Adjuvant Chemotherapy for Stage II Colon Cancer

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Adjuvant therapy is defined as any treatment administered after surgical resection of a primary tumor with the intent of improving the patient’s outcome by eliminating any occult, viable tumor cells that may have remained after surgery.

ABSTRACT: The use of adjuvant chemotherapy following resection for all patients with stage III colon cancer is now part of the standard of care around the world. Recent trials have led to changes in the standard regimens, which now include the use of oxaliplatin (Eloxatin) for most patients with stage III colon cancer. The addition of oxaliplatin has resulted in a 23% reduction in the risk of recurrence compared with fluorouracil/leucovorin alone, with a small but statistically significant survival benefit. Unfortunately, no adequately powered trial has determined whether adjuvant chemotherapy is beneficial for stage II patients, and its use is much more controversial. Most investigators agree that adjuvant chemotherapy has some activity against stage II disease. However, its impact on progression-free and overall survival remains highly controversial. Despite the lack of data, there is growing acceptance of an informal classification system, which stratifies stage II patients by risk on the basis of clinical data, as a guide for deciding whether to use adjuvant therapy. The only phase III clinical trial for stage II patients currently ongoing in the United States uses molecular classification as the basis for patient randomization.

Adjuvant therapy is defined as any treatment administered after surgical resection of a primary tumor with the intent of improving the patient’s outcome by eliminating any occult, viable tumor cells that may have remained after surgery. For adjuvant chemotherapy to be considered in any disease, the agents used should effectively eradicate the type of tumor cells present in that disease, and the risk-to-benefit ratio for the adjuvant treatment must be favorable, since some, if not most, patients who receive adjuvant treatment are already cured by the surgical procedure. Recent declines in mortality rates from colorectal cancer in the United States have been attributed to the increased utilization of surveillance and improvements in adjuvant chemotherapy. However, colon cancer continues to be a leading cause of cancer death around the world. TABLE 1

AJCC TNM Staging System for Colorectal Cancer

The decision of whether to use adjuvant chemotherapy is based on a patient’s risk of recurrence, which is determined in large measure by the disease stage (Table 1) and the risk reduction expected with treatment. The now-standard TNM staging system is based on tumor penetration through the bowel wall (T) and the presence of regional lymph node (N) and distant metastases (M). Patients with stage I disease have a high probability of cure after resection, and adjuvant chemotherapy is unlikely to add much benefit. Adjuvant therapy is not an option for patients with stage IV (metastatic) cancer, although the term is frequently used to identify chemotherapy given after resection of localized metastasis.[1] Therefore, only patients with stage II or III disease are generally considered eligible for adjuvant chemotherapy. The use of adjuvant chemotherapy in colon cancer dates back to 1990, when it was demonstrated...
that fluorouracil (5-FU) and the antihelminthic agent levamisole improved overall survival after resection—a finding that was repeated in 1994 in a study combining 5-FU with leucovorin (LV). In 1998, 5-FU/LV was demonstrated to be superior to 5-FU/levamisole, resulting in the discontinuation of further levamisole use. In 2003, the combination of oxaliplatin (Eloxatin) and 5-FU/LV demonstrated greater benefit than 5-FU/LV alone, and the oral agent capecitabine (Xeloda) was later shown to be equivalent to intravenous 5-FU/LV. Current trials in stage III colorectal cancer are exploring the integration of capecitabine into combination regimens and the addition of monoclonal antibodies to adjuvant therapies. However, despite decades of adjuvant trials with 5-FU, the question of whether adjuvant chemotherapy is beneficial in node-negative, stage II (T3/4, N0) colon cancer has not yet been answered. Patients with stage II disease represent approximately one-quarter of the patients diagnosed with colon cancer and have a good prognosis, with a 5-year survival rate of approximately 80%. This review addresses the current debate over the use of adjuvant chemotherapy in stage II colon cancer, describing relevant concepts for critiquing the available data in the literature and attempting to place the potential benefits in a framework appropriate for discussion with patients.

**Efficacy of Adjuvant Chemotherapy in Stage II Colon Cancer**

The benefit of adjuvant chemotherapy for stage III colon cancer has been established and refined over several decades of clinical trials. The relevant historical trials focusing on stage III patients have been extensively reviewed.[2-4] Despite the fact that patients with stage II disease have been included in many of these adjuvant trials, the benefit of chemotherapy after resection in these patients has still not been definitively established. The following review of the past 20 years of trials provides a background for understanding the current controversy in this field.

**Early Trials**

An early prospective trial of adjuvant therapy for colorectal cancer reported a significant benefit of short-term 5-FU for stage II patients, with a 5-year disease-free survival rate of 82% compared with 59% in patients who did not receive adjuvant chemotherapy (P < .02).[5] However, the dramatic results of this small study have never been replicated, and subsequent trials have only added to the confusion.

The early National Surgical Adjuvant Breast and Bowel Project (NSABP) trials randomized patients to 5-FU-based regimens (semustine, vincristine, and 5-FU or preoperative portal vein infusion of 5-FU) vs observation, whereas later trials compared a 5-FU-plus-leucovorin arm to other 5-FU regimens (semustine, vincristine, and 5-FU or 5-FU and levamisole with or without leucovorin).[6-9] These trials were designed with a primary endpoint of overall survival in stage II/III patients, and subgroup analyses failed to show a statistically significant improvement in the outcomes of stage II patients treated with adjuvant chemotherapy.

One of the first studies to report data separately for stage II patients was the North Central Cancer Treatment Group (NCCTG) trial in which patients were randomized to observation or adjuvant treatment with levamisole or 5-FU and levamisole for 12 months.[10] The investigators found a trend toward improved disease-free survival with adjuvant chemotherapy (59% vs 73% for observation vs 5-FU/levamisole, P = .10). However, overall survival in this small stage II cohort was unchanged with treatment. **Dilemmas in Clinical Decision-Making: A Case Example**

A 70-year-old man with hypertension presented to his primary care physician with anemia and fatigue, prompting a colonoscopy, which demonstrated a nonobstructing sigmoid adenocarcinoma. He underwent a left hemicolectomy, which identified a moderately differentiated adenocarcinoma invading through the muscularis propria (T3) without lymphovascular invasion. Ten lymph nodes were evaluated, without evidence of tumor involvement.

How should we treat this stage II colon cancer patient? There are no consistent data on the benefit of adjuvant chemotherapy in stage II patients, although the cumulative evidence suggests a small benefit for fluorouracil/leucovorin chemotherapy.

How does the limited number of evaluated lymph nodes impact the treatment recommendation? It may represent inadequate surgical resection, incomplete pathologic evaluation, or a paucity of pericolonic regional lymph nodes in this patient.

What risk factors, if any, should influence the treatment recommendation? Several “high-risk”
features have been proposed, including inadequate sampling of the lymph nodes, with varying amounts of supporting data.

**GI Intergroup Trials**

A subsequent trial conducted through the GI Intergroup evaluated the benefit of 5-FU/levamisole in both stage II and stage III patients. This trial enrolled 1,247 patients; however, it was underpowered to answer the question of benefit in stage II patients, as only 318 with this diagnosis were studied. When compared with patients randomized to observation alone, those receiving 5-FU and levamisole were part of a trend toward a reduced rate of recurrence (71% vs 79% for observation and 5-FU/levamisole, respectively, P = .10), with nearly identical overall survival in the final report.[11,12]

A second GI Intergroup trial explored adjuvant chemotherapy with 5-FU-based regimens in patients with high-risk stage II/III disease, with a goal of identifying the optimal chemotherapy modulator. Patients with high-risk stage II disease, which was defined by the presence of obstruction, perforation, or invasion of adjacent structures at the time of diagnosis, accounted for 20% of the study enrollment. The four arms of the study included combinations of 5-FU with and without leucovorin or levamisole. Despite the fact that no observation arm was included, the results in high-risk stage II patients were felt to be similar to those in historical controls.[13]

**QUASAR 1 Trial**

The largest trial to date involving stage II patients is the Quick and Simple and Reliable (QUASAR) 1 study, which randomized colon and rectal cancer patients with an unclear indication for adjuvant chemotherapy to 5-FU and leucovorin or observation. Of the 3,239 patients enrolled, 92% had stage II disease. The primary endpoint of overall survival for all enrolled patients had not been reached at the time of the most recent abstract presentation of the study.[14]

In the subset of stage II patients, there was a 3% to 4% absolute improvement in the 5-year overall survival rate (P = .04), with a similar 3% to 4% absolute improvement in the rate of disease recurrence (15.4% vs 19.1%, P = .004). However, this study included rectal cancer patients (29%), some of whom also received adjuvant or neoadjuvant radiation therapy. A subset analysis suggested that the majority of the benefit seen with adjuvant chemotherapy occurred in the stage II rectal cancer patients (recurrence rate of 20% vs 27%, P = .005) as opposed to the stage II colon cancer patients (17% vs 20%).[14] It has been subsequently reported that only a minority of these patients had high-risk disease, characterized by a T4 primary tumor, lymphovascular invasion, or perineural invasion.[15] Further results are expected when the study report is published.

**MOSAiC and NSABP C-07 Trials**

With the introduction of oxaliplatin into adjuvant regimens, an additional question of benefit for stage II patients has been raised. In the MOSAiC trial (Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer), 6 months of 5-FU/LV was compared to 6 months of 5-FU/LV with oxaliplatin (FOLFOX regimen).[16] The primary endpoint of improved 3-year disease-free survival for stage II/III colon cancer patients was met. However, subset analysis of disease-free survival for stage II patients failed to demonstrate a benefit (absolute risk reduction of 3.8%, hazard ratio [HR] = 0.84, 95% confidence interval [CI] = 0.62–1.14), prompting the US Food and Drug Administration to limit approval of oxaliplatin to use in stage III colon cancer. Limiting the analysis to high-risk stage II disease (defined as a T4 lesion, tumor perforation or obstruction, poorly differentiated tumor, venous invasion, or fewer than 10 lymph nodes analyzed) likewise did not demonstrate a statistically significant benefit for oxaliplatin (absolute risk reduction of 7.2%, HR = 0.74, 95% CI = 0.52–1.06). Recently updated 6-year overall survival results did not differ for stage II patients treated with 5-FU/LV or FOLFOX.[17]

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![Adjuvant Therapy With and Without Oxaplatin](image)
Similar results from the NSABP C-07 trial demonstrated an overall benefit for the addition of oxaliplatin to 5-FU/LV but failed to demonstrate an improvement in the stage II subset.[18] Of note, in both trials above, the relative positive effect of adjuvant treatment on disease-free survival was similar for stage II and III patients, as denoted by comparable hazards ratios for the subgroups (Figure 1).

Capecitabine Data
Capecitabine, an oral prodrug of 5-FU, has been shown to be equivalent to bolus 5-FU/LV in the adjuvant treatment of 1,987 stage III patients.[19] To date, completed capecitabine adjuvant trials have not included stage II patients, although a study that included a capecitabine-and-oxaliplatin arm for high-risk stage II patients has completed enrollment.

5-FU Meta-analyses and Cohort Studies
Given the potential absolute benefit of 4% seen in the QUASAR study, a definitive trial to demonstrate a benefit for adjuvant chemotherapy for stage II patients would require 4,700 patients to be adequately powered.[20] As a result, the question of benefit in this population lends itself to meta-analysis. Unfortunately, the meta-analyses performed thus far have also been discordant and controversial.

Early Meta-analyses
One of the initial meta-analyses combined the outcomes of 4,000 colorectal cancer patients who received portal vein infusion of 5-FU as adjuvant therapy and demonstrated a statistically significant reduction in the 5-year mortality rate despite no change in the incidence of subsequent liver metastases.[21] This improved 5-year overall survival rate was also seen in the Dukes’ B subset of approximately 1,400 patients, with a 6% absolute risk reduction compared to observation alone. This did not, however, reach statistical significance, although Dukes’ B patients had the same relative risk reduction with treatment as was seen in Dukes’ C patients (18%).

These discrepant results were repeated in two meta-analyses published concurrently in the Journal of Clinical Oncology. The IMPACT B2 study (International Multicentre Pooled Analysis of B2 Colon Cancer Trials) evaluated five trials that had compiled individual patient data for modified Dukes’ B2 (T3/4, N0) patients.[22] These patients were randomized to treatment with 5-FU and leucovorin or observation. A total of 998 patients were included in the analysis, with a 5.8-year follow-up period. The 5-year overall survival rate was 82% in patients treated with 5-FU/LV and 80% for observation alone, which represented a statistically nonsignificant difference. The hazard ratio at 5 years was 0.83 (90% CI = 0.72–1.07) for disease-free survival and 0.86 (90% CI = 0.68–1.07) for overall survival. The authors concluded that 5-FU/LV could not be recommended for routine use in stage II colon cancer patients.

The second of the two reports evaluated the benefit of adjuvant treatment in the NSABP C-01 through C-04 trials.[23] Comparison of the more effective to less effective treatment arms in the four trials revealed a 30% reduction in mortality for stage II patients (P < .05), with a corresponding decrease in risk of recurrence. The mortality reduction in stage II patients occurred irrespective of the presence or absence of the adverse prognostic factors of obstruction, perforation, and invasion into adjacent structures. Although the stated intent of the analysis was to determine the benefit of chemotherapy in stage II disease, the combined analysis of trials without comparison arms was appropriately criticized as inadequate to fulfill that objective.[24]

However, a second and arguably more instructive goal was to compare the efficacy of adjuvant therapy in stage II and III tumors, with the hypothesis that if the biology of these tumors is similar, the relative benefit of any given chemotherapy regimen should also be similar. This was indeed suggested by the results of the analysis, as the relative benefit of the more effective treatment arm in each trial was similar in stage II and III patients, with a trend towards a greater relative benefit for stage II patients.

A similar finding was reported in an analysis of a GI Intergroup/NCCTG study.[11,12] Evaluation of several prognostic factors failed to demonstrate any interactions with tumor stage in the multivariate analysis, again suggesting that the relative benefit of adjuvant treatment is the same for stage II and III patients.

A multivariate analysis of seven trials of adjuvant therapy for stage II/III colon cancer explored the benefits of adjuvant treatment.[25] Univariate analysis of node-negative patients demonstrated a
4% absolute risk reduction in disease-free survival (HR = 0.83, P = .049). This approach, which adjusted for tumor stage, nodal status, and histologic grade, demonstrated a 35% reduction in the risk of recurrence (HR = 0.65; 95% CI = 0.58–0.73) and a 30% reduction in the risk of death (HR = 0.73; 95% CI = 0.63–0.79) with adjuvant chemotherapy.

CCO, ASCO, Medicare, and SEER Analyses

A systematic review focused on stage II patients was conducted by the Cancer Care Ontario (CCO) Program in Evidence-Based Care (PEBC).[26] This review, which included 37 trials and 11 meta-analyses, pooling data from 4,187 patients, found a risk ratio of 0.87 for adjuvant chemotherapy (95% CI = 0.75–1.01, P = .07), representing a trend toward improvement in overall survival.

A separate analysis conducted at the behest of an American Society of Clinical Oncology (ASCO) expert panel tasked with developing recommendations for stage II colon cancer adjuvant therapy limited the analysis to trials with an observation arm and a treatment arm containing 5-FU. Their results also concluded that adjuvant chemotherapy for stage II colon cancer patients does not significantly improve survival (risk ratio = 0.86, P = .08).[27] The authors concluded that there is probably a small benefit for adjuvant treatment that has not been detected as significant because of inadequate trial size.

A different approach was taken using the administrative and registry databases of Medicare and Surveillance, Epidemiology and End Results (SEER) to explore the potential benefits of adjuvant chemotherapy for stage II patients.[28] In that analysis, more than 3,000 patients aged 65 to 75 with stage II colon cancer were identified. Approximately 27% of the patients received adjuvant chemotherapy. This group tended to be younger and in better health and to have a lower tumor grade. After adjustment for available prognostic variables, the hazards ratio for survival associated with adjuvant treatment was found to be 0.91 (95% CI = 0.77–1.09). This analysis was limited, however, by an inability to collect and incorporate confounding prognostic factors (such as obstruction) that may have influenced both the outcomes and the decision to treat with adjuvant chemotherapy.

Summary

Our interpretation of the available evidence is that there is likely a small improvement in rates of recurrence and overall survival with adjuvant 5-FU chemotherapy for stage II colon cancer. The benefit has not been demonstrated owing to the inadequate sample sizes of previous studies. Oxaliplatin has not demonstrated a benefit in overall survival for stage II patients. This interpretation of the data is influenced by the consistent finding across trials of a similar relative benefit from adjuvant 5-FU chemotherapy for stage II and III patients. Some have suggested that estimates of relative treatment benefit are the best overall measure of treatment effect for stage II patients.[20] Therefore, the identification of high-risk features may define a subset of stage II patients who, as a result of their worse prognosis, may derive a greater absolute benefit from adjuvant treatment.

Toxicity of Chemotherapy in the Stage II Colon Cancer Population

Given the relatively good prognosis of stage II colon cancer patients, a recommendation to administer chemotherapy requires a discussion of the potential risks associated with treatment. The side effects of 5-FU/LV regimens, with or without oxaliplatin, have been well documented in the literature.[16,18] In one recent phase III trial, severe side-effects, defined as grade 3 or higher toxicities, occurred in 14% of stage II patients treated with 5-FU/LV, resulting in premature treatment discontinuation in 6% of patients. The addition of oxaliplatin to the regimen increased these rates (19% of patients experiencing severe adverse events, 12% of which resulted in treatment discontinuation).[29] Although well tolerated in the majority of patients, 5-FU-based regimens can cause severe complications, including death. In most modern trials, rates of treatment-related death range from 0.5% to 1%.[16,18]

The long-term side effects of adjuvant treatment are less well defined. In one study, quality of life decreased after adjuvant 5-FU treatment, requiring up to 1 year to return to baseline levels.[30] The addition of oxaliplatin increases the potential for neurotoxicity, which can significantly affect a patient’s quality of life. This neuropathy can worsen for some time after oxaliplatin is discontinued. Although most oxaliplatin-induced neuropathy resolves over time, it can be an unrelenting symptom in a minority of patients. Neuropathy was still present in 10% of patients 2 years after
discontinuation of treatment in the C-07 trial, despite the use of lower cumulative doses of oxaliplatin than in the adjuvant FOLFOX regimen [31].

Several trials that include patients with stage II disease are incorporating the monoclonal antibodies cetuximab (Erbitux), panitumumab (Vectibix), or bevacizumab (Avastin) into the adjuvant setting. The toxicities of adjuvant therapy are increased with these biologic agents. For example, bevacizumab is associated with very rare but severe side effects such as arterial thromboembolic events. In addition, the long-term toxicities of these newer agents are not as well defined. Until the risks and benefits of monoclonal agents are better defined, they should not be used in the adjuvant setting.

**Risk Stratification in the Stage II Colon Cancer Population**

Patients with stage II disease are a heterogeneous population. Understanding the different subgroups of stage II cancer can help determine the appropriate treatment course. For example, stage II patients with T4 primary tumors have a 72% 5-year overall survival rate, which is worse than that of patients with a T2 primary tumor with involvement of fewer than four lymph nodes (83% 5-year overall survival).[32]

While the magnitude of benefit from adjuvant therapy is small for the average stage II patient, it is informative to note that the relative improvement in outcomes with 5-FU adjuvant therapy is similar between stage II and stage III patients (as measured by the hazards ratio or odds ratio). This suggests that the relative benefit of 5-FU may be independent of the absolute risk of recurrence (ie, treatment may result in a 15%-20% relative reduction in recurrence or death regardless of the stage). This finding supports the use of clinical and pathologic variables to further clarify risk of recurrence for stage II tumors, as is suggested by the current guidelines.

However, these recommendations are made on the assumption that the prognostic characteristics will not alter the relative benefit of chemotherapy. Stated another way, it is assumed that these characteristics will not predict response to chemotherapy, but only reflect the risk of recurrence in the absence of treatment. In contrast, predictive markers reflect the response to a particular chemotherapy.

Below, we review the generally accepted prognostic factors, with a brief mention of several nontraditional prognostic factors under investigation. The limitations of prognostic markers and the difficulty in establishing predictive markers will be further discussed below.

**Prognostic Pathologic Markers**

- **T Stage**—As noted above, T stage is a major prognostic marker, with T4 tumors having particularly poor outcomes. The T4 classification includes both tumor extension into adjacent structures and perforation of the visceral peritoneum. The median survival of patients with visceral peritoneum involvement has been demonstrated to be significantly shorter than that in patients with tumor extension into adjacent structures.[33] It has been suggested that parietal peritoneum penetration is a worse prognostic factor than nodal involvement, prompting a call for revision of the TNM staging system.[34]

When gross perforation by the primary tumor is present, prognosis is adversely affected not only by the morbidity and mortality associated with the immediate event but also by an apparent increase in the rate of recurrence. Pathologically noted “microperforations” or contained perforations also represent a poor-prognosis subgroup, as is reflected in the current stage II guidelines.[27,35] Similarly, obstruction was found by multivariate analysis to result in 1.6-fold higher odds of recurrence or death within 5 years.[36]

- **Lymph Node Evaluation**—As part of the TNM staging criteria, lymph node analysis offers clear prognostic information. Interestingly, even for patients without nodal involvement, the number of nodes analyzed is a prognostic factor. A large population-based cohort study from the National Cancer Database evaluated the relationship between the number of lymph nodes resected and overall survival in 35,787 patients. Compared with patients who have 1 to 7 lymph nodes resected, the risk of death was 19% and 32% lower, respectively, for patients with 8 to 12 and more than 13 lymph nodes resected (P < .01).[37]

A systematic review of 61,371 stage II colon cancer patients demonstrated that this finding of improved survival with increased lymph node evaluation was consistent across 16 of the 17 reported trials.[38] This finding has been incorporated into many of the national guidelines for the determination of high-risk stage II colon cancer. Although a cutoff value of 12 resected lymph nodes has been used to distinguish high- and low-risk patients, the degree of risk is continuous in many studies such that, for example, stage II patients with 20 lymph nodes analyzed have better outcomes.
than those with 15 lymph nodes analyzed.[39] The association between the number of lymph nodes analyzed and survival not only indicates the importance of adequate mesenteric resection, and of an adequate and thorough evaluation of the specimen by the pathologist, but also a possible biologic relationship with prognostic relevance.[40] When an inadequate number of lymph nodes is reported, medical oncologists should request a pathology reevaluation to ascertain whether additional lymph nodes are present in the submitted tissue, as additional nodes can commonly be identified with diligent gross and/or microscopic examination.

Traditional staging characterizes nodal involvement as groups of tumor cells larger than 0.2 mm. However, smaller groups of cells or isolated tumor cells may also be prognostically informative. Several reports have documented the impact of single cytokeratin-positive cells identified by immunohistochemical (IHC) analysis or carcinoembryonic antigen (CEA) detection in lymph nodes by sensitive polymerase chain reaction (PCR) assays. For example, in a meta-analysis of stage II patients, PCR analysis resulted in the “upstaging” of 37% of the patients, which was associated with a significant decrease in the 3-year overall survival rate (78% vs 97%, P < .001).[41] Similarly, in a separate study, PCR for cytokeratin 20 was performed to detect hematogenous tumor cell dissemination. These investigators found a strong association between cytokeratin detection and subsequent disease-specific survival in stage II patients (HR = 7.7, P < .001).[42] Although changes in the standard techniques for nodal evaluation are being considered, use of IHC analysis or PCR should be considered investigational and is not yet sufficiently defined to guide clinical care.

- **Lymphovascular Invasion**—Another histologic feature associated with poor outcomes is the presence of lymphovascular invasion. The term describes the visualization of tumor cells within an endothelial-lined vessel. In a multivariate analysis of over 600 patients, the presence of lymphovascular invasion raised the odds of recurrence 2.8-fold (P < .001).[43] In a separate study, venous invasion combined with T and N stage outperformed the standard TNM staging system as a predictor of individual prognosis.[44] Despite the clear impact of this finding on outcomes, there is significant heterogeneity in the reporting of this risk factor, with high interobserver variation seen.[40] Nevertheless, lymphovascular invasion is considered to be a clinically useful marker of high-risk disease in stage II colon cancer patients.

- **Tumor Grade**—Another commonly cited prognostic factor, the designation of tumor grade is an attempt to categorize tumor behavior on the basis of architectural and cytologic features, including the extent of gland formation. Although grading systems vary without an accepted standard, most are capable of consistently identifying a subset of poorly differentiated or undifferentiated tumors with a worse prognosis. A large registry study of approximately 80,000 colorectal cancer patients demonstrated 5-year survival rates of 59% and 51%, respectively, for well-differentiated and moderately differentiated tumors, compared to 39% for poorly differentiated tumors.[45] Similar findings have been reported in stage II patients.[25,46] Mucinous and signet-ring histologies are considered poorly differentiated, and likewise have worse outcomes than well- or moderately differentiated adenocarcinomas. A two-tiered system of well or moderate differentiation vs poor or no differentiation has been adopted for the characterization of tumor risk in adjuvant chemotherapy guidelines for stage II disease.[27,35]

- **Other Histologic Markers**—Other histologic characteristics, including tumor growth patterns (infiltrating vs expanding), tumor budding on the invasive front, and extent of muscularis invasion, have been shown to be prognostic but not yet applicable to clinical practice.[47,48] Other potential prognostic histology markers are reviewed elsewhere.[33,49]

### Clinical Definitions of High-Risk Stage II Disease

Based on these data, guidelines have been developed that define a consensus group of high-risk features for stage II colon cancer.[27,50] These expert panel recommendations recognize that the benefit of adjuvant therapy for stage II patients is unknown and suggest enrollment in a clinical trial, if possible. Patient-physician decision-making is encouraged after a discussion of the risks and potential benefits of adjuvant therapy.

The National Comprehensive Cancer Network clinical practice guidelines define high-risk stage II disease as being characterized by at least one of the following factors: T4 tumor; poor histologic grade (undifferentiated or poorly differentiated); lymphovascular involvement; bowel obstruction at presentation; T3 lesion with localized perforation or close, indeterminate, or positive margins; and inadequately sampled lymph nodes (defined as fewer than 12 nodes analyzed).[50] According to these guidelines, patients with high-risk disease should be considered for adjuvant chemotherapy.
There is no evidence, however, that the factors associated with poorer prognosis are predictive of response to treatment. The guidelines developed by ASCO are similar but also list neural invasion as a high-risk feature.[27] The possible absolute benefit of adjuvant chemotherapy for stage II patients is estimated in this guideline as a 2% to 4% increase in the 5-year survival rate. The consensus opinion was that the direct evidence does not yet support the use of adjuvant chemotherapy for high-risk stage II patients, but that indirect evidence based on inadequate sample size in prior negative trials and the established benefit for stage III patients may support treatment of selected patients.

On the basis of these criteria, high-risk features are found in the majority of stage II patients. In the subset of stage II patients enrolled in the MOSAIC trial, 64% were characterized as high risk. Specifically, 19% had T4 lesions, 34% had inadequate lymph node sampling (defined as fewer than 10 lymph nodes in this study), 17% had bowel obstruction, 9% had perforation, and the high-risk pathologic findings of poor differentiation and vascular invasion were seen in 10% and 4% of patients, respectively.[29]

Other high-risk models have been suggested. For example, the Petersen prognostic model defines high risk as either tumor perforation or more than one of the following: peritoneal involvement, vascular invasion, and positive surgical margins. In an independent validation cohort of 1,625 stage II patients, this model demonstrated a significant difference in 5-year survival rate for high-risk vs low-risk patients (45% vs 70%, respectively, P < .01).[51]

**Prognostic Molecular Markers**

In addition to the well-recognized pathologic and clinical high-risk characteristics, molecular markers can also provide prognostic information. Several molecular markers are being prospectively validated and are reviewed here. The ASCO recommendations on the use of markers in colon cancer provide a more definitive review of this topic.[52]

- **Microsatellite Instability**—Microsatellite instability (MSI) is a measure of DNA repair mechanisms that when disrupted lead to replication errors in repetitive nucleotide regions (called microsatellites). MSI is classically associated with the familial hereditary nonpolyposis colorectal cancer syndrome, although it is also present in a minority of sporadic colon cancers. The presence of MSI has been associated with better outcomes in stage II and III patients.[53] Studies to determine the impact of MSI status on response to 5-FU are few in number but appear to suggest a lack of benefit from 5-FU adjuvant therapy.[54,55]

- **18q LOH**—Loss of heterozygosity on the long arm of chromosome 18 (18q LOH) is a common finding in tumors arising from the chromosomal instability pathway. The deleted in colon cancer (DCC) protein is encoded on this chromosome, and in stage II colon cancer, 18q LOH is associated with a worse prognosis in two retrospective studies.[56,57] Similar studies have used the presence or absence of DCC staining to evaluate 18q status, with mixed results. These markers require prospective validation before they can be recommended for use in determining the prognosis of stage II colon cancer. One study in high-risk stage II and stage III patients suggested a benefit from 5-FU adjuvant chemotherapy in patients with retention of both alleles of 18q, but the study design was unable to separate the predictive and prognostic roles of 18q LOH.[58]

**RECOMMENDATIONS**

- Discuss adjuvant chemotherapy with all stage II colon cancer patients whose comorbidities do not preclude treatment.
- Gauge patient interest in participating in the decision-making process.
- Evaluate clinical and pathologic features that may predict a higher rate of recurrence.
- As appropriate, relay risks and estimated benefits of treatment using “number needed to treat” language, while acknowledging uncertainty in the degree of benefit. Alternatively, online numeracy guides may aid in the discussion of the benefits of treatment.
For patients who receive adjuvant chemotherapy, reevaluate risks and benefits with the patient as appropriate during the course of treatment.

Other Molecular Marker Considerations—Other markers, such as mutations in p53, PIK3CA, and KRAS and expression of vascular endothelial growth factor, lactate dehydrogenase, and telomerase, have been shown to have prognostic significance in preliminary studies in early-stage colon cancer. Further validation is required before they can be utilized in the clinic, however. Molecular markers may not be independent of histologic markers. For example, a tumor lymphocytic infiltrate is associated with better outcomes and is seen more frequently in MSI tumors. Similarly, 18q LOH appears to be necessary for vascular invasion. Success in advancing molecular techniques will require that they show improvement in prognostic ability over current pathologic techniques.

Prognostic factors are frequently reported, but it is much more complicated to determine factors predictive of efficacy after treatment. Separation of the predictive and prognostic characteristics of a marker requires samples from both treated and untreated patients. This is a critical limitation of many studies, as markers denoting poor prognosis do not always predict response to therapy. For example, patients with stage II/III colorectal cancer lacking a particular epithelial growth factor receptor polymorphism have worse overall survival but also a decreased sensitivity to chemotherapy. Likewise, stage II/III patients with tumors expressing low levels of dihydropyrimidine dehydrogenase had worse overall survival if they received surgery alone but a greater relative benefit from oral 5-FU adjuvant chemotherapy.

Multiple-Marker Models—Given the complexities of cancer, a single molecular marker is unlikely to completely distinguish high- and low-risk patients. As a result, there has been significant interest in prognostic models that incorporate multiple molecular features, such as genetic microarrays and multiplexed PCR assays. In one study in stage II colon cancer, a 23-gene signature was found to confer 13-fold higher odds of relapse than a good prognostic signature. A second study produced a 43-gene set that segregated stage II and III patients into good- and poor-prognosis groups with corresponding 5-year overall survival rates of 65% and 30%, respectively. In both studies, validation was limited to a small sample set, and further external validation is needed. A similar approach is being taken by the NSABP using PCR techniques, which can be performed using paraffin-embedded tissues. Moving these platforms into the clinic requires additional work to generate a laboratory test certified for clinical use, and ideally, a robust determination of the critical components of the predictive panel. In addition, the information obtained from the gene arrays must be shown to be independent from previously established clinicopathologic factors.

FIGURE 2

ECOG 5202 Study

In a current GI Intergroup trial, E5202, patients are being prospectively selected for adjuvant therapy on the basis of MSI and 18q status. Poor-prognosis patients, defined as those with 18q loss of heterozygosity and either MSS (microsatellite stable) or MSI-Low (low levels of microsatellite instability not meeting the formal MSI definition) status, will be treated with FOLFOX-based regimens identical to that in the ongoing NSABP C-08 trial. Conversely, patients with a good prognosis (retained 18q heterozygosity or MSI [denoted as MSI-High]) will be observed only (Figure 2). In addition, tumor banking is incorporated in this study to allow for the future evaluation of molecular prognostic models, including DNA microarray studies.

Conclusions

The benefit of adjuvant 5-FU chemotherapy for stage II colon cancer has not been robustly demonstrated, with most trials and meta-analyses demonstrating trends toward improved outcomes that do not meet statistical significance. In multiple trials, however, the relative benefit of treatment
with 5-FU adjuvant chemotherapy is similar for stage II and III patients, with relative risk reductions of 15% to 20% with 5-FU treatment. This credibly implies that stage II patients derive benefit from adjuvant treatment, but that the degree of benefit is too small to observe given the size of previous clinical trials.

For patients with low-risk stage II cancer, the small-interval benefit from treatment is balanced by the fixed risks of severe toxicity and death from chemotherapy. Although the decision regarding adjuvant treatment needs to be individualized, observation only is an acceptable option for these patients. For the patient with high-risk stage II disease, the benefit from chemotherapy is greater and outweighs the risks associated with chemotherapy in most situations. Quantitating the degree of benefit is helpful for some patients with sufficient numeric literacy. Using the “number needed to treat” method of communicating absolute benefit is preferred in patient discussions, as it avoids the use of relative benefits.[68,69] The number of stage II patients needed to treat to prevent one recurrence or death is 25 to 50 patients, at the cost of a severe adverse event in every 6 patients treated and death due to treatment in every 100 to 200 patients treated. For high-risk stage II patients, the number needed to treat to prevent one death or recurrence is likely in the range of 15 to 30. For stage II patients without high-risk features, it can be implied that the number needed to treat to prevent one recurrence or death is greater than 50.

REFERENCE

GUIDE

Therapeutic Agents

- Bevacizumab (Avastin)
- Capecitabine (Xeloda)
- Cetuximab (Erbitux)
- Fluorouracil (5-FU)
- Leucovorin
- Levamisole
- Oxaliplatin (Eloxatin)
- Panitumumab (Vectibix)
- Semustine (methyl-CCNU)
Alternatively, two freely available online numeracy guides have been developed for adjuvant chemotherapy for colon cancer. Adjuvant! Online (www.adjuvantonline.com) incorporates more prognostic characteristics, allows alteration of the underlying assumptions of benefit, and provides a graphic display of benefit designed to be shared with patients.[70] The Mayo Clinic calculator (www.mayoclinic.com/calcs) relies on fixed assumptions of benefit for stage II patients and is supported by a peer-reviewed publication describing its validation methods.[71]

Although not studied in stage II patients, capecitabine has been demonstrated to be at least equivalent to intravenous 5-FU regimens in stage III and IV patients, and it is an appropriate single-agent treatment option to discuss with the patient. Inclusion of oxaliplatin into the adjuvant regimen increases the uncertainty regarding the degree of benefit from the treatment and increases the toxicities associated with treatment. As in the prior 5-FU trials, the relative benefit of treatment with oxaliplatin in the two recent adjuvant trials is remarkably similar for stage II and III disease. As a result, treatment with an oxaliplatin/5-FU combination cannot be viewed as the new standard but is reasonable for select stage II patients.

The list of potential prognostic factors dramatically outpaces our ability to prospectively validate them and determine whether they will translate into factors predictive of response to chemotherapy. Molecular markers are under investigation and should not be used to guide current clinical decision-making. Similarly, microarray-based assays for stage II colon cancer will require extensive prospective validation prior to implementation, but they offer the potential to improve patient selection for adjuvant therapy.

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References: References


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