NCCN Guidelines® Insights

Metastatic Colon Cancer, Version 3.2013
Featured Updates to the NCCN Guidelines

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Abstract
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, peri-operative treatment, patient surveillance, management of recurrent and metastatic disease, and survivorship. The NCCN Colon Cancer Panel meets annually to review comments from reviewers within their institutions and to reevaluate and update their recommendations. In addition, the panel has interim conferences as new data necessitate. These NCCN Guidelines Insights summarize the NCCN Colon Cancer Panel's discussions surrounding metastatic colorectal cancer for the 2013 update of the guidelines. Importantly, changes were made to the continuum of care for patients with advanced or metastatic disease, including new drugs and an additional line of therapy. (JNCCN 2013;11:141–152)

Please Note
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the Panel's discussion, including the literature reviewed.

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The following authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products or devices discussed in this report or their competitors: Dr. Chen, Dr. Cooper, Dr. Engstrom, Dr. Fakih, Dr. Fenton, Dr. Hunt, Dr. Kamel, Dr. Leong, Dr. May, Dr. Mulcahy, Dr. Rohren, Dr. Sharma, Dr. Shibata, Dr. Skibber, Dr. Small, and Dr. Willett.

The following authors have disclosed that they have financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products or devices discussed in this report or their competitors:


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Dr. Venook: PI for and has received research support from Agen Inc.; Genentech, Inc.; Genomic Health, Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc. Research support from Bayer HealthCare. Consultant for Abbott Laboratories and Bristol-Myers Squibb Company. Advisory board member for Bayer HealthCare, Genentech, Inc., Genomic Health, Inc., Novartis Pharmaceuticals Corporation.

The NCCN Guidelines Staff have no conflicts to disclose.

Supported by educational grants from Eisai, Inc.; Millennium: The Takeda Oncology Company; Teva Pharmaceuticals; Bayer HealthCare Pharmaceuticals Inc.; Celgene Corporation; Endo Pharmaceuticals and HealthTronics; Genentech; and ARIAD Pharmaceuticals, Inc.

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Release date: February 18, 2013; Expiration date: February 18, 2014

Learning Objectives:
Upon completion of this activity, participants will be able to:

• Integrate into professional practice the updates to the NCCN Guidelines for Colon Cancer

• Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Colon Cancer

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Metastatic Colon Cancer, Version 3.2013

Overview
Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2012, an estimated 103,170 new cases of colon cancer and approximately 40,290 cases of rectal cancer occurred. During the same year, an estimated 51,690 people died of these cancers combined. Despite these high numbers, the incidence of colon and rectal cancers per 100,000 people has decreased from 60.5 in 1976 to 46.4 in 2005. In addition, mortality from colorectal cancer has decreased by almost 35% from 1990 to 2007, likely because of earlier diagnosis through screening and better treatment modalities.

Peritoneal Carcinomatosis: Cytoreductive Surgery and Perioperative Hyperthermic Intraperitoneal Chemotherapy
Approximately 17% of patients with metastatic colorectal cancer have peritoneal carcinomatosis,
with 2% having the peritoneum as the only site of metastasis.\(^4\) The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative, and consists of systemic therapy (see “Chemotherapy for Advanced or Metastatic Disease,” pages 144–147 [COL-C] and in the full guidelines, available at NCCN.org) with palliative surgery or stenting if needed (see page 143 [COL-5, -7, -8]). Patients with peritoneal metastases generally have shorter progression-free and overall survivals than those without peritoneal involvement.\(^4\)

The panel discussed the data regarding cytoreductive surgery (ie, peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis without extraabdominal metastases. Several surgical series have addressed the role of this procedure in this setting.\(^5,9\) In the only randomized controlled trial involving this approach, Verwaal et al\(^10\) randomized 105 patients to either standard therapy (5-FU/leucovorin [LV] with or without palliative surgery) or aggressive cytoreductive surgery and HIPEC with mitomycin C; postoperative 5-FU/LV was given to 33 of 47 patients. Overall survival was 12.6 months in the standard arm and 22.3 months in the HIPEC arm ($P = .032$). However, treatment-related morbidity was high, and the mortality was 8% in the HIPEC group, mostly related to bowel leakage. In addition, long-term survival does not seem to be improved by this treatment as seen in follow-up results.\(^11\) Importantly, this trial was performed without oxaliplatin, irinotecan, or molecularly targeted agents. The panel agreed with experts who have argued that the overall survival difference might have been much smaller if these agents were used (ie, the control group would have had better outcomes).\(^12\)

Other criticisms of the Verwaal trial have been published.\(^12\) One important point discussed by the panel is that the trial included patients with peritoneal carcinomatosis of appendiceal origin, a group

![Continuum of Care - Chemotherapy for Advanced or Metastatic Disease](COL-C_1-9.png)
that has seen greater benefit with the cytoreductive surgery/HIPEC approach.\textsuperscript{5,8,13} A retrospective multicenter cohort study reported overall median survival times of 30 and 77 months for patients with peritoneal carcinomatosis of colorectal origin and appendiceal origin, respectively.\textsuperscript{8} The overall median survival time for patients with pseudomyxoma peritonei, which arises from mucinous appendiceal carcinomas, was not reached at the time of publication.\textsuperscript{8} A recent retrospective international registry study reported 10- and 15-year survival rates of 63\% and 59\% in patients with pseudomyxoma peritonei from mucinous appendiceal carcinomas, respectively, treated with cytoreductive surgery and HIPEC, suggesting that the approach is beneficial in this population.\textsuperscript{14}

The panel noted that the individual components of this approach have not been well studied. In fact, studies in rats have suggested that the hyperthermia component of the treatment is irrelevant.\textsuperscript{15} Results of a retrospective cohort study also suggest that heat may not affect outcomes from the procedure.\textsuperscript{8} In addition, the panel expressed concerns about the significant morbidity and mortality associated with this procedure. A 2006 meta-analysis of 2 randomized controlled trials and 12 other studies reported morbidity rates ranging from 23\% to 44\% and mortality rates ranging from 0\% to 12\%.\textsuperscript{9} Although the risks are reportedly decreasing with time (ie, recent studies report 1\%–5\% mortality rates at centers of excellence\textsuperscript{12}), the benefits of the approach have not been definitively shown. Therefore, the panel reaffirmed their previous recommendation that the treatment of disseminated carcinomatosis of colorectal cancer with cytoreductive surgery and HIPEC should be considered investigational (see footnote “ee,” page 143 [COL-5, -7, -8]). The panel does not endorse this therapy outside of a clinical trial. However, it does recognize the need for randomized clinical tri-
-contained care for advanced or metastatic disease:

**Initial Therapy**
- FOLFOX$^3,5 \pm$ bevacizumab
- CapeOX$^4,5 \pm$ bevacizumab
- Irinotecan$^{10} \pm$ oxaliplatin$^{\pm}$ bevacizumab
- Irinotecan$^{10} \pm$ bevacizumab
- FOLFIRI$^{10} \pm$ bevacizumab
- FOLFIRI$^{10} \pm$ ziv-aflibercept

**Therapy After First Progression**
- Irinotecan$^{10}$
- Cetuximab or panitumumab$^{6,12-15}$ (KRAS WT gene only)$^8$ + irinotecan$^{10}$
- Cetuximab or panitumumab$^{6,12-15}$ (KRAS WT gene only)$^8$
- Regorafenib (KRAS mutant only)

**Therapy After Second Progression**
- FOLFOX$^3$ or CapeOX$^4$
- Cetuximab or panitumumab$^{6,12-15}$ (KRAS WT gene only)$^8$ + irinotecan$^{10}$
- Cetuximab or panitumumab$^{6,12-15}$ (KRAS WT gene only)$^8$
- Regorafenib (if not given previously)
- Clinical trial
- Best supportive care

**Therapy After Third Progression**
- Regorafenib (if not given previously)
- Clinical trial
- Best supportive care

See footnotes on COL-C 5 of 9

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**Management of the Primary Tumor in the Setting of Unresectable Metastases**

The panel discussed results from a recent pooled analysis of patients from 4 randomized trials suggesting that patients may experience some benefit in both overall and progression-free survival from resection of the primary tumor in the setting of unresectable colorectal metastases.$^{16}$ Other retrospective analyses also have shown a potential benefit to this approach.$^{17,18}$ On the other hand, the prospective, multicenter phase II NSABP C-10 trial showed that patients with an asymptomatic primary colon tumor and unresectable metastatic disease who received mFOLFOX6 with bevacizumab experienced an acceptable level of morbidity without upfront resection of the primary tumor.$^{19}$ The median overall survival was 19.9 months. Notably, symptomatic improvement in the primary is often seen with systemic chemotherapy even within the first 1 to 2 weeks. Furthermore, complications from the intact primary lesion are uncommon in these circumstances,$^{20}$ and its removal delays initiation of systemic chemotherapy. In fact, a recent systematic review concluded that resection of the primary does not reduce complications, nor does it improve overall survival.$^{21}$ Overall, the panel believes that the risks of surgery outweigh the possible benefits of resection of asymptomatic primary tumors in the setting of unresectable colorectal metastases. Therefore, the panel maintained their recommendation that palliative resection of a synchronous primary lesion should only be considered if the patient has an unequivocal imminent risk of obstruction or acute significant bleeding (see page 143 [COL-5, -7, -8]). The panel acknowledged that rel-
1For chemotherapy references, see Chemotherapy Regimens and References [COL-C 6-9].
2PET-CT should not be used to monitor progress of therapy, CT with contrast or MRI is recommended.
3Discontinuation of oxaliplatin should be strongly considered from FOLFOX or CapeOX after 3-4 months of therapy (or sooner if significant neurotoxicity develops ≥ grade 2) with other drugs maintained (fluoropyrimidine + bevacizumab) until time of tumor progression. Oxaliplatin may be reintroduced if it was discontinued previously for neurotoxicity rather than disease progression. Tournigand C, Vervant A, Figer A, et al. OPTIMOXI: A randomized study of FOLFOX4 or FOLFOTX with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer - A GERCOR Study. J Clin Oncol 2006;24:394-400. There are insufficient data to support the routine use of CaMg infusion to prevent oxaliplatin-related neurotoxicity.
4The majority of safety and efficacy data for this regimen have been developed in Europe, where a capcitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capcitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capcitabine. The relative efficacy of CapeOx with lower starting doses of capcitabine has not been addressed in large-scale randomized trials.
5There is an increased risk of stroke and other arterial events, especially in those aged ≥ 65 years. The use of bevacizumab may interfere with wound healing.
7If cetuximab or panitumumab is used as initial therapy, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy.
8See Principles of Pathologic Review (COL-A 4 of 5) - KRAS and BRAF Mutation Testing.
9There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status.
10Irinotecan should be used with caution and with decreased doses in patients with Gilbert’s disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established.
11There are no data to suggest activity of FOLFIRI-ziv-aflibercept in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.
12Cetuximab is indicated in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.
13EGFR testing has no demonstrated predictive value; therefore, routine EGFR testing is not recommended. No patient should be included or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.
14There are no data, nor is there a compelling rationale, to support the use of panitumumab after clinical failure on cetuximab, or the use of cetuximab after clinical failure on panitumumab. As such, the use of one of these agents after therapeutic failure on the other is not recommended.
15Patients with a V600E BRAF mutation appear to have a poorer prognosis. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after a patient has progressed on first-line therapy.
16Single-agent or combination therapy with capcitabine, mitomycin, or gemcitabine has not been shown to be effective in this setting.
17Infusional 5-FU is preferred.
18Patients with diminished creatinine clearance may require dose modification of capcitabine.
19A treatment option for patients not able to tolerate oxaliplatin or irinotecan.
20Data are not mature for the addition of biologic agents to FOLFOXIRI.
21The use of single-agent capcitabine as a salvage therapy after failure on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.

Chemotherapy for Advanced and Metastatic Disease

The current management of disseminated metastatic colon cancer involves various active drugs, either in combination or as single agents, given across a continuum: 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, and regorafenib.22-62 The putative mechanisms of action of these agents are varied and include interference with DNA replication and inhibition of the activities of vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) receptors.63-66 The choice of therapies and their sequence is based on consideration of the goals of therapy, the type and timing of prior therapy, the differing toxicity profiles of the constituent drugs, and the KRAS status of the tumor.

This year, the panel discussed data pertaining to new drugs and other changes to the continuum of systemic therapy for patients with advanced or metastatic disease after progression, as discussed in the following sections.

Continuation of Bevacizumab After Progression on Bevacizumab

In the TML trial, patients with good performance status and metastatic colorectal cancer who progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy regimen with or without bevacizumab.67 This study met its primary end point, with patients continuing on bevacizumab having a modest improvement in overall survival (11.2 vs. 9.8 months; hazard ratio [HR], 0.81; 95% CI, 0.69–0.94; P = .0062).
The continuation of bevacizumab after progression on bevacizumab was also studied in a community oncology setting through a retrospective analysis of 573 patients from the US Oncology iKnowMed electronic medical record system. Bevacizumab beyond progression was associated with a longer overall survival (HR, 0.76; 95% CI, 0.61–0.95) and a longer postprogression overall survival (HR, 0.74; 95% CI, 0.60–0.93) on multivariate analysis.

Overall, the panel believes that these data (along with those from the VELOUR trial, discussed later) show that the continuation of VEGF blockade in second-line therapy offers a very modest but statistically significant overall survival benefit. The panel noted that the TML trial excluded patients whose disease progressed quickly or who had a poor performance status, and considered limiting their recommendation similarly. In the end, the panel added the continuation of bevacizumab to the second-line treatment options for the 2013 versions of the NCCN Guidelines for Colon and Rectal Cancers without these patient limitations (see all COL-C figures, pages 144–147, and in the full guidelines, available at NCCN.org). Bevacizumab may be added to any second-line regimen that does not contain an EGFR inhibitor or ziv-aflibercept. The panel recognizes the lack of data suggesting a benefit to bevacizumab with irinotecan alone in this setting, but believes that the option is acceptable, especially in patients for whom a 5-FU– or capecitabine-based regimen failed. This addition to the systemic therapy continuum was made as a category 2A recommendation because currently only 1 trial has been performed, the observed benefit was quite modest, and toxicities were considerable.

Ziv-Aflibercept

The panel discussed the recent data from the phase III VELOUR trial at their annual panel meeting and again on an interim call after ziv-aflibercept was approved by the FDA. Ziv-aflibercept is a recombinant protein that has part of the human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1. It is designed to function as a VEGF trap to prevent activation of VEGF receptors and thus inhibit angiogenesis. The VELOUR trial tested second-line ziv-aflibercept in patients with metastatic colorectal cancer for whom one regimen containing oxaliplatin failed. The trial met its primary end point, with a clinically modest but statistically significant improvement in OS (13.5 months for FOLFIRI/ziv-aflibercept vs. 12.1 months for FOLFIRI/placebo; HR, 0.82; 95% CI, 0.71–0.94; P = .003).

Adverse events associated with ziv-aflibercept treatment in the VELOUR trial led to discontinuation in 26.6% of patients compared with 12.1% in the placebo group. The most common causes for discontinuation were asthenia/fatigue, infections, diarrhea, hypertension, and venous thromboembolic events.

Ziv-aflibercept has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients. No data suggest activity of FOLFIRI plus ziv-aflibercept in patients who experienced disease progression on FOLFIRI plus bevacizumab, or vice versa, and no data suggest activity of single-agent ziv-aflibercept. Thus, the panel added ziv-aflibercept as a second-line treatment option in combination with FOLFIRI or irinotecan only after progression on therapy not containing irinotecan (see all COL-C figures, 144–147, and in the full guidelines, available at NCCN.org). This addition to the systemic therapy continuum was made as a category 2A recommendation because currently only 1 trial has been performed, the observed benefit was quite modest, and toxicities were considerable.

Regorafenib

The panel discussed the recent data from the phase III CORRECT trial at the annual panel meeting and again on an interim call after regorafenib was approved by the FDA. Regorafenib is a small molecule inhibitor of multiple kinases (including VEGF receptors, fibroblast growth factor receptors, platelet-derived growth factor [PDGF] receptors, BRAF, KIT, and RET) that are involved with various processes, including tumor growth and angiogenesis. In the CORRECT trial, 760 patients who progressed on standard therapy were randomized to best supportive care with placebo or regorafenib. The trial met its primary end point of overall survival (6.4 months for regorafenib vs. 5.0 months for placebo; HR, 0.77; 95% CI, 0.64–0.94; P = .005). Progression-free survival was also significantly but modestly improved (1.9 vs. 1.7 months; HR, 0.49; 95% CI, 0.42–0.58; P < .000001).

The most common grade 3 or higher adverse events in the regorafenib arm of the CORRECT trial were hand-foot skin reactions (17%), fatigue (10%), hypertension (7%), diarrhea (7%), and rash/
desquamation (6%).

Severe and fatal liver toxicity occurred in 0.3% of 1100 patients treated with regorafenib across all trials.

Regorafenib has only shown activity in patients who have experienced progression on all standard therapies. Therefore, the panel decided to add regorafenib as an additional line of therapy for patients with metastatic colorectal cancer refractory to chemotherapy (see all COL-C figures, 144–147, and in the full guidelines, available at NCCN.org). For patients with mutant KRAS, regorafenib can be used in the third-line setting; patients with wild-type KRAS can receive regorafenib as a third or fourth line of therapy. This addition to the systemic therapy continuum was made as a category 2A recommendation because it is based on only 1 trial with a modest clinical benefit, and toxicities associated with regorafenib are significant.

Summary of Changes to the 2013 NCCN Guidelines for Colon Cancer

In summary, the panel discussed many pertinent issues this year. Some recommendations were reviewed in detail and not changed (denoted by purple text in algorithms):

- The panel reaffirmed their previous recommendation that the treatment of disseminated carcinomatosis of colorectal cancer with cytoreductive surgery and HIPEC should only occur on a clinical trial, because the risks are high and the benefits unproven.

- The panel maintained their recommendation that palliative resection of a synchronous primary lesion in the setting of unresectable metastases should only be considered if the patient has an unequivocal, imminent risk of obstruction or acute significant bleeding.

Other discussions resulted in changes to the 2013 recommendations:

- The panel added the continuation of bevacizumab with a different chemotherapy backbone to the second-line treatment options for patients with advanced or metastatic disease who progressed on regimens containing bevacizumab.

- The panel added ziv-aflibercept as a second-line treatment option in combination with FOLFIRI or irinotecan for patients with advanced or metastatic disease who progressed on therapy not containing irinotecan.

- The panel added regorafenib as an additional line of therapy for patients with advanced or metastatic colorectal cancer refractory to all standard systemic therapy options.

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Metastatic Colon Cancer, Version 3.2013
Metastatic Colon Cancer, Version 3.2013


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Posttest Questions

1. True or False: In the setting of unresectable colorectal metastases, the panel believes that the benefits outweigh the risks of resection of asymptomatic primary tumors.
2. True or False: The phase III CORRECT trial compared patients with metastatic colorectal cancer who progressed on all standard therapies to best supportive care with placebo or regorafenib and met its primary end point with a modest, but statistically significant improvement in OS.
3. True or False: The phase III TML trial, in which patients with metastatic colorectal cancer who progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy regimen with or without bevacizumab, met its primary endpoint with a modest, but statistically significant improvement in OS.