Chemotherapy for Stage II Colon Cancer

Anna Varghese, MD¹

¹ Division of Solid Tumor Oncology, Department of Medicine, Gastrointestinal Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, New York

Address for correspondence Anna Varghese, MD, Division of Solid Tumor Oncology, Department of Medicine, Gastrointestinal Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY (e-mail: varghesa@mskcc.org).

Clin Colon Rectal Surg 2015;28:256–261.

Abstract

The adjuvant treatment of patients with stage II colon cancer is an area of controversy in medical oncology. Adjuvant chemotherapy aims to eradicate micrometastatic disease present at the time of surgery, preventing the development of distant metastatic disease and thereby curing those patients of their cancer. National and international guidelines for the adjuvant treatment of stage II colon cancer recommend a range of treatment options from observation to chemotherapy with single-agent or combination regimens, depending on the presence or absence of high-risk features (poorly differentiated histology, presence of lymphovascular invasion, presence of perineural invasion, report of < 12 lymph nodes, bowel obstruction, localized perforation, or positive margins). In the one prospective study designed to address the role of adjuvant chemotherapy in stage II colon cancer, a small but statistically significant benefit in overall survival was seen for those patients who received adjuvant chemotherapy; however, multiple meta-analyses and retrospective subgroup analyses have called these findings into question. Though there may be a role for adjuvant chemotherapy in the treatment of patients with stage II colon cancer, its incremental benefit is small, at best, and comes with the risks of real and rarely fatal complications of chemotherapy.

Keywords

- stage II colon cancer
- adjuvant therapy
- chemotherapy

The role of adjuvant chemotherapy in stage II colon cancer remains an area of great controversy despite multiple clinical trials and meta-analyses. Questions remain not only about which patients will benefit from treatment but also what chemotherapy to use if adjuvant chemotherapy is recommended.

Patients with early-stage, theoretically curable colon cancer can be divided into three groups: (1) patients who are cured of the disease by surgery and the cancer will not return regardless of the adjuvant treatments given, (2) patients in whom micrometastatic disease is present at the time of surgery and cancer will return regardless of the adjuvant treatments given, and (3) patients in whom micrometastatic disease is present at the time of surgery but adjuvant chemotherapy will eradicate that disease, thereby rendering the patient “cured” of cancer. Patients with stage I colon cancer whose tumors have not invaded through the colonic wall are highly likely to fall into the first group, and these patients therefore do not receive adjuvant chemotherapy. Patients with stage III colon cancer whose cancers have

spread to local lymph nodes are more likely to fall into the second and third groups and are therefore routinely given chemotherapy based on multiple large clinical trials.^{1,2} Patients with stage II colon cancer comprise a heterogeneous combination of all three groups. Consequently, there is “no one right answer” for how to approach these patients, and the decision whether to administer chemotherapy and what chemotherapy to administer is controversial. This article reviews the current guidelines regarding adjuvant chemotherapy for stage II colon cancers, the data behind these recommendations, and the role of adjuvant chemotherapy in special populations of the elderly and patients with mismatch repair deficient colon cancers.

Stage II Colon Cancers

An estimated 93,090 cases of colon cancer will be diagnosed in the United States in 2015.³ For patients with nonmetastatic cancer, risk of recurrence is closely linked to pathologic stage.

Stage II colon cancers include stage IIA (pT3N0), stage IIB (pT4aN0), and stage IIC (pT4bN0) tumors in which the tumor has not yet spread to lymph nodes.⁴ T3 lesions are cancers that invade through the muscularis propria into the pericolic tissues, T4a lesions are cancers that penetrate the surface of the visceral peritoneum, and T4b lesions are cancers that directly invade or are adherent to other organs or structures. As with all early-stage colon cancers, stage II colon cancers carry the risk of micrometastatic disease, and adjuvant therapy is directed at destroying this micrometastatic disease before it develops into macrometastatic disease.

In randomized studies comparing surgical resection versus surgical resection and adjuvant chemotherapy for patients with stage II and III colon cancers, 5-year overall survival (OS) for patients with stage II colon cancer after curative surgery alone has typically been around 80%, slightly higher than the 5-year OS for patients with stage II colon cancers cited in a recent analysis using the Surveillance, Epidemiology, and End Results (SEER) database.^{4–6} In a SEER analysis, 5-year OS for patients with stages IIA, IIB, and IIC colon cancer was 66.7%, 60.6%, and 45.7%, respectively.⁴ These findings suggest that patients with stage II colon cancer represent a heterogeneous population that includes some patients who might derive meaningful benefit from adjuvant chemotherapy and others for whom adjuvant chemotherapy after surgery is likely to provide minimal, if any, benefit.⁵

Current Guidelines for the Treatment of Stage II Colon Cancers

The National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO) have slight variations among their recommendations for adjuvant chemotherapy for stage II colon cancers (→ **Table 1**). The NCCN guidelines vary depending on the presence of high-risk features of recurrence, including poorly differentiated histology, presence of lymphovascular invasion, presence of perineural invasion, report of less than 12 lymph nodes,

bowel obstruction, localized perforation, or positive margins.⁷ For the patients with stage IIA colon cancers with the absence of high risk features, observation, a clinical trial, or a 6-month course of adjuvant therapy with 5-fluorouracil (5-FU) and leucovorin (LV) or capecitabine is recommended.⁷ For the patients with stage IIA colon cancers with high-risk features or patients with stage IIB or IIC colon cancers, treatment options include observation, treatment on a clinical trial, or a 6-month course of adjuvant chemotherapy with one of the following regimens: 5-FU/LV, capecitabine, or combination chemotherapy with a regimen of 5-FU, LV, oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (Capeox).⁷ The ASCO guidelines, last updated in 2004, cite that “the routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer is not recommended. However, there are populations of patients with stage II disease that could be considered for adjuvant therapy.”⁸ No specific recommendations are given regarding the type of chemotherapy to be used.⁸ The ESMO guidelines, last updated in 2013, are similar to those of ASCO and recommend that “adjuvant therapy should not be routinely recommended for unselected patients. In high-risk patients who present with at least one of the previously mentioned clinical high-risk features, adjuvant therapy could be considered in clinical practice.”⁹ Most importantly, all guidelines emphasize the importance of discussing the very real risks of chemotherapy, including permanent neuropathy and even fatal complications from chemotherapy, balanced against the potential minimal improvement in OS.

Though all guidelines recommend considering adjuvant chemotherapy for the patients with stage II colon cancer with high-risk features, in practice many patients with stage II colon cancers without high-risk features receive adjuvant chemotherapy. In an analysis of the SEER database, 27% of patients with stage II colon cancers without high-risk features were given adjuvant chemotherapy, and no significant difference was seen in the 5-year OS in treated versus untreated patients.¹⁰

Table 1 Recommended guidelines for the adjuvant treatment of stage II colon cancers

Organization	Stage	Recommendations
NCCN	IIA (pT3N0) with no high-risk features	Observation OR Clinical trial OR 5-FU/LV or capecitabine
	IIA (pT3N0) with high-risk features; IIB; IIC	Observation OR Clinical trial OR 5-FU/LV or capecitabine FOLFOX or CapeOx
ASCO	IIA, IIB, or IIC	No adjuvant therapy recommended
	IIA, IIB, or IIC with high-risk features	Consider adjuvant therapy
ESMO	IIA, IIB, or IIC	No adjuvant therapy recommended
	IIA, IIB, or IIC with high-risk features	Consider adjuvant therapy

Abbreviations: ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; NCCN, National Comprehensive Cancer Network.

Studies for the Use of Chemotherapy in Patients with Stage II Colon Cancer

The existing evidence in favor of giving adjuvant chemotherapy for patients with stage II colon cancer relies primarily on the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials (C-01 through C-04) and the QUick and Simple And Reliable Study (QUASAR).

The NSABP evaluated the role of adjuvant chemotherapy in patients with stage II and III colon cancers through testing multiple adjuvant chemotherapy regimens against each other or surgery alone.^{11–14} These studies included patients enrolled from 1977 to 1990 who received various chemotherapy regimens, many of which are no longer used today in the treatment of colon cancer. These include the MOF regimen (semustine, vincristine, and 5-FU), 5-FU via portal vein infusion (PVI), and 5-FU/LV with and without levamisole. In C-01 and C-02, two trials comparing adjuvant therapy (MOF in C-01 and 5-FU via PVI in C-02) to surgical resection, adjuvant therapy demonstrated a trend toward improved 5-year OS, but neither trial reached statistical significance.^{11,12} In C-01, 5-year OS for patients receiving adjuvant MOF was 67% compared with 60% for patients undergoing surgical resection alone with p -value = 0.07.^{11,15} In C-02, 5-year OS for patients receiving adjuvant 5-FU via PVI was 74% compared with 67% for patients undergoing surgical resection alone with p -value = 0.08.^{12,15} C-03 compared the MOF regimen with 5-FU and LV and demonstrated a statistically significant improvement in 5-year OS of 76% versus 66% with p -value = 0.0008.^{13,15}

To further evaluate the role of adjuvant chemotherapy by stage in the NSABP trials, an evaluation was undertaken compiling the results of all four trials in which a comparison was made between the inferior and superior treatment arms in each study.¹⁵ Of the 1,565 patients with stage II colon cancer, there was decreased odds ratio of death of 0.7 for the patients receiving the superior treatment arm. Even for the patients with stage II colon cancer and no high-risk features, there was a favorable odds ratio of death of 0.68. The authors concluded that adjuvant chemotherapy decreases the risk of death and improves cure for patients with stage II colon cancers regardless of the presence or absence of high-risk features. There are, however, several serious limitations to these findings. Most importantly, none of these studies was designed to address whether adjuvant chemotherapy is useful in stage II colon cancer and analysis of stage II patients is limited by its retrospective, post hoc nature. Additionally, our current backbone of adjuvant chemotherapy, 5-FU and LV, was used in only two of the included studies. Finally, the validity of combining these trials and the comparison of superior versus inferior treatment arms in trials using various chemotherapy regimens are questionable.¹⁶

The QUick and Simple And Reliable (QUASAR) trial was designed specifically to “determine the size and duration of any survival benefit from adjuvant chemotherapy for patients with colorectal cancer at low risk of recurrence.”¹⁷ About 3,239 patients with stage II colon or rectal cancer

were randomized to chemotherapy with 5-FU–based therapy or surgery alone. Only 628 patients had available data regarding high-risk features of vascular invasion and T4 status. The majority of these patients had colon cancer (71%) and had stage II disease (91%). There was a statistically significantly decreased risk of dying (relative risk 0.82 with 95% confidence interval [CI] 0.7–0.95) and of recurrence (relative risk 0.78 with 95% CI 0.67–0.91) in the chemotherapy group compared with the surgery alone group. The benefit of adjuvant chemotherapy to prevent recurrence was present in the first 2 years following surgery with the relative risk of 0.64 (95% CI 0.52–0.78); however, this benefit to adjuvant chemotherapy disappeared after 2 years. The decreased risk of dying translates into an absolute increase in survival of 3.6%. Thus, though this study demonstrates a benefit to adjuvant chemotherapy for patients with stage II colon cancers, the absolute improvement in survival is quite small.¹⁷

Because the absolute benefit to adjuvant chemotherapy in the stage II setting is likely to be small as suggested by the QUASAR data, if present at all, many have attempted to address the role of adjuvant chemotherapy in the stage II setting using meta-analyses of multiple large randomized trials. First, the International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) study aimed to “determine whether fluorouracil and folinic acid is an effective adjuvant therapy for patients after potentially curative resection of colon cancer in patients” with stage II colon cancers.⁵ This meta-analysis included a total of 1,016 patients from five separate trials with a median follow-up of 5.75 years. No significant difference was seen in event-free survival (p = 0.61) or OS (p = 0.57) for patients who received adjuvant chemotherapy compared with those who received surgical resection alone.⁵ Five-year event-free survival for patients who received adjuvant chemotherapy was 76% and for those who underwent surgical resection only was 73%. Five-year OS for patients who received adjuvant chemotherapy was 82% and 80% for those who underwent surgical resection only. Another meta-analysis by Gill et al included the five studies evaluated in IMPACT-B2 analysis plus two additional studies. The stage II patients included in this analysis had a statistically significant improvement in a 5-year disease-free survival (DFS) from 72 to 76% (p = 0.049) in favor of chemotherapy and no difference in OS (80 vs. 80%).⁶

These studies highlight several important features in the study of adjuvant chemotherapy for patients with stage II colon cancer. First, patients with stage II colon cancer have a generally good outcome with 5-year OS of approximately 80% with surgery alone. Second, any potential gain with adjuvant chemotherapy is likely to be small, if present at all. Third, large numbers of patients would need to be enrolled and then followed for many years to identify such a small gain in OS or DFS. Consequently, the most important component of decision making is a conversation between clinicians and patients regarding the real and potential risks and benefits with adjuvant chemotherapy for stage II colon cancers.

The Role of Oxaliplatin in Stage II Colon Cancer

The Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) and NSABP C-07 studies established the role of oxaliplatin in the adjuvant treatment of stage III colon cancers. These studies also raised questions regarding the role of oxaliplatin in stage II colon cancer. MOSAIC was a phase III randomized trial in which patients with stage II and III colon cancer were randomized to receive 5-FU/LV or 5-FU/LV/oxaliplatin (FOLFOX). In the full study population of 2,246 stage II and III patients, FOLFOX conferred an improvement in 5-year DFS (73.3 vs. 67.4% with HR 0.8, 95% CI 0.68–0.93, $p = 0.003$) and 6-year OS (78.5 vs. 76%, HR 0.84, 95% CI 0.71–1, $p = 0.046$) compared with patients who received 5-FU/LV. While this benefit in OS was seen in the subset of patients with stage III colon cancers and remained a statistically significant finding, no clear benefit in OS was seen with the addition of oxaliplatin to 5-FU/LV in patients with stage II colon cancers.¹⁸

In a retrospective unplanned analysis of the MOSAIC data, investigators sought to better assess the role of adjuvant chemotherapy with oxaliplatin in patients with stage II cancers.¹⁹ Of the 899 patients with stage II disease, no benefit in OS (HR 1 with 95% CI 0.7–1.41) or DFS (HR 0.84 with 95% CI 0.62–1.14) was seen with adjuvant oxaliplatin and 5-FU/LV compared with 5-FU/LV alone. Of the 330 low-risk stage II and the 569 high-risk patients with stage II colon cancer, there was no benefit in DFS or OS with oxaliplatin.¹⁹

The NSABP C-07 trial is a phase III randomized controlled trial for patients with stage II and III colon cancer in which the investigators evaluated “the impact on DFS of adding oxaliplatin to bolus weekly fluorouracil (FU) combined with leucovorin as surgical adjuvant therapy for stage II and III colon cancer.”²⁰ Patients were randomized to surgery with adjuvant 5-FU/LV or adjuvant bolus 5-FU, LV, and oxaliplatin (FLOX). Of the 2,407 eligible patients, there was a 20% risk reduction with the use of FLOX compared with 5-FU/LV with an HR of 0.8 with (95% CI 0.69–0.93). In an updated report of this trial, further analyses were performed by stage, and no significant benefit was seen in OS or DFS for patients with stage II colon cancer.²¹ Understanding that these studies were not powered or designed to address whether oxaliplatin has a role in the adjuvant treatment of stage II colon cancer, these do suggest that there is, at best, a very limited role for oxaliplatin in the stage II setting.

Use of Adjuvant Chemotherapy in Special Populations of Patients with Stage II Colon Cancer

High-Risk Disease

In clinical practice and according to clinical care guidelines, adjuvant chemotherapy is recommended as an option for patients with stage II colon cancer that has high-risk features. According to the NCCN guidelines, high-risk features include the following: T4 primary tumors, poorly differentiated histology (except in cases of mismatch repair deficient

tumors, described as follows), presence of lymphovascular invasion, presence of perineural invasion, bowel obstruction, less than 12 lymph nodes evaluated in the pathology report, or close or indeterminate margins.⁷

Several studies have attempted to address the role of adjuvant chemotherapy in the high-risk stage II setting in observational reports or retrospective, unplanned analyses. In a retrospective study taking advantage of the large numbers of patients in the SEER database, O'Connor and colleagues sought to “determine the overall survival benefit of chemotherapy among patients with stage II colon cancer having poor prognostic features.”²² They identified 24,847 patients with stage II colon cancer, including 18,613 with poor prognostic features. With this large sample size, the study was powered to detect an absolute difference in 5-year OS of 2%, and this was not seen.²² No difference in 5-year OS was seen for patients with stage II colon cancer with poor prognostic features who received adjuvant therapy (56.7%) compared with those who did not (56.1%). Similarly, adjuvant chemotherapy had no impact on 5-year OS for patients with stage II colon cancer with the absence of poor prognostic features (70% for treated patients compared with 69.5% for untreated patients).²²

In a retrospective analysis of the MOSAIC trial, subgroup analyses were performed for patients with stage II colon cancer who received FOLFOX versus 5-FU/LV.¹⁹ Of the 899 patients with stage II colon cancer, 330 had low-risk disease and 569 had high-risk disease. Of the patients with high-risk disease, there was no improvement in DFS or OS with FOLFOX compared with 5-FU/LV with HR 0.72 (95% CI 0.51–1.02) and HR 0.91 (95% CI 0.61–1.36), respectively. Although these were unplanned analyses, these findings also question the utility of oxaliplatin in the adjuvant therapy for even patients with stage II colon cancer who have high-risk features.

Mismatch Repair Deficient or Microsatellite Instable Tumors

Approximately 15% of all colorectal cancers have abnormalities in the DNA mismatch repair pathway, which can be identified by the molecular phenotype of microsatellite instability. Microsatellites are short nucleotide sequences repeated throughout the genome, and deficient mismatch repair results in alterations in these microsatellites, causing microsatellite instability. The presence or absence of deficient mismatch repair mechanisms and microsatellite instability are important determinants in the decision whether to pursue adjuvant chemotherapy for patients with stage II colon cancers. Colorectal cancers with microsatellite instability (MSI-H) or dMMR (mismatch repair deficient) are more likely poorly differentiated, mucinous, right-sided, and have the presence of tumor infiltrating lymphocytes. MSI-H tumors are also more common among patients with stage II cancers compared with stage III cancers, suggesting lower likelihood to metastasize.²³ In a retrospective analysis of 570 tumors from patients across multiple phase 3 trials of adjuvant chemotherapy with 5-FU/LV or 5-FU and levamisole, Ribic and colleagues

identified that 95 cases (16.7%) were MSI-H.²⁴ OS was associated with microsatellite instability in which multivariate models demonstrated that MSI-H was associated with improved OS. Of the 287 patients who did not receive adjuvant chemotherapy, the patients with MSI-H tumor had a significantly better OS than the patients with microsatellite stable (MSS) tumor (HR 0.31 with 95% CI 0.14–0.72). Of the patients who received adjuvant chemotherapy, a benefit in OS was seen in the patients with MSS tumors with HR 0.72 (95% CI 0.53–0.99) and no benefit was seen in the patients with MSI-H tumors. In another retrospective analysis of patients treated on multiple adjuvant chemotherapy trials with 5-FU/LV or 5-FU and levamisole, investigators demonstrated that patients with stage II colon cancers that were dMMR actually had worse OS when they received adjuvant chemotherapy with HR of 2.95 (95% CI 1.02–8.54) compared with those patients with dMMR tumors who received surgery alone.²⁵ Although these analyses are all limited by their retrospective, unplanned nature, these findings suggest that patients with dMMR or MSI-H tumors do not benefit from adjuvant chemotherapy with 5-FU-based regimens and may possibly be harmed with adjuvant chemotherapy. Interestingly, these studies included patients who received adjuvant chemotherapy regimens with 5-FU. The role of FOLFOX for patients with stage II dMMR colon cancers remains unclear.^{26,27}

Elderly Patients

Several studies have suggested that patients older than 65 with surgically resected colon cancer receive benefit from adjuvant chemotherapy without significantly increased toxicity compared with their younger counterparts; however, many have questioned the role of oxaliplatin in this group.^{28,29} In retrospective subgroup analysis of 70 to 75-year-old patients with stage II and III colon cancer enrolled in the MOSAIC trial, 155 received FOLFOX and 160 received 5-FU and LV.¹⁹ In comparisons of these two groups, 5-year DFS and 6-year OS were similar between elderly patients who received FOLFOX compared with those who received 5-FU/LV with HR 0.93 (95% CI 0.64–1.35) and HR 1.1 (95% CI 0.73–1.65), respectively.¹⁹ Similarly, in retrospective analysis of the NSABP C-07 study, for patients older than 70 years who received 5-FU/LV and FLOX, 5-year OS and DFS did not vary significantly with HR 1.18 (95% CI 0.86–1.62) and HR 1.03 (95% CI 0.77–1.36), respectively.²¹

These post hoc analyses of elderly patients in combined populations of stages II and III colon cancer demonstrate limited benefit of oxaliplatin in elderly patients. Given that these analyses included patients with stage III colon cancer, any benefit to combination therapy with 5-FU- and oxaliplatin-based therapies for patients with stage II colon cancer would theoretically have been overestimated. Given that these studies demonstrate limited benefit to oxaliplatin- and 5-FU-based therapies in the elderly population, these findings strongly suggest that the benefit in elderly patients with stage II colon cancer is quite limited, if present at all.

Novel Technologies to Assess Risk of Recurrence

Several commercially available multigene expression arrays are currently marketed to help determine the likelihood of recurrence and whether to administer adjuvant chemotherapy for patients with stage II colon cancer; however, their role and utility in the care of patients with colon cancer remain unclear. The ColDx assay (Almac, Craigavon, UK) is a microarray-based assay to identify high- and low-risk patients; Oncotype Dx (Genomic Health, Redwood City, CA) uses gene expression analysis of 12 genes to identify patients at high, intermediate, and low risk for recurrence; and ColoPrint (Agendia, Huntington Beach, CA) uses a gene expression analysis of 18 genes to classify patients into high- and low-risk categories. Each of these assays has been validated and found to be associated with the likelihood of recurrence; however, they provide no clear evidence about which patients will benefit from adjuvant chemotherapy.^{30–32} Consequently, routine use of these assays is not recommended at this time.

Summary

The role of adjuvant chemotherapy for patients with stage II colon cancer remains a controversial area. Most studies have included patients with both stage II and III colon cancers, making it difficult to assess the true benefit of adjuvant chemotherapy in the stage II setting. In the one prospective study designed to explicitly address this question, the QUASAR study, a small but statistically significant benefit to adjuvant chemotherapy, was seen for patients with surgically resected colon cancers with a low likelihood of recurrence. However, in multiple post hoc analyses of patients with stage II colon cancers, the role and utility of adjuvant chemotherapy in the stage II setting has been questioned. Research has suggested that subgroups of patients with stage II colon cancer such as the dMMR population do not derive benefit from adjuvant chemotherapy.

What is clear from the research available is that surgical resection remains the most important treatment for patients with stage II colon cancer. Adjuvant chemotherapy may add a small incremental benefit to OS and DFS; however, this small benefit comes at the risk of very real and rarely fatal complications of chemotherapy. Consequently the most important component of deciding whether to proceed with adjuvant chemotherapy for patients with stage II colon cancer is an informed discussion between patients and their medical oncologists about the risks and benefits of adjuvant chemotherapy and the controversies that exist in this area.

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