

Counterpoint: Adjuvant Therapy in Stage II Colon Cancer: Pain Not Justified by the Gain

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Abstract

No definitive evidence shows benefit from adjuvant therapy for stage II colon cancer, and its role remains controversial. Although a trend toward improved disease-free survival (DFS) has been reported in subgroup analyses from clinical trials that included patients with stage II disease, time trends for recurrences of stage II disease indicate that DFS is not a reliable surrogate for overall survival (OS). Several clinical trials have been conducted to answer the question of whether adjuvant therapy benefits patients with stage II disease, but none have been adequately powered to detect what would be a small OS benefit. Features that are currently used to assign high risk for recurrence (tumor perforation, lymphovascular invasion, <12 lymph nodes analyzed, and poorly differentiated histology) may or may not be associated with clinical outcome, and they are not predictive of treatment benefit. Risks of adjuvant therapy are nonnegligible and must be weighed against a large number of patients needed to be treated to realize benefit. Future research should aim to answer the questions of whether microsatellite instability, nodal sampling, molecular markers, and genetic signatures are useful tools to guide decision-making. Given what is now known, the viewpoint is that the aggregate data do not support adjuvant therapy for patients with normal-risk stage II colon cancer. (*JNCCN* 2012;10:1379–1386)

Adjuvant therapy for colon cancer evolved in an additive fashion. In the 1980s, 5-fluorouracil (5-FU) administered as a daily bolus regimen made the first positive impact of any therapy on colon cancer survival.¹ The ensuing decade of research led to the incorporation of

the modulating agent leucovorin (folinic acid) to form a 2-drug combination.^{2–4} This combination evolved further with the change to a 48-hour infusion schedule of 5-FU,^{5,6} and finally with the addition of oxaliplatin (FOLFOX).^{7,8} This stepwise progression culminated in the MOSAIC trial, which conclusively showed that FOLFOX improved disease-free survival (DFS) and overall survival (OS) compared with 5-FU alone in patients with stage III disease.⁷ Among patients who undergo a complete resection of node-positive stage III tumors, adjuvant FOLFOX achieves an estimated one-third reduction in the risk of recurrence compared with surgery alone.⁹

The existing evidence for the role of adjuvant therapy is largely the result of clinical trials that lumped together patients with either node-negative or node-positive disease, and this treatment algorithm has not yielded definite evidence of OS benefit for those with node-negative disease. Thus, the impact of adjuvant therapy in patients with stage II disease is of a lesser magnitude and its role remains controversial. This need not be seen as a failure: with an OS at 5 years of approximately 80%, patients with stage II disease have a high rate of cure after surgery alone.¹⁰ In the best of scenarios, additional therapy has the potential for small incremental benefit and improvement of outcomes for only 20% of all patients with stage II disease.

Current consensus guidelines from NCCN state that adjuvant therapy with FOLFOX should not routinely be offered to patients with normal-risk stage II colon cancer (to view the most recent version of the NCCN Guidelines for Colon Cancer, visit NCCN.org).¹¹ This article reviews the data behind these recommendations and balances their limitations against the potential costs, risks, and benefits of adjuvant therapy for patients with stage II colon cancer. The authors advocate that the aggregate data does not support adjuvant therapy for patients with normal-risk stage II colon cancer.

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A Review of the Literature

The existing literature on the role for adjuvant chemotherapy in stage II colon cancer is summarized in Table 1. The QUASAR trial randomized 2291 patients with completely resected stage II colon cancer to receive adjuvant chemotherapy with 5-FU/leucovorin versus observation and showed a relative risk (RR) of death of 0.86 (95% CI, 0.66–1.12), which translates to a marginal improvement in survival of 3.6% (95% CI, 1.0–6.0).¹⁰ These results were of borderline significance, and the study was limited by broad entry criteria, with many factors left to physician discretion.

The MOSAIC trial, like many others, combined patients with stage II and III disease. The addition of oxaliplatin significantly improved 5-year DFS and 6-year OS in the adjuvant setting among patients with stage III disease, but no differences in DFS or OS were seen in the subgroup of those with stage II.¹² The NSABP C-07 trial also randomized patients with stage II and III disease to receive bolus 5-FU/leucovorin alone versus with oxaliplatin (FLOX) and showed no evidence for survival benefit within the stage II cohort, corroborating the results of MOSAIC.⁸ The subgroup of patients with stage II disease in NSABP C-07 was a minority of the study population, and the trial was underpowered to detect the same relative difference that was seen in the stage III subgroup. Importantly, patients in both arms of these studies received 5-FU; thus, these results do not refute the benefit of 5-FU in the adjuvant setting for patients with stage II disease.

In the search for a conclusive result in patients with stage II disease, several pooled analyses and 1 large retrospective cohort study were previously reported. Looking at the sum of the results of its first 4 trials (C-01 through C-04), NSABP reported that the same benefits in DFS and OS from 5-FU–based adjuvant chemotherapy seen in patients with stage III disease held true for those with stage II, regardless of the presence or absence of adverse prognostic factors.¹³ Given the evolution of therapeutic standards reflected in these 4 trials, this result drew much skepticism. However, these data were loosely corroborated by a pooled analysis of 1440 patients with node-negative colon cancer from 7 randomized adjuvant trials comparing 5-FU–based therapy with surgery alone, wherein Gill et al⁹ reported a 4% absolute 5-year DFS benefit (72% vs.

76%; $P=.049$) and a very slight OS advantage that was not significant in patients with node-negative disease (80% vs. 81%; $P=.1127$). Likewise, the IMPACT B2 study, which pooled data from 1016 patients in 5 separate trials randomizing patients to 5-FU/leucovorin versus observation, did not show any significant benefit of 5-FU/leucovorin combinations in patients with stage II disease.¹⁴ The 5-year OS rate was 80% for the control arm and 82% in the treatment arm, suggesting that for every 100 individuals treated, adjuvant 5-FU/leucovorin benefited only 2.

The ACCENT collaborative group pooled individual patient data from 20,898 patients in 18 clinical trials of adjuvant therapy, including nearly 6900 patients with stage II disease. This analysis demonstrated an 8-year OS of 66.8% for patients receiving surgery alone and 72% for patients treated with 5-FU–based chemotherapy after surgery ($P=.026$).¹⁵ A recent retrospective review of 24,847 Medicare patients with stage II colon cancer identified from the SEER database between 1992 and 2005 concluded that no survival benefit from any adjuvant chemotherapy was observed in patients either with or without any poor prognostic features.¹⁶

Proceeding With Caution: OS Is the Meaningful End Point

Additional analysis from the ACCENT group determined that patterns of treatment failure for patients with stage II disease are both distinct and delayed compared with those for patients with stage III disease. Among patients with stage II disease, the benefit in reducing DFS events attenuates over time and is entirely absent after 2 to 3 years.¹⁵ In this pooled cohort of more than 6800 patients with stage II disease, 74% of stage II recurrences (1075 of 1458) occurred within the first 3 years, compared with 82% of stage III recurrences.¹⁷ Additional factors, including noncancer deaths, fewer events, a smaller absolute benefit, and disease heterogeneity, all potentially confound the association between DFS and OS for stage II colon cancer. In the ACCENT data, the association between DFS with a 3-year median follow-up and 5-year OS was weak in patients with stage II disease, with a correlation between hazard ratios (HRs) for DFS and OS of 0.7 (95% CI, 0.44–0.80). This reduced association

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Table 1 Noteworthy Studies on the Role of Adjuvant Therapy for Patients Who Have Undergone Resection of Stage II Colon Cancer

Study	Study Type	Accrual Period	Stage II Disease (N)	Treatment Arms	OS	Significant OS Benefit
NSABP C-01, C-02, C-03, and C-04 ¹³	Pooled analysis of 4 RCTs	1977–1990	1565	C-01: MOF vs. OBS C-02: PVI of 5-FU vs. OBS C-03: 5-FU/LV vs. MOF C-04: 5-FU/LV vs. 5-FU/LEV vs. 5-FU/LV/LEV	Absolute improvement in survival of 5%	Yes
IMPACT B2 ¹⁴	Pooled analysis of 5 RCTs		1016	5-FU/LV vs. OBS	5-year OS: 82% with 5-FU/LV vs. 80% with OBS (P=.057)	No
Gill et al ⁹	Pooled analysis of 7 RCTs		1440	5-FU/LV vs. OBS or 5-FU/LEV vs. OBS	80% with OBS vs. 81% with 5-FU/LV or 5-FU/LEV (P=.1127)	No
ACCENT ¹⁵	Pooled analysis of 18 phase III RCTs	1978–1999	≈6900	5-FU–based CT vs. OBS	8-year OS: 72.2% with 5-FU–based CT vs. 66.8% with OBS (P=.026)	No
O'Connor et al ¹⁶	Retrospective cohort study from SEER-Medicare database	1992–2005	24,847	Any adjuvant CT vs. OBS	5-year OS: 69.5% with adjuvant CT vs. 70% with OBS	No
QUASAR ¹⁰	Phase III RCT	1994–2003	1436	5-FU/LV vs. OBS	Absolute improvement in survival of 3.6% with 5-FU/LV (95% CI, 1.0–6.0)	Trend toward yes
MOSAIC ¹²	Phase III RCT	1998–2001	899	5-FU/LV vs. FOLFOX4	6-year OS: 86.8% with 5-FU/LV vs. 86.9% with FOLFOX4 (HR, 1.00; 95% CI, 0.7–1.41; P=.986)	No
NSABP C-07 ⁸	Phase III RCT	2000–2002	≈700	5-FU/LV vs. FLOX	5-year OS: 89.6% with 5-FU/LV vs. 89.7% with FLOX (P=.84)	No

Abbreviations: 5-FU, fluorouracil; CT, chemotherapy; HR, hazard ratio; LEV, levamisole; LV, leucovorin; MOF, semustine, vincristine, and fluorouracil; OBS, observation; OS, overall survival; PVI, portal venous infusion; RCT, randomized controlled trial.

between DFS and OS in patients with stage II disease suggests that OS should be the primary end point for stage II–specific trials.¹⁷

Because of the low recurrence rate in patients with stage II disease (20%)¹⁰ and the large number of noncancer deaths in this population (32%),¹⁷ clinical trial design remains a challenge. A prospective adjuvant trial with a no-treatment control arm powered to detect an absolute risk reduction of 3.3% among patients with stage

II colon cancer with a baseline prognosis of 80% would require a sample size of 5800.¹⁸ The adjuvant clinical trials conducted to date all have been underpowered to show OS benefit within those parameters. Although QUASAR data and the pooled analysis from Gill et al⁹ reported improvements in DFS, the authors caution that this is an imperfect surrogate for OS in patients with stage II colon cancer and must be interpreted with skepticism.

Risk Stratification: “High Risk” May Not Be High Risk

The MOSAIC trial reported a trend toward improved 5-year DFS in patients with “high-risk” stage II disease. The consensus opinion of the NCCN Colon Cancer Panel specifies that patients with stage II disease should be stratified by low and high recurrence risk.¹¹

And how does one do that? Features that are used to stratify for a high risk of recurrence in stage II disease include advanced tumor stage (eg, pT4 lesions), tumor perforation, lymphovascular invasion, postsurgical analysis of fewer than 12 nodes, and poorly differentiated histology.^{9,19} This definition of high-risk features is predicated on results from a subgroup analysis of 318 patients with stage II colon cancer enrolled in INT-0035; of this relatively small cohort, perforation was present in 6%, obstruction in 16%, T4 tumors in 18%, and poorly differentiated histology in 11%.²⁰ Retrospective analysis of pooled data from 403 patients with stage II disease in INT-0035 and the North Central Cancer Treatment Group adjuvant trial showed perforation and obstruction to be significantly associated with increased recurrence risk, with perforation being the only feature that was independently prognostic in a multivariate analysis ($P \leq .01$).²⁰

According to these stratification criteria, 75% of the 24,847 patients in the SEER-Medicare database review were classified as “high risk” based on the presence of 1 or more of these features.¹⁶ Similarly, in the MOSAIC trial, 64% of patients with stage II were “high-risk,” mostly due to inadequate nodal sampling. In an exploratory subgroup analysis of the patients with stage II disease in MOSAIC, these high-risk patients showed shorter DFS in both treatment arms.¹² In a validation study conducted with the QUASAR cohort, a T4 tumor was the only feature associated with increased recurrence risk in a multiple-covariate Cox regression model, with an HR of 1.87 ($P = .004$). Lymphovascular invasion and tumor histology were not associated with increased risk of recurrence.²¹

Contrary to these stratification criteria, poorly differentiated histology was inversely associated with risk of recurrence (HR, 0.65; $P = .05$) in patients with stage II disease in the QUASAR cohort.²¹ Although this might seem surprising, it is actually consistent with the fact that a greater proportion of tumors with high-level microsatellite instability (MSI) exhibit

poorly differentiated histology.^{22,23} Patients with MSI-high tumors, leading to defective DNA mismatch repair, actually have a better prognosis than their counterparts with intact DNA mismatch repair. And surprisingly, the superior prognosis is negated by 5-FU-based therapy; patients with MSI-high tumors who receive adjuvant 5-FU-based chemotherapy have inferior OS.²⁴ Although MSI status still needs independent validation as a predictive biomarker, current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommend that, if therapy is being considered, MSI testing should be performed, and that patients with stage II MSI-high disease do not benefit from 5-FU-based adjuvant therapy (to view the most recent version of these guidelines, visit NCCN.org).¹¹

Distinguishing Predictive Versus Prognostic

The original recognition of putative high-risk features gleaned from the small INT-0035 cohort somehow became gospel, with the features derived from this analysis defining high-risk stage II disease. The current guidelines for risk stratification neglect the important distinction between prognostic factors (those that are associated with clinical outcome) and predictive factors (those that correlate with likelihood of benefit from therapy). In fact, grade and lymphovascular invasion have never been prospectively substantiated as prognostic factors. Moreover, the mechanism through which inadequate nodal sampling affects prognosis remains enigmatic. Online risk calculators are a tool for providing patients with prognostic information regarding recurrence risk but they are not predictive of treatment benefit. They are probably also overly simplistic for the multiplicity of factors that must be considered. Despite efforts to identify patients at the highest risk for recurrence, considerable stage-independent variability exists, reflecting the limitations of the NCCN Guidelines and the need for better prognostic and predictive tools.

Weighing Risks and Benefits

Although QUASAR data suggest an incremental survival benefit for patients with stage II disease, showing a reduction of the 20% chance of 5-year

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mortality without adjuvant therapy to 16.4% with adjuvant therapy, this marginal benefit must be weighed carefully against the risks of treatment-related morbidity and noncancer-related death. In both arms of the MOSAIC trial, 0.5% of patients in each arm died during treatment and as many as 40% of patients experienced grade 3 or 4 neutropenia.⁷

Moreover, although the addition of oxaliplatin possibly provides an absolute survival benefit of 1.5% compared with 5-FU/leucovorin therapy alone, it also has the potential to result in permanent sensory neuropathy. This toxicity typically occurs after 7 to 9 cycles, at cumulative doses between 667 and 810 mg/m².^{12,25,26} In the MOSAIC adjuvant trial, 12.1% of patients developed grade 3 peripheral sensory neuropathy during treatment, and 24.1% reported symptoms of any grade 18 months after completion of therapy¹²; the possibility of surviving and living with this debilitating sequela should not be discredited.

Treatment-related risks must also be considered in terms of a patient's actuarial age, comorbidities, and life expectancy. Based on results from the QUASAR trial, a reduction of the 5-year risk of cancer death by 3.6% increases life expectancy by 1 year in a 55-year-old patient with a life expectancy exceeding 30 years if not succumbing to re-

current colon cancer. For a 75-year-old with a life expectancy of 10 years, adjuvant therapy might increase life-expectancy by 4 months.¹⁰

The costs associated with these decisions warrant mention. The out-of-pocket drug cost for 8 cycles of adjuvant capecitabine is estimated at \$41,059 (based on a body surface area [BSA] of 2.0 m² and cost of capecitabine at \$36.66 per 500-mg tablet). The treatment-related costs of 12 cycles of mFOLFOX-6 exceed an estimated \$170,000 (based on a BSA of 2.0 m². This estimate reflects only pharmaceutical and infusion center costs assuming branded oxaliplatin and 48-hour infusion devices; it does not include the costs of supportive care, laboratory assessments, or provider visits.). With more than 35,000 cases of stage II colon cancer projected to be diagnosed in the United States in 2012,²⁷ the cost of adjuvant therapy with capecitabine alone would exceed \$1.4 billion and the cost of adjuvant therapy with FOLFOX would exceed \$6 billion.

Future Directions

MSI status, nodal sampling for accurate ascertainment of metastatic disease, molecular markers, and genetic signatures are all topics of active investigation in a broader query regarding

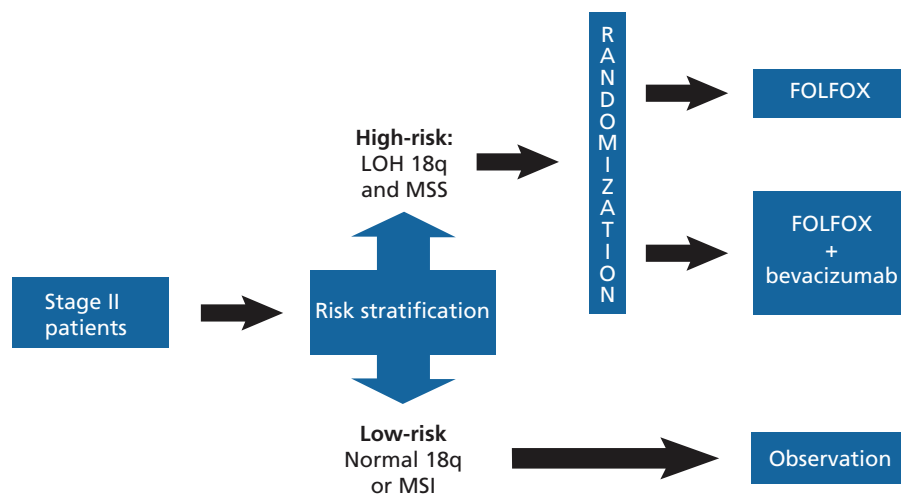


Figure 1 ECOG 5202 was a randomized phase III study of oxaliplatin and 5-FU/leucovorin with or without bevacizumab for the treatment of patients who had undergone surgery for stage II colon cancer, stratified according to MSI status and 18q heterozygosity. The study was closed early because of ethical concerns regarding randomization to the FOLFOX plus bevacizumab arm. The study accrued 1925 of the planned 3125 patients before study closure. Results are anticipated in August 2017. Abbreviations: FOLFOX, 5-FU, leucovorin, oxaliplatin; LOH, loss of heterozygosity; MSI, microsatellite instability; MSS, microsatellite stable.

which patients with stage II disease should receive adjuvant therapy. Development of novel diagnostic measures, such as guanylyl cyclase C, to detect tumor cells in lymph nodes may add prognostic value in patients who, by current standards, are falsely diagnosed with pN0 disease and require validation in a clinical trial.²⁸ Loss of heterozygosity at 18q has been implicated with prognostic value,²⁹ but this has been called into question by the heterogeneity of allelic loss within a colorectal tumor.³⁰

Two genetic signatures derived from microarray-based gene expression profiles have been validated and are commercially available: *Oncotype DX Colon* (Genomic Health, Inc., Redwood City, CA) and *ColoPrint* (Agendia, Irvine, CA). Developed with different strategies for selecting the component genes, each assay seems to be prognostic but not predictive of benefit from therapy. *Oncotype DX Colon*, which can be assayed on paraffin-slides, has been validated in 3 data sets.^{31–33} Market research shows that it is used by some oncologists for decision-making, but its clinical application is limited by the assay's small range of recurrence scores and the absence of predictive value. As of this writing, *ColoPrint* is commercially available but its use is still limited by requirement for fresh tissue. Notably, *Oncotype DX Colon* is not performed on patients who are determined to be MSI-high. These and other gene signatures in development require further refinement and validation as tools for providing predictive information in challenging stage II cases.

Intratumor heterogeneity presents major challenges to the development of these tools, and may portend that results based on single tumor–biopsy samples will never prove to be useful for customizing care.³⁴

Whether and how to use gene signatures and other molecular tests to guide decision-making are difficult questions. Commercial tests that are currently available include MSI testing and assays for loss of chromosome 18q, but only MSI testing has been validated for clinical use. A phase III intergroup trial, ECOG 5202, was designed to prospectively answer this question by using MSI and 18q status to stratify patients with stage II disease randomized to FOLFOX alone versus FOLFOX plus bevacizumab versus observation only (Figure 1). The ethics of randomization to the FOLFOX-plus-bevacizumab arm became problematic, however, with release of data showing no benefit from bevacizumab in the adjuvant setting,³⁵ and the study was prematurely closed short of the accrual goal. Although underpowered for the planned end points, results from this trial are anticipated in August 2017.

Conclusions

The logical argument has been made that the adjuvant treatment paradigm for patients with stage III disease should apply to those with stage II disease. Although it is intuitive that a subset of stage II tumors are in fact lesions detected by surveillance earlier in a continuum before spread to lymph nodes,

Table 2 Arguments For and Against Adjuvant Therapy in Stage II Colon Cancer

For	Against
<ul style="list-style-type: none"> • DFS and OS benefit is consistently seen in patients with stage III colon cancer • A trend is seen toward improved DFS in patients with stage II disease; however, clinical trials have been underpowered to detect the OS benefit in these patients • 20% risk of recurrence without adjuvant therapy • In the absence of reliable risk stratification tools, caution is preferred • Patient unease with observation alone after a cancer diagnosis 	<ul style="list-style-type: none"> • Colon cancer is a heterogeneous disease, across and within stages; results from one stage should not be extrapolated to another stage • DFS is not a surrogate for OS in stage II disease • Given 80% chance of cure with surgery alone, the number needed to treat to derive benefit is large • Current tools for risk stratification are not predictive of treatment benefit • Risk of treatment-related morbidity and mortality • Cost: 8 cycles of capecitabine is \$41,059; 12 cycles of mFOLFOX-6 is >\$170,000

Abbreviations: DFS, disease-free survival; mFOLFOX-6, modified 5-FU, leucovorin, oxaliplatin; OS, overall survival.

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evidence shows that the biology of node-negative tumors is both heterogeneous and distinct from that of those tumors that spread to lymph nodes earlier. Current tools for risk stratification neglect variability in clinicopathologic features and tumor biology, and in fact are not prognostic.

In the authors' best estimate, more than 80 patients with normal-risk stage II colon cancer would need to be treated for 1 patient to derive benefit. Meanwhile, the risk of treatment-related death may be as high as 0.5%,⁷ and treatment-related morbidity is nonnegligible. Until additional data are available to definitively show that patients are truly being helped by being exposed to 6 months of chemotherapy, the authors recommend considering adjuvant therapy only for patients with tumors exhibiting high-risk features, particularly those with T4 tumors and/or inadequate lymph node sampling. The authors advise that a normal-risk patient with stage II disease who has undergone a complete resection should only receive chemotherapy in the context of a clinical trial. And for those for whom adjuvant therapy is a consideration, thoughtful patient-centered discussions that attempt to convey the relative risks and benefits are imperative (summarized in Table 2). The authors believe that the pain associated with adjuvant therapy in stage II colon cancer is not justified by the gain.

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