

# Adjuvant Chemotherapy for Colon Cancer

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**CASE SUMMARY:** A 55-year-old man with no medical history presents to his primary care physician with fatigue and dark stools and is found to have anemia. He is referred for diagnostic colonoscopy and found to have an ulcerated mass in the ascending colon. Metastatic workup is negative. He is referred to a colorectal surgeon and undergoes an uneventful laparoscopic right hemicolectomy. Final pathology reveals a 4-cm ulcerated mass involving the muscularis propria with 3 positive lymph nodes of 12 (T2N1bM0, stage IIIA). The patient arrives at his postoperative appointment with questions about chemotherapy.

## CLINICAL QUESTIONS

- What adjuvant chemotherapy should be used for colon cancer?
- Which patients with colon cancer benefit from adjuvant chemotherapy?

## BACKGROUND

Along with adequate surgical resection, adjuvant chemotherapy has played an important role in improving

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the survival for patients with colon cancer, and current guidelines recommend the use of adjuvant chemotherapy for patients with surgically resected stage III or IV colon cancer.<sup>1</sup> Systemic chemotherapy is also used in the neoadjuvant setting for patients with metastatic or locally invasive disease that may become surgically resectable. The role of adjuvant therapy in earlier-stage tumors with certain high-risk features is an area of active investigation. The Table summarizes the important trials that have influenced adjuvant chemotherapy for colon cancer.

Oxaliplatin-based adjuvant chemotherapy is standard of care for stage III disease based on multiple clinical trials.<sup>2–5</sup> The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer<sup>2</sup> compared adjuvant chemotherapy regimens of bolus plus continuous-infusion fluorouracil (5-FU) plus leucovorin (LV) with or without the addition of oxaliplatin for resected stage II or III colon cancer. Patients in the oxaliplatin group (5-FU and oxaliplatin (FOLFOX)) had a higher rate of 5-year disease-free survival (73% vs 67%), and FOLFOX has become the standard of care for adjuvant chemotherapy. A 10-year follow-up report showed that the FOLFOX regimen was associated with a significantly higher rate of overall survival for stage II/III patients (72% vs 67%), most notably in stage III patients (67% vs 59%).<sup>3</sup>

The National Surgical Adjuvant Breast and Bowel Project C-07 trial demonstrated a benefit for bolus fluorouracil plus leucovorin and oxaliplatin (FLOX),<sup>4</sup> and the capecitabine-based regimen (CAPEOX) has also shown a survival benefit,<sup>5</sup> but both are associated with higher toxicity. At this time, FOLFOX is the preferred regimen for stage III colon cancer, whereas FLOX and CAPEOX are reserved as alternatives if infusional therapy is not feasible.

Trials have also investigated other agents for adjuvant chemotherapy in stage III colon cancer without success. The Cancer and Leukemia Group B 89803 study<sup>6</sup> compared adjuvant 5-FU and LV with and without irinotecan and found no difference in survival, with potentially worse adverse effects in the irinotecan group. The Bevacizumab Plus Oxaliplatin-Based Chemotherapy as Adjuvant Treatment for Colon Cancer<sup>7</sup> study investigated FOLFOX or CAPEOX with and without bevacizumab (Avastin) and

**TABLE 1.** Randomized controlled trials of adjuvant chemotherapy for colon cancer

Author/trial	PMIDs*	Year	Experimental arms	Results	Conclusion
Windle	3304518	1987	5-FU vs 5-FU + Lev vs observation	Improved DSS (68% vs 48%) with 5-FU + Lev	Additive effect of levamisole when used in combination with 5-FU
Wolmark NSABP C-03	8410113	1993	Stage II/III 5-FU + LV vs MOF	32% reduction in mortality and 30% improvement in DFS with 5-FU + LV	5-FU-based adjuvant therapy is preferable regimen
Moertel INT-0035	8523058	1995	Stage II 5-FU + Lev vs Lev alone vs observation	Reduced recurrence rate (31%) with 5-FU + Lev	Benefit of adjuvant therapy for stage III
O'Connell	8996149	1997	5-FU + LV vs observation	Improved OS (74% vs 63%) with 5-FU + LV	6 mo of adjuvant therapy improves outcomes
O'Connell	9440756	1998	5-FU + Lev vs 5-FU + LV + Lev, 6 vs 12 mo	Improved OS (70% vs 60%) with 6 mo of 5-FU + LV + Lev	Additive effect of 5-FU + LV, survival benefit of 6 mo of adjuvant therapy
Wolmark NSABP C-04	10550154	1999	5-FU + LV vs 5-FU + Lev vs 5-FU + LV + Lev	Higher DFS (65% vs 60%) for 5-FU + LV, no added benefit with Lev	5-FU + LV is preferable adjuvant regimen
IMPACT B2	10334519	1999	Stage II 5-FU + LV vs observation	No survival difference	Routine use of adjuvant 5-FU + LV for resected stage II is not indicated
Andre/MOSAIC	15175436 19451431 26527776	2004 2009 2015	Stage II/III 5-FU + LV vs 5-FU + LV + Ox (FOLFOX)	FOLFOX associated with higher OS (72% vs 67%), especially for stage III (67% vs 59%)	FOLFOX established as standard adjuvant treatment for resected stage III
Twelves/X-ACT	15987918	2005	5-FU + LV vs capecitabine	Capecitabine was noninferior to 5-FU + LV	Oral capecitabine is an acceptable alternative to IV 5-FU + LV
Kuebler/NSABP C-07	17470851	2007	Stage II/III Bolus 5-FU + LV vs bolus 5-FU + LV + Ox (FLOX)	Improved DFS for FLOX (76% vs 73%)	FLOX is an acceptable option for adjuvant chemotherapy
Saltz/CALGB 89803	17687149	2007	Stage III 5-FU + LV vs 5-FU + LV + Iri	No difference in survival	Irinotecan is not beneficial for resected stage III
QUASAR	18083404	2007	Stage II 5-FU + LV vs observation	Statistically insignificant improved recurrence for stage II/III colon cancer	Adjuvant chemotherapy for stage II may or may not improve survival
de Gramont/AVANT	23168362	2012	Stage II/III FOLFOX vs FOLFOX + Ava vs XELOX + Ava	Higher rate of recurrence/death with FOLFOX + Ava (29% vs 25%), no difference with XELOX + Ava	No benefit, and possible harm, with adjuvant Avastin

Ava = Avastin (bevacizumab); DFS = disease-free survival; DSS = disease-specific survival; FLOX = bolus fluorouracil (5-FU) + leucovorin + oxaliplatin; FOLFOX = 5-FU + leucovorin + oxaliplatin; Iri = irinotecan; IV = intravenous; Lev = levamisole; LV = leucovorin; MOF = lomustine, vincristine, and 5-FU; OS = overall survival; Ox = oxaliplatin; RR = relative risk; XELOX = capecitabine + oxaliplatin.

\*To access the hyperlinks to the PubMed abstracts for each study, go to <https://tinyurl.com/y8lcsuzc>.

found no benefit and potential harm with the addition of bevacizumab to adjuvant treatment regimens. As such, adjuvant treatment at this time is based on FOLFOX without the addition of other agents.

The role of adjuvant chemotherapy for stage II colon cancer is less clear. The International Multicentre Pooled Analysis of B2 Colon Cancer Trials<sup>8</sup> pooled data from 5 trials and found no survival benefit for adjuvant therapy in stage II disease, although adjuvant chemotherapy in these studies was 5-FU plus LV, without oxaliplatin or

other agents. The Quick and Simple and Reliable study randomly assigned patients with colorectal cancer and an “uncertain indication for adjuvant chemotherapy” to receive either no adjuvant chemotherapy or adjuvant therapy including 5-FU and LV with or without levamisole depending on the timing of randomization.<sup>9</sup> The benefit of adjuvant chemotherapy in patients with stage II cancer was borderline significant, whereas the benefit for patients with stage III cancer was not significant. Therefore, the results of this study must be interpreted with caution.

### PRESENTATION AND DIAGNOSIS

Most patients with colon cancer are identified by either screening colonoscopy or after a patient presents with anemia, weight loss, or other symptoms. The entire colon must be visualized to identify synchronous lesions. Workup should include a complete blood count, a basic metabolic panel, carcinoembryonic antigen, and CT of the chest, abdomen, and pelvis.

The TNM classification system developed by the American Joint Committee on Cancer<sup>1</sup> is used for staging. Stage I disease is localized to the colon and is associated with a 92% rate of 5-year overall survival. Stage II disease is more locally invasive, with survival rates of 87% and 63% for stages IIA and IIB. Stage III disease involves regional lymph nodes and is associated with 5-year survival rates of 89%, 69%, and 53% for stages IIIA, IIIB, and IIIC. Stage IV represents metastatic disease and has been associated with a survival rate of 11%, although recent advances in treatment are prolonging survival for many patients.<sup>10</sup>

### MANAGEMENT

An algorithm for the management of colon cancer can be found in the section on Evaluation and Treatment Algorithm. This is based on the current National Comprehensive Cancer Network guidelines for management of colon cancer and highlights the role of systemic chemotherapy for these patients.

Adjuvant chemotherapy is not indicated for resected stage I colon cancer with negative margins and is not the standard of care for stage II disease. Both the National Comprehensive Cancer Network and the American Society of Clinical Oncology advocate a detailed risk/benefit conversation with stage II patients regarding adjuvant chemotherapy. Published studies including heterogeneous populations of patients with stage II colon cancer have not shown improved survival with adjuvant chemotherapy, but new data are emerging regarding the benefit for tumors with certain high-risk features.<sup>1</sup>

Microsatellite instability is a specific tumor characteristic that may be helpful in evaluating patients with stage II cancer for adjuvant therapy.<sup>1</sup> Patients with high microsatellite instability (MSI) have been shown to have a better prognosis than patients with low MSI, which may have

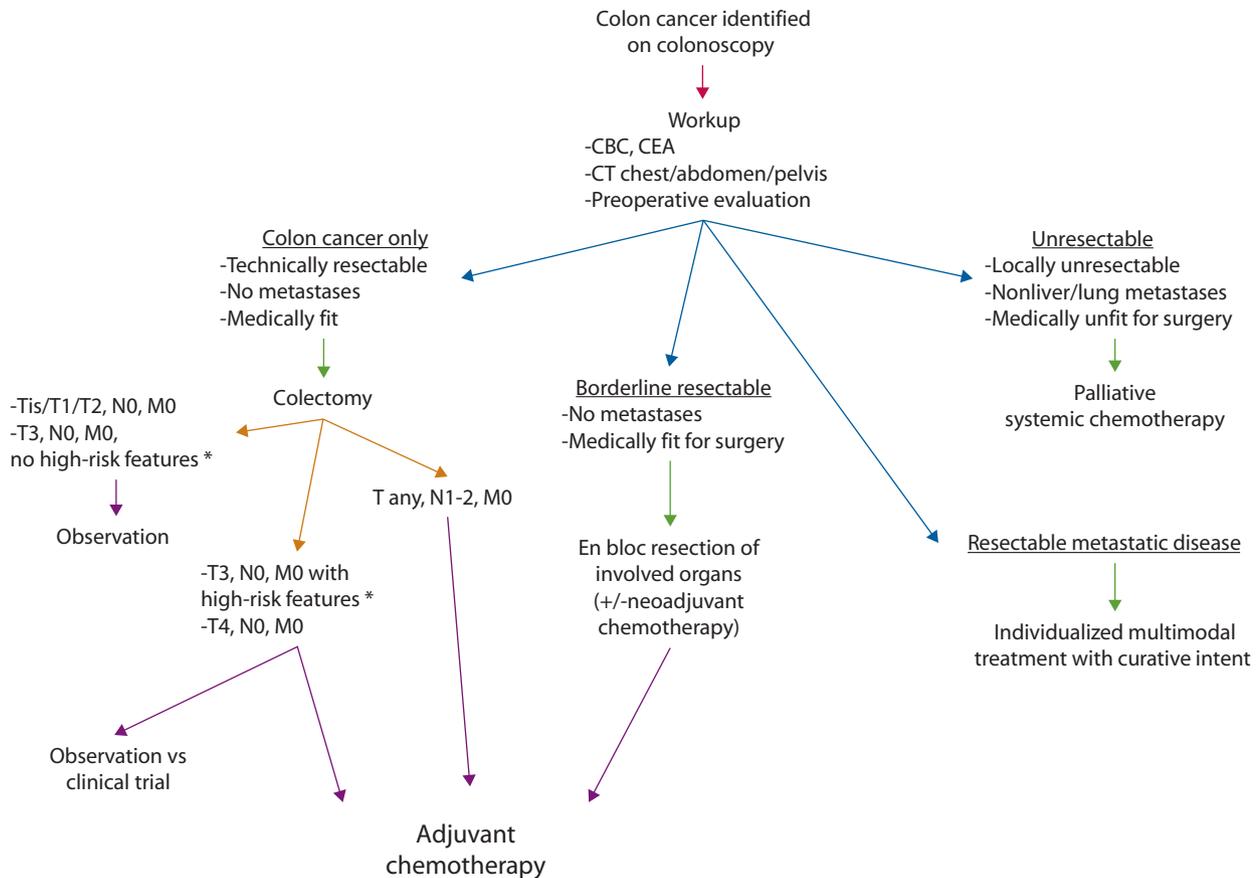
an increased likelihood to metastasize. Moreover, studies have suggested that patients with high MSI tumors may not benefit from adjuvant chemotherapy, whereas patients with low MSI tumors do. As such, all resected colon cancers should undergo MSI testing to inform prognosis and guide treatment decisions.

Medically fit patients with stage III cancer should be referred to medical oncology after surgical recovery for consideration of systemic adjuvant chemotherapy to improve survival based on the results of the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer and other trials. Systemic therapy for stage IV disease is generally aimed at palliation and prolonging survival, with rare evidence of cure. Nevertheless, patients with metastatic disease who receive multimodal systemic therapy have greatly improved survival compared with supportive management alone. This is also because of more frequent use of surgery and other interventional therapies in the setting of metastatic disease. The available regimens include combinations of FOLFOX, FLOX, or CAPEOX with irinotecan, cetuximab, and bevacizumab. Chemotherapy in this setting should be individualized and determined with a coordinated multidisciplinary team.

There are also ongoing trials investigating the role of immunotherapy for patients with stage III or IV cancer in the adjuvant and palliative setting. The ATOMIC Trial (NCT02912559)<sup>11</sup> is currently enrolling patients with stage III colon cancer and deficient DNA mismatch repair to receive adjuvant therapy with FOLFOX with or without atezolizumab, a monoclonal antibody against the protein programmed cell death ligand 1. Similar antibodies are being investigated for multiple malignancies and are showing promise. Results of this trial and others may further revolutionize the treatment of colon cancer.

These adjuvant therapies are of course not given without adverse effects. Most commonly, these regimens can result in hair loss, mouth sores, GI issues, and fatigue. Oxaliplatin is known for causing a neuropathy that manifests as numbness, tingling, or pain in the hands and feet. It can also cause intense sensitivity to hot and cold in other parts of the body. These effects have been seen in <12% of patients a year after treatment.<sup>3</sup> Symptomatic management is the best available treatment at this time.

## EVALUATION AND TREATMENT ALGORITHM



\* High risk features: poorly differentiated, lymphovascular invasion, perineural invasion, <12 nodes examined, obstruction, localized perforation, positive margin

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