

NCCN Guidelines® Insights

Localized Colon Cancer, Version 3.2013

Featured Updates to the NCCN Guidelines

Al B. Benson III, MD¹; Tanius Bekaii-Saab, MD²; Emily Chan, MD, PhD³; Yi-Jen Chen, MD, PhD⁴; Michael A. Choti, MD, MBA⁵; Harry S. Cooper, MD⁶; Paul F. Engstrom, MD⁶; Peter C. Enzinger, MD⁷; Marwan G. Fakih, MD⁸; Moon J. Fenton, MD, PhD⁹; Charles S. Fuchs, MD, MPH⁷; Jean L. Grem, MD¹⁰; Steven Hunt, MD¹¹; Ahmed Kamel, MD¹²; Lucille A. Leong, MD⁴; Edward Lin, MD¹³; Kilian Salerno May, MD¹⁴; Mary F. Mulcahy, MD¹; Kate Murphy, BA (in memoriam)¹⁵; Eric Rohren, MD, PhD¹⁶; David P. Ryan, MD¹⁷; Leonard Saltz, MD¹⁸; Sunil Sharma, MD¹⁹; David Shibata, MD²⁰; John M. Skibber, MD¹⁶; William Small Jr, MD¹; Constantinos T. Sofocleous, MD, PhD¹⁸; Alan P. Venook, MD²¹; Christopher G. Willett, MD²²; Kristina M. Gregory, RN, MSN, OCN²³; and Deborah A. Freedman-Cass, PhD²³

Abstract

The NCCN Clinical Practice Guidelines in Oncology 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, perioperative 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 regarding the treatment of localized disease for the 2013 update of the guidelines. (*JNCCN* 2013;11:519–528)

From ¹Robert H. Lurie Comprehensive Cancer Center of Northwestern University; ²The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; ³Vanderbilt-Ingram Cancer Center; ⁴City of Hope Comprehensive Cancer Center; ⁵The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; ⁶Fox Chase Cancer Center; ⁷Dana-Farber/Brigham and Women's Cancer Center; ⁸University of Michigan Comprehensive Cancer Center; ⁹St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; ¹⁰UNMC Eppley Cancer Center at The Nebraska Medical Center; ¹¹Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; ¹²University of Alabama at Birmingham Comprehensive Cancer Center; ¹³Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; ¹⁴Roswell Park Cancer Institute; ¹⁵Fight Colorectal Cancer; ¹⁶The University of Texas MD Anderson Cancer Center; ¹⁷Massachusetts General Hospital Cancer Center; ¹⁸Memorial Sloan-Kettering Cancer Center; ¹⁹Huntsman Cancer Institute at the University of Utah; ²⁰Moffitt Cancer Center; ²¹UCSF Helen Diller Family Comprehensive Cancer Center; ²²Duke Cancer Institute; and ²³National Comprehensive Cancer Network.

Disclosures for the NCCN Localized Colon Cancer Panel

Individual disclosures of potential conflicts of interest for the NCCN Localized Colon Cancer Panel members can be found on page 520.

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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Dr. Benson: grant or research support from Abbott Laboratories, Amgen Inc., Genentech, Inc., and Gilead Sciences, Inc. Data Safety Monitoring Board for Alchemia Limited. Advisory board member for Agendia BV, Daiichi-Sankyo Co., Eli Lilly and Company, Genentech, Inc., Precision Therapeutics, Inc. Consultant for Genomic Health, Inc. and National Cancer Institute.

Dr. Bekaii-Saab: PI for Enzon Pharmaceuticals, Inc.; Genentech, Inc.; National Cancer Institute; Array BioPharma Inc.; Oncolytics Biotech Inc.; and Roche Laboratories, Inc. Data Safety Monitoring Board for Polaris Pharmaceuticals, Inc. Consultant for Amgen Inc.; Bristol-Myers Squibb Company; Genentech, Inc.; and Onyx Pharmaceuticals, Inc.

Dr. Chan: PI for Abbott Laboratories; Amgen Inc.; Genentech, Inc.; ImClone Systems Incorporated; Merck & Co., Inc.; Pfizer Inc.; and Roche Laboratories, Inc. Advisory Board Member for Amgen Inc., Bayer HealthCare, and Bristol-Myers Squibb Company.

Dr. Choti: PI for Ipsen. Consultant for Bayer HealthCare, Genentech, Inc., and sanofi-aventis U.S. Advisory Board Member for Bristol-Myers Squibb Company.

Dr. Enzinger: Consultant for Boehringer Ingelheim GmbH; Genentech, Inc.; sanofi-aventis U.S.; and Taiho Pharmaceuticals Co., Ltd.

Dr. Fuchs: PI for Amgen Inc. and ImClone Systems Incorporated. Advisory board member for Amgen Inc., Metamark Genetics, Inc., Pfizer Inc., and sanofi-aventis U.S. Consultant for Bristol-Myers Squibb Company; Genentech, Inc.; Genomic Health, Inc.; ImClone Systems Incorporated, Infinity Pharmaceuticals, Momenta Pharmaceuticals, Inc., and Roche Laboratories, Inc.

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Ms. Murphy: Data safety monitoring committee for the Radiation Treatment Oncology Group.

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Dr. Sofocleous: PI for the National Cancer Institute and Sirtex Medical Inc. Consultant for Sirtex Medical Inc.

Dr. Venook: PI for and has received research support from Amgen 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.

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Learning Objectives:

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

- Integrate into professional practice the updates to NCCN Guidelines for localized colon cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for localized colon cancer

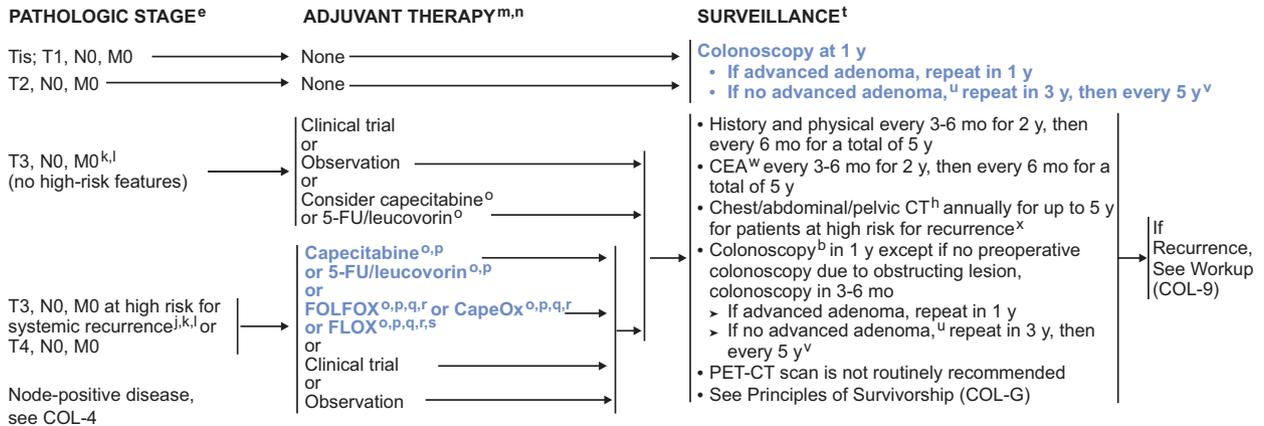
EDITOR: Kerrin M. Green, MA, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*, has disclosed that she has no relevant financial relationships.

CE AUTHORS: Nicole B. Harrold, BS, Manager, Continuing Education and Grants, has disclosed that she has no relevant financial relationships. Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations, has disclosed that she has no relevant financial relationships. James Prazak, RPh, Assistant Director, Continuing Education and Grants, has disclosed the following relationships with commercial interests: Bristol-Myers Squibb Company: Pension; Pfizer, Inc: Stockholder; United Healthcare Group: Stockholder; Johnson & Johnson: Stockholder. Deborah A. Freedman-Cass, PhD, Oncology Scientist/Senior Medical Writer, has disclosed that she has no relevant financial relationships.

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^bAll patients with colon cancer should be counseled for family history and considered for risk assessment. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Colorectal Cancer Screening.

^cSee Principles of Pathologic Review (COL-A) - Pathological stage.

^dCT should be with IV and oral contrast. Consider abd/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

^eHigh-risk factors for recurrence: poorly differentiated histology (exclusive of those cancers that are MSI-H), lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, or positive margins. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.

^fTesting for mismatch repair (MMR) proteins should be considered for all patients <50 years of age or with stage II disease. Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy. Sargent DJ, Marsomi S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol* 2010;28:3219-3226. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20498393>

^gSee Principles of Risk Assessment for Stage II Disease (COL-D).

^hThere are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.

ⁱBevacizumab, cetuximab, panitumumab, or irinotecan should not be used in the adjuvant setting for stage II or III patients outside the setting of a clinical trial.

^jSee Principles of Adjuvant Therapy (COL-E).

^kConsider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy (COL-F).

^lA survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. Tournigand C, André T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly (between ages 70 and 75 years) with colon cancer: a subgroup analyses of the Multicenter International Study of oxaliplatin, fluorouracil, and leucovorin in the adjuvant treatment of colon cancer trial. *J Clin Oncol* 2012; published online ahead of print on August 20, 2012.

^mA benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.

ⁿGrade 3-4 diarrhea is considerably higher with FLOX than FOLFOX in cross study comparison.

^oDesch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2005;23:8512-8519.

^pVillous polyp, polyp >1 cm, or high-grade dysplasia.

^qRex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2006;130:1865-71.

^rIf patient is a potential candidate for further intervention.

^sCT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion by tumor; poorly differentiated tumors).

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COL-3

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

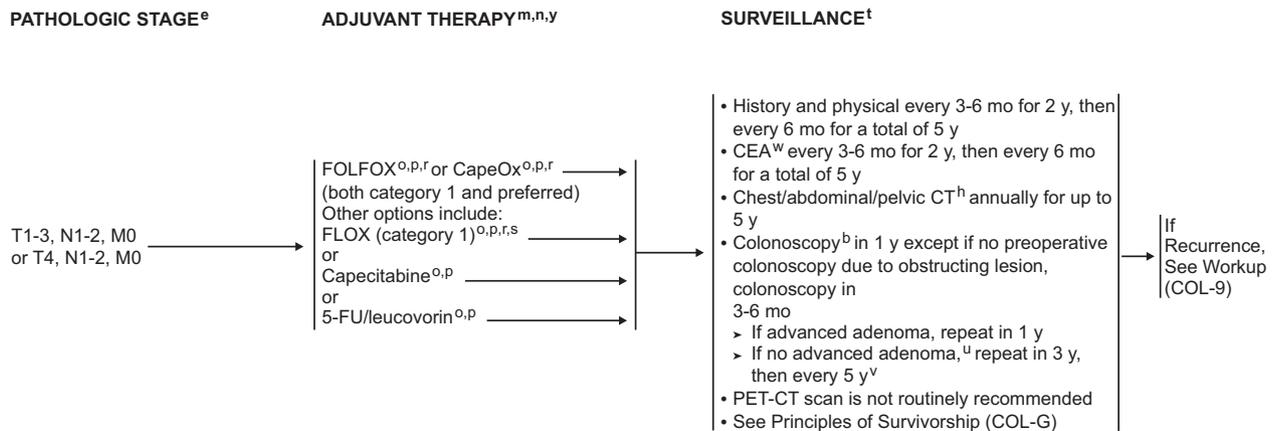
Overview

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.¹ 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 2005.² In addition, mortality from colorectal cancer has decreased by almost 35% from 1990 to 2007,³ likely because of earlier diagnosis through screening and better treatment modalities.

Surveillance for Early-Stage Disease

While reviewing the guidelines during the annual panel meeting, a panelist brought up the issue of surveillance for early-stage colon cancer after col-

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^bAll patients with colon cancer should be counseled for family history and considered for risk assessment. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Colorectal Cancer Screening.

^eSee Principles of Pathologic Review (COL-A) - Pathological stage.

^hCT should be with IV and oral contrast. Consider abd/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

^mThere are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.

ⁿBevacizumab, cetuximab, panitumumab, or irinotecan should not be used in the adjuvant setting for stage II or III patients outside the setting of a clinical trial.

^oSee Principles of Adjuvant Therapy (COL-E).

^pConsider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy (COL-F).

^rA benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.

^sGrade 3-4 diarrhea is considerably higher with FLOX than FOLFOX in cross study comparison.

^tDesch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2005;23:8512-8519.

^uVillous polyp, polyp >1 cm, or high-grade dysplasia.

^vRex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2006;130:1865-71.

^wIf patient is a potential candidate for further intervention.

^yTesting for mismatch repair (MMR) proteins should be considered for all patients <50 years of age.

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COL-4

ectomy. The surveillance recommendations were the same for patients with stage I and II disease, but the panel noted that the risk of recurrence is significantly lower in stage I. The possible harms associated with intensive surveillance discussed by the panel include the radiation exposure of repeated CT scans, the psychological stress associated with surveillance visits and scans, and the stress and risks from following up on false-positive results. The panel discussed whether including history and physicals or carcinoembryonic antigen (CEA) measurements would be reasonable to ensure regular office visits to the oncologist to coordinate care, but acknowledged that no data exist to support the benefits of these measures. Overall, the panel believes that patients with stage I disease are at very low risk for recurrence and that these survivors do not require intensive surveillance. Therefore, the panel decided to change its surveillance recommendation for patients with stage I disease to include only colonoscopy at 1 year (see

COL-3, page 521). Repeat colonoscopy is recommended at 3 years, and then every 5 years thereafter, unless advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia) is found. In this case, colonoscopy should be repeated in 1 year.⁴

Adjuvant Therapy for Stage II Disease

The panel discussed the impact of adjuvant chemotherapy on outcomes for patients with resected stage II colon cancer. This topic has been addressed in several clinical trials and practice-based studies. Results from a meta-analysis of 5 trials in which patients with stage II or III colon cancer were randomly assigned to receive surgery alone or surgery followed by adjuvant 5-FU/leucovorin (LV) showed that most of the benefit from adjuvant therapy was seen in patients with stage III disease.^{5,6} Similarly, an analysis of pooled data from 7 randomized trials indicated that overall survival of patients with resected colon

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cancer treated with 5-FU–based adjuvant therapy was statistically significantly increased with the addition of chemotherapy in the subset with stage III disease but not in those with stage II.⁷ These results suggest that the benefit of adjuvant therapy is greater in patients at higher risk because of nodal status.⁷ These clinical trial results are supported by data from the community setting. Using the SEER databases, an analysis of outcomes of patients with stage II disease based on whether they had received adjuvant chemotherapy showed no statistically significant difference in 5-year overall survival between the groups (78% vs 75%, respectively), with a hazard ratio (HR) for survival of 0.91 (95% CI, 0.77–1.09) when patients receiving adjuvant treatment were compared with untreated patients.⁸ In contrast to results from most other trials, the QUASAR trial indicated a small but statistically significant survival benefit for patients with stage II disease treated with 5-FU/LV compared with patients not receiving adjuvant therapy (relative risk of recurrence at 2 years, 0.71; 95% CI, 0.54–0.92; $P=.01$).⁹

A recent meta-analysis of 12 randomized controlled trials from 1988 to 2010, in which surgery alone was the control arm, found a significant benefit to adjuvant therapy in patients with stage II colon cancer.¹⁰ The 5-year overall survival HR was 0.81 (95% CI, 0.71–0.91), and the 5-year disease-free survival HR was 0.86 (95% CI, 0.75–0.98). The trials in this analysis used various chemotherapy regimens, many of which are not currently recommended in this setting.

Notably, a recent analysis of more than 24,000 patients with stage II colon cancer from the SEER Medicare database showed no 5-year survival benefit for adjuvant chemotherapy over observation, even in patients with stage II disease with one or more poor prognostic features (HR, 1.03; 95% CI, 0.94–1.13).¹¹ Although this study was limited to patients older than 65 years and involved a period before the use of oxaliplatin-based therapies,¹² it is still an important piece of data to consider during the decision-making process regarding the use of adjuvant chemotherapy in patients with stage II disease.

The panel believes that decision-making regarding the use of adjuvant therapy for patients with stage II disease should incorporate individualized patient/physician discussions, and should include explanations of the specific characteristics of the

disease and its prognosis, and the evidence related to the efficacy and possible toxicities associated with treatment, centering on patient choice.^{13,14} Observation and participation in a clinical trial are options that should be considered. Patients with average-risk stage II colon cancer have a very good prognosis, so the possible benefit of adjuvant therapy is small. Patients with high-risk features, however, have been traditionally considered more likely to benefit from adjuvant chemotherapy. However, as the panel discussed, the current definition of high-risk stage II colon cancer is clearly inadequate, in that many high-risk patients do not experience a recurrence, whereas some patients with average risk do.¹⁵ Furthermore, no data identify features that are predictive of benefit from adjuvant chemotherapy, and no data correlate risk features and selection of chemotherapy in high-risk patients with stage II disease.

Overall, the NCCN panel supports the conclusion of a 2004 ASCO panel that *direct* evidence from randomized controlled trials does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer: “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, including patients with inadequately sampled nodes, T4 lesions, perforation, or poorly differentiated histology.”¹³ The NCCN panel believes that it is reasonable to accept the relative benefit of adjuvant therapy in stage III disease as indirect evidence of possible benefit for stage II disease, especially for those with high-risk features. Additional information that may influence adjuvant therapy decisions in stage II and/or III disease (microsatellite instability [MSI], multigene assays, and patient age) was also addressed by the panel, as summarized here.

Microsatellite Instability

Mutation in DNA mismatch repair (MMR) genes or their modification, usually by promoter methylation, can result in MMR protein deficiency or dysfunctional gene products and MSI.¹⁶ Germline mutations in the MMR genes *MLH1*, *MSH2*, *MSH6*, and/or *PMS2* or in *EpCAM* are found in individuals with Lynch syndrome, which is responsible for 2% to 4% of colon cancer cases.^{17–20} Somatic MMR defects have been reported to occur in approximately 19% of colorectal tumors,²¹ almost always because of so-

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matic hypermethylation of the *MLH1* gene promoter and its associated *MLH1* gene inactivation, and loss of expression of the gene product and its binding partner PMS2; in 8% to 17% of colon tumors; and in 57% to 89% of tumors with MSI.^{22–24} Tumors showing the presence of MSI are classified as either MSI-high (MSI-H) or MSI-low (MSI-L), depending on the extent of instability in the DNA markers tested, whereas tumors without DNA marker instability are classified as microsatellite-stable (MSS).²⁵ Patients are commonly evaluated for MMR protein expression using immunohistochemistry or for MSI through testing for changes in the length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units, but rarely for defective MMR function. Tumors with loss of MSH2 and MSH6 or of *MLH1* and PMS2 expression have MSI-H status. Loss of MSH6 alone or PMS2 alone is variably associated with MSI status.

As in past years, the panel discussed MSI testing (ie, MMR protein expression testing or DNA-based assays) in patients with stage II disease, because MSI is an important consideration when deciding whether to use adjuvant chemotherapy in these patients because of the improved stage-specific survival rates. The use of common adjuvant regimens in patients with MSI-H carcinomas is controversial, and the mechanism of MSI-H may influence benefit.^{26,27} Data from the PETACC-3 trial showed that tumor specimens characterized as MSI-H are more common in stage II disease than in stage III disease (22% vs 12%, respectively; $P < .0001$).²⁸ In another large study, the percentage of stage IV tumors characterized as MSI-H was only 3.5%.²⁹ These results suggest that MSI-H (ie, MMR-deficient [dMMR]) tumors have a decreased likelihood to metastasize. In fact, substantial evidence shows that MSI is a marker of a more favorable outcome and a predictor of decreased benefit (and possibly a detrimental impact) from adjuvant therapy with a fluoropyrimidine alone in patients with stage II disease.^{30–32}

A retrospective study involving long-term follow-up of patients with stage II and III disease evaluated according to MSI tumor status showed that those characterized as MSI-L or MSS had improved outcomes with 5-FU adjuvant therapy; however, patients with tumors characterized as MSI-H did not show a statistically significant benefit from 5-FU after surgery, instead exhibiting a lower

5-year survival rate than those undergoing surgery alone.³⁰ Similarly, results from another retrospective study of pooled data from adjuvant trials by Sargent et al³¹ showed that in tumors characterized as dMMR, adjuvant 5-FU chemotherapy seemed to be detrimental in patients with stage II disease but not those with stage III disease.

In contrast to the findings of Sargent et al,³¹ however, a recent study of 1913 patients with stage II colorectal cancer from the QUASAR study, half of whom received adjuvant chemotherapy, showed that although dMMR was prognostic (the recurrence rate of dMMR tumors was 11% vs 26% for MMR-proficient tumors), it did not predict benefit or detrimental impact of chemotherapy.³³ A recent study of patients on the CALGB 9581 and 89803 trials reached a similar conclusion.³⁴ MMR status was prognostic but not predictive of benefit or detrimental impact of adjuvant therapy (irinotecan, LV, and 5-FU [IFL] regimen) in patients with stage II colon cancer.

Many of the NCCN Member Institutions reported that they perform MSI testing on all patients with stage II disease. Others reported that they only perform MSI testing on patients with stage II colon cancer if adjuvant therapy is being considered. Because observation after resection is an acceptable option in the guidelines, even for patients with proficient MMR status, the panel decided not to mandate MSI testing for all patients with stage II disease. Because patients with stage II MSI-H disease have a good prognosis and do not benefit from 5-FU adjuvant therapy, the panel reaffirmed its recommendation that MSI testing be considered for patients with stage II disease, especially those who are being considered for adjuvant therapy (see COL-3, footnote k, page 521). The panel also emphasized that poorly differentiated histology is not considered a high-risk feature for patients with stage II disease whose tumors are MSI-H.

In addition to its predictive value, MSI testing is important to assess for the possibility of Lynch syndrome. The panel believes that MSI testing should be performed for all patients younger than 50 years, because they are most likely to have Lynch syndrome. Some institutions perform MSI testing reflexively on all colorectal and endometrial tumors, because the benefits of identifying Lynch syndrome in relatives can be far-reaching.³⁵

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Multigene Assays

Several multigene assays have been developed with the hope of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer.¹⁵ The panel discussed whether to add these assays to the guidelines to help define patients with high-risk stage II disease and guide adjuvant therapy choices. The data on 3 multigene assays were reviewed by the panel, as described here.

Oncotype DX Colon (Genomic Health Inc., Redwood City, CA) quantifies the expression of 7 recurrence-risk genes and 5 reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence.³⁶ Clinical validation in patients with stage II and III disease from the QUASAR³⁷ and NSABP C-07³⁸ trials showed that recurrence scores are prognostic for recurrence, disease-free survival, and overall survival in patients with stage II and III colon cancer, but are not predictive of benefit to adjuvant therapy. For the low, intermediate, and high recurrence risk groups, recurrence rates at 3 years were 12%, 18%, and 22%, respectively.³⁷ Multivariate analysis showed that recurrence scores were related to recurrence independently from TNM staging, MMR status, tumor grade, and number of nodes assessed in both stage II and III disease.

ColoPrint (Agendia Inc., Irving, CA) quantifies the expression of 18 genes as a prognostic classifier of low versus high recurrence risk.³⁹ In a set of 206 patients with stage I through III colorectal cancer, the 5-year relapse-free survival rates were 87.6% (95% CI, 81.5%–93.7%) and 67.2% (95% CI, 55.4%–79.0%) for those classified as low- and high-risk, respectively. In patients with stage II disease in particular, the HR for recurrence between the high- and low-risk groups was 3.34 ($P=.017$).³⁹ This assay was further validated in a pooled analysis of 320 patients with stage II disease, 227 of whom were assessed as a T3/MSS subset.⁴⁰ In the T3/MSS subset, patients classified as low- and high-risk had 3-year recurrence-free survival rates of 91% (range, 86%–96%) and 73% (range, 63%–83%), respectively ($P=.002$).⁴⁰ As with the Oncotype DX Colon assay, recurrence risk determined by ColoPrint is independent of other risk factors, including T stage, perforation, number of nodes assessed, and tumor grade. This assay is being further validated for its

ability to predict 3-year relapse rates in patients with stage II colon cancer in a prospective trial.⁴¹

ColDx is a microarray-based multigene assay that uses 634 probes to identify patients with stage II colon cancer at high risk of recurrence.⁴² In a 144-sample independent validation set, the HR for identification of high-risk patients was 2.53 (95% CI, 1.54–4.15; $P<.001$) for recurrence and 2.21 (95% CI, 1.22–3.97; $P=.0084$) for cancer-related death. Similar to the other assays described here, the recurrence risk determined by ColDx is independent of other risk factors.

On reviewing these data, the panel agreed that the information from these tests can further inform the risk of recurrence over other risk factors, but the panel questioned the value added. Panelists pointed out that no evidence exists for any predictive value in terms of the potential benefit of chemotherapy to any of the available multigene assays. The panel believes that data are insufficient to recommend the use of multigene assays to determine adjuvant therapy, and therefore made no change to the guidelines (see COL-3 and COL-4, footnote m, page 521 and 522).

Oxaliplatin in High-Risk Stage II Disease

On publication of the mature results of post hoc exploratory analyses of the MOSAIC trial,⁴³ the panel held an interim conference to discuss the implications of these results on the guideline recommendations. The analysis showed that FOLFOX had no significant disease-free survival benefit over 5-FU/LV for patients with stage II disease at a follow-up of 6 years (HR, 0.84; 95% CI, 0.62–1.14; $P=.26$).⁴³ In addition, patients with high-risk stage II (ie, disease characterized by at least one of the following: T4 tumor, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion, <10 lymph nodes examined) receiving FOLFOX did not show a significantly improved disease-free survival compared with those receiving infusional 5-FU/LV (HR, 0.72; 95% CI, 0.50–1.02; $P=.06$). Furthermore, no overall survival benefit was seen in the patients with stage II overall (HR, 1.00; 95% CI, 0.70–1.41; $P=.99$) or those with stage II with high-risk features (HR, 0.91; 95% CI, 0.61–1.36; $P=.65$).

The panel discussed the difficulties in defining risk factors (see “Adjuvant Therapy for Stage II Disease,” page 522), and questioned whether most of

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the patients classified as high-risk in the MOSAIC analysis were truly high-risk. The panel noted that most (54%) of the high-risk patients were in that group because of inadequate lymph node sampling, which may be a risk factor that has less of an impact than others. Also, 17% of the high-risk patients had tumors with poorly differentiated histology, which is often associated with MSI status. Because the analysis did not take into account MSI status and because poor differentiation is not considered a high-risk factor for patients with MSI, these patients may not have been truly high-risk.

The panel thus decided to leave oxaliplatin as an option for high-risk stage II patients, but they removed the preferred status for FOLFOX and CapeOx (see COL-3, page 521). The panel also added a footnote stating that a survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/LV in stage II colon cancer (COL-3, footnote q, page 521). The panel believes that the decision to add oxaliplatin to adjuvant therapy for a patient with stage II disease should be individualized.

Oxaliplatin in Adjuvant Therapy for Elderly Patients With Stage II/III Disease

The panel also discussed the implications of the mature post hoc exploratory analyses of the MOSAIC trial⁴³ as they relate to the panel's recommendations for adjuvant therapy in older patients. In this analysis, 315 patients aged 70 to 75 years with stage II or III colon cancer derived no benefit from the addition of oxaliplatin to their adjuvant regimens (overall survival HR, 1.10; 95% CI, 0.73–1.65).⁴³ The panel also considered similar data from a subset analysis of the C-07 trial, which compared FLOX versus 5-FU/LV in patients with stage II and III disease and found no difference in overall survival (HR, 1.18; 95% CI, 0.86–1.62; $P=.30$) or disease-free survival (HR, 1.03; 95% CI, 0.77–1.36; $P=.87$) in the 396 patients who were aged 70 years or older.⁴⁴ The panel noted that the MOSAIC and C-07 analyses were unplanned and included a relatively small number of patients. In addition, a population study of 5489 patients aged 75 years or older diagnosed with stage III colon cancer between 2004 and 2007 from 4 datasets, including the SEER-Medicare Databases and the NCCN Outcomes Database, showed a survival benefit for adjuvant chemotherapy in this population (HR, 0.60; 95% CI, 0.53–0.68).⁴⁵ However, when the benefit of adding oxaliplatin to adjuvant therapy was assessed

in these older patients with stage III disease, only a small, nonsignificant benefit was found.

Weighing these data, the panel decided that oxaliplatin should remain an option for older patients with stage II and III disease. Overall, the panel believes that the benefit and toxicities of 5-FU/LV as adjuvant therapy seem to be similar in older and younger patients.^{45–47} However, the panel cautions that a benefit for the addition of oxaliplatin to 5-FU/LV in patients aged 70 years and older has not been proven in stage II or III colon cancer (COL-3 and COL-4, footnote r, pages 521 and 522). The panel agreed that the choice of whether to add oxaliplatin to the adjuvant regimen in elderly patients should be individualized.

Summary of Changes to the 2013 NCCN Guidelines for Localized Colon Cancer

In summary, the panel discussed many pertinent issues this year. Some recommendations were reviewed in detail and not changed (indicated with purple font on COL-3 and COL-4, pages 521 and 522):

- The panel reaffirmed its recommendation that MSI testing be considered for patients with stage II disease, especially for those who are being considered for adjuvant therapy, because patients with stage II MSI-H disease have a good prognosis and do not benefit from 5-FU adjuvant therapy.
- The panel believes that data are still insufficient to recommend the use of multigene assays to determine adjuvant therapy in patients with stage II or III disease.
- The panel decided that oxaliplatin should remain as an option for older patients with stage II and III disease, although they added a footnote to caution that a benefit for the addition of oxaliplatin to 5-FU/LV in patients aged 70 years and older has not been proven in stage II or stage III colon cancer.

Other discussions resulted in changes to the 2013 recommendations (indicated with blue font on COL-3 and COL-4, pages 521 and 522):

- The panel made its surveillance recommendation for patients with stage I disease less intensive, with only colonoscopy at 1 year.
- The panel removed the preferred status for

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FOLFOX and CapeOx as adjuvant therapy for patients with high-risk stage II disease. The panel also added a footnote stating that a survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/LV in stage II colon cancer.

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Posttest Questions

1. Surveillance recommendation for patients with stage I disease includes which one of the following at 1 year:
 - a. History and physical
 - b. Colonoscopy
 - c. Chest/abdominal/pelvic CT
 - d. CEA measurement
2. True or False: After reviewing the mature post-hoc exploratory analyses of the MOSAIC trial, the panel removed oxaliplatin as an adjuvant therapy option for patients with high-risk stage II colon cancer.
3. When making decisions regarding adjuvant therapy in patients with stage II, the panel recommends consideration of all of the following, EXCEPT:
 - a. Microsatellite instability
 - b. Patient age
 - c. Score on a multigene assay
 - d. Prognostic characteristics of the disease
 - e. Patient choice

