

The Capsule and Colorectal-Cancer Screening — The Crux of the Matter

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In the United States and other countries, colonoscopy has emerged as the primary screening test for colorectal cancer. Colonoscopy is believed to prevent colorectal cancer because polyps are removed during the procedure, but randomized trials have not been conducted to show this benefit. Because colonoscopy is an invasive, uncomfortable procedure, with a small but finite risk of complications, there is a demand for less invasive techniques.

Imagine a small capsule with a built-in camera, the size of a tablet, that is easily swallowed and can detect cancer and polyps in your large bowel. It causes no discomfort while it travels through your colon taking photographs before being excreted with the stool. Yes, the colon capsule has been engineered and marketed and is in clinical use in Europe. However, the device's ability to detect cancer and polyps is not established.

In this issue of the *Journal*, Van Gossom et al. report the findings of a European multicenter study comparing capsule endoscopy of the colon with standard colonoscopy for the detection of colorectal polyps and cancer.¹ The study included 320 patients with abnormal findings at previous diagnostic procedures or with symptoms suggestive of colorectal cancer or polyps. Capsule endoscopy was followed by conventional colonoscopy.

The results show that the capsule fails to detect colorectal pathological features in a significant number of examinations; the capsule missed polyps that were at least 6 mm in size in 36% of the persons for whom colonoscopy showed such polyps. Lesions of this size are more likely to progress to colorectal cancer than are smaller polyps and, as seen with the use of computed tomographic (CT) colonography and flexible sigmoidoscopy, are considered the threshold for referral for colonoscopy.² Surprisingly, the sensitivity of capsule endoscopy was similarly poor for the largest lesions — capsule endoscopy detected adenomas 10 mm or larger in only 64% of persons who had them, and it detected colorectal cancer in only 14 of 19 persons with cancer (sensitivity for cancer, 74%; 95% confidence interval, 52 to 88). Since the size of colorectal

lesions is a predictor of the development of cancer, the relatively low sensitivity of capsule endoscopy for the detection of large adenomas is cause for concern. In contrast, the sensitivity of both colonoscopy and CT colonography are better for the detection of large lesions than small lesions.² The current findings are in line with the results of two previous capsule-feasibility trials, which showed a sensitivity of 60% and specificity of 73% for polyps larger than 5 mm,³ and of 50% and 84%, respectively, for either more than three polyps or at least one polyp larger than 5 mm.⁴

Eight patients (2.5%) were excluded from the accuracy analysis, six because of problems with the capsule (the capsule did not reach the colon before the end of the life of the battery in five patients, and one patient was unable to swallow the capsule) and two because of incomplete colonoscopy. The inclusion of these patients in the analysis in accordance with the intention-to-treat principle would presumably have resulted in an even poorer performance of the capsule.

Although a more extensive bowel-cleansing regimen is required for capsule endoscopy than for colonoscopy, suboptimal cleansing was observed in 28% of capsule-endoscopy procedures and 13% of colonoscopies. Impaired viewing of the capsule images owing to fecal residue partly explains the poor performance of capsule endoscopy. Since extensive bowel-cleansing regimens are associated with lower patient satisfaction,⁵ this may be another pitfall of the capsule.

Colon capsule endoscopy has not yet been cleared for sale in the United States, but it is actively marketed in Europe. The current price for a capsule is approximately €950 (\$1,150), which is not lower than the price of colonoscopy or CT colonography.⁶ With the capsule's relatively low sensitivity for the detection of colorectal lesions, its requirement for more extensive bowel-cleansing regimens as compared with colonoscopy and CT colonography, and its high cost, colon capsule endoscopy cannot be recommended at this time.

Detection rates for polyps and cancer, as investigated in the present study, are only surrogate markers for the ultimate primary end point —

the ability of screening methods to reduce the incidence of the disease and the associated mortality rate. This is the crux of the matter in any approach to cancer screening.

Colorectal-cancer screening by means of colonoscopy is actively promoted for persons older than 50 years of age in the United States and in an increasing number of other countries. Current U.S. guidelines state that colonoscopy has a significant effect on the incidence of colorectal cancer and the mortality rates associated with this cancer.² However, randomized trials studying the effect of colonoscopy on the incidence of or the mortality due to colorectal cancer have not been conducted. Recommended guidelines are based on statistical prediction models and case-control studies. Recent estimates suggest that colonoscopy has a lower effect on mortality associated with colorectal cancer than previously thought,⁷ and researchers have warned that overly optimistic claims about its benefits have been used to sell colonoscopy to the general public.⁸

Before recommending screening to presumably healthy persons, one should have evidence from randomized trials showing that the screening tool reduces the incidence of or mortality associated with the target disease. Randomized trials have been a long-standing requirement for the introduction of new drugs to the market. It is difficult to understand why the standard of evidence should be lower for diagnostic tools or screening tests.⁹

The enthusiastic promotion of methods of colorectal-cancer screening that have not been tested in randomized trials should be replaced by critical appraisal of the evidence for colorectal-cancer screening and its potential pitfalls. The target population should be informed that current recommendations are mainly based on theoretical assumptions and studies with suboptimal design, and that the magnitude of benefit of screening is unclear. Many persons will still participate in screening programs but with a better understanding of the potential benefits and harms.

The colorectal-cancer screening community should learn from other areas of cancer screening. Prostate-cancer screening by prostate-specific antigen-based testing, although strongly advocated by physicians and broadly adopted by the

public, has recently been shown to provide only a marginal effect, if any, on prostate-cancer mortality.^{10,11} Colonoscopy, CT colonography, and colon capsule endoscopy should be tested in randomized, comparative trials that allow valid and precise quantification of their effect on colorectal-cancer incidence and mortality. This may be easily done within the framework of already established colorectal-cancer screening programs by introducing new techniques such as colon capsule endoscopy to the programs in a randomized way.

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