**CLINICAL VIGNETTE**

# Why Practice Guidelines Matter: Optimizing Complex Adjuvant Chemotherapy Decision-Making for Patients with Stage II Colon Cancer

Erin Chamberlain, MD and Deborah Villa, MD

A 77-year-old man presented after colon cancer screening. He reported feeling well without symptoms. Two biopsies taken from polyps within the ascending colon revealed moderately differentiated adenocarcinoma, with intact mismatch repair proteins. His past medical history includes hypertension, well controlled type II diabetes mellitus and stage IIIA chronic kidney disease. He had no significant past surgical history or relevant family history. He is married, enjoys cycling, and retired from owning and operating a radio station.

His physical exam was unremarkable. Routine lab work showed a hemoglobin (HGB) of 9.7 g/dL and ferritin of 29 ng/mL. His metabolic panel was remarkable for an estimated glomerular filtration rate (eGFR) of 54. His carcinoembryonic antigen (CEA) was within normal limits at 2.86 ng/mL. He underwent CT staging revealing significant colonic wall thickening extending from the hepatic flexure to the proximal descending colon. Imaging was otherwise negative for lymphadenopathy or distant metastatic disease. He underwent right hemicolectomy with excision of the distal duodenum revealing a 7.5cm adenocarcinoma arising from the ascending colon, grade 2, with invasion into the visceral peritoneum including the serosal surface of the duodenum. None of 15 lymph nodes contained carcinoma and margins were negative for tumor involvement. The patient was diagnosed with stage IIC colon cancer, pathologic stage pT4bpN0cM0.

Given the involvement of the duodenal serosal surface, he was diagnosed with high risk disease and offered adjuvant 5FU-based chemotherapy with or without oxaliplatin. With shared decision making, he opted for capecitabine in combination with oxaliplatin (CAPEOX) for a planned duration of three months of therapy. Following his second cycle of CAPEOX therapy, he developed loose, watery bowel movements, ten above his daily baseline average. He was diagnosed with grade 4 treatment-related colitis and instructed to use anti diarrheal therapy. His colitis was unresponsive to both loperamide and diphenoxylate-atropine therapy. He was referred to the emergency room where he was found to have low serum sodium, low serum potassium, and an acute kidney injury from gastrointestinal losses prompting his admission. He required continuous intravenous hydration, continued diphenoxylate-atropine, and subcutaneous octreotide. On hospital day ten, his bowel movements returned to baseline in both caliber and frequency, and his acute kidney injury resolved. He permanently discontinued adjuvant chemotherapy with CAPEOX.

The American Society of Clinical Oncology (ASCO) published updated guidelines regarding the use of adjuvant therapy in stage II colon cancer.[2] Historically, adjuvant chemotherapy was not recommended to patients whose cancer had not spread to lymph nodes (i.e. stage II disease). The primary treatment was surgery alone. However, evidence suggests higher recurrence rates for patients with stage II colon cancer with high risk features. These features include fewer than 12 sampled lymph nodes, T4 tumor stage, clinical bowel obstruction at the time of diagnosis, perforation of the colon at the tumor site, poor histologic grade, lymphovascular invasion and/or perineural invasion, presence of circulating tumor DNA (ctDNA), and tumor budding. Recurrence rates in these patients approaches 40-50%, similar to that of stage III disease, for which adjuvant therapy is recommended.[1] The updated ASCO guideline sought to clarify treatment for stage II disease. Specifically, they seek to answer in which stage II patients the benefit of fluorouracil-based adjuvant chemotherapy might outweigh the risk of adverse events and inconvenience of therapy. Additionally, this guidelines update sought to answer whether patients with tumors that exhibit deficient mismatch repair proteins (dMMR) benefit from adjuvant therapy, if oxaliplatin should be added to fluoropyrimidine-based chemotherapy, as well as duration of treatment (three or six months of adjuvant therapy).

After a thorough review of the literature, ASCO updated its previous guideline from 2004 and published its recommendations online on December 22, 2021. This update recommends that adjuvant chemotherapy should not be recommended routinely for patients with stage II colon cancer who are not in the high-risk subgroup, as defined above. Adjuvant chemotherapy should be discussed and offered to patients with high risk stage II disease. The addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy is not routinely recommended, but may be offered as a result of shared decision making. Patients with dMMR should not be routinely offered adjuvant chemotherapy, however, if offered then the addition of oxaliplatin is recommended. Duration of chemotherapy can be offered as 3 or 6 months of treatment with capecitabine and oxaliplatin or fluorouracil, leucovorin, and oxaliplatin, with decision making informed by key evidence of 5-year disease free survival in each treatment subgroup and by taking into

account the rate of adverse events, including peripheral neuropathy.[2]

This patient was offered adjuvant chemotherapy due to the presence of his T4 tumor that invaded the serosal surface of the adjacent small bowel, denoting high risk stage II disease. The ASCO guideline reflect six studies of patients with T4 tumors, with OS advance with adjuvant chemotherapy compared with surgery alone (HR 0.64). With informed consent, he decided to pursue treatment with capecitabine with the addition of oxaliplatin, based on the added time to recurrence (TTR) benefit seen in the MOSAIC trial when oxaliplatin is added.[3] Furthermore, he opted for 3 months of treatment over 6 months, given the results of the IDEA collaboration demonstrating similar 5-year disease free survival (DFS) rates (81.7% and 82% respectively p=0.09) with 3 versus 6 month duration of treatment.[4] Additionally, he preferred shorter duration to minimize the risk of grade 2 or higher peripheral neuropathy, noted as 13% with three months versus 36% with six months of treatment as outlined in the ASCO update.

This ASCO updated guideline serves a powerful reference for physicians in the management of stage II colon cancer. The patient highlighted in this case appropriately was offered therapy in accordance with the guidelines, with the intention of maximizing his disease-free survival, which was expected as 82% at five years. Unfortunately, he developed life-threatening adverse event related to his chemotherapy, grade 4 diarrhea resulting in kidney injury and required permanent treatment discontinuation. He had required a prolonged recovery, incurring both physical injury as well as financial injury. His story highlights the need for guidelines to help inform both the patient and the clinician in complex decision-making. Guidelines assist in discussing the potential benefits in relation to recurrence rates and overall survival compared to risks of grade 3 and 4 adverse events.

As with all guidelines, there remain unanswered questions. While this ASCO update on adjuvant therapy in stage II colorectal cancer validates many of the shared decisions made between this patient and his physician, it does not provide a comprehensive guide to his therapy. For example, this update notes insufficient evidence to routinely recommend the addition of oxaliplatin to fluoropyrimidine-based chemotherapy for patient with high-risk stage II colon cancer. This relates to the low quality of evidence suggesting a TTR benefit, as well as low quality evidence demonstrating a significant survival benefit with addition of oxaliplatin. The treating physician must do her best to engage the patient in shared decision making based on what evidence exists. Additionally, this guideline update did not specifically address recommendations in relation to age of patient. This patient is considered older with age > 70 and data are conflicting regarding the benefit of oxaliplatin in this age group. This patient's adverse events gives rise to questioning whether oxaliplatin was an appropriate choice in his care. Thus, this case further emphasizes both the important role of guidelines to assist in the complex decision making required of cancer patients and their physicians, but also the questions that remain and require additional time and data to provide further guidance.

**REFERENCES**


1. **Meyers BM, Cosby R, Quereshy F, Jonker D**. Adjuvant Chemotherapy for Stage II and III Colon Cancer Following Complete Resection: A Cancer Care Ontario Systematic Review. *Clin Oncol (R Coll Radiol)*. 2017 Jul;29(7):459-465. doi: 10.1016/j.clon.2017.03.001. Epub 2017 Mar 22. PMID: 28341242.
2. **Baxter NN, Kennedy EB, Bergsland E, Berlin J, George TJ, Gill S, Gold PJ, Hantel A, Jones L, Lieu C, Mahmoud N, Morris AM, Ruiz-Garcia E, You YN, Meyerhardt JA**. Adjuvant Therapy for Stage II Colon Cancer: ASCO Guideline Update. *J Clin Oncol*. 2022 Mar 10;40(8):892-910. doi: 10.1200/JCO.21.02538. Epub 2021 Dec 22. PMID: 34936379.
3. **André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators**. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004 Jun 3;350(23):2343-51. doi: 10.1056/NEJMoa032709. PMID: 15175436.
4. **Iveson TJ, Sobrero AF, Yoshino T, Souglakos I, Ou FS, Meyers JP, Shi Q, Grothey A, Saunders MP, Labianca R, Yamanaka T, Boukovinas I, Hollander NH, Galli F, Yamazaki K, Georgoulias V, Kerr R, Oki E, Lonardi S, Harkin A, Rosati G, Paul J**. Duration of Adjuvant Doublet Chemotherapy (3 or 6 months) in Patients With High-Risk Stage II Colorectal Cancer. *J Clin Oncol*. 2021 Feb 20;39(6):631-641. doi: 10.1200/JCO.20.01330. Epub 2021 Jan 13. Erratum in: *J Clin Oncol*. 2021 May 20;39(15):1691. PMID: 33439695; PMCID: PMC8078416.