NCCN Guidelines® Insights

Colorectal Cancer Screening, Version 1.2015

Featured Updates to the NCCN Guidelines

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Abstract
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colorectal Cancer Screening provide recommendations for selecting individuals for colorectal cancer screening, and for evaluation and follow-up of colon polyps. These NCCN Guidelines Insights summarize major discussion points of the 2015 NCCN Colorectal Cancer Screening panel meeting. Major discussion topics this year were the state of evidence for CT colonography and stool DNA testing, bowel preparation procedures for colonoscopy, and guidelines for patients with a positive family history of colorectal cancer. (J Natl Compr Canc Netw 2015;13:959–968)

Featured Updates to the NCCN Guidelines

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 to the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the NCCN Guideline Panel discussion, including the literature reviewed.

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Overview

Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the third most frequent cause of cancer death in both US men and women. In 2015, an estimated 93,090 new cases of colon cancer and 39,610 new cases of rectal cancer will occur in the United States. During the same year, an estimated 49,700 people will die of colon and rectal cancer. CRC mortality can be reduced through early diagnosis and cancer prevention with polypectomy. Hence, the goal of a CRC screening program is to reduce mortality through cancer prevention and early detection. Currently, the relative 5-year survival rate for patients with localized CRC is 90.5%, whereas for those with regional and distant disease it is 71.9% and 12.5%, respectively, showing that earlier diagnosis can have a large impact on survival.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CRC Screening

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.
describe various CRC screening modalities and provide recommended screening schedules for patients with an average or increased risk of developing sporadic CRC (to view the most recent version of these guidelines, visit NCCN.org). Recommendations regarding the management of inherited syndromes, such as Lynch syndrome (ie, hereditary nonpolyposis CRC), familial adenomatous polyposis, MutY human homolog (MUTYH)–associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis syndrome, and serrated polyposis syndrome, are addressed in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal available online at NCCN.org).6–8

Impact of CRC Screening on Mortality Rates
Mortality from CRC decreased by almost 35% from 1990 to 2007,9 and in 2011 had decreased 47% from peak mortality rates.1 These improvements in incidence of and mortality from CRC over past years are thought to be, at least partly, a result of cancer prevention and earlier diagnosis through screening and better treatment modalities: modeling suggests that approximately 63% of CRC deaths can be attributed to non-screening.10 According to the CDC, the screening rate among US adults aged 50 to 75 years has increased from approximately 42% in 2000 to 59% in 2010.11 The National Colorectal Cancer Roundtable established the goal to increase CRC screening rates in the United States to 80% by 2018, which they estimate could prevent approximately 280,000 new CRC cases and 200,000 CRC deaths through 2030.12

Results from the Nurses’ Health Study and the Health Professionals Follow-Up Study showed that death from CRC was reduced after flexible sigmoidoscopy (hazard ratio [HR], 0.59; 95% CI, 0.45–0.76) and colonoscopy (HR, 0.32; 95% CI, 0.22–0.46).13,14 These improvements in incidence of and mortality from CRC over past years are thought to be, at least partly, a result of screening and better treatment modalities: modeling suggests that approximately 63% of CRC deaths can be attributed to non-screening.10

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0.24–0.45), and that mortality from proximal colon cancer was reduced after colonoscopy (HR, 0.47; 95% CI, 0.29–0.76) but not after sigmoidoscopy.\textsuperscript{13} Additionally, results of 5 randomized controlled trials (RCTs) provide strong evidence for the use of flexible sigmoidoscopy as a screening modality.\textsuperscript{14–18} Recent meta-analyses of RCTs show that screening via flexible sigmoidoscopy significantly reduces CRC incidence and mortality.\textsuperscript{19–22} Evidence from these prospective studies and reviews of RCTs shows that screening significantly reduces CRC mortality rates.

The NCCN Guidelines Panel emphasizes that the main goal of a CRC screening program is to reduce mortality through prevention and early detection. A major theme that emerged during the panel meeting is how new and/or developing screening modalities (eg, CT colonography [CTC], stool DNA testing) fit into an overall CRC screening program. The panel emphasizes the preferred conditions of a program in a footnote—specifically, that screening should include standardized methods for identifying those who are eligible for and wish to undergo screening, administering screening at agreed-upon intervals, reporting of results, and follow-up for positive results (see CSCR-2, page 961). High-quality studies that provide information about how emerging screening modalities fit into a screening program are crucial for making recommendations, such as those regarding screening intervals. However, the panel also noted the importance of patient preferences and resources: although colonoscopy may be the primary method used for screening, the patient ultimately decides which screening modality is used.

## Screening Modalities

Current CRC screening technology generally falls into 2 broad categories: structural tests and stool/fecal-based tests.\textsuperscript{23} Structural tests (ie, colonoscopy, flexible sigmoidoscopy, CTC) are able to detect
early cancer and polyps via endoscopic or radiologic imaging. However, endoscopic tests have several limitations, including their relative invasiveness, the need for dietary preparation and bowel cleansing, and the time dedicated to the examination (typically an entire day). Endoscopic examinations require informed consent, usually involve sedation, and have related risks, including perforation and bleeding. Fecal-based tests (ie, fecal occult blood test [FOBT], stool DNA test) are designed to detect signs of CRC in stool samples, specifically occult blood or, more recently, alterations in exfoliated DNA. In contrast to structural tests, they are noninvasive and bowel cleansing is not necessary. However, stool tests are less likely to detect polyps for cancer prevention. Also, sensitivity can be limited by inadequate specimen collection or suboptimal processing and interpretation, and it is significantly lower than that of structural tests. Therefore, the panel recommends that any positive stool test be followed by a colonoscopy.

For the 2015 guidelines update, the panel did not discuss all possible screening modalities. Therefore, the following discussion is limited only to the modalities that were discussed (ie, colonoscopy, CTC, stool DNA testing, FOBT) during the panel meeting.

**Colonoscopy**

Colonoscopy is the most complete screening procedure, allowing examination of the entire large bowel and the removal of polyps in one session. It is the required procedure for confirmation of positive findings from other tests. Colonoscopy is also considered the current gold standard for assessment of the efficacy of other screening methods. Although no RCTs directly show mortality reduction by colonoscopy, findings from case-control and cohort studies show a significant impact of colonoscopy and polypectomy on CRC, with an estimated reduction in incidence of greater than 50%. Rabeneck et al recently reported an inverse correlation between colonoscopy use and death from CRC in a large population study involving approximately 2.5 million Canadians. For every 1% increase in colonoscopy rate, the risk of death decreased by 3%.

Colonoscopic screening, in addition to cancer prevention, is also expected to lead to earlier diagnosis. This is supported by a recent retrospective review of a prospective database comparing 217 patients diagnosed with colon cancer through screening colonoscopy and 854 patients with colon cancer not diagnosed through screening. Unscreened patients were at a higher risk for more-invasive tumors (relative risk [RR], 1.96; P < .001), nodal disease (RR, 1.92; P < .001), and metastatic disease at presentation (RR, 3.37; P < .001). Furthermore, unscreened patients had higher rates of death and recurrence, shorter survival, and shorter disease-free intervals.

The panel enhanced its recommendations regarding bowel preparation for colonoscopy (see CSCR-A 3 of 5, page 963) based on the recently published recommendations from the US Multi-Society Task Force on Colorectal Cancer. The task force recommended the use of split-dose preparation because it is superior to the traditional regimen and is administered the day before colonoscopy. The recommended timing of the second dose of the split-dose preparation is 4 to 6 hours before colonoscopy and should end at least 2 hours before colonoscopy. The panel agrees with the Multi-Society Task Force that a same-day, morning-only regimen is acceptable, particularly for patients undergoing afternoon procedures.

The panel continues to recommend a 10-year screening interval for average-risk patients who undergo complete colonoscopy with adequate bowel preparation and have negative results. Inadequate preparation indicates a shorter screening interval. To determine preparation quality, a preliminary assessment should be made in the rectosigmoid colon. If an inadequate preparation would interfere with the detection of polyps larger than 5 mm, then the procedure should be rescheduled. Alternatively, additional bowel cleaning can be attempted for the colonoscopy to proceed that day. For cases in which colonoscopy is complete to the cecum but the preparation is ultimately considered inadequate, colonoscopy should be repeated within 1 year; a more aggressive preparation regimen should be recommended in these cases. When advanced neoplasia is detected and preparation was inadequate, then an interval shorter than 1 year is recommended.

**CT Colonography**

CTC is evolving as a promising technique for CRC screening, and has the advantages of being noninvasive and not requiring sedation. The risk
of test-related complications is also very low, and results of a recent systematic review suggest that CTC may be cost-effective when compared with colonoscopy. However, a positive CTC finding requires a colonoscopy, and extracolonic findings, which are present in up to 16% of patients, pose a dilemma. These findings require further investigation and have the potential for both benefit and harm. Currently, data to determine the clinical impact of these incidental findings are insufficient.

The NCCN Guidelines Panel discussed at length how CTC might fit into a screening program. Available data indicate that CTC may be useful for the detection of larger polyps. Further, a small prospective study of 47 patients with pathologically proven lateral spreading tumors found that CTC may not be as sensitive as colonoscopy for detecting tumors with significant lateral spread. The panel noted that CTC is still an evolving technique, and currently few data are available that address screening intervals, polyp size leading to referral for colonoscopy, what follow-up is required for a patient with a positive CTC and a negative colonoscopy, and protocol for evaluating extracolonic lesions. Therefore, although it was acknowledged that CTC is a promising emerging screening modality and is currently being used in clinical practice, the panel is currently unable to provide recommendations about how CTC best fits into a screening program. The best evidence currently available seems to support repeating CTC every 5 years and referring patients with polyps larger than 5 mm for colonoscopy. The panel has revised a footnote regarding CTC for the 2015 guidelines update, reiterating this information (see CSCR-2, page 961).

Fecal Occult Blood Test

FOBTs (guaiac-based and immunochemical) are recommended annually when used alone. When used in combination with flexible sigmoidoscopy every 5 years, the panel recommends FOBT screening at year 3. Annual FOBT should not be performed in combination with colonoscopy in an average-risk patient. Any positive result on FOBT, however, should be followed up with colonoscopy. It is important for FOBT alone to be performed annually, because the sensitivity in detecting advanced adenomas in a single test is fairly low.

Guaiac FOBT is the most common stool test used for CRC screening. A major disadvantage of this test is that it may miss tumors that bleed in smaller amounts, intermittently, or not at all. Another limitation is the high false-positive rate resulting from reaction with nonhuman heme in food and blood from the upper gastrointestinal tract. To compensate for these limitations, guaiac FOBT should be performed on 3 successive stool specimens obtained while the patient adheres to a prescribed diet. There is direct evidence from RCTs that guaiac FOBT reduces CRC mortality. However, the panel recommends that that only high-sensitivity guaiac tests be used. The US Preventive Services Task Force defines high-sensitivity FOBT as a test with a sensitivity of greater than 70% and a specificity of more than 90% for detecting cancer; guaiac tests that meet these criteria are newer and have not been tested in RCTs.

Stool DNA Testing

Stool DNA testing has emerged as a new primary screening tool for CRC, and 5 panel members raised questions about considering it as a screening option. It detects the presence of known DNA alterations during colorectal carcinogenesis in tumor cells sloughed into stool. Early tests produced relatively poor sensitivity. However, other stool DNA tests have also been developed and tested. Particularly, Cologuard uses quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and ACTB in conjunction with a hemoglobin immunoassay. A recent study that included 9989 participants with average-risk CRC, each of whom underwent a fecal immunochemical test (FIT), stool DNA testing with Cologuard, and a colonoscopy, found that the stool DNA test was more sensitive than FIT in the detection of CRC (92.3% vs 73.8%; P=.002), advanced precancerous lesions (42.4% vs 23.8%; P<.001), polyps with high-grade dysplasia (69.2% vs 46.2%; P=.004), and sessile serrated polyps larger than 1 cm (42.4% vs 5.1%; P<.001). Specificity, however, was better with FIT (86.6% vs 94.9% among participants with nonadvanced or negative findings; P<.001), and more participants were excluded because of problems with stool DNA testing (n=689) than with FIT (n=34). In August 2014, the FDA approved Cologuard as the first stool DNA test for primary screening of CRC. Other stool DNA tests (eg, ColoSure, which detects methylated vimentin) are currently available in the United States, although they are not FDA-approved.
Five panel members questioned whether recommendations regarding stool DNA testing should be revised because Cologuard was FDA-approved as a primary screening modality. The panel noted that, like CTC, it is not clear how stool DNA testing may fit into an overall screening program. Data are limited regarding determination of appropriate screening intervals and adherence to/participation rates in screening programs. It is not clear, for example, how stool DNA testing will compare with several rounds of annual FIT. For these reasons, the panel included a footnote in the 2015 NCCN Guidelines indicating that, although stool DNA testing has been FDA-approved as a primary screening modality, an appropriate screening interval cannot be recommended at this time because of limited available data (see CSCR-2, page 961). Therefore, the panel does not currently recommend stool DNA testing as a primary screening modality.

**Screening Individuals With a Positive Family History**

Individuals with a family history of CRC have an increased risk of the disease and should undergo earlier and/or more frequent screening. The panel recommended some minor revisions to the guidelines for those with a family history of CRC, because of concerns from panel members that the previous guidelines were too aggressive. The recommendations for patients with a family history of CRC are now as follows (see CSCR-6, page 962):

- For patients with an affected first-degree relative diagnosed before age 60 years or 2 first-degree relatives with CRC at any age: colonoscopy is recommended every 5 years, beginning 10 years before the earliest diagnosis in the family or at age 40 years at the latest. If colonoscopy results are positive, follow-up colonoscopy should be based on findings.
- For patients with one affected first-degree relative diagnosed at age 60 years or older, colonoscopy every 5 to 10 years should begin at age 50 years. If colonoscopy results are positive, follow-up colonoscopy should be based on findings. Multiple (≥2) negative colonoscopies may support stepwise lengthening of the colonoscopy interval in these individuals.
- For those with one second-degree relative diagnosed with CRC before age 50 years, colonoscopy should begin at 50 years of age, with repeat colonoscopy every 5 to 10 years or based on findings.
- Individuals with a first-degree relative with a confirmed history of advanced adenomas (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) should undergo colonoscopy at the relative’s age of onset of adenoma or age 50 years at the latest, with repeat colonoscopy every 5 to 10 years or based on findings. Data suggesting an increased risk for CRC in this population are limited. The panel emphasized the need to confirm family history of advanced adenoma, including obtaining documentation through medical records.

The CRC Screening Panel has also developed guidelines to screen for patients who may meet the criteria for an inherited CRC syndrome (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal; to view the most recent version, visit NCCN.org). Further risk evaluation and counseling of these patients, as outlined in those guidelines, is required.

**Summary and Conclusions**

In summary, the NCCN CRC Screening Panel discussed several pertinent issues this year, and revised the 2015 recommendations to:

- Emphasize that the ultimate goal of screening is to reduce mortality through prevention and early detection;
- Enhance recommendations regarding bowel preparation for colonoscopy; and
- Revise screening guidelines for those with a positive family history.

The panel continues to monitor the potential for CTC and stool DNA testing, although it did not revise the current recommendations because of limited evidence regarding how these screening modalities fit into an overall CRC screening program. CRC screening significantly impacts mortality rates. With continued advances in screening methods, mortality rates from CRC may continue to decrease, but there is an ongoing need for high-quality research.
References


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Posttest Questions

1. A patient, whose biological father was diagnosed with CRC at 56 years of age, began colonoscopy screening at age 45 years. No polyps were found. At what age should this patient be screened next, according to the 2015 NCCN Guidelines for CRC Screening?
   a. 48 years
   b. 50 years
   c. 55 years
   d. No need for further screening

2. True or False: If a 6-mm polyp is found during CTC, the next step is referral for colonoscopy.

3. Which of the following is/are true regarding colonoscopy preparation and procedures, according to the 2015 NCCN Guidelines for CRC Screening?
   a. Split-dose preparation is recommended
   b. If bowel preparation is inadequate, additional bowel cleaning should not be performed to proceed with the colonoscopy that day
   c. Withdrawal time may influence quality of colonoscopy
   d. a and b
   e. a and c
   f. All of the above