Adjuvant Therapy for Stage II Colon Cancer: Prognostic and Predictive Markers

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Key Words
Stage II, colon cancer, treatment, molecular markers, clinical trials

Abstract
The treatment of stage II colon cancer is a controversial issue that has persisted for the past decade. Clinicians must understand that accurate assessment of risk factors is the key to identifying patients who will benefit from treatment. Pathologic staging for colon cancer is based on the American Joint Committee on Cancer 6th edition staging system. In addition, distinct pathologic factors characterize a patient at high risk for stage II disease. More recent retrospective data suggest that molecular markers and gene expression microarrays may be valuable as prognostic and predictive tests. Unfortunately, previous research studies were not powered to properly assess efficacy in stage II disease. However, two recent clinical trials, National Surgical Adjuvant Breast and Bowel Project C-07 and MOSAIC, have provided more insight into defining the optimal treatment approach. With the development of the newer therapeutic agents, oxaliplatin and bevacizumab, ongoing trials such as Intergroup E5202 should help determine risk versus benefit of chemotherapy in the adjuvant treatment of stage II colon cancer. (JNCCN 2007;5:927–936)

Colon cancer is the third most common cancer in the United States, with an estimated 112,340 diagnoses in 2007.1 In the past decade, the treatment for this disease has undergone major changes, particularly with the emergence of new chemotherapy regimens. Although the mortality rate for colon cancer is slowly decreasing, it is still the second most common cause of cancer death. Prognosis is based mainly on the clinicopathologic stage defined by the TNM (Tumor, Node, Metastasis) staging system of the American Joint Committee on Cancer (AJCC). For localized disease, standard care for stage I colon cancer is surgical resection alone, whereas it is widely accepted that adjuvant chemotherapy improves overall survival compared with surgery alone for patients with stage III disease. However, controversy exists for the approximately 25,000 patients diagnosed with stage II colon cancer in the United States each year. Of those patients, about 75% to 78% will remain disease-free after 5 years irrespective of whether adjuvant chemotherapy is given.2 With such a high survival rate, a clinical trial would need at least 4,700 patients to detect a 4% survival advantage at 5 years for stage II patients.3 This quota has not been reached in any past study and will be difficult to accomplish in future trials. In addition, most adjuvant trials include patients with stage II and III disease with inadequate power to assess efficacy for the stage II cohort. Thus, the benefits of using adjuvant chemotherapy in stage II disease remains unclear. The challenge for clinicians continues to be in identifying not only patients with stage II disease who are at high-risk for recurrence, but also those who will actually benefit from treatment.

Pathologic Risk Factors
The first step in addressing the adjuvant question is to accurately stage the patient and attempt to ascertain specific tumor characteristics. Colon cancer was originally classified using the Dukes’ staging system, with Dukes’ B best correlating with T3, N0, M0 by the TNM staging system.4 In 1954, a modified Dukes’ classification (Astler-Coller system) redefined Dukes’ B as B1 (T2, N0, M0), B2 (T3, N0, M0), and B3 (T4, N0, M0), and this system was used in many older trials for colon cancer. However, the TNM staging system is now the preferred staging system used in practice and clinical trials. The AJCC
6th edition further separated TNM stage II disease into subgroups IIA (T3, N0, M0) and IIB (T4, N0, M0). Although these patients may seem similar, with only a difference in T3 or T4 tumor stage, they actually have wide pathologic variability, ranging from tumors that barely penetrate the bowel wall to those that actually invade adjacent structures with lymphatic and venous spread. Even T4 lesions can vary based on serosal invasion or perforation. This is an important and often underdiagnosed finding that is separately classified as pT4b. Based on the Surveillance, Epidemiology, and End Results (SEER) data from 1991 to 2000, which reported clinical practice outcomes, the difference between stage IIA and IIB translates to a 10% to 15% survival disadvantage for patients who have stage IIB colon cancer. Patients who have stage IIB colon cancer have a worse 5-year survival (72.2%) than even node-positive stage IIIA (83.4%), suggesting that T4 lesions can be an even worse prognostic feature than lymph node involvement (Figure 1).

Specific pathologic markers have been identified to help determine which patients have the highest risk for recurrence. Lymph node status is an obvious determinant because it is an integral part of the TNM staging system. Surprisingly, however, several studies have found that the actual number of analyzed nodes is also significant. A multivariate analysis of Intergroup trial 0089 showed that survival was influenced by the number of nodes obtained during surgery regardless of whether they were positive or negative. In node-negative disease, patients who had more than 20 nodes removed had an 8-year survival of 79% versus 59% for those patients with fewer than 10 nodes ($P < .001$).

The Intergroup Trial for Adjuvant Therapy on Colon Cancer studies showed similar results, with an absolute improvement in 5-year overall survival (OS) of 8%
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(P < .001) and relapse-free survival (RFS) of 17% (P < .001) for Dukes’ B, with fewer than 7 nodes versus more than 17 nodes recovered.9 In a recent systematic review, 16 of 17 studies showed that survival improved as the number of lymph nodes sampled increased.10 Because these studies were retrospective, whether a causal relationship exists is unknown. Other possible explanations for this interesting phenomenon include more accurate staging, improved quality of surgery, or a change in the tumor’s lymphatic drainage.

An expert panel from the National Cancer Institute recommended a minimum of 12 lymph nodes be examined before a patient is considered node-negative for entry into a colon adjuvant trial.11 Any grossly negative nodes should still be examined microscopically for the presence of micrometastasis.4 These are groups of tumor cells more than 0.2 mm but less than 2 mm and are defined as pN1. The significance of this is obvious since it upstages a patient to stage III. On the other hand, isolated tumor cells (ITC) are groups of cells less than 0.2 mm that are identified histologically or with special techniques. Although this is still classified as pN0 disease, ITCs may play a more significant yet undefined prognostic role.

Other well-known pathologic markers that have been shown to have prognostic value for stage II colon cancer include T4 disease, poorly differentiated histology, lymphovascular invasion, perforation, and obstruction.12–14 A recent retrospective study15 attempted to assess the validity of the Petersen prognostic model, which used peritoneal involvement, vascular invasion, perforation, and positive surgical margins to define low- and high-risk groups. Of 1625 patients with Dukes’ B, only 23.3% actually had all the pathologic variables to be fully assessed. Nonetheless, a survival difference of 24.3% was seen between high- and low-risk groups (P < .01). More importantly, this study underlines the idea that, similar to surgical skill in nodal sampling, the pathologic evaluation must be of high quality for clinicians to reliably assess prognostic factors for patients with stage II colon cancer.

Molecular Markers
Although pathologic risk factors have been verified as prognostic markers, they have not been validated as predictive tools. Because a distinct difference exists between the terms prognostic and predictive, the meaning of each must be understood to appreciate their significance in colon cancer adjuvant treatment. A prognostic test identifies a high-risk population of patients who have a more aggressive form of disease and is linked to survival. A predictive test correlates with response to treatment. In the setting of stage II colon cancer, the question remains as to which patients will most likely benefit from treatment. Thus, predictive markers are being investigated aggressively, with research now focusing on molecular biology to predict response.

Recent advances in the discovery of molecular markers and gene expression profiles have provided a significant first step in achieving this goal. Microsatellite instability (MSI) is one of the most studied markers and is found not only in hereditary nonpolyposis colorectal cancer syndrome but also in approximately 15% of sporadic colon cancer cases. Although the specific genetic mechanisms differ in either case, the molecular pathway frequently involves transforming growth factor (TGF) β and defective DNA mismatch repair genes.16 MSI refers to new alleles of small repeated DNA sequences; 5 markers (BAT25, BAT26, D5S346, D2S123, D17S250) are measured to quantify instability. High-frequency MSI (MSI-H) is classified as 2 or more markers with instability, whereas low-frequency MSI (MSI-L) is defined as 1 marker with that feature.17 Microsatellite stability (MSS) tumors have no changes in any of the examined loci. Pathologically, MSI-H tumors are characterized by larger proximal tumors that are poorly differentiated and mucinous with tumoral lymphocytic infiltration.18,19

The predictive value of MSI has been studied extensively in retrospective analyses. Ribic et al.20 found that, in patients not treated with adjuvant chemotherapy, MSI-H conferred an improved 5-year OS compared with MSS or MSH-L, with a hazard ratio (HR) of 0.31 (P = .004). Among patients who underwent treatment, those with MSS or MSH-L had an improved OS (HR, 0.72; P = .04), but chemotherapy was not beneficial for MSI-H. Another recent trial21 with 718 patients (393 stage II and 325 stage III) showed similar findings. Patients with stage II colon cancer with MSI-H tumors had a better clinical outcome than those with MSI-L/MSS (P = .0059). However, other trials have not consistently supported MSI as a predictive tool. Kim et al.22 found no relationship between MSI and chemotherapy in terms of OS (P = .62). A systematic review of 32 studies23 found that patients with MSI had improved OS (HR, 0.65) but did not benefit from adjuvant chemotherapy (HR, 1.24).
Chromosomal abnormalities, including translocations, amplifications, and allelic losses, are commonly seen in 85% of colorectal cancers. Specifically, loss of heterozygosity of chromosome 18q (18q LOH) has been well studied and found to be associated with a poor prognosis. Watanabe et al.\(^\text{14}\) conducted a retrospective study on 460 patients with high-risk stage II and stage III colon cancer treated with adjuvant chemotherapy in 2 Gastrointestinal (GI) Intergroup trials. The 18q LOH group was associated with a 5-year OS of 50% versus 74% for those patients without 18q LOH \(P = .006\). In addition, patients with MSI-H in the presence of a mutated TGF-\(\beta\) gene was associated with an improved 5-year OS of 76% versus 46% for those without a mutation \(P = .03\). Although a review of biomarkers showed that MSI probably had the only prognostic value,\(^\text{22}\) other markers, including thymidylate synthase, Ki-67, p53, and epidermal growth factor receptor (EGFR), have shown promise.\(^\text{26-28}\) Nonetheless, additional research is needed to further support these other molecules as predictive tests.

Recent investigations have also been encouraging for gene expression profiling, which uses oligonucleotide microarrays on tumor mRNA samples. A 23-\(^{\text{23}}\)-30-gene signature\(^\text{6}\) yielded around a 78% to 80% prognosis prediction accuracy for recurrence in stage II patients. Other recent investigations have shown that smaller (8-gene\(^\text{31}\) and larger (70-gene\(^\text{32}\)) prognosis predictors can also be effective. Johnston et al.\(^\text{33}\) used a transcriptome-based approach in developing a 48-gene microarray that was 100% accurate in predicting recurrence in stage II disease \(P < .001\). Although still early in development, the hope is that a test will become available that can personalize each patient’s colon cancer to predict who requires adjuvant chemotherapy.

**Chemotherapy in Adjuvant Trials**

To shed light on the question of whether chemotherapy is needed for stage II patients, one must examine the history of adjuvant treatment. In the 1980s, based on early studies from the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the North Central Cancer Treatment Group (NCCTG), 5-fluorouracil (5-FU) was first noted to have activity in this disease. Initially, 5-FU in combination with semustine and vincristine was studied in the NSABP trial C-01,\(^\text{44}\) which enrolled patients with Dukes’ B and C colon cancer. Other subsequent trials from NSABP (C-02, C-03, C-04, C-05) included stage II and III but were individually underpowered for stage II analysis.\(^\text{31}\) The combination of 5-FU with levamisole was studied in an NCCTG trial, which showed a 33% decrease in the risk for death at a median follow-up of 3 years.\(^\text{35}\) No survival benefit was seen for the subset of patients with stage II disease.

The GI Intergroup was also involved in studies evaluating stage II disease. Intergroup trial 0035 enrolled 318 patients with stage II disease to undergo either treatment with 5-FU and levamisole or observation. After a median follow-up of 7 years, a 31% reduction was seen in the recurrence rate that was not significant \(P = .10\) and no difference was seen in mortality, with both groups having a 72%-7-year survival rate.\(^\text{37}\) Based on these trials, in 1990 the National Institutes of Health recommended chemotherapy with a 5-FU–based regimen for patients with resected stage III disease only.\(^\text{38}\) No adjuvant therapy was specified for patients with stage II disease because of the lack of data. Intergroup study 0089 randomized 3759 patients with stage II and III disease to undergo treatment with 4 different combinations of 5-FU and leucovorin or levamisole. The patients with stage II disease exhibited high-risk features, such as bowel obstruction, perforation, or invasion of adjacent structures. The 5-year OS for stage II was similar in all 4 groups, ranging between 75% and 77%. Because this survival rate is comparable to previous data for patients after surgery alone, adjuvant therapy seemed to provide no benefit, even though no observation arm was included.

Another large randomized trial attempted to evaluate the role of chemotherapy in stage II disease. The Quick and Simple and Reliable (QUASAR)\(^\text{40}\) study enrolled 3238 patients with either colon or rectal cancer, of which 91% had Dukes’ stage B disease and 71% had colon cancer. After a median follow-up of 4.2 years, there was a significant 18% reduction in the relative risk of recurrence \(P = .02\) but a nonsignificant 12% reduction in the risk for death \(P = .15\) for the combined population of patients. This translated to a 1% to 5% OS benefit for chemotherapy. The data have been reported in abstract form only. Thus, although not a pure study for stage II colon cancer, this is the closest any dedicated stage II adjuvant trial has come to supporting the use of chemotherapy in this group of patients.
Meta-Analysis and Systematic Reviews

Because past studies contain a mix of patients and treatments, more statistical analysis has been performed through the pooling of data, including the meta-analysis of adjuvant trials. One of the first retrospective analyses was composed of 4 NSABP trials (C01–C04). These contained several different treatment and control arms, therefore for analysis, the most superior arm was compared with the most inferior arm. For the pooled 1565 patients with Dukes’ B disease, a 30% reduction in mortality was seen with chemotherapy. However, because the treatment regimens in C-01 and C-02 are no longer used for colon cancer, these results have been controversial. The International Multicenter Pooled Analysis of Colon Cancer Trials (IMPACT) B2 meta-analysis evaluated 5 trials with 1016 patients with stage II disease, all comparing 5-FU and leucovorin with surgery alone. The investigators found a nonsignificant trend in OS (HR, 0.86) for adjuvant chemotherapy. A meta-analysis by Gill et al. expanded on the IMPACT B2 data by adding 2 additional trials, for a total of 7 trials, with 5-FU and leucovorin or levamisole. In the analysis of 3302 patients with stage II disease, adjuvant chemotherapy resulted in a 5-year disease free survival (DFS) of 76%, which was barely significant (P = .049), and a 5-year OS of 81%, which was not significant (P = .1127).

Because of the continued controversy surrounding the routine use of chemotherapy for stage II colon cancer, a systematic review was performed by the Cancer Care Ontario Program in Evidence-Based Care in 2003. They included 37 trials and 11 meta-analyses published after 1987 that compared any adjuvant therapy with observation. Overall, the review included more than 20,317 patients with stage II disease varying from 23% to 100% between trials. The CCPOGI concluded that the mortality risk ratio was 0.87 (P = .7), and therefore not enough evidence was available to recommend adjuvant chemotherapy in patients with stage II disease.

In 2004, the American Society of Clinical Oncology (ASCO) released their guidelines based on a more stringent review of the trials in the earlier CCPOGI review. A subset of 12 of the original 37 trials was used to compare surgery alone with a 5-FU-based chemotherapy arm. The results were similar to the CCPOGI analysis, with a mortality risk ratio of 0.86. Thus, ASCO also did not recommend the routine use of chemotherapy in stage II colon cancer. Nevertheless, they did include stipulations in which adjuvant treatment could be offered. These involved high-risk prognostic features, including a T4 lesion, perforation, poorly differentiated histology, and inadequate lymph node sampling; however, the actual number of lymph nodes was not defined. Notably, these factors do not predict response to treatment. Finally, ASCO recommended that a thorough discussion between patients and physicians should occur to evaluate the risks and benefits of adjuvant chemotherapy (Figure 2).

Newer Therapies and Trials

The aforementioned studies have all evaluated the use of 5-FU–based chemotherapy in stage II colon cancer. However, in the past 10 years, adjuvant therapy has evolved from 5-FU alone to the addition of oxaliplatin as the new standard adjuvant regimen. Irinotecan was also investigated in adjuvant clinical trials based on its activity in previous metastatic trials. Three recent adjuvant studies, however, do not support the integration of irinotecan as a treatment strategy. The Pan-European Trials in Adjuvant Colorectal Cancer-3 (PETACC-3) trial enrolled 945 patients with stage II and 2333 patients with stage III disease. Unfortunately, the 3-year DFS was not significantly different between the treatment groups. In addition, the French ACCORD trial and Cancer and Leukemia Group B (CALGB) 89803 for patients with stage III disease also showed that 5-FU plus irinotecan had no advantage compared with 5-FU alone and therefore should not be given in the adjuvant setting. This also emphasizes the importance of phase III adjuvant trials to validate treatment efficacy. History has provided the important lesson that a therapeutic agent’s benefit in metastatic disease does not necessarily translate to the adjuvant setting and should be considered when conducting future studies with novel agents.

However, the acceptance of oxaliplatin as part of the standard adjuvant treatment was based on 2 recently completed prospective studies, NSABP C-07 and MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer), which have also shed more light on the dilemma of stage II disease. In NSABP C-07, patients were randomized to treatment with either bolus 5-FU/leucovorin (FULV) or oxaliplatin...
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- Ask the patient how much prognostic information they wish to hear and whether they prefer numbers (e.g., 3%) or words (e.g., very small).
- Understand the patient’s perception of risk and benefit and individual factors that may influence decision-making.
- Focus discussion on whether potential benefits of treatment outweigh potential risks.
  - Patients with stage II colon cancer have a good prognosis with surgery alone (5-year survival of 75% to 80%).
  - The potential improvement in cure rate with chemotherapy is limited. Although clinical trials have been adequate to show that 5-FU does not improve survival by more than 3%, they have not been large enough to confirm that the actual survival advantage may be in the range of 2% to 4%.
  - Possible risks and toxicities from chemotherapy given over 6 to 8 months should be discussed in detail, including the risk for treatment-related death (<1%).
- Define risk based on T and N stage, tumor differentiation and perforation, vascular and lymphatic invasion, neuroinvasion, and number of lymph nodes.
  - Emphasize that these tumor characteristics may be prognostic markers, but no data suggest that they are also predictive markers.
- Other potential prognostic and predictive markers may be addressed, including 18q and MSI, with the understanding that only retrospective data are available.
- Discuss any comorbidities and their effect on benefit versus risk of therapy.
- Consider using a numeracy program (www.mayoclinic.com/calcs), which is a model estimate of survival stratified by age, tumor grade, nodal status, and T stage, to help analyze patient risk.

Figure 2 Points of discussion between the patient and physician: the value of adjuvant chemotherapy for stage II colon cancer.

Abbreviation: 5-FU, 5-fluorouracil.

with bolus 5-FU/leucovorin (FLOX). Of the 2407 patients, 695 patients had stage II disease, with relatively equal representation in both treatment groups. A recent update after 4 years showed that DFS was 67% for FULV and 73.2% for FLOX, with an HR of 0.80 (P = .0034). Because the stage II cohort was small, the study was not powered to evaluate efficacy; however, the benefit of oxaliplatin was observed for both stage II and III.

Another landmark study showed similar overall results. The MOSAIC trial involved 2246 patients with stage II and III disease randomized to treatment with either 5-FU/leucovorin (LV5FU2) or oxaliplatin and 5-FU/leucovorin (FOLFOX4). Approximately 40% of patients in either group had stage II disease. Initial 3-year results showed an overall DFS of 78.2% for FOLFOX4 and 72.9% for LV5FU2, with an HR of 0.77 (P = .002). In addition, although the trial was not adequately powered for stage II disease, a DFS rate of 87% was seen with FOLFOX4 and 84.3% with LV5FU2. Further subset analysis was reported in abstract form. Of the 899 patients with stage II disease, 109 had high-risk features, such as bowel obstruction, perforation, venous invasion, or a T4 lesion. Patients with stage II disease treated with FOLFOX4 had a 20% relative risk reduction for recurrence compared with those treated with LV5FU2. The 6-year final survival analysis was recently presented at the 2007 ASCO meeting. A nonsignificant 3.8% difference in DFS was seen for patients with stage II disease (P = .258); however, high-risk stage II disease showed a trend toward benefit, with an absolute 7.2% difference in DFS (HR, 0.74). A minimal difference of 0.1% in OS was seen between LV5FU2 and FOLFOX4 in patients with stage II disease after 6 years (P = .996). Thus, the addition of oxaliplatin to 5-FU comes at the cost of substantial neuropathy (12.4%) during treatment without the benefit of improved survival for at least low- to average-risk patients with stage II disease and cannot be recommended.

Recent results from the Adjuvant Colon Cancer Endpoints (ACCENT) dataset that evaluated patients experiencing recurrence after treatment was also presented at the 2007 ASCO meeting. The investigators showed that the initial pathologic stage (II vs. III) and time from initial surgery to recurrence were important prognostic factors. In addition, adjuvant therapy significantly improved DFS, especially within the first 2 years; however, patients treated with chemotherapy had a worse prognosis after recurrence than those treated with surgery alone (P = .005). This may be caused by a selection and sensitivity bias, because
patients who underwent 5-FU adjuvant treatment possibly had less-advanced disease that then recurred and was resistant to further 5-FU therapy.

In the past few years, targeted agents have been discovered that are specific to biologic pathways such as vascular endothelial growth factor (VEGF) and EGFR. The only currently approved anti-VEGF drug is bevacizumab, whereas available anti-EGFR therapy for colon cancer includes cetuximab and panitumumab. Whether these agents have any benefit for patients with stage II disease remains to be seen. Two current trials, NCCTG N0147 and PETACC-8, are evaluating FOLFOX with and without cetuximab for patients with stage III disease. The AVANT trial is a multinational study in 33 countries randomizing patients with high-risk stage II and III disease to treatment with FOLFOX, FOLFOX plus bevacizumab or XELOX (capecitabine + oxaliplatin) plus bevacizumab. The trial is now closed after a planned enrollment of 3450 patients. Another trial, NSABP C-08, which randomized more than 2600 patients with stage II and III disease to treatment with FOLFOX with or without bevacizumab, recently completed accrual. With no observation arm, these trials may be of limited value in answering the adjuvant question in patients with stage II disease. However, in NSABP C-08, prognostic markers are being evaluated retrospectively to provide more insight into stage II colon cancer.

The need for appropriate risk assessment has influenced clinical trialists to integrate the analysis of markers to better define a patient’s response to treatment. This is best exemplified in Eastern Cooperative Oncology Group E5202 study design.

**Figure 3** Eastern Cooperative Oncology Group E5202 study design.

**RANDOMIZE**

**Arm A:**
- Oxaliplatin 85 mg/m², IV over 2 h
- Leucovorin 400 mg/m², IV over 2 h
- 5-FU 400 mg/m², IV bolus injection, immediately following leucovorin.
- Continuous infusion 5-FU 2.4 g/m² over 46 h immediately following bolus 5-FU.

**Arm B:**
- Oxaliplatin 85 mg/m², IV over 2 h
- Leucovorin 400 mg/m², IV over 2 h
- 5-FU 400 mg/m², IV bolus injection, immediately following leucovorin.
- Continuous infusion 5-FU 2.4 g/m² over 46 h immediately following bolus 5-FU.
- + Bevacizumab 5 mg/kg IV over 2 h

Cycle + 2 treatment days q2wk
Repeat for 12 cycles (both treatment arms)

*Continue for 12 additional cycles following completion of chemotherapy.

Tumor block risk assessment based on biology (18Q/MSI)

**Arms/Regimens**

- Stage II colon cancer (resected < 60 days before registration)
- High Risk
  - MSS with 18q LOH
  - MSI-L with 18q LOH
- Low Risk
  - MSS with retention of 18q alleles
  - MSI-L with retention of 18q alleles
  - MSI-H with or without retention of 18q alleles

**Abbreviations:** 5-FU, 5-fluorouracil; LOH, loss of heterozygosity; MSI, microsatellite instability; MSI-L, low-frequency microsatellite instability; MSI-H, high-frequency microsatellite instability; MSS, microsatellite stable.

From Benson AB III. New approaches to the adjuvant therapy of colon cancer. Oncologist 2006;11:978; with permission.
On study is not only focusing on patients with stage II disease but is also going one step further in stratifying patients according to the molecular prognostic factors, MSI and 18q LOH. Patients are classified as low risk if they have retention of 18q or MSI-H and will be observed after surgery. The high-risk group includes patients with either MSS or MSI-L in conjunction with loss of 18q and will be randomized to either FOLFOX or FOLFOX and bevacizumab (Figure 3). Based on the trial hypothesis that the low-risk group will have a survival of nearly 90%, and with a planned accrual of 3610 patients, there will be an 88% power to detect a 37% difference between the cohorts for median DFS after 3 years. The hope is that this study will provide a basis for the use of molecular markers on which future adjuvant trials can build. In addition, it will be an invaluable resource, with one of the largest stage II tumor banks that can be used to perform multivariate analyses incorporating pathologic and molecular factors and for future evaluation of gene expression signatures.

Conclusions

Controversy surrounding adjuvant therapy for stage II colon cancer is based on the lack of data showing a definite benefit for chemotherapy for these patients as a whole. Current recommendations from the National Comprehensive Cancer Network (NCCN) on the use of chemotherapy in patients with stage II disease are classified as 2B because of the low level of existing evidence. Patients are separated into low-risk stage IIA or high-risk stage IIA/IIB groups. High-risk features are defined as histologic grade 3–4, lymphovascular invasion, obstruction, perforation, fewer than 12 lymph nodes examined, or positive surgical margins. Treatment options for patients with high-risk IIA or IIB disease include capcitabine or 5-FU/leucovorin with or without oxaliplatin and consideration of enrollment into clinical trials.

Significant pathologic differences account for the variability in survival rates among subgroups. In identifying these specific factors, physicians will be able to classify patients who are at greater risk for relapse. Unfortunately, this does not necessarily determine who will have a better response to chemotherapy. Thus, molecular markers and gene microarrays as predictive tests may be the answer, although further prospective trials are needed to prove their effectiveness. Surgical and medical oncologists are strongly encouraged to enroll patients to Intergroup trial E5202, which addresses both patient and tumor characteristics in hopes of establishing an individualized treatment approach. Through further research, physicians may one day be able to provide better care through integrating prognostic and predictive markers into clinical practice.

References


