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Colorectal Carcinoma: What Should the Oncologist Recommend for Screening?

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Clinical oncology has traditionally focused on the treatment of human cancer, but with an increasing emphasis on cancer prevention and screening. As the cancer expert, the oncologist must therefore be well versed in the existing and emerging tools for clinical cancer screening. With the emergence of new screening modalities, what should oncologists recommend to colleagues and patients for colorectal cancer screening?

Colorectal cancer (CRC) remains the second-leading cause of cancer death within the U.S. and throughout much of the developed world.¹ This fact is particularly disturbing given that CRC is almost entirely preventable by screening for the detection of advanced adenomas. In fact, of the approximately 50,000 deaths from CRC in the U.S. each year, most are believed to be attributable to nonscreening.² Advanced adenomas are defined by a large size (10 mm) and/or by histologic features of high-grade dysplasia or a significant villous component. Previous studies have shown that endoscopic CRC screening with removal of adenomas significantly reduces mortality from this malignancy.^{3,4} The American Cancer Society guidelines for CRC screening have placed appropriate emphasis on the tests that provide for sensitive detection of significant colorectal polyps (ie, primary prevention),⁵ whereas the guidelines of the US Preventive Service Task Force fall short in this regard, without clear distinction between cancer prevention and cancer detection. In particular, colonoscopy – whether optical or virtual – allows for the highest degree of primary prevention via total colonic examination and accurate detection of advanced adenomas. The key target for CRC screening is advanced neoplasia, which includes both advanced adenomas (primary prevention) and cancers (secondary prevention), but the former is about 25 times more prevalent. Although most of the current stool-based screening tests perform reasonably well in terms of cancer detection, none is sensitive enough for large adenomas to be considered an effective screening test for prevention. This lack of cancer prevention is a huge missed opportunity for otherwise healthy adults in the 50–75 year-old age range.

Optical colonoscopy (OC) currently represents the dominant CRC screening modality within the U.S., whereas in Europe and elsewhere OC is far less utilized for primary screening relative to stool-based tests and flexible sigmoidoscopy. As the treatment endpoint for all

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primary screening modalities, colonoscopy has the advantage of combining screen detection with therapy (polypectomy). Disadvantages include the level of invasiveness, risk for significant complications, and high costs. The most feared complication is colonic perforation, which can be life-threatening and most often affects individuals without advanced neoplasia, violating the “first do no harm” credo. More common complications include significant bleeding and cardiovascular events, with the latter mainly related to sedation. Many individuals view the often arduous bowel preparation as a major barrier, while others may cite inconveniences such as the recovery time and need for assisted transport after procedure completion.

Additional issues related to primary OC screening worth considering include over-diagnosis and diminished performance in the proximal (right) colon. The adenoma detection rate (ADR) is a quality measure for endoscopists that is sometimes misconstrued as a diagnostic measure of test positivity. Current endoscopic advances may now allow for adenoma detection rates that exceed 50% in average-risk adults but are largely diminutive tubular adenomas of little or no clinical relevance rather than advanced adenomas. Because the lifetime risk of CRC is 5%, the vast majority of these tiny polyps will never develop into cancer, and represent “pseudo-disease”. In terms of right- versus left-sided colonic evaluation, conventional endoscopy (OC) provides better protection from cancer in the distal or left colon, an area largely covered by sigmoidoscopy. Factors contributing to missed right-sided lesions at OC include the physical constraints and the tendency for flatter polyps in this area.

CT colonography (CTC), also referred to as virtual colonoscopy, is a less invasive method for total colonic examination than conventional OC. Some of the advantages of CTC for primary screening compared with OC include a significantly improved risk profile, equivalent detection of advanced neoplasia, avoidance of sedation (and its attendant risks), no need for pain medication or recovery time, improved patient experience, and the addition of extracolonic screening.^{6–8} Because CTC is considerably less costly than the more invasive OC and because fewer than 10% of those screened by CTC require polypectomy (because tiny polyps in isolation are intentionally ignored), this approach is more cost effective as well.⁹ From the patient perspective, a more convenient low-volume bowel preparation can be utilized that is much less arduous than 4L of polyethylene glycol and no additional preparation is required for same-day polypectomy (if needed). The patient experience is further improved by the lack of recovery time and ability to immediately return to regular activities including driving. In our experience, the addition of CTC as a primary screening option has had the complementary effect of drawing in unscreened individuals from the “put it off” side line. As a special note for the practicing clinical oncologist, CTC can be combined with the diagnostic abdominopelvic CT often obtained for non-CRC diagnostic evaluation. In addition, for CRC patients returning for colonoscopy and CT one year after resection, we are conducting a prospective trial to determine if simultaneous CT/CTC obviates the need for OC.

Potential drawbacks of CTC screening include radiation exposure, extracolonic findings, and the handling of diminutive and flat lesions. The low-dose radiation technique used for CTC is however well below the level of any measurable theoretic harm in adults, and drops

below sub-mSv levels on average when newer iterative reconstruction techniques are applied. In terms of extracolonic evaluation, the net benefit related to “opportunistic” screening for aortic aneurysms, osteoporosis, and other cancers clearly outweighs any unnecessary work-up for unimportant incidental findings when handled responsibly.⁸ I also believe that intentionally ignoring diminutive colorectal lesions is a good idea, markedly reducing the number of non-therapeutic polypectomies that contribute to over-diagnosis. In terms of flat lesions, state-of-the-art CTC appears to be comparable to OC for detecting significant pathology. In the end, the biggest current drawback for CTC screening is the lack of broad coverage by the major insurers, including CMS. This lack of coverage has in turn led to limited availability beyond a few centers of excellence. This important barrier may be lifted if the upcoming USPSTF guideline revision issues an “A” or “B” grade for CTC screening, as recently happened with low-dose CT for lung cancer screening.

Stool-based tests are largely intended for cancer detection rather than cancer prevention. This may be more appropriate in older or debilitated individuals where limited life expectancy may not warrant prevention. A common advantage to the stool-based tests is of course their non-invasive nature. Guaiac-based fecal occult blood tests have largely given way to qualitative and quantitative fecal immunochemical tests (FIT). Heterogeneity in study design and test parameters preclude precise comments regarding performance, but overall sensitivity and specificity for CRC typically lie in the ranges of 60–90% and 85–95%, respectively. Sensitivity of FIT for advanced adenomas is generally in the range of 10–40%, much lower than OC or CTC. Cologuard[®] is a multi-target stool DNA (sDNA) test that also incorporates FIT and was recently approved by both the FDA and Medicare for CRC screening. A recently published trial showed a sensitivity for CRC that was at the high end of the FIT range (92%) and at the low end for specificity (87%).¹⁰ Sensitivity for large adenomas was near the high end of the FIT range (42%), but still falling well short of that needed for robust cancer prevention. One disadvantage of Cologuard[®] relative to FIT is cost, estimated at an order of magnitude greater. Despite intensive research for effective serum-based biomarkers for CRC, the only approved blood test for CRC screening is Epi proColon[®], which detects methylated septin9 DNA. One study showed that this approach was less than 50% sensitive for cancer.¹¹ A simple blood test that is both sensitive and specific for advanced neoplasia likely represents the “holy grail” for CRC screening, but does not appear imminent.

In conclusion, advanced neoplasia represents the optimal target for CRC screening, with the greatest clinical and economic value derived from primary cancer prevention by advanced adenoma identification and not simply cancer detection. Both optical and virtual colonoscopy achieve this goal of primary cancer prevention via total colonic examination, but the less-invasive latter option provides a number of additional advantages. The main disadvantage of CTC screening is the current lack availability, primarily due to lack of insurance coverage. Given the complementary strengths of CTC and flexible sigmoidoscopy for right- and left-sided colonic evaluation, respectively, an alternating strategy of these two modalities might be an optimal approach (eg, an alternating regimen every 5–10 years starting at age 50). In comparison, the stool- and serum-based tests continue to improve but still lack adequate preventive capabilities. As such, they cannot yet serve as recommended primary screening options for the general population.

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