bring about any changes in the treatment of those patients. In fact, caution should be exercised; validation in prospective trials is essential before the introduction of routine MSI testing as an aid to prognosis and choice of treatment regimen. By contrast, patients with high-risk stage II CRC tend to be offered adjuvant treatment, but in this case if MSI was determined it could be beneficial. Its presence could indicate a better prognosis and could inform the avoidance not only of adjuvant treatment, but also of certain other agents.

Also, in patients older than 65 years with a poor general state of health and in those who are planned to be treated exclusively with fluoropyrimidines, the finding of MSI could lead to the implementation of FOLFOX treatment. On the other hand, for patients older than 70 years, FOLFOX seems to have no more efficacy than monotherapy with fluoropyrimidines and so MSI detection could lead to abstinence from adjuvant treatment [89].

However, it is important to take into account that MSI can be produced by two different pathways: 1) germline mutations, and 2) epigenetic silencing leading to different behaviour of tumours. The first refers to MMR gene mutation (especially MLH1, MSH2, and MSH6), which is associated with the most common genetic syndrome with a predisposition for colon cancer, hereditary non-polyposis CRC (Lynch syndrome). The second results from hypermethylation of CpG islands in MLH1 in sporadic CRC. Although MSI is associated with a better prognosis in sporadic tumours than in hereditary ones, it frequently coexists with the BRAF mutation, which is a poor prognostic factor [90]. Moreover, it is not clear whether these MSI groups (sporadic or hereditary) have a different response to chemotherapy [91].

In summary, it is not clear if over-treatment of 95% of patients with stage II is justified for the 2–4% added benefit from chemotherapy after surgery that has been the marginal, but consistent, finding in the studies and meta-analyses completed to date.

The decision to offer adjuvant therapy for stage II disease therefore needs to be individualised to the circumstances of each patient, explaining the
benefits and the possible risks the choice involves. In clinical practice, it is likely that stage II patients without T4 tumours, neither occluded nor perforated, with more than 12 examined lymph nodes and treated in hospitals that can guarantee a multidisciplinary approach, have a very high surgical cure rate.

In spite of this, many studies have shown that patients are willing to accept adjuvant therapy for little or even no clinical improvement; therefore, the explanation about adjuvant treatment advantages and disadvantages should be provided by a medical oncologist with a lot of experience in this field. Furthermore, with approximately 40–60% of patients with stage II currently receiving adjuvant chemotherapy, it would be more appropriate to encourage them to participate in randomised trials [92].

In the meantime, treatment should be individualised and oral fluoropyrimidines should be considered a valuable alternative in this good prognosis population.

2.2. Clinical practice attitude

Several reviews found significant variations in the use of chemotherapy in stage III colon cancer (48–62%) among different centres, which could put patients at risk if they failed to receive appropriate adjuvant therapy. The variation depended on:

A) Patient characteristics

It was noticed that older patients (>75 years) received adjuvant chemotherapy significantly less often than younger patients, older age being considered a predictor of treatment failure. Increased comorbidity (congestive heart failure, chronic obstructive pulmonary disease and diabetes) as well as duration of hospitalisation after surgical resection or rehospitalisation were found to be negative predictors for the use of adjuvant treatment.

Subjective judgments about sex and race, probably in relation to social and environmental factors, have also influenced the use of chemotherapy, and explain why women and non-white patients have received less adjuvant treatment [93].

B) Tumour characteristics

Patients with more positive lymph nodes had a greater overall use of chemotherapy; on the other hand, tumour size was not considered a significant predictor.
C) Oncologist versus surgeon approach

There are three factors that could influence good results of chemotherapy in stage III colon cancer:

a) Referral to an oncologist: better results were seen when the treatment was conducted by an oncologist than by a surgeon as the former is more capable of completing administration of all the therapy cycles. However, there were no differences found in the number of patients who started treatment with either an oncologist or a surgeon.

b) Acceptance of the treatment by the patients: patient refusal accounted for 29.6% of non-use and this was due to failure to communicate information or to the recommendation of no treatment being given by the physician rather than to the non-acceptance of the patient.

c) The ability to maintain a regimen of chemotherapy: 22–31% of patients were unable to complete treatment, which led to a higher mortality rate (20–47%) than in the group of patients that finished therapy [94].

Although the data from these reviews are provided to improve day to day clinical practice, we should not forget that every patient is a different entity and the opportunity of prolonging life should surpass any social or economic barrier.

2.3. Should 3-year disease free survival be a surrogate of overall survival?

The traditional end point for adjuvant chemotherapy clinical trials is OS. However, Sargent et al demonstrated in meta-analyses published in 2005 [95] and then in 2007 [96], that 3-year DFS is an appropriate surrogate end-point and an excellent predictor of 5-year OS in clinical trials of adjuvant therapy in colon cancer. This requires a smaller sample size with a shorter follow-up period, which reduces the cost and time of reporting such trials and accelerates the improved therapeutic strategies. For this reason, in 2004, the FDA accepted that DFS was an adequate basis for regular drug approval. The ACCENT meta-analysis [89] included 20,898 patients enrolled onto 18 phase III trials and it concluded that DFS outcomes after a 2- or 3-year median follow-up were excellent predictors of 5-year OS for trials in which the majority of patients were stage III. The correlation of HR within trials was 0.92 (95% CI: 0.85–0.95) for stage III patients and 0.70 (95% CI: 0.44–0.80) for stage II patients. Moreover, DFS with 1-year minimum follow-up demonstrated a perfect negative predictive value because all trials negative at
1-year for DFS were negative for 5-year OS. This will help when discontinuation of a trial is necessary and when drugs have a negative one-year interim evaluation.

Nowadays, the existence of more accurate imaging techniques for the diagnosis of metastases and the availability of new, more effective options to treat them means that instead of attributing OS effects solely to adjuvant chemotherapy, other parameters can now be identified. This may result in DFS becoming a more appropriate outcome than OS in CRC.

Moreover, while the DFS in the first 2 years was transiently favourable in the bevacizumab arm, the 3-year DFS predicted negative results in OS in the NSABP C-08 study [51].

Nevertheless, one aspect we must take into account, as we have shown in this chapter, is that all adjuvant clinical trials do not measure an identical end point, OS or DFS, and this can make it difficult to compare them.

3. Recommendations

In this section, we will design an algorithm for an alternative adjuvant approach in the context of different patients.

3.1. Stage III resected disease (node-positive) (Grade 1A recommendation)

A 6-month course of an oxaliplatin-based regimen is recommended: XELOX or mFOLFOX6. While FOLFOX4 was the regimen used in the adjuvant registration trials, mFOLFOX6 could be chosen because of its convenient administration and FOLFOX7 or modified FOLFOX7 (mFOLFOX7) (table 1), which eliminates the use of bolus 5FU completely, is a less aggressive alternative, with significantly less hematological toxicity.

In particular situations, these regimens could be modified as detailed below:

- When patients cannot tolerate oral drugs or have a dihydropyrimidine dehydrogenase (DPD) deficiency: mFOLFOX6.
- When patients have a high risk of pneumothorax, septicemia or thromboses: the use of an implantable port should be avoided, and it is therefore better to use XELOX or FLOX.
- When patients have low risk of neuropathy: FLOX.
- When patients have high risk of neuropathy: fluoropirimidine alone.
- When patients have severe cardiovascular disease: raltitrexed plus oxaliplatin.
- When patients have renal failure: UFT/LV.
3.2. Stage II resected disease

Based on the available data [61-68], adjuvant chemotherapy should not be considered as a standard of care for all patients. It is also necessary to discuss the risks and benefits of adjuvant chemotherapy with patients who have high-risk disease as defined by any of the following:

- Inadequate node retrieval: fewer than 13 nodes in the surgical specimen
- T4 lesion
- Poorly differentiated histology, signet ring and mucinous histology
- Aneuploidy, high S-phase fraction or deletion of 18q
- Perforated lesion
- Vascular, lymphatic or perineural invasion

We suggest capecitabine or 5FU/LV alone, rather than an oxaliplatin-based regimen for most patients in stage II, but it is important to take into consideration that stage IIB (T4N0) has a lower OS than stage IIIA (T1-2N1) because of the increase of recurrences (Grade 2B recommendation).

An online tool, Adjuvant! Online, can help the clinician estimate the risk of death within 5-years based on clinicopathologic features (age, comorbidities, T stage, N stage, number of nodes retrieved and histological grade) and the relative benefits of chemotherapy. Available at: http://www.adjuvantonline.com/index.jsp.

3.3. Radiation therapy

The evidence is inconclusive regarding the benefit of adding radiotherapy to chemotherapy for patients at high risk of a local recurrence in colon cancer. In accordance with NCCN guidelines, adjuvant radiotherapy should be given to patients with T4 tumours that infiltrate a fixed structure or have positive resection margins (Grade 2C) [97].

4. Follow-up

There are two aims of surveillance after curative resection of CRC:

- To identify recurrence that could be completely resectable.
- To identify second CRCs.

Although there is no standard schedule for follow-up, different groups have published guidelines concerning this issue: ASCO, ESMI, Cochrane, American Cancer Society, the US Multi-Society Task Force on CRC and others.
Based on these guidelines and on the available literature, we recommend the following [98]:

- Evaluation of the general condition, concomitant pathology and organ function that determine therapeutic strategy. Thus, in cases where salvage surgery or systemic treatment would not be feasible, the need for a strictly controlled strategy will not be so important.
- Clinical suspicion of metastatic disease should always be confirmed by adequate radio-imaging (usually a computed tomography scan). Histopathologic or cytologic confirmation should be obtained whenever there is atypical presentation or very late presentation after the primary cancer. Resectable metastases do not need histologic confirmation before resection. An FDG-TEP can identify further lesions when performing a planned resection of metastases.
- History evaluation, physical examination and CEA should be determined every 4 months for the first 3 years, every 6 months during 4 and 5 years, and subsequently at the discretion of the physician.
- Ultrasonography of the liver and chest X-ray should be carried out every 6 months for 5 years. CT scan of the chest and abdomen instead of ultrasonography and X-ray could be considered in patients with stage III-C cancer or other tumoural conditions with a higher risk for recurrence. For rectal cancer, a pelvic CT scan should be also considered, especially for patients with several poor prognostic factors, including those who have not been treated with radiation. Other imaging tests should also be conducted if there are some symptoms or specific signs.
- Another colonoscopy should be performed after a year since diagnosis and thereafter every 3–5 years to look for metachronous adenomas or cancer. In high-risk rectal cancer, a flexible proctosigmoidoscopy should be performed every 6 months for 2–5 years.
- Blood count, routine blood chemistry (liver function tests) and other laboratory examination are not recommended unless patients have suspicious symptoms.
- Molecular or cellular markers should not influence the surveillance strategy based on available evidence.

**Conclusion**

During the past 10 years, substantial progress has been made in the treatment of CRC. In patients with potentially resectable tumors, advances in
surgery, radiation, and chemotherapy have all contributed to increased rates of cure. Higher volume medical centers have become models for improving surgical quality.

Oxaliplatin has been incorporated into adjuvant treatment programs for colon cancer, and new targeted agents are currently in preclinical development and ongoing clinical trials. As in the past, further progress depends on the completion of well-designed RCTs.

References