Colonic Capsule as a Screening Test for Colorectal Cancer: We are Improving

INTRODUCTION

Colorectal cancer (CRC) is a major health concern with an incidence of 1.2 million new cases per year and a mortality rate close to 600,000 yearly. At the same time, CRC is one of the most preventable and curable malignancies if diagnosed at an early stage. Consequently, CRC screening programs were established in more than 50 countries. Despite participation rates in these programs being below the set targets, CRC incidence and mortality rates are declining. Colorectal cancer screening in the United States increased significantly from 2000 to 2010 and was essentially unchanged in 2013. Over the same period, the incidence of and deaths from colon cancer have decreased and these are attributed to improvements in screening for CRC, improved treatment strategies and changing patterns in risk factors. Specifically, CRC death rates declined by 2% per year during the 1990s and approximately 3% each year during the past decade (2001–2010) with the most impact in adults aged 65 and older. In Europe, CRC screening programs have been implemented in 19 of 27 European Union (EU) countries with participation rates nearing 60%. CRC mortality has fallen in an increasing number of European countries since 1970, despite persistent differences between specific regions in Europe. The
largest reductions in CRC mortality have occurred in western and northern European countries because of increased screening participation and improved access to specialized care. In most central European countries, CRC mortality has been stable or slightly decreasing since the early 2000s, but is still increasing in most eastern European countries. These epidemiological findings infer that participation in a CRC screening program will culminate in an improved health outcome.

**CRC Screening Tests**

The American College of Gastroenterology (ACG) has classified colorectal cancer screening tests as either CRC prevention tests or CRC detection tests. Tests that are labeled as prevention are “imaging tests” given their potential to identify both cancer and polyps. These tests either enable visual assessment of the structural integrity of the colon and rectum (e.g., flexible sigmoidoscopy, colonoscopy and capsule colonoscopy) or are non-invasive tests that are able to obtain two-and/or three-dimensional (3D) images of the colon and its mucosa (e.g., computed tomography (CT) colonography and a double-contrast barium enema). On the other hand, detection tests are “indirect tests” that probe the stool for the presence of markers of CRC (e.g., fecal occult blood test (FOBT), fecal immunochemical test (FIT) and the fecal DNA test). While non-invasive, these tests have low sensitivity for detecting polyps. Colonoscopy is the standard of care for evaluating the colon, either as a primary test or as a follow up to an abnormal imaging modality or positive stool testing.

The ACG also recommends that a CRC prevention test, preferably a colonoscopy, be first offered to patients with family history of CRC. Hence, colonoscopy has become an invaluable component of most national screening programs. While the entirety of the colon can be evaluated during colonoscopy and abnormal tissue(s) can be sampled or removed during the procedure, the procedure has disadvantages that may limit its use. Some of these considerations include the need for thorough colonic cleansing, sedation and the potential need to stop taking certain medications (especially anticoagulants) as well as the rare but potentially life-threatening complications of bleeding and perforation. Additionally, colonoscopy is avoided by patients as the procedure elicits feelings of fear, embarrassment, loss of dignity or vulnerability, absence from work, lack of awareness on the importance of screening, transportation difficulties, obstacles with scheduling of appointments and financial cost.

**Colonoscopy with Colon-Capsule**

In an effort to improve acceptability and safety of lower-GI endoscopy, colonoscopy with colon-capsule (CCE, PillCam Colon, Given Imaging Ltd., Yoqneam, Israel) is an endoscopic technique developed for a non-invasive, painless exploration of the colon without the need of sedation and injection of air. Initial studies comparing CCE with colonoscopy (traditional and virtual) performed in Israel and Belgium show that CCE allows direct visualization of the mucosa (such as traditional examination), does not use radiation (such as virtual colonoscopy) and does not cause pain, eliminating the need for sedation.

**Technology**

The new generation of CCE (CCE-2) represents a technological evolution of the previous capsule. It measures 11.6 x 31.5 mm. It is equipped with two optical domes with a viewing angle of 172° (the previous version had an angle of 156°), two light sources (one for each optical dome), an antenna that transmits images to an external recorder and a battery (10 hour battery life). In addition, CCE-2 owns an advanced system of acquisition and transmission of images. It is in continuous two-way communication with the external data recorder, which is no longer a single recorder of images, but an actual computer. The data recorder receives images from CCE-2, and it processes them to “understand” if the capsule is at rest or in motion and sends signals to the capsule, establishing the speed of acquisition of the images. When the CCE-2 is immobile, it acquires four images per second, however, when it is in motion it acquires 35 images per second. The data recorder also assists and guides the patient during the stages of bowel preparation indicating through a sound system and a display how to proceed with the intake of drugs and when the procedure is finished. Unique to this procedure, aside from picking up the CCE-2 from the hospital, the remainder of the testing is performed at home.

**Preparation for the Procedure**

Bowel preparation for CCE includes the use of laxatives and drugs to activate intestinal peristalsis in order to achieve three objectives: 1) to ensure an adequate level of cleaning, 2) to stimulate the motility for CCE
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progression and 3) to fill the colon of transparent liquids to adequately distend the bowel. CCE is not able to insufflate air to distend the bowel, or to aspirate any residues, which therefore need to be completely removed through a dedicated preparation. The use of drugs stimulating colon motility (usually sodium phosphate or sodium sulfate, more recently) is necessary given minimal colonic peristaltic movements throughout the day. The excretion rate of CCE (about 20%) was too low with the use of traditional colonoscopy preparations. Sodium phosphate (NaP) and sodium sulfate result in a strong activation of peristalsis responsible for the CCE progression and excretion, which occurs in 90% of cases within 10 hours of ingestion. Two recent studies with the new generation capsule assess a novel bowel preparation involving the use of a split regimen with 4 liters of PEG and a reduced dose of NaP. Adequate cleaning has been achieved in 78-81% of patients and CCE excretion (which corresponds to complete colonoscopy) in 81-88% with this preparation. This new preparation is more tolerable for the patient thus increasing compliance, reduces the NaP which decrease the risk of adverse events and the rate of colon cleansing and excretion of the capsule are encouraging. The Aronchick colon cleansing rating scale is generally

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utilized to assess the prep (poor, fair, good and excellent) with good inter-observer agreement (kappa = 0.619). Although the four-level system has been widely adopted in research, a recent guideline suggests the use of a simplified two-levels scale for clinical activity.

Accuracy of the Capsule
Most of the studies published in the literature center around data obtained with the first generation of CCE. A meta-analysis with the first generation of CCE summarized the preliminary experience. Eight studies with a total 837 patients showed a 71% CCE-sensitivity for polyps of any size and a 68% sensitivity for significant lesions (>6 mm polyps or ≥3 polyps). The specificity for polyps of any size and for significant lesions was 75% and 82%, respectively. Finally, CCE identified 16 of 21 cancerous lesions, showing a sensitivity of 76%.

The second generation of CCE was evaluated in an Israeli multicenter study and a European multicenter study. Both studies were blinded and compared CCE to conventional colonoscopy with a standardized, split-dose bowel preparation (PEG 2L the day prior to the procedure and 2L the morning of the procedure with a reduced dose of NaP). The prevalence of polyps of any size (in 104 patients, mean age 49.8 years) was 44%, 53% of which were adenomas. (16) CCE sensitivity for polyps ≥6 mm was 89% (95% CI 70%-97%) and 88% (95% CI 56-98) for polyps ≥ 10 mm; specificity was 76% (95% CI 72-78) and 89% (95% CI 86-90), respectively. An adequate level of cleansing was observed in 78% of patients (95% CI 68-86) and CCE colonoscopy was complete (natural excretion of video capsule) within eight hours in 81% of patients.

In the European multicenter study (20), 109 patients were enrolled (mean age 60 years). The sensitivity (“per patient”) of CCE for polyps ≥ 6 mm and ≥ 10 mm was 84% and 88%, with a specificity of 64% and 95%, respectively. All three invasive adenocarcinomas were detected by the capsule. The rate of excretion of

Figure 5. Case Study 1: Images of polyps from the capsule compared to colonoscopy.
5A., 5B. Colonoscopy appearance of 20 mm pedunculated polyp in sigmoid colon.
5C., 5D. Imaging capsule appearance. Tube type and fillet type 3D construction.
the capsule was 88%. Adequate cleansing of the colon was observed in 81% of patients.

Despite only two published studies, some general observations can be made. First, the second-generation capsule has shown a much higher sensitivity for significant lesions compared to the first generation. Secondly, for polyps ≥ 6 mm, the specificity is still sub-optimal. The low specificity is partly due to true polyps ≥ 6 mm that were regarded as false positive because they were missed by colonoscopy, the golden standard in this trial.²⁴,²⁵ Next, the preparation of the new scheme show encouraging results both in terms of quality of cleansing and in terms of completeness of the examination. Finally, CCE is a safe technique without any report of serious adverse events.¹⁶,²⁰

Check Cap Capsule
The diagnostic accuracy of colonoscopy is very dependent on the quality of the colonic cleansing.²⁶,²⁷ Inadequate colonic cleansing results in cancellation or rescheduling of the procedure, lessens the procedure’s diagnostic accuracy and discriminative ability, lowers the cecal intubation rates and increases the patient’s discomfort and inconvenience.

The Check Cap Ingestible Imaging Capsule
The Check Cap ingestible imaging capsule (Check Cap, Mount Carmel, Israel), is comprised of a mobile imaging capsule (34 mm x 11.5 mm, 13 grams), which is ingested together with a radiopaque contrast agent by the patient, and a stationary external recorder, which is located in a dermal patch on the patient’s back (Figure 1). The imaging capsule contains three miniaturized systems, an X-ray emitting system, a data acquisition system and a local positioning system (Figure 2).

X-rays from a short-lived radioisotope, housed within a rotating collimator whose rotation is powered by a battery-driven electric motor, are emitted in all directions when the capsule’s position changes. The

Figure 6. Case Study 2: Images of polyps from the capsule compared to colonoscopy.
6A. Colonoscopy appearance of 12 mm sessile polyp in ascending colon.
6B.,6C. Imaging capsule appearance. Tube type and fillet type 3D construction.
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Data acquisition system contains sensors, which can discriminate X-ray fluorescence from ingested radiopaque contrast agent and scattering from the intestinal mucosa. The positioning system uses electromagnetic signals, which are emitted by the capsule and tracked by the dermal patch. Imaging data and position signals are continuously transmitted by telemetry to the external recording unit (Figure 3). The recorder’s data are then uploaded and processed by computer to construct 3D images of the colon’s lumen, structure, and contour.

Human Studies on the Safety and Clinical Utility of the Device

The device’s safety and potential utility were assessed in Germany and Israel at several medical centers. In the first section, 75 healthy volunteers aged 41–70 years swallowed dummy capsules. All capsules were retrieved and were undamaged upon inspected. In the second part, 49 capsules were swallowed by 46 volunteers aged 45–68 years (three patients swallowed the capsule on two different occasions). During this study, a lightweight external recording unit was strapped to the waist of each participant while normal daily routine was maintained. After ingesting the capsule, each participant drank 50–70 ml of an iodine-based contrast agent daily until the capsule was eliminated. Forty-eight of the 49 capsules were ingested, transited the gastrointestinal tract and were naturally eliminated without any adverse effects. The missing capsule was retrieved from the cecum of an asymptomatic patient during a scheduled colonoscopy for a planned polypectomy. The average radiation dose to each volunteer was 0.03±0.0007 mSv, which is less than the amount of radiation exposure from one chest X-ray. (Figure 4) The 3D images revealed the typical structure and contour of the different colonic segments, such as the hepatic flexure and the triangular shape of the transverse colon. Polyps in several patients were detected by the device and their presence was later validated by colonoscopy. (Figures 5,6)

Beebe and his colleagues investigated whether removal of a laxative preparation would improve CRC screening rates using data that were collected from a mixed-mode and telephone survey. They reported that removing this relatively common disincentive to CRC screening participation can potentially increase patient receptivity to CT colonography. As such, the Check Cap Capsule system could be an alternative method of CRC testing. This imaging system is a safe, easy-to-use, patient-friendly, painless, and private medical device with high diagnostic accuracy discriminating patients with disease from those without disease without the need for a bowel preparation. Another advantage of the system is that the dose of ionizing radiation to the patient is lower not only than that of CT colonography but also less than chest X-ray. (Figure 4) Additionally, use of this concealed imaging system eliminates the need to schedule an appointment at a health facility, be absent from work and enables the patient to continue their daily routine without the negative emotional and physical feelings which may be experienced during colonoscopy. For all of these reasons, this innovative imaging system could potentially increase participation rates in a local and/or national CRC screening program. Many features of image reconstruction and measurement of polyp size and colon diameter still need refinement and validation. To resolve these issues, modifications to the imaging capsule are on going and international, randomized, multicenter studies are planned for the end of 2016.

CONCLUSION

While colonoscopy is currently the most utilized and accepted form of colorectal cancer screening, technology has allowed inroads to developing new testing that may improve patient care. Colonic capsules are safe novel systems that are easy-to-use, painless, patient-friendly and private. These devices should significantly increase participation rates in a CRC screening programs.

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References


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