



### Paul F. Engstrom, MD

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In the past, Dr. Engstrom chaired the gastrointestinal Committee of ECOG, the Board of Scientific Counselors, DCPC, NCI, and the Scientific Advisory Board of the Armed Forces Institute of Pathology.

Dr. Engstrom's research interests include biomarkers research, cancer prevention and control interventions, and behavioral medicine interventions. He is Director of the Fox Chase Early Detection Research Network Clinical Epidemiology and Validation Center Program.

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## Ten Years of Progress in Colon Cancer Therapy

In the past 10 years, the NCCN Guidelines Panels for Colon and Rectal Cancers have worked diligently to keep up with changes in the management of these cancers. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon and Rectal cancers in 2002 were short and simple; essentially, they are the model A version of the NCCN Guidelines on those same cancers in 2012 (Figure 1; to view the most recent version of these guidelines, visit the NCCN Web site at [NCCN.org](http://NCCN.org)).

In 2002, the NCCN panel advocated 5-fluorouracil (5-FU)/leucovorin adjuvant therapy for stage III or node-positive disease and 5-FU leucovorin with or without irinotecan (IFL) as first-line therapy for metastatic disease. Second-line therapies for metastatic disease included irinotecan alone, continuous intravenous 5-FU, and capecitabine. The 2002 NCCN Guidelines recommended en bloc resection of the colon or a hemicolectomy; laparoscopic-assisted colectomy was not mentioned. The usefulness of molecular markers had not been established in treatment determination or prognosis. Intrahepatic artery chemotherapy was a consideration for patients with advanced liver metastasis, and liver resection could be considered if the patient had 3 or fewer discreet liver metastasis. Surveillance after successful resection of early-stage colon carcinoma consisted of periodic colonoscopy, physical examination, and serial carcinoembryonic antigen (CEA) determinations.

Oxaliplatin was introduced as a therapeutic agent for colon cancer in 2002 when preclinical studies showed synergy between infusional 5-FU and oxaliplatin. Combination therapy was studied, and the research resulted in the 5-FU, leucovorin, and oxaliplatin (FOLFOX) regimen. Similarly, IFL gave way to a more tolerable and effective infusional 5-FU, leucovorin, and irinotecan regimen (FOLFIRI). Capecitabine plus oxaliplatin (CapeOx) showed response rates similar to FOLFOX. Perhaps the most important discovery of the decade was the finding from the MOSAIC Trial that FOLFOX for 6 months was superior to 5-FU/leucovorin as adjuvant therapy for patients with stage III colon cancer.<sup>1</sup>

In 2004, antibody therapy of colon cancer became a reality with the discovery that bevacizumab selectively inhibited tumor vasculature through an anti-vascular endothelial growth factor effect, and enhanced first-line FOLFOX in

2002	2003	2004	2007	2008	2009	2012
5-FU/leucovorin adjuvant therapy for stage III or node-positive disease and IFL are recommended as first-line therapy for metastatic disease Oxaliplatin is introduced	MOSAIC trial shows FOLFOX for 6 months to be superior to 5-FU/leucovorin as adjuvant therapy for patients with stage III colon cancer	Bevacizumab shown to selectively inhibit tumor vasculature through an anti-VEGF effect and enhance first-line FOLFOX in patients with metastatic disease Cetuximab, a chimeric antibody, and its congener, panitumumab, a fully humanized antibody to EGFR are introduced as single agents in the management of advanced metastatic disease	Guidelines reach the current level of complexity and detail; including recommendations for polypectomy or colectomy with en bloc resection, and laparoscopic-assisted colectomy for patients with uncomplicated resectable disease	NCCN Guidelines now show continuum of care with chemotherapy for advanced metastatic disease Standard of care first-line therapy includes FOLFOX plus bevacizumab, CapeOx plus bevacizumab, or FOLFIRI with bevacizumab NCCN Guidelines also define therapy after second progression	NCCN Guidelines include survivorship principles for the first time, including recommendations for screening for cancer at other sites, management of late sequelae, and use of appropriate health monitoring	Pathologic factors and genetic testing considered

**Figure 1** Important changes between 2002 and 2012 in the NCCN Guidelines for Colon and Rectal Cancers.

Abbreviations: 5-FU, 5-fluorouracil; CapeOx, capecitabine, oxaliplatin; EGFR, epidermal growth factor receptor; FOLFIRI, 5-FU, leucovorin, irinotecan; FOLFOX, 5-FU, leucovorin, oxaliplatin; IFL, irinotecan, 5-FU, leucovorin; VEGF, vascular endothelial growth factor.

the treatment of patients with metastatic disease. That same year, cetuximab, a chimeric antibody, and its congener, panitumumab, a fully humanized antibody to epidermal growth factor (EGFR), were introduced as single agents in the management of patients with advanced metastatic disease. Randomized studies showed that treatment with at least 3 of these agents could result in higher antitumor response and could prolong progression-free survival for up to 24 months.

The 2007 version of the NCCN Guidelines for Colon Cancer introduced the complexity and detail that carries forth to the NCCN Guidelines in 2012. The management of patients presenting with a malignant polyp was shown with greater detail, including polypectomy or colectomy with en bloc resection, and laparoscopic-assisted colectomy was recommended for patients with uncomplicated resectable disease. PET scans were a consideration for the management of patients with suspected or proven synchronous metastatic adenocarcinoma of the large bowel or in the evaluation of patients with rising CEA after resection. The NCCN Guidelines stipulated the desirability of at least 12 lymph nodes in the surgical specimen to adequately assess the nodal status of patients with putative stage II disease.

Patients who presented with synchronous metastatic liver carcinoma were treated with FOLFOX plus bevacizumab or FOLFIRI plus bevacizumab. If the liver metastases showed response, the patient was considered a candidate for resection. Surgeons were no longer limited by what would be removed during surgery, but by how much normal liver could be preserved. The goal was an R0 resection with negative margins that still preserved a sufficient amount of normal liver for the patient to survive. The use of aggressive combination FOLFOX or FOLFOX plus irinotecan resulted in downsizing unresectable colorectal metastasis and allowed consideration of resection for patients whose disease was previously considered inoperable, unresectable.

This model of care also influenced the management of patients who presented with stage IV disease. Previously, patients received a palliative resection and then started chemotherapy; the 2007 NCCN Guidelines, however, recommended immediate systemic chemotherapy. Patients with response in the liver and bowel may not require subsequent bowel resection.

A sizable body of literature shows that the status of the *KRAS* gene in the tumor is highly predictive of outcome with anti-EGFR therapies. Tumors with a mutation in codon-12 or -13 of the *KRAS* gene are essentially insensitive to EGFR inhibitors, such as cetuximab and panitumumab. Therefore, the 2008 NCCN Guidelines strongly recommended *KRAS* genotyping of tumor tissue, either primary tumor or metastasis, in all patients with metastatic colorectal cancer and recommended against cetuximab or panitumumab for patients with known mutations. The 2008 NCCN Guidelines were also the first to establish a continuum of care with chemotherapy for advanced metastatic disease. In general, the oncologist was encouraged to use FOLFOX plus bevacizumab, CapeOx plus bevacizumab, or FOLFIRI with bevacizumab as first-line therapy. Therapy after first progression consisted of non-overlapping treatments and emphasized the need for cetuximab or panitumumab for patients with wild-type *KRAS*. The 2008 Guidelines also defined therapy after a second progression.

For the first time, the 2009 NCCN Guidelines described principles of survivorship for patients after surgery and adjuvant treatment for stage I, II, or III colon cancer. These survivorship guidelines included recommendations for screening for cancer at other sites, management of late sequelae to treatment, and use of appropriate health monitoring, particularly for cholesterol, bone density, and depression. Most importantly, the guidelines emphasized exercise and appropriate diet. Studies in patients who survive after cancer treatment showed that those who participate in physical exercise show improved survival over those who were sedentary and overweight.

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This complexity was maintained through the 2010 and 2011 versions. The 2012 NCCN Guidelines for Colon Cancer continue to be comprehensive and allow management that is specific for individual patients. Patients with stage II disease should undergo thorough pathologic evaluation of the tumor. These patients are also considered for genetic testing to better define risk of recurrence. Pathologic factors contributing to recurrence include lymphovascular invasion, high-grade tumor, bowel obstruction, fewer than 12 lymph nodes evaluated, perineural invasion, localized perforation, and close or positive margins. Testing for mismatch repair proteins should be considered for all patients 50 years of age or younger. Patients with stage II disease whose tumors express microsatellite instability–high may have a good prognosis and benefit less from 5-FU adjuvant therapy.

Gene expression determination from formalin-fixed paraffin embedded tumor samples can profile patients with high risk of recurrence and poor survival. However, to date, these studies do not translate into a survival advantage with available chemotherapy; therefore, routine use of molecular testing is not recommended in the current NCCN Guidelines.

The 2012 NCCN Guidelines do, however, recommend *KRAS* gene testing of tumor tissue in all patients with metastatic disease. If the *KRAS* gene is not mutated, *BRAF* testing should be considered. FOLFOX is recommended for adjuvant treatment of patients with stage III disease. In patients who receive neoadjuvant chemotherapy before resection of metastatic disease and the primary colon lesion, a shortened course of postsurgical chemotherapy should be considered. The section of the NCCN Guidelines on the Continuum of Care of Advanced or Metastatic Disease has not changed greatly over the past 5 years (available online, in these guidelines, at [NCCN.org](http://NCCN.org) [COL-C]).

The past 10 years of colon cancer guideline development have been exciting, both for oncologists and for patients. I predict that the next 10 years will result in more targeted therapy and thus more personalized care of colon cancer patients: for instance, regorafenib, an investigational oral multi-kinase inhibitor of angiogenic, stromal, and oncogenic receptor tyrosine kinases, shows promise based on a recently completed randomized double-blind, placebo-controlled study in patients with metastatic colon cancer. In addition, a recent publication indicates that hypermethylation of the gene encoding transcription factor AP-2 epsilon (TFAP2E) is associated with clinical non-responsiveness to 5-FU chemotherapy of colon cancer. The next generation of NCCN Guideline Panel members will be challenged to develop more specific and more detailed treatment guidelines.

## Reference

1. André T, Boni C, Mounedji-Boudiaf L, et al. for the 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;350:2343–2351.