# Current Status of Adjuvant Therapy for Colon Cancer

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## ABSTRACT

Due to its frequency and persistently high mortality, colorectal cancer represents a major public health problem. The use of adjuvant chemotherapy has improved prognosis in stage III disease, but much work remains to be done in optimizing adjuvant treatment, including refinement of ability to predict disease course and response to chemotherapy. The FOLFOX4 regimen is now considered standard treatment for stage III disease. Combinations of irinotecan and 5-fluorouracil (5-FU) have not proven to be more effective than 5-FU/folinic acid (FA). Oral fluoropyrimidines (eg, capecitabine, UFT + FA) now offer an alternative to intravenous 5-FU. Adjuvant chemotherapy for stage II colorectal cancer is more controversial. Use of adjuvant chemotherapy does not appear to be justified in patients with no particular risk factors (T3N0 with no poor prognosis factor). In contrast, the risk:benefit ratio in patients with one or more poor prognostic factors (T4 tumor, occlusion or perforation, poorly differentiated tumor, vascular invasion, or < 10 lymph nodes examined) appears to favor adjuvant treatment with FOLFOX4. Ongoing adjuvant trials are evaluating bevacizumab and cetuximab combined with 5-FU and oxaliplatin, and are examining the utility of such potential predictive markers as tumor microsatellite instability and loss of heterozygosity. Duration of therapy and prevention of oxaliplatin neurotoxicity are other critical areas for future research.


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Despite advances in the treatment of colorectal cancer, associated mortality remains high and the disease continues to represent a major public health issue. In western countries, mortality is still close to 40%.[1] Colon cancer and other supraperitoneal malignancies (tumors located at the rectosigmoid junction or in the upper part of the rectum) present a low risk of local recurrence, and radiotherapy is consequently not indicated. The mortality risk associated with colon or supraperitoneal rectal cancers is, therefore, related primarily to risk of metastasis.

Systemic treatments can diminish risk of metastasis by eradicating disseminated microscopic tumor foci that are distant to the primary tumor and undetectable during preoperative and perioperative assessment of tumor extension. In the absence of any further treatment after resection of the primary tumor, 5-year survival rates are principally determined by the histologic stage of the tumor at the time of resection. The crucial prognostic factor for the survival of patients with no visceral metastases is the stage of the tumor,[2] determined by the depth of tumor penetration into the intestinal wall and the number of lymph nodes involved.

The therapeutic potential of systemic treatments for colorectal cancer has expanded rapidly during the past 10 years, with the introduction of oral fluoropyrimidines, oxaliplatin, and irinotecan. The marked improvements in response rate, progression-free survival (PFS), and overall survival (OS) achieved with these new cytotoxic agents in patients with metastatic colorectal cancer[3,4] encouraged their testing in the adjuvant treatment of non-metastatic disease, especially in patients with stage III tumors. At the same time, advances in tumor biology led to the discovery of prognostic factors, such as microsatellite instability (MSI), that are potentially predictive of tumor response to cytotoxic agents. Prognostic factors are particularly valuable in the context of stage II colorectal cancer, in which the benefit of adjuvant cytotoxic therapy is more controversial than in stage III disease.

This article reviews the status of adjuvant treatment for stage II and III colon cancer on the basis of data available as of 2006. Since initial prognosis of the disease is crucial to selecting the optimal treatment for each patient, the first part of the review focuses on the factors identified to date as being predictive of disease outcome and, in some cases, response to treatment.

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## PROGNOSTIC FACTORS IN COLORECTAL CANCER

Histologic stage remains the most important prognostic factor in colorectal cancer.[2] The extent to which the tumor has invaded the intestinal wall and locoregional lymph node involvement form the basis for current tumor classification systems, the most widely used system being that developed by the American Joint Committee on Cancer (AJCC).[5] O'Connell et al[6] reported survival data on close to 120,000 patients with colon cancer as a function of tumor stage, defined according to the 6th edition of the AJCC classification. This analysis revealed that patients with stage IIIA tumors had a better prognosis than those with stage IIB tumors ($P = .001$).

### Lymph Node Analysis

The Intergroup 0089 study (N = 3,441) conducted in the United States showed that the survival of patients who have undergone resection of a stage II or III tumor was related to the number of lymph nodes analyzed in the resected tissue.[7] In this study, patients with stage III or high-risk stage II disease received one of four chemotherapy regimens: monthly 5-fluorouracil/leucovorin (5-FU/LV, Mayo Clinic regimen), weekly 5-FU/LV (Roswell Park regimen), 5-FU/levamisole, and 5-FU/LV/ levamisole.

Overall survival was similar in the four treatment arms. The mean number of lymph nodes examined in the excised colon tissue was 11 (range, 1 to 87 lymph nodes). Among the 3,411 patients evaluable for this analysis, 648 had no lymph node metastasis. Separate multivariate analyses were performed on patients with stage II and stage III disease. After adjustment for the number of lymph nodes invaded, OS increased to a highly significant extent ($P = .0001$) with increasing number of lymph nodes analyzed. A significant increase in OS with the number of lymph nodes analyzed was similarly seen in patients with no lymph node involvement ($P = .0005$). The authors concluded that the number of lymph nodes analyzed is an independent prognostic factor that should be taken into account in future studies. These results emphasize the prognostic importance of two parameters: the number of lymph nodes excised and the number of lymph nodes subjected to histologic analysis.

Intergroup 0089 also investigated the prognostic utility of intestinal occlusion and peritoneal and/or mesenteric implants.[8] Intestinal occlusion (present in 31.8% of the patients) did not appear to be a factor indicative of poor prognosis, with 5-year disease-free survival (DFS) and OS being similar irrespective of presence or absence of occlusion. In contrast, the presence of peritoneal and/or mesenteric implants was associated with poor prognosis, with both DFS (40% vs. 59%, $P < .0001$) and OS (43% vs. 64%, $P < .0001$) being significantly lower in patients with such implants.

### Microsatellite Instability

Numerous studies have demonstrated a relationship between tumor MSI and prognosis. Approximately 15% of sporadic colorectal cancers show MSI[9] without loss of heterozygosity (LOH). These tumors are most often proximal, poorly differentiated, mucinous in nature, and feature peritumoral lymphatic infiltrations. Ribic et al[10] performed a retrospective analysis of MSI in samples from 570 patients with stage II or III colon cancer included in five randomized trials. Among the 287 patients who had received no adjuvant chemotherapy, those with MSI had greater 5-year OS than those with a microsatellite-stable (MSS) tumor (hazard ratio [HR], 0.31; 95% confidence interval [CI], 0.14–0.72; $P = .004$). In contrast, among patients who received fluoropyrimidine-based adjuvant chemotherapy, 5-year OS did not differ based on MSI vs. MSS status (HR, 1.07; 95% CI, 0.62–1.86; $P = .80$). These results suggest that 5-FU–based chemotherapy benefits patients with MSS tumors, but possibly not those with MSI.

Parc et al[11] retrospectively analyzed the prognostic value of MSI in 142 patients with T3-4N0M0 colon cancer. All patients underwent curative tumor resection and none received adjuvant treatment. Immunohistochemical analysis revealed MSI tumors in 17% of the patients, and these patients had significantly prolonged recurrence-free survival (RFS) compared with patients with MSS tumors ($P = .02$).

Lanza et al[12] determined MLH1 and MSH2 expression status by immunohistochemical analysis in 718 patients with stage II or III colorectal cancer and evaluated the prognostic value of MSI using this technique.[12] Patients not expressing MLH1/MSH2 showed a reduced risk of cancer-related death in multivariate analysis ($P = .0001$) compared with those expressing MLH1/MSH2. These authors also demonstrated a correlation between microsatellite status determined by immunohistochemical analysis and that determined by polymerase chain reaction (PCR) in 363 patients. All patients identified as MSS and MSI-L (instability at < 30% of loci) using PCR were positive for MLH1/MSH2 when tested by immunohistochemical analysis. Among the 75 patients identified as MSI-H (instability at ≥ 30% of loci) using PCR, 68 (90.7%) were negative for MLH1/MSH2 according to immunohistochemical analysis and 7 (9.3%) were positive. Four of these patients were negative for MSH6 and one was negative for PMS2 by immunohistochemical analysis.[12] The results of this study demonstrate the prognostic value of MLH1/MSH2 status determined immunohistochemically in patients with stage II or III colorectal cancer and validates immunohistochemical analysis as a possible routine test for assessing MSI.

The three retrospective studies discussed above[10–12] confirm the prognostic value of MSI after resection of stage II or III colon cancer. It remains to be proven that 5-FU–based chemotherapy is of no benefit in patients with MSI, particularly in those with stage III cancer. It is feasible to assess MSI status routinely by PCR analysis of healthy tissues (blood, buccal cavity, colon mucosa) using an automatic sequencer[13] and/or by immunohistochemical analysis.[11]

Prospective studies are now needed to define the place of chemotherapy in MSI tumors and to determine the type of chemotherapy to use. MSI and MSS tumors have different resistance profiles. Topoisomerase I inhibitors have been shown to be effective in vitro in MSI tumor cells with mismatch repair deficiency.[13] Furthermore, MSI is a factor associated with improved DFS in patients with stage III colon cancers receiving adjuvant treatment with irinotecan, 5-FU, and LV.[14,15]

### Allelic Loss

Chromosome 17p and 18q allelic loss (LOH) has also been demonstrated to be a prognostic factor independent of histologic

stage. The prognosis of patients with a stage II tumor with chromosome 18q allelic loss is identical to that of patients with stage III tumors receiving adjuvant chemotherapy. Conversely, the prognosis of patients with stage II tumors showing no allelic loss is comparable to that in patients with stage I tumors.[16] Allelic loss was also found to be a marker of poor prognosis in patients with stage III tumors.[17] In contrast, Halling et al[18] did not observe a statistically significant correlation between chromosome 18q allelic loss and the prognosis of patients with either stage II or stage III tumors.

### Studies of Other Markers

Several other molecular markers have also been investigated as potential prognostic factors in stage II and III disease. These include expression of thymidylate synthetase (TS) and dihydropyrimidine dehydrogenase (DPD), both implicated in tumor resistance to 5-FU; the cell proliferation index Ki-67; the apoptosis markers p53 and bcl-2; and ploidy. Kornmann et al[19] showed that overexpression of TS was correlated with a better prognosis in patients with stage II and III cancers receiving 5-FU–based adjuvant chemotherapy. In a meta-analysis by Popat et al,[20] the HR for OS was 1.35 (95% CI, 1.07–1.80) for low TS expression vs. high TS expression. Garrity et al[21] showed a correlation between a high cell proliferation index Ki-67 (> 27%) and increase in DFS and OS in patients with stage II or III tumors (of whom 70% had received adjuvant chemotherapy) in both univariate and multivariate analyses.

As is the case with other cancers, notably breast cancer, lung cancer, and lymphoma, studies of the transcriptome of colorectal adenocarcinomas using DNA microarrays have produced some interesting results. In a first series of studies, it was shown that the profiles of expression of mRNA in tumor tissue differed from those observed in the adjacent healthy mucosal tissue.[22] The results of a second series of studies suggested that these mRNA expression profiles could be used for prognostic purposes in both stage II and stage III colorectal cancer.[19–23]

Wang et al[23] identified a signature comprising 23 genes that predicted recurrence in stage II patients. Barrier et al[24] identified a prognostic signature in stage II disease comprising 30 genes that completely differed from the signature proposed by Wang et al,[23] while the study nevertheless validated the prognostic accuracy of the latter signature. Another study suggested that the mRNA expression profiles might allow prediction of the risk of relapse among stage III patients in the absence of adjuvant chemotherapy.[25] In contrast to these three studies focusing on the RNA expression profiles of tumor tissue, another showed that the mRNA expression profiles of the adjacent colon mucosa yielded comparable results with regard to prognostic ability.[26] The results of all these studies are certainly of great interest, but need to be confirmed in much larger series of patients and, above all, validated in the context of prospective clinical trials.

Overall, the current status of prognostic and predictive factors in colorectal cancer can be summarized as follows. Prognostic markers routinely used today are histologic stage (T), lymph node involvement (N), number of lymph nodes examined in the resected tissue, tumor perforation of the intestinal wall, degree of tumor differentiation, and invasion of the lymphatic and/or vascular systems. The prognostic value of intestinal occlusion remains controversial. The value of MSI and LOH as markers is currently being investigated in prospective clinical trials.

## ADJUVANT TREATMENT OF STAGE III DISEASE

### 5-Fluorouracil

The first study to demonstrate the value of adjuvant chemotherapy in patients with stage III colon cancer (Dukes C, TxN+M0) was reported by Moertel and colleagues in 1990.[27] This study showed an increase in OS and DFS in patients receiving 5-FU/levamisole-based chemotherapy for 1 year compared with levamisole alone or no chemotherapy. At a mean follow-up of 6.5 years, patients treated with 5-FU/levamisole showed a 40% reduction in recurrence rate and an estimated 33% reduction in overall death rate.[28]

As of 1996, the standard treatment for patients with colon cancer that has metastasized to the lymph nodes was 6–8 months of chemotherapy with a combination of 5-FU (bolus or short infusion) and LV, either 5 days per month (Mayo Clinic regimen) or weekly (Roswell Park regimen), with the addition of levamisole no longer being recommended.[29–32] The Intergroup 0089 study[8] showed that the Roswell Park regimen was equivalent to the Mayo Clinic regimen in terms of efficacy and resulted in reduced rates of grade 3/4 neutropenia (4% vs. 24.1%) and mucositis (1.4% vs. 18.1%); the incidence of diarrhea was higher (30% vs. 21%) with the Roswell Park regimen.

The GERCOR study C96.1[33] compared the monthly bolus FUFOL regimen (bolus 5-FU followed by leucovorin [LV] over 15 minutes) with the twice-monthly infusional LV5FU2 regimen (LV over 2 hours, followed by bolus 5-FU, followed by cotinuous-infusion 5-FU over 2 days), each given over 24 and 36 weeks, in 905 patients with stage II (43%) or III (57%) colon cancer. The LV5FU2 regimen was less toxic, particularly with regard to hematologic and gastrointestinal adverse events ($P < .001$). No significant difference in DFS or OS was observed between either the two treatment regimens or the two durations of treatment at a median follow-up of 6 years.[34] Among patients experiencing metastatic relapse in this study, median OS after relapse was 24 months. The identical efficacy and reduced toxicity with the 6-month course of LV5FU2 supported its use as a reference treatment in subsequent studies in adjuvant chemotherapy.

The Pan-European Trials in Adjuvant Colon Cancer (PETACC) 2 study, presented at the 2006 American Society of Clinical Oncology (ASCO) meeting, supported these findings by showing that the monthly FUFOL regimen was equivalent in terms of DFS to the three European infusional 5-FU regimens (LV5FU2, TTD, and AIO regimens). LV5FU2 was the least toxic infusional regimen.[35] Two other studies demonstrated the equivalence of bolus 5-FU combined with LV with or without levamisole and continuous infusion of 5-FU.[36,37] The Medical Research Council (MRC) study[36] showed that a 3-month course of continuous-infusion 5-FU was equivalent to a 6-month course of 5-FU/LV (Mayo Clinic regimen).

### Oral Fluoropyrimidines

Two trials to date have investigated oral fluoropyrimidines as adjuvant treatment. The X-ACT (Xeloda [capecitabine] in Adjuvant Colon Cancer Therapy) trial[38] in stage III patients (N = 1,987) compared capecitabine (2,500 mg/m$^2$/day, 14 of 21 days) to the Mayo Clinic regimen. At a median follow-up of 3.8 years, these two treatments exhibited similar efficacy in terms of DFS and OS.

Analysis of the intention-to-treat population showed the efficacy of capecitabine to be at least equivalent to that of the Mayo Clinic regimen with regard to DFS. At 3 years, DFS was 64.2% in the capecitabine arm vs. 60.6% in the Mayo Clinic arm, corresponding to a 13% reduction in risk (HR, 0.87; 95% CI, 0.75–1.00). The upper limit of the 95% CI was below the predefined limit for noninferiority (set at 1.20, with $P < .001$), thus demonstrating the noninferiority of capecitabine. Three-year RFS was significantly better with capecitabine than with the Mayo Clinic regimen (65.5% vs. 61.9%; HR, 0.86; $P = .04$). Three-year OS was 81.3% with capecitabine vs. 77.6% with the Mayo Clinic regimen (HR, 0.84; $P = .07$).

A multivariate analysis confirmed these efficacy results and showed that capecitabine treatment was an independent prognostic factor with a statistically significant effect on all the criteria used for efficacy evaluation (DFS, RFS, OS). In this study, capecitabine was associated with significantly fewer acute toxicities of all grades combined ($P < .001$). The incidence of grade 3/4 toxicities was lower with capecitabine, including diarrhea (11% vs. 13%), stomatitis (2% vs. 14%) and neutropenia (2% vs. 26%). The most frequent adverse event in patients treated with capecitabine was hand-foot syndrome—60% vs. 9% (all grades combined) and 17% vs. < 1% for grades 3/4 ($P < .001$). The capecitabine dose of 2,500 mg/m$^2$/day had to be reduced in 60% of the patients.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-06 study[39] compared oral uracil/tegafur (UFT) plus LV to the Roswell Park regimen in patients with stage II or III colon cancer (N = 1,953). The DFS (HR, 1.004; 95% CI, 0.887–1.190), OS (HR, 1.014; 95% CI, 0.825–1.246), and toxicity (grade 3/4 toxicities; 38.2% vs. 37.8%) were identical for the two treatments.

These findings demonstrate that oral fluoropyrimidines have efficacy comparable to that of regimens based on bolus 5-FU, with a greater ease of administration. In light of these results, the Mayo Clinic and Roswell Park regimens should no longer be used as adjuvant treatments for colon cancer.

### Oxaliplatin

The MOSAIC trial assessed the efficacy of FOLFOX4 (oxaliplatin 85 mg/m$^2$ combined with LV5FU2) vs. LV5FU2 in adjuvant therapy.[40] Three-year DFS was selected as the primary end point in this trial, a choice that now appears to be perfectly justified on the basis of a recently published meta-analysis.[41] This meta-analysis, which included 18 randomized phase III studies involving 20,898 patients receiving a fluoropyrimidine-based adjuvant treatment for colon cancer, showed a close correlation between 3-year DFS and 5-year OS, indicating that 3-year DFS is an appropriate end point for studies evaluating the efficacy of adjuvant treatment in this setting. It should be noted that the vast majority (80%) of metastatic relapses of colon cancer occur during the first 3 years after surgery. Following validation of DFS as a primary end point by this meta-analysis, oxaliplatin became the first cytotoxic agent to receive marketing authorization based on DFS data.

In MOSAIC, at a median follow-up of 37.9 months (N = 2,246), 3-year DFS was 78.2% with FOLFOX4 vs. 72.9% with LV5FU2 alone ($P = .002$), corresponding to a 23% reduction in the risk of relapse (all disease stages combined). The benefit of this new treatment was also observed in each subgroup of patients. In patients with stage III colon cancer (n = 1,347), 3-year DFS was 72.2% vs. 65.3% (HR, 0.76; 95% CI, 0.62–0.92). Grade 3 neurologic toxicity was observed in 137 patients receiving FOLFOX4 (12.4%). However, neuropathy was reversible in most cases; only 1.1% of the population treated with FOLFOX4 still experienced grade 3 neuropathy 1 year after the end of treatment and the rate had fallen to 0.5% by 18 months. Overall mortality during treatment in MOSAIC was 0.5% in each treatment group.

After approval of oxaliplatin for use in adjuvant treatment of stage III colon cancer, a subsequent follow-up of the MOSAIC trial demonstrated the superiority of FOLFOX4 in a population of patients with stage II and stage III disease. Analysis at a median follow-up of 48.6 months and when duration of survival was at least 3 years for all surviving patients showed that FOLFOX4 was associated with a highly significant reduction of 24% ($P = .0008$) in the risk of relapse in the entire population.[42]

In patients with stage III colon cancer, DFS at 4 years was 69.7% in the FOLFOX4 group and 61.0% in the LV5FU2 group, corresponding to a relative risk reduction of 25%. In patients with stage II disease, 4-year DFS was 85.1% vs. 81.3%, corresponding to a risk reduction of 20%. In the entire population treated, 84.3% of patients in the FOLFOX4 group and 82.7% of the patients in the LV5FU2 group were still alive at the time of this analysis. Localized paresthesias of moderate intensity (at least grade 2) persisted in 2.7% of the patients treated with oxaliplatin, but only 0.7% of the patients developed paresthesias likely to interfere with their activities (grade 3).

The value of oxaliplatin in the adjuvant setting was confirmed by the NSABP C-07 study[43] comparing oxaliplatin in combination with 5-FU and LV (Roswell Park regimen, bolus 5-FU + LV weekly, during 24 weeks) vs. the Roswell Park regimen alone. The proportion of patients with stage III disease in this trial (71.4%) was higher than that in the MOSAIC study. After a median follow-up of 34 months, 3-year DFS (both stages combined) was 76.5% in the oxaliplatin arm and 71.6% in the Roswell Park arm (HR, 0.79; 95% CI, 0.67–0.93; $P = .004$), corresponding to a 21% reduction in the risk of relapse. Overall mortality during treatment in the NSABP C-07 study was 1.1% in patients receiving a treatment regimen without oxaliplatin and 1.2% in patients treated with an oxaliplatin-containing regimen.

The NO 16968 study compared capecitabine and oxaliplatin (XELOX) to the

Mayo Clinic regimen in 1,850 patients. Safety results were reported at ASCO in 2006, but efficacy data were not available at the time.[44]

The protocol-defined cumulative dose of oxaliplatin was 1,020 mg/m$^2$ in the MOSAIC study vs. 765 mg/m$^2$ in the NSABP C-07 study. Future studies should evaluate the possibility of reducing the number of cycles of FOLFOX4 administered as adjuvant therapy in order to diminish the neurotoxicity induced by oxaliplatin. In addition, there is growing evidence that polymorphisms in genes coding for DNA repair enzymes and metabolic inactivation routes contribute to the interindividual differences in antitumor efficacy and toxicity of oxaliplatin. Studies are ongoing to evaluate the potential role of ERCC-1 and other DNA-repair enzymes in the management of patients with colon cancer.

**Table 1.** Adjuvant chemotherapy in stage II disease: synthesis of meta-analyses and the QUASAR study.

| Reference | Treatment/ observation | No. of stage II patients | 5-year DFS (%) | 5-year OS (%) |
|---|---|---|---|---|
| IMPACT B2[50] | 5-FU/LV | 1,016 | **+ 3%** (*P* = .061; HR, 0.83) | **+ 2%** (*P* = .057; HR, 0.86) |
| Figueredo et al[51] (18 studies) | 5-FU or immunotherapy | 4,187 colorectal | – | *P* = .07; HR, 0.87 |
| Mayo Clinic[52] (7 studies) | 5-FU/LV or levamisole | 1,440 colon | **+ 4%** (*P* = .049; HR, 0.831) | **+ 1%** (*P* = .011; HR, 0.855) |
| NSABP[53] (4 studies) | A vs. B | 1,565 colon | – | **+ 5%** (B vs. A; HR, 0.70) |
| Meta-analysis Group Japan[54] (3 studies) | Oral fluoropyrimidines | 2,295 colorectal | + 4.7% | + 4.3% |
| QUASAR[55] (1 study) | 5-FU/LV ± levamisole | 3,238 (91% stage II) colorectal | **+ 4%** (*P* = .001; HR, 0.78) | **+ 2.9%** (*P* = .02; HR, 0.83) stage II: *P* = .04 |

Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; DFS = disease-free survival; HR = hazard ratio; IMPACT B2 = International Multicentre Pooled Analysis of B2 Cancer Trials; NSABP = National Surgical Adjuvant Breast and Bowel Project; OS = overall survival.

### Irinotecan

Combinations of irinotecan with 5-FU generally have not shown better results compared with 5-FU–based regimens. The Cancer and Leukemia Group B (CALGB) C89803 Intergroup trial comparing the IFL regimen (irinotecan/bolus 5-FU/LV) with 5-FU/LV alone showed no improvement in DFS and greater toxicity with the addition of irinotecan in patients with stage III disease.[45] The FNCLCC Accord 002/FFCD 9802 study[46] in 400 high-risk stage III patients (N2, T4, perforation/occlusion) showed no improvement in 3-year DFS with irinotecan/LV5FU2 over LV5FU2 alone (51% vs. 60%, *P* = .22). However, the PETACC 3 study,[47] comparing irinotecan/LV5FU2 (IF) vs. LV5FU2 (F) in stage III patients (and stage II patients in the associated V307 study) showed a nonsignificant benefit with regard to 3-year DFS including second noncolorectal cancers. In stage III patients, DFS, the primary end point of the study, was 63.3% in the irinotecan arm vs. 60.3% in the control arm (HR, 0.89; *P* = .091). However, when second, noncolorectal cancers were excluded from the analysis (corresponding to the definition of DFS used in MOSAIC), the difference in DFS favoring irinotecan became significant in patients with stage III disease (66% vs. 62.2%; HR, 0.86; *P* = .045) and in stage II and stage III disease combined (69.6% vs. 66.8%; HR, 0.88; *P* = .05). Furthermore, in this study, more patients in the irinotecan arm had a tumor classified as T4 or N2; analysis adjusted for these prognostic factors revealed a statistically significant difference (*P* = .009) in 3-year DFS favoring irinotecan.

### Elderly Patients

The value and feasibility of adjuvant 5-FU–based chemotherapy for patients over 70 years of age was supported by a pooled analysis reported by Sargent et al[48] that found no evidence of interaction between age and efficacy of chemotherapy. Moreover, the toxic effects of chemotherapy were no greater in patients over 70, with the exception of leukopenia in one study. Adjuvant treatment with FOLFOX4 was effective and well tolerated in these patients.[49] Of 3,742 patients treated with FOLFOX4 in the adjuvant or metastatic setting, the incidence of grade 3/4 toxicity was identical in patients ≥ 70 years old (n = 614) and those < 70 years old (63% vs. 67%, *P* = .15). Only the rates of neutropenia and thrombocytopenia were higher in patients ≥ 70 years old — 43% vs. 49% (*P* = .04) and 2% vs. 5% (*P* = .04), respectively.

## ADJUVANT TREATMENT OF STAGE II DISEASE

Stage II tumors comprise all lesions extending beyond the muscular layer, but with no lymph node involvement or metastatic dissemination (ie, T2-4N0M0). This group of tumors is consequently highly heterogeneous, with 5-year OS rates ranging from 84.7% (IIA) to 72.2% (IIB).[6]

The value of adjuvant chemotherapy for patients with stage II disease is controversial, with the major issue in this setting being definition of patient subgroups most likely to benefit from such treatment.

The results of the principal studies or meta-analyses of adjuvant therapy in patients with stage II disease are somewhat ambiguous (Table 1).[50–55] The International Multicentre Pooled Analysis of B2 Cancer Trials (IMPACT B2),[50] the meta-analysis reported by Figueredo et al,[51] and that published by the Mayo Clinic[53] show no improvement in OS or DFS in patients receiving adjuvant chemotherapy. In IMPACT B2 and the Mayo Clinic meta-analysis, the number of patients included in the analyses would seem to be insufficient, since a population of 4,000 patients would be required to show a 4% difference in 5-year OS.[56]

The meta-analysis reported by Figueredo et al[51] includes 18 trials comparing surgery alone to adjuvant treatment with various chemotherapeutic regimens (16 trials) or immunotherapy (2 trials), and the diversity of the adjuvant treatments used makes the results difficult to interpret. In contrast, the results of the NSABP analysis[53] and the Japanese meta-analysis[54] are in favor of adjuvant chemotherapy. In the NSABP analysis, the relative risk of relapse was reduced to a significant extent in stage II patients receiving the most effective treatment. However, it is difficult to draw a general conclusion from the analysis regarding the benefit of treatment due to the diversity of both the control and treatment arms in the trials included in the analysis.

In the QUASAR study,[55] a total of 3,238 patients with colon (71%) or rectal (29%) cancer, of whom 91% had stage II disease, were randomized to either adjuvant 5-FU/LV (± levamisole) or no chemotherapy. Five-year OS was 80.3% vs. 77.4% ($P = .04$) with an HR of 0.83 (95% CI, 0.71–0.97) in favor of the chemotherapy arm. An analysis including only stage II patients showed a significant reduction in the risk of death at 5 years ($P = .04$).

Overall, the available data suggest a trend in favor of adjuvant chemotherapy in stage II disease. However, it is clear that the utility of such treatment could be maximized by being able to define which subgroups of patients are most likely to benefit from treatment and which can be spared toxicity of treatment from which there is likely to be no benefit.

With regard to defining higher-risk subgroups, the Intergroup 0089 study did not find that occlusion was a prognostic factor in stage II disease in a multivariate analysis.[8] Among the 40% of patients in the MOSAIC study with stage II disease,[40] 3-year DFS was 87.4% with FOLFOX4 vs. 84.4% with LV5FU2 (HR, 0.80; 95% CI, 0.56–1.15). Among high-risk stage II patients, defined as those with T4 disease, occlusion/perforation, poorly differentiated tumors, or < 10 lymph nodes examined, the relative risk of relapse was reduced by 28% (HR, 0.72; 95% CI, 0.48–1.08) with FOLFOX4 (compared with a 25% reduction in stage III patients).[57]

Thus, a case can be made for considering adjuvant therapy with FOLFOX4 (or with other fluoropyrimidine-based therapy — eg, oral fluoropyrimidines or LV5FU2) in those patients with higher-risk characteristics (T4, perforation, poorly differentiated tumor, vascular invasion, < 10 lymph nodes examined) in whom prognosis is similar to that in stage III disease. Similarly, it can be argued that adjuvant therapy can be avoided in patients with T3N0 disease and absence of other risk factors, in whom prognosis is similar to patients with stage I disease. However, many questions remain regarding which patients with stage II disease are most likely to benefit from adjuvant therapy.

## ONGOING STUDIES

Studies of adjuvant chemotherapy ongoing in 2006 include those integrating biologic approaches into therapeutic strategies.

### Stages II and III

The place of bevacizumab in the adjuvant setting is being studied in two international trials, based on the efficacy of this agent in metastatic disease. The AVANT trial in patients with high-risk stage II or stage III disease (N = 3,450) is comparing FOLFOX4 for 24 weeks (reference regimen), FOLFOX4 plus bevacizumab for 24 weeks followed by bevacizumab alone for 24 weeks, and XELOX plus bevacizumab for 24 weeks followed by bevacizumab alone for 24 weeks. The primary end point of the trial is 3-year DFS in patients with stage III disease. The NSABP C-08 study (N = 2,700) is comparing FOLFOX6 for 24 weeks vs. FOLFOX6 plus bevacizumab for 24 weeks followed by maintenance treatment with bevacizumab alone for 24 weeks. The primary end point of the study is 3-year DFS in patients with high-risk stage II disease and stage III disease.

### Stage III

The PETACC 8 trial is comparing two treatment arms (N = 2,000): FOLFOX4 for 24 weeks vs. FOLFOX4 plus cetuximab for 24 weeks. The North Central Cancer Treatment Group (NCCTG) N0147 study is similarly comparing FOLFOX6 for 24 weeks vs. FOLFOX6/cetuximab for 24 weeks (N = 2,300).

### Stage II

The Eastern Cooperative Oncology Group E5202 study is assessing both adjuvant use of bevacizumab and strategy based on prognosis according to MSI and LOH status in patients with stage II disease (N = 3,125). After surgery, patients are stratified according to MSI and LOH. Low-risk patients (MSI and no LOH) receive no adjuvant treatment (observation arm), whereas high-risk patients (MSS and LOH) are randomized to receive FOLFOX6 with or without bevacizumab.

## DISCUSSION

The value of adjuvant treatment of colon cancer was clearly demonstrated only as recently as the early 1990s.[27] The combination 5-FU/LV became the standard treatment for stage III colon cancer in 1996, with the use of such treatment for patients with stage II disease being, and remaining, controversial. The international MOSAIC trial[40–42] demonstrated the superiority of FOLFOX4 over the combination 5-FU/LV and also modified treatment habits, with this regimen becoming in 2004 the new therapeutic standard in adjuvant treatment of stage III colon cancer. FOLFOX4 is generally well tolerated; its principal specific complication, peripheral sensory neuropathy, is reversible in the vast majority of cases.

The role of adjuvant chemotherapy for stage II colon cancer is still debated. The principal studies in this setting, including the MOSAIC trial, generally lack the power to demonstrate statistically significant differences in this heterogeneous population of patients, although a marked trend in favor of chemotherapy is observed in most cases. Prognostic factors and comorbidity should be taken into account in evaluation of the risk:benefit ratio as an aid to choosing the therapeutic strategy for each individual patient. A model incorporating these factors is now available to provide physicians with tailored estimates of 5-year DFS and OS probabilities with surgery alone and with surgery plus 5-FU–based adjuvant chemotherapy (available online at www.mayoclinic.com/calcs and www.adjuvantonline.com/index.jsp).

In addition to providing an individual estimate of the benefit of adjuvant therapy, these calculators also provide an individual evaluation of the prognostic effect of age-related effects of concomitant disease. Age and concomitant disease generally are

ignored as risk factors in clinical trials, which usually are restricted to a relatively young and fitter population of patients.

Biologic prognostic factors (MSI, LOH, etc.) are now being evaluated in prospective studies, and in the future may help better define populations likely to benefit from adjuvant chemotherapy.

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## Disclosures of Potential Conflicts of Interest

Dr. de Gramont is a consultant to Roche, Genentech, and sanofi-aventis.