Clinical Roundtable Monograph

Gastroenterology & Hepatology September 2017

Polyp Resection and Removal Procedures: Insights From the 2017 Digestive Disease Week

Faculty

Carol Burke, MD, FACG, AGAF, FASGE, FACP
Vice Chair, Department of Gastroenterology and Hepatology
Director of the Center for Colon Polyp and Cancer Prevention
Cleveland Clinic
Cleveland, Ohio

Vivek Kaul, MD, FACG, FASGE, AGAF
Segal-Watson Professor of Medicine
Chief, Division of Gastroenterology & Hepatology
Center for Advanced Therapeutic Endoscopy
University of Rochester Medical Center
Rochester, New York

Heiko Pohl, MD
Associate Professor of Medicine
Geisel School of Medicine at Dartmouth
Hanover, New Hampshire
Department of Gastroenterology, Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Department of Gastroenterology, VA Medical Center
White River Junction, Vermont

Abstract: Colorectal cancer (CRC) is an important public health issue not only because of its high incidence but also for its high mortality rate. When CRC is diagnosed at an early stage, the 5-year relative survival rate reaches 89.9%. However, only 39% of patients with CRC are diagnosed at this stage. Screening decreases both the incidence of CRC and the number of CRC-related deaths. There are several options available for screening, and colonoscopy is one of the most common methods utilized in the United States. Screening colonoscopy is associated with durable protection from CRC. However, it has become increasingly apparent in recent years that polyp detection and resection have not been completely effective in clinical practice. Because the protective benefit of colonoscopy is variable, quality benchmarks have been established to improve its clinical effectiveness. The adenoma detection rate (ADR) directly correlates with the incidence and mortality of postcolonoscopy (or interval) CRCs. It is now routine to remove large polyps (≥20 mm) using advanced techniques for endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Recent studies have helped identify which colorectal lesions are at higher risk of invasive cancer and would benefit from a complete en bloc resection. Such data may guide endoscopists in making a decision on whether to use ESD or EMR for removal of large lesions. An increased number of studies have reported on the efficacy and safety of cold snare resection, even for larger polyps. These data suggest that cold snare resection may be as effective, and perhaps safer, than hot snare resection for polyps up to 1 to 2 cm in size. However, data on the threshold for cold snare resection and the value of submucosal injectates are still lacking. Use of submucosal injection is generally preferred for larger polyps, particularly those located in the proximal colon, where the colonic wall is thinner.

Supported through funding from Aries Pharmaceuticals Inc.

Evolving Strategies for the Prevention of Colorectal Cancer

Carol Burke, MD, FACG, AGAF, FASGE, FACP

Vice Chair, Department of Gastroenterology and Hepatology
Director of the Center for Colon Polyp and Cancer Prevention
Cleveland Clinic
Cleveland, Ohio

In 2017, an estimated 135,430 new cases of colorectal cancer (CRC) will be diagnosed in the United States, making it the third most frequently diagnosed cancer in both men and women.[1,2] The lifetime risk for developing CRC in the United States is slightly higher in men (4.6%) than women (4.2%),[1,2] and it increases with age. The median age of diagnosis is higher for colon cancer than rectal cancer, at 69 years in men and 73 years in women vs 63 years in men and 65 years in women.[3] Rates of CRC vary according to race and ethnicity. The age-adjusted incidence of CRC is highest in African American men (56.4 per 100,000) and women (43.2 per 100,000) compared with all other ethnic groups.[1]

CRC is an important public health issue not only because of its high incidence but also for its high mortality rate. It is the second-leading cause of cancer-related deaths in men and the third in women.[1] An estimated 50,260 deaths will be attributed to CRC in the United States in 2017.[2] The overall 5-year relative survival rate for patients with CRC is 64.9%. This rate is dependent upon many factors, one of the most important being stage at diagnosis. When CRC is diagnosed at a localized stage (confined to the colon or rectum), the 5-year relative survival rate reaches 89.9%. However, only 39% of all patients with CRC are diagnosed at a curable stage, and most are diagnosed after CRC has spread to regional lymph nodes (35%) or metastasized to distant organs (21%), when it is associated with a 5-year survival of 13.9%. Just as African Americans have the highest incidence of CRC, they also have the highest stage-adjusted morality rate compared with other races.

Certain lifestyle factors increase the risk of colorectal polyps and CRC. They include obesity, excess alcohol intake, physical inactivity, a diet high in processed foods and low in dairy and plant-based materials, and smoking.[1] Chronic colonic inflammation, as occurs with ulcerative colitis and Crohn's disease, is another important risk factor that can stimulate colorectal neoplasia. An increased risk of CRC has been linked to a personal or family history of colorectal polyps or CRC; the inherited CRC syndromes, such as hereditary nonpolyposis CRC and its subtypes, Lynch syndrome and familial CRC type X; and the most common adenomatous polyposis syndromes, including familial adenomatous polyposis and *MYH*-associated polyposis.

There has been a substantial decrease in the overall incidence of CRC since the 1980s, primarily owing to the use of CRC screening and the detection and removal of precancerous polyps. Incidence rates have declined a minimum of 1% per year among men and women of every major racial/ethnic group, except for American Indian/Alaskan Native men (among whom the rates were relatively stable).[4] A concerning epidemiologic observation, however, is a marked increase in the annual

Indexed through the National Library of Medicine (PubMed/Medline), PubMed Central (PMC), and EMBASE

Disclaimer

Funding for this monograph has been provided by Aries Pharmaceuticals Inc. Support of this monograph does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Gastro-Hep Communications, Inc., the supporter, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

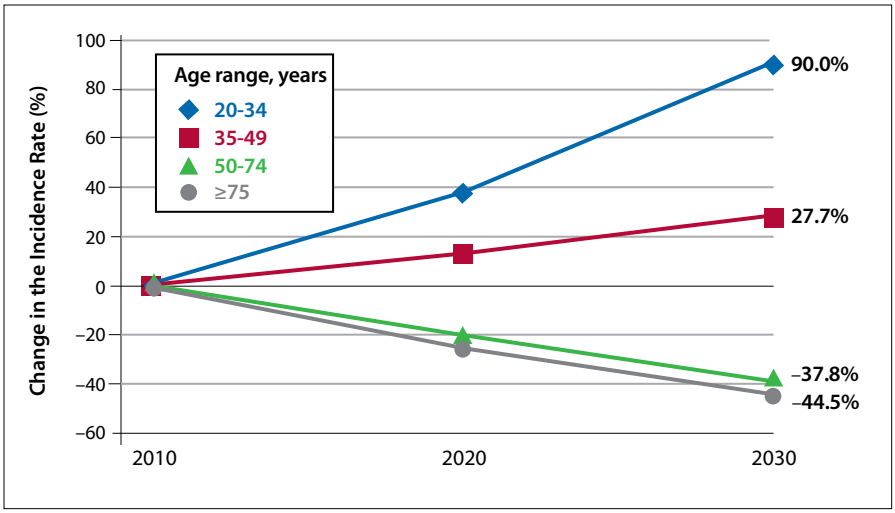

Figure 1. Anticipated changes in the incidence rates of colorectal cancer. Adapted from Bailey CE et al. *JAMA Surg*. 2015;150(1):17-22.[6]

percentage change in the rates of CRC among young adults. In a study reported in 2017 by Siegel and colleagues, the incidence of colon cancer increased by 1.0% to 2.4% annually since the mid-1980s among adults ages 20 to 39 years, and by 0.5% to 1.3% since the mid-1990s among adults ages 40 to 54 years.[5] The incidence of rectal cancer increased even more dramatically—by 3.2% annually from 1974 to 2013—among adults ages 20 to 29 years.[6] Based on the current trends, it is estimated that in 2030, the incidence rate for colon and rectal cancer will increase by 90.0% and 124.2%, respectively, for patients ages 20 to 34 years and by 27.7% and 46.0% for patients ages 35 to 49 years (Figure 1).[6] The rise in CRC incidence seen since the mid-1990s in adults younger than 55 years is confined to white men and women. A recent report demonstrated that CRC mortality parallels the increased incidence, but, again, only in white men and women. After decades of decline, rates have increased since 1995 at an annual incidence of 1.6% in those ages 30 to 39 years and of 1.9% in those ages 40 to 49 years. Since 2005, the rate has increased by 0.9% in those ages 50 to 54 years.[7]

Even with this rise in incidence, the frequency of CRC among individuals younger than 50 years is relatively rare, at less than 10,000 cases in the United States, representing a small proportion overall of CRC. Most experts have no conclusive explanation for the increase of CRC among younger white individuals. It may relate to a lifestyle of physical inactivity and poor diet. It is also possible that the growing obesity epidemic may play a role, as might some other unidentified environmental exposures.

Progression to CRC

CRC is believed to arise from a polyp precursor through a genetic pathway that may be identifiable through CRC screening. Conventional adenomas are the most common CRC precursor, but up to 30% of CRC cases are thought to emanate from a sessile serrated polyp. The progression from conventional adenomas and sessile serrated polyps to CRC is thought to occur primarily through 1 of 2 pathways: the chromosomal instability (CIN) pathway or the CpG island methylator phenotype (CIMP) pathway, resulting in microsatellite instability. The CIN pathway is typified by somatic mutations occurring in both tumor suppressors (such as *APC* and *TP53*) and oncogenes (such as *KRAS*, *PI3KCA*, and *NRAS*).[8]

Alternatively, in the non–Lynch syndrome microsatellite instability pathway, CRC develops from hypermethylation of CpG islands in the promoter region of genes, particularly *MLH1*, which leads to high microsatellite instability and is associated with the *BRAF* mutation v600E, resulting in a serrated neoplasia-carcinoma pathway.[8,9]

Impact of CRC Screening

In the United States, the mortality rate from CRC has dropped precipitously, showing a 51% decrease from 1976 to 2014.[10] The incidence of CRC has also declined by approximately 32% in adults ages 50 years or older. Among the multiple factors that may have contributed to these reductions, the most important is a large increase in rates of CRC screening and removal of detected polyps.

The rising incidence of CRC in younger white adults (<50 years) has prompted debate on who should be screened. As of now, it is premature, and likely not cost-effective, to extend screening to white individuals between the ages of 20 to 49 years. Instead, the important point for practitioners is that symptoms suggestive of CRC should not be summarily dismissed in younger adults. Diagnostic evaluation of the colon with colonoscopy should be

considered in all adults—particularly white individuals younger than 50 years—who present with rectal bleeding, an unexplained change in bowel habits, abdominal pain, or unanticipated weight loss.

Strong evidence demonstrates that screening decreases the incidence of both CRC and CRC-related deaths. However, in 2015, more than 1 in 3 eligible Americans were not adherent to screening recommendations for CRC.[1] The percentage of American adults who were up-to-date with CRC screening recommendations increased from just 54% in 2002 to 63% in 2015.[1] This screening rate has increased only approximately 1.5% in the last decade.

The National Colorectal Cancer Roundtable (NCCRT) was established in 1997 with the main objective of reducing the incidence and mortality of CRC in the United States. The goal of this national coalition is to have 80% of the eligible American population screened for CRC by 2018. The impact of reaching this goal would be the prevention of 277,000 cases of CRC and 203,000 CRC deaths by 2030.[11]

In a discussion at the 2017 Digestive Disease Week (DDW), Pochapin provided several steps that gastroenterologists can take to help achieve the important goal of an 80% CRC screening rate by 2018.[12] One step is for gastroenterologists and institutions to formally pledge to work toward this goal; an online pledge form can be found on the NCCRT website.[13] Additionally, gastroenterologists should become familiar with the panoply of CRC screening methods and remember to recommend screening to their patients. One of the greatest cited barriers to CRC screening is that the patient never received the recommendation from his or her health care provider.[14] Similarly, gastroenterologists should remind their patients when they are due for follow-up screening. Gastroenterologists should partner with primary care providers, hospitals, local community health clinics, and the media to champion the message of CRC screening in the community. Healthcare providers should understand the quality standards for CRC screening programs, including colonoscopy as a screening strategy. In the United States, an important asset for gastroenterologists is the GI Quality Improvement Consortium (GIQuIC), a clinical data registry qualified by the Centers for Medicare & Medicaid Services. The consortium is a collaboration between the American College of Gastroenterology (ACG) and the American Society of Gastrointestinal Endoscopy. The registry allows physicians to report and benchmark their quality metrics in endoscopic procedures and compare them with other participants. It has been shown that the use of public reporting, such as with physician report cards assessing the quality of colonoscopies, has improved the adenoma detection rate (ADR).[15,16]

Methods for CRC Screening

There are now several options available for CRC screening, such as colonoscopy, the fecal occult blood test, multitarget stool DNA test, virtual colonoscopy, and sigmoidoscopy, to name a few. With the plethora of CRC screening modalities, patients and clinicians may wonder which testing strategy is the best. According to the adage, the best test is the one that gets done, and is done well. It is, of course, not that simple. Several cultural and social factors impact a patient's CRC screening method preference. To ease discussion, health care providers may frame the conversation with their patients by dividing screening tests into 2 categories: those that prevent cancer based on a high sensitivity to detect CRC precursors and remove them vs those that merely detect cancer with less accuracy for polyp detection. Providers should also consider whether the environment of patient care is best suited for a programmatic vs opportunistic approach to CRC screening. An opportunistic approach would be to offer a future colonoscopy or fecal immunochemical testing if colonoscopy is refused at the time of an office visit. Alternatively, patients can be enrolled in programs that provide a system for CRC screening over time, with navigation and support to enhance the quality of the program. This programmatic approach is often followed in health care settings such as those administered by the US Department of Veterans Affairs (VA) or Kaiser Permanente. In any case, encouraging patients to undergo CRC screening should include a discussion of any concerns or barriers the patient may have, and should address the costs, risks, and benefits of each approach, as well as the implications and required follow-up for a positive noncolonoscopy test.

Physicians should inform eligible patients that CRC screening is an insurance benefit mandated by legislation. However, a colonoscopy performed for follow-up of an abnormal screening test becomes a diagnostic procedure—and no longer a screening procedure—which has implications for copays and coinsurance. Patients are often surprised to learn that a diagnostic colonoscopy performed as follow-up for a positive screening test is not considered a preventive healthcare benefit.

CRC Screening Guideline Recommendations

In 2016, the United States Preventive Services Task Force (USPSTF) published updated recommendations regarding CRC screening in adults.[17] For individuals who are asymptomatic and at average risk for the development of CRC, it is recommended that screening for CRC begin at age 50 years and continue until age 75 years (grade A recommendation). For people ages 76 to 85 years, the USPSTF recommended that the decision to screen should be individualized, taking into account

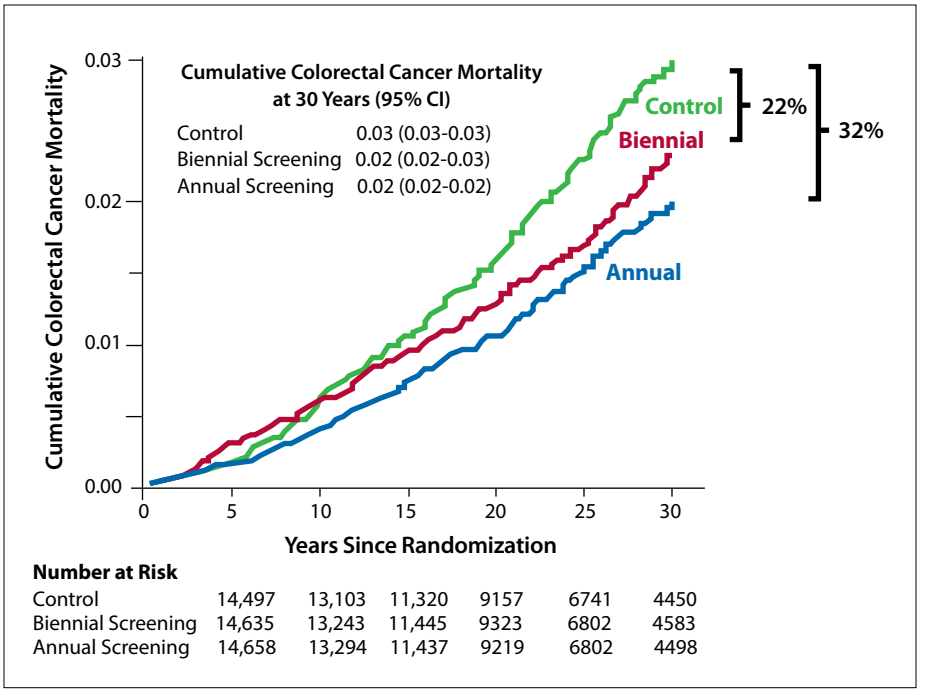

Figure 2. Rates of colorectal cancer mortality in a study of 46,551 participants randomly assigned to usual care or guaiac-based fecal occult blood testing on an annual or biennial schedule. Adapted from Shaukat A et al. *N Engl J Med.* 2013;369(12):1106-1114.[24]

the patient's overall health and prior screening history (grade C recommendation). The task force made the additional point that among these older individuals, those who have never undergone CRC screening are the most likely to benefit from screening. Additionally, in older adults, screening is most appropriate among those without significant comorbid conditions and those who are healthy enough to undergo treatment if CRC is detected.

The frequency of CRC screening depends on the screening strategy chosen. In a divergence from previous versions of the USPSTF guidelines, the 2016 update does not strongly endorse one type of screening test over another. The new guidelines acknowledge that there are currently no head-to-head clinical studies showing that one strategy is more effective than another.[17] The guideline recognizes that each screening strategy has differing levels of evidence, as well as unique advantages and disadvantages.

In their 2009 CRC screening guidelines, the ACG recommended that African Americans begin screening at age 45.[18] The rationale is based on the higher incidence, earlier age at onset, worse survival, and late-stage presentation seen in African Americans compared with other ethnicities.[19-22] For the first time, the latest Multi-Society Task Force (MSTF) on CRC guidelines, published in June 2017, also recommended that screening begin at age 45 in African Americans.[19-22]

The cornerstones of CRC screening in the United States include colonoscopy administered every 10 years or stool occult blood testing administered annually. They are considered tier 1 tests by the MSTF. Fecal immunochemical testing (FIT) has largely supplanted guaiac-based fecal occult blood testing (gFOBT). A less frequently utilized endoscopic screening method is flexible sigmoidoscopy every 5 to 10 years.[9,17,18] The USPSTF suggests that the frequency of flexible sigmoidoscopy be decreased from 5 years to every 10 years, with the addition of annual FITs. The MSTF prefers an interval of 10 years rather than 5 years. All guidelines suggest that if computed tomography colonography (CTC) is chosen, it should be repeated at a frequency of every 5 years.

The optimal interval for the use of the multitarget FIT-DNA stool test has not been determined. The guidelines vary, recommending every 1 year or every 3 years. Capsule colonoscopy every 5 years is endorsed by the MSTF as a tier 3 recommendation.

Data Supporting Stool-Based Testing

In randomized controlled trials throughout the world, gFOBT has reduced CRC-related mortality.[23] gFOBT was evaluated in the Minnesota Colon Cancer Control Study of 46,551 participants who were randomly assigned to either usual care or gFOBT on an annual or biennial schedule.[24] After 30 years of follow-up, participants in the annual screening cohort demonstrated a 32% reduction in CRC-related mortality (relative risk [RR], 0.68; 95% CI, 0.56-0.82; Figure 2). The reduction was 22% with biennial screening (RR, 0.78; 95% CI, 0.65-0.93). However, gFOBT screening was not found to impact all-cause mortality.

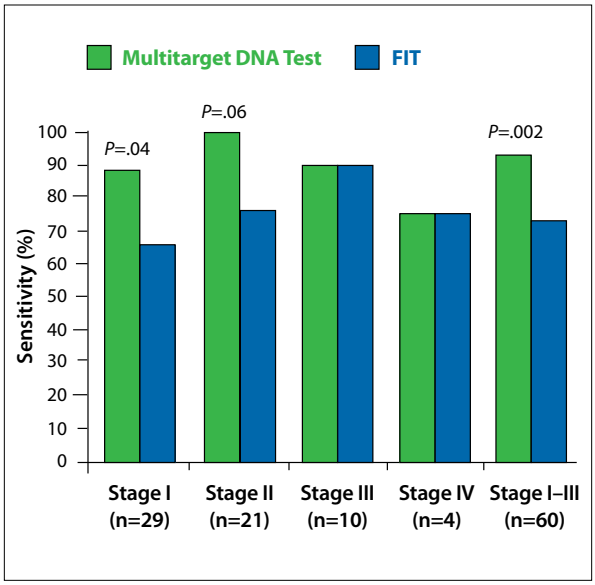

Figure 3. Sensitivity for detection of lesions in a study comparing a multitarget DNA stool test with FIT. FIT, fecal immunochemical testing. Adapted from Imperiale TF et al. *N Engl J Med*. 2014;370(14):1287-1297.[27]

The gFOBT uses an enzymatic reaction in hemoglobin to detect blood in the stool. Therefore, it identifies the presence of blood indirectly. The gFOBT requires 3 spontaneously passed stools, as well as diet and medication restrictions. Test characteristics showed that the specificity for CRC reached 98%, but the sensitivity ranged from 31% to 64%.[25] FIT uses an antibody to directly detect human globin in the stool. This test requires only 1 stool sample, and it does not place restrictions on diet or medication. Data generally demonstrate that the specificity for CRC is slightly greater with gFOBT than FIT (98% vs 96%), but the sensitivity of gFOBT has been shown to be at least 20% lower than FIT.[25,26] Additionally, FIT has a higher accuracy for the detection of advanced adenomas and is associated with greater adherence to screening.[25] It is important to note that FIT detects only lower gastrointestinal bleeding because hemoglobin degrades when it passes through the upper gastrointestinal tract.

The multitarget stool DNA test takes advantage of the use of FIT for the detection of fecal occult blood in combination with molecular markers such as the *KRAS* mutation and the methylation markers *BMP3* and *NDRG4*. A large study compared screening with a multitarget stool DNA test vs FIT.[27] The multitarget stool DNA test showed a 92.3% sensitivity for CRC, with a specificity of 89.8%. For FIT, sensitivity and specificity were 73.8% and 96.4%, respectively. Multitarget stool DNA tests were better for the detection of earlier-stage cancers and demonstrated a 42% sensitivity for the detection of advanced neoplasia vs 24% with FIT (P<.001; Figure 3). These lesions included high-grade dysplasia and sessile serrated polyps larger than 1 cm.

Some physicians may be concerned that a positive multitarget stool DNA test followed by a negative high-quality colonoscopy warrants investigation into other areas of the gastrointestinal tract. This issue is being examined in the LONG-HAUL study, which was presented at the 2016 DDW.[28] The abstract reported data from 37 patients whose multitarget stool DNA test was positive and who had a negative follow-up colonoscopy. Over a duration of follow-up ranging from 3 to 5 years, none of these individuals developed CRC or aerodigestive cancer. Although this trial evaluated a small cohort with a short follow-up time, the data are nonetheless reassuring. It is not recommended that patients with a positive multitarget stool DNA test followed by a negative high-quality colonoscopy undergo additional testing to determine a cause for the positive multitarget test.

The MSTF guidelines suggest that FIT is superior to gFOBT, citing that FIT is associated with enhanced patient adherence to screening and improved detection of advanced neoplasms vs gFOBT.[29] The MSTF issued detailed recommendations on the technical performance and quality of FIT screening programs.[29] The task force also found evidence that colonoscopy was superior to onetime FIT for the detection of advanced neoplasia.

When FIT is used in the context of programmatic screening, the MSTF suggests several quality metrics for FIT-based testing programs.[29] The FIT completion rate should be 60% or more, the testing laboratory should be able to process more than 95% of the FIT tests, and the colonoscopy completion rate should be higher than 80% in individuals with a positive FIT result. In cases of a positive FIT result (using a hemoglobin threshold of 20 µg/g of stool), the ADR should be greater than 45% in men and greater than 35% in women. Importantly, none of the large programs currently offering FIT in a programmatic fashion have met these benchmarks.

Interim results published from a randomized, controlled trial provide some indication of how FIT compares with colonoscopy.[30] These results demonstrated that compared with biennial FIT, onetime colonoscopy had a higher detection of advanced adenomas (odds ratio [OR], 2.30; 95% CI, 1.97-2.69; P<.001), nonadvanced adenomas (OR, 9.80; 95% CI, 8.10-11.85; P<.001), advanced neoplasia (OR, 2.14; 95% CI, 1.85-2.49; P<.001), and any neoplasia (OR, 4.67; 95% CI, 4.17-5.24; P<.001). However, the rates of cancer detection between FIT and colonoscopy were not substantially different (OR, 0.99; 95% CI, 0.61-1.64; P=.99). Notably, the participation rate was significantly higher in the FIT group than in the colonoscopy group (34.2% vs 24.6%, respectively; P<.001). The follow-up results of this study

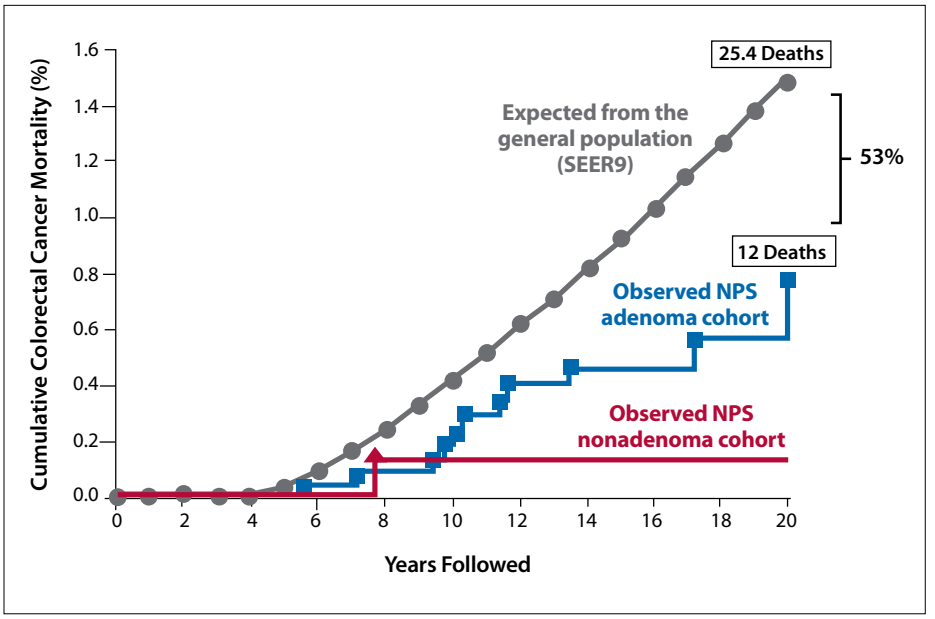

Figure 4. Long-term follow-up of patients in the NPS showed a 53% reduction in mortality among those who underwent colonoscopy and had polyps removed. NPS, National Polyp Study; SEER, Surveillance, Epidemiology, and End Results. Adapted from Zauber AG et al. *N Engl J Med.* 2012;366(8):687-696.[36]

are eagerly awaited to more confidently compare biennial FIT with onetime colonoscopy.

Data Supporting Direct Visualization of the Mucosa

Screening colonoscopy has been shown to be very effective, and it is associated with durable protection from CRC. Despite a lack of completed randomized trials evaluating screening colonoscopy, multiple cohort and case-control studies have demonstrated the efficacy of screening colonoscopy for decreasing CRC incidence and preventing CRC-related mortality.[31-37] The durability of protection of a negative screening colonoscopy has been noted to last up to 10 years.[38,39] In long-term follow-up (up to 23 years) of patients in the National Polyp Study, there was a 53% reduction in mortality among individuals who underwent colonoscopy and had polyps removed (hazard ratio [HR], 0.47; 95% CI, 0.26-0.80; Figure 4).[36] The protective benefit of colonoscopy in decreasing CRC incidence and mortality is more robust in the distal colon (decreasing by approximately 80%) compared with the proximal colon (decreasing by 40% to 60%).[31,32,40-42]

The evidence supporting the role of flexible sigmoidoscopy in CRC screening was bolstered by numerous randomized, controlled trials that demonstrated a decrease in CRC incidence and mortality. A randomized, controlled study that included 14 centers in the United Kingdom assigned people to undergo a onetime flexible sigmoidoscopy (n=57,099) or no procedure (n=112,939). With flexible sigmoidoscopy, the incidence of CRC was reduced by 23% (HR, 0.77; 95% CI, 0.70-0.84) and the mortality from CRC was decreased by 31% (HR, 0.69; 95% CI, 0.59-0.82).[43] In the United States, a screening trial randomly assigned 77,445 participants to undergo flexible sigmoidoscopy every 3 to 5 years vs usual practice. Flexible sigmoidoscopy was associated with a 21% reduction in CRC incidence (RR, 0.79; 95% CI, 0.72-0.85; *P*<.001) and a 26% decrease in CRC-related deaths (RR, 0.74; 95% CI, 0.63-0.87; *P*<.001).[44]

Capsule colonoscopy is a much less widely used CRC screening strategy. It is approved by the US Food and Drug Administration for imaging the proximal colon in patients with previous incomplete colonoscopies and for patients who require colorectal imaging but are not candidates for colonoscopy or sedation. In addition, it is indicated for the detection of colon polyps in patients with evidence of gastrointestinal bleeding originating from the lower tract and patients who have major risk factors for colonoscopy or moderate sedation. Drawbacks to capsule colonoscopy include lack of reimbursement by insurance and the need for an aggressive bowel preparation. In a screening trial of 884 patients, capsule colonoscopy had an 88% sensitivity and 82% specificity for detecting adenomas that were 6 mm or larger.[45] It was ineffective for the detection of sessile serrated polyps (26% false-negative rate). Furthermore, in 9% of patients, the examination technically failed because of either inadequate cleansing or rapid transit of the capsule.

CTC is also a relatively noninvasive method used to visualize the colonic mucosa. It has been associated with low complication rates when compared with conventional colonoscopy. CTC has demonstrated a sensitivity of 82% to 92% for the detection of adenomas 1 cm or larger.[46-49] CTC requires a bowel preparation, and patients are subjected to radiation exposure. Extracolonic findings are observed in approximately 15% to 50% of cases. A randomized, controlled trial comparing

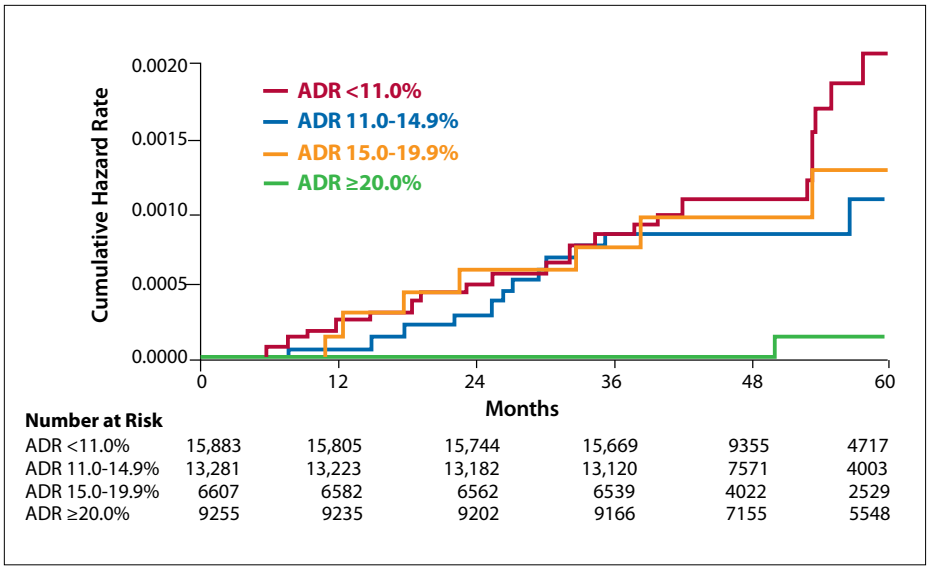

Figure 5. In a Polish colonoscopy screening program, an ADR of 20% or higher was associated with a reduced rate of interval cancers. ADR, adenoma detection rate. Adapted from Kaminski MF et al. *N Engl J Med.* 2010;362(19):1795-1803.[52]

CTC with colonoscopy-based screening for the detection of high-risk sessile serrated polyps in average-risk individuals determined that colonoscopy was substantially and significantly more effective for the detection of advanced serrated polyps.[50] With colonoscopy, 4.3% of individuals were diagnosed with at least 1 high-risk sessile serrated polyp, compared with 0.8% in the CTC arm (P<.001).

Interval CRCs and the ADR

Interval CRCs refer to cancers that develop in the interval of time between the performance of a CRC screening test and the date of the patient's next recommended screening test. The ADR is an extremely important quality metric because it inversely correlates with the incidence and mortality of interval CRCs. For every 1% increase in the ADR, there is a 3% decrease in CRC incidence and a 5% decrease in CRC-related mortality.[51] In a Polish colonoscopy screening program, it was found that physicians who had an ADR of 20% or better had a substantially reduced rate of interval cancers compared with physicians who had an ADR under 20% (Figure 5).[52]

For these reasons, the ADR is considered a premier colonoscopy quality benchmark. The ACG/American Society for Gastrointestinal Endoscopy task force on quality colonoscopy recommended a new minimum average risk screening ADR target of 25% in a combined male and female population (30% ADR in men and 20% ADR in women).[53] The ability to increase the ADR requires physicians to utilize an excellent technical approach for visualizing the colon lining, which should include luminal distention, flattening folds, and adequate cleansing of the colonic mucosa. The importance of adequate bowel preparation on the effectiveness of colonoscopy is highlighted by higher completion rates and improved ADR. The MSTF recommended that adequate bowel preparation should be obtained in more than 85% of outpatient examinations, and that split-dose bowel preparation regimens should be used.[54] Split-dose is defined as ingestion of at least 50% of the bowel preparation on the day of the procedure. Two studies, including one presented at the 2017 DDW, demonstrated that low-volume, split-dose bowel preparation significantly increases the detection rate of sessile serrated polyps.[55,56]

Strategies to Improve the ADR

Given its important impact on CRC incidence and mortality, there has been much effort to improve the ADR, including imaging strategies to enhance adenoma detection. One of these approaches is a high-definition colonoscopy, which has been shown to increase ADR compared with standard white-light colonoscopy in physicians with a low ADR.[57] Reports have suggested that chromoendoscopy can increase ADR vs standard white-light colonoscopy, but data are not conclusive.[58] In contrast, no strong and convincing data suggest that electronic chromoendoscopy with narrow band imaging, Fujinon intelligent chromoendoscopy, or digital autofluorescence increases ADR compared with white-light colonoscopy.[59,60]

Several other advancements in endoscopic technology have been made. Features that allow visualization behind colonic folds—such as wide-angle colonoscopy, a retrograde viewing device, a ring attachment on the tip of the scope, and a balloon colonoscope—have been associated with lower miss rates of adenomas smaller than 10 mm compared with standard colonoscopy.[61-64]

Cap-assisted colonoscopy has not been shown to increase the ADR, but decreases time to intubate the cecum and enhances the ability to enter the terminal ileum.[65,66]

In a meta-analysis of more than 5624 patients, Endocuff-assisted colonoscopy was associated with a higher ADR (OR, 1.49; 95% CI, 1.23-1.80; *P*=.03) and detection of sessile serrated polyps (OR, 2.34; 95% CI, 1.63-3.36; *P*<.001) compared with standard colonoscopy.[67] There was an increased risk of complications (5% vs <1% standard colonoscopy), which included a small risk of mucosal injury or displacement of the cuff.

Water immersion colonoscopy has the theoretical advantage of magnification of mucosal lesions, luminal distension, and decreased patient discomfort in order to enhance ADR. In a meta-analysis of randomized, controlled trials of water immersion vs standard colonoscopy, a slight improvement in ADR with water immersion was noted (RR, 1.16; 95% CI, 1.04-1.30; *P*=.007).[68] A low-cost strategy is the use of retroflexion in the right colon. A systematic review and meta-analysis of right colon retroflexion vs standard colonoscopy demonstrated a per adenoma and per colonoscopy miss rate in the right colon of 16.9% and 6.1%, respectively.[69] The rate of successful retroflexion was 92%, and the rate of adverse events was low, at 0.03%.

Summary

Using CRC screening, CRC and CRC-related deaths are preventable. With one-third of eligible Americans not adherent to screening, there is a need to employ strategies to enhance CRC screening rates. Clinicians must be aware that adenomas and sessile serrated polyps are biologically different precursors, and variability exists in the ability of different CRC screening modalities to detect sessile serrated polyps. Although there is evidence now supporting the use of several different CRC screening modalities, it is imperative for clinicians to remember that quality is paramount for a successful screening regimen, no matter which option is chosen.

Disclosure

Dr Burke has received research support from Cancer Prevention Pharmaceuticals and Ferring Pharmaceuticals.

References

1. American Cancer Society. Cancer Facts and Figures: 2017. Atlanta, Georgia. 2017. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html. Accessed August 15, 2017.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Colon and Rectum Cancer. 2017. https://seer.cancer.gov/statfacts/html/colorect.html. Accessed July 17, 2017.
3. Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/csr/1975_2014. Updated June 28, 2017. Accessed August 14, 2017.
4. Edwards BK, Noone AM, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer*. 2014;120(9):1290-1314.
5. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974-2013. *J Natl Cancer Inst*. 2017;109(8). doi: 10.1093/jnci/djw322.
6. Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. *JAMA Surg*. 2015;150(1):17-22.
7. Siegel RL, Miller KD, Jemal A. Colorectal cancer mortality rates in adults aged 20 to 54 years in the United States, 1970-2014. *JAMA*. 2017;318(6):572-574.
8. Strum WB. Colorectal adenomas. *N Engl J Med*. 2016;374(11):1065-1075.
9. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol*. 2017;112(7):1016-1030.
10. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin*. 2017;67(3):177-193.
11. Meester RG, Doubeni CA, Zauber AG, et al. Public health impact of achieving 80% colorectal cancer screening rates in the United States by 2018. *Cancer*. 2015;121(13):2281-2285.
12. Pochapin MB. 80% by 2018! What gastroenterologists can do to reach this goal. Presentation at: the 2017 Digestive Disease Week; May 6-9, 2017; Chicago, IL. Session Sp945.
13. Tools & Resources – 80% by 2018 Pledge. National Colorectal Cancer Roundtable. http://nccrt.org/tools/80-percent-by-2018/80-percent-by-2018-pledge. Accessed August 14, 2017.
14. Jones RM, Devers KJ, Kuzel AJ, Woolf SH. Patient-reported barriers to colorectal cancer screening: a mixed-methods analysis. *Am J Prev Med*. 2010;38(5):508-516.
15. Kahi CJ, Ballard D, Shah AS, Mears R, Johnson CS. Impact of a quarterly report card on colonoscopy quality measures. *Gastrointest Endosc*. 2013;77(6):925-931.
16. Keswani RN, Yadlapati R, Gleason KM, et al. Physician report cards and implementing standards of practice are both significantly associated with improved screening colonoscopy quality. *Am J Gastroenterol*. 2015;110(8):1134-1139.
17. Bibbins-Domingo K, Grossman DC, Curry SJ, et al; US Preventive Services Task Force. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;315(23):2564-2575.
18. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM; American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol*. 2009;104(3):739-750.
19. Williams R, White P, Nieto J, Vieira D, Francois F, Hamilton F. Colorectal cancer in African Americans: an update. *Clin Transl Gastroenterol*. 2016;7(7):e185.
20. Ashktorab H, Vilmenay K, Brim H, Laiyemo AO, Kibreab A, Nouraie M. Colorectal cancer in young African Americans: is it time to revisit guidelines and prevention? *Dig Dis Sci*. 2016;61(10):3026-3030.
21. Carethers JM. Screening for colorectal cancer in African Americans: determinants and rationale for an earlier age to commence screening. *Dig Dis Sci*. 2015;60(3):711-721.
22. QuickStats. Colorectal cancer screening among adults aged 50-75 years, by race/ethnicity—National Health interview study, United States, 2000-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(38):1042.
23. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol*. 2008;103(6):1541-1549.
24. Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. *N Engl J Med*. 2013;369(12):1106-1114.
25. Rabeneck L, Rumble RB, Thompson F, et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. *Can J Gastroenterol*. 2012;26(3):131-147.
26. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med*. 2014;160(3):171.
27. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. 2014;370(14):1287-1297.
28. Cotter TG, Burger KN, Johnson D, et al. Long-term follow-up of patients having false positive multi-target stool DNA tests after negative screening colonoscopy: the LONG-HAUL study [DDW abstract M01716]. *Gastroenterology*. 2016;4(suppl 1).

29. Robertson DJ, Lee JK, Boland CR, et al. Recommendations on fecal immunochemical testing to screen for colorectal neoplasia: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2017;152(5):1217-1237.e3.
30. Quintero E, Castells A, Bujanda L, et al; COLONPREV Study Investigators. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. *N Engl J Med*. 2012;366(8):697-706.
31. Brenner H, Chang-Claude J, Jansen L, Knebel P, Stock C, Hoffmeister M. Reduced risk of colorectal cancer up to 10 years after screening, surveillance, or diagnostic colonoscopy. *Gastroenterology*. 2014;146(3):709-717.
32. Doubeni CA, Corley DA, Quinn VP, et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. *Gut*. 2016;gutjnl-2016-312712.
33. Doubeni CA, Weinmann S, Adams K, et al. Screening colonoscopy and risk for incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study. *Ann Intern Med*. 2013;158(5 Pt 1):312-320.
34. Kahi CJ, Imperiale TF, Juliar BE, Rex DK. Effect of screening colonoscopy on colorectal cancer incidence and mortality. *Clin Gastroenterol Hepatol*. 2009;7(7):770-775.
35. Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology*. 2010;139(4):1128-1137.
36. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med*. 2012;366(8):687-696.
37. Winawer SJ, Zauber AG, Ho MN, et al; The National Polyp Study Workgroup. Prevention of colorectal cancer by colonoscopic polypectomy. *N Engl J Med*. 1993;329(27):1977-1981.
38. Singh H, Turner D, Xue L, Targownik LE, Bernstein CN. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. *JAMA*. 2006;295(20):2366-2373.
39. Lakoff J, Paszat LF, Saskin R, Rabeneck L. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. *Clin Gastroenterol Hepatol*. 2008;6(10):1117-1121.
40. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. *Ann Intern Med*. 2011;154(1):22-30.
41. Baxter NN, Warren JL, Barrett MJ, Stukel TA, Doria-Rose VP. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. *J Clin Oncol*. 2012;30(21):2664-2669.
42. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med*. 2009;150(1):1-8.
43. Atkin WS, Edwards R, Kralj-Hans I, et al; UK Flexible Sigmoidoscopy Trial Investigators. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet*. 2010;375(9726):1624-1633.
44. Schoen RE, Pinsky PF, Weissfeld JL, et al; PLCO Project Team. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med*. 2012;366(25):2345-2357.
45. Rex DK, Adler SN, Aisenberg J, et al. Accuracy of capsule colonoscopy in detecting colorectal polyps in a screening population. *Gastroenterology*. 2015;148(5):948-957.e2.
46. Rosman AS, Korsten MA. Meta-analysis comparing CT colonography, air contrast barium enema, and colonoscopy. *Am J Med*. 2007;120(3):203-210.e4.
47. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncol*. 2012;13(1):55-64.
48. Johnson CD, Herman BA, Chen MH, et al. The National CT Colonography Trial: assessment of accuracy in participants 65 years of age and older. *Radiology*. 2012;263(2):401-408.
49. Halligan S, Wooldrage K, Dadswell E, et al; SIGGAR investigators. Computed tomographic colonography versus barium enema for diagnosis of colorectal cancer or large polyps in symptomatic patients (SIGGAR): a multicentre randomised trial. *Lancet*. 2013;381(9873):1185-1193.
50. IJspeert JE, Tutein Nolthenius CJ, Kuipers EJ, et al. CT-colonography vs. colonoscopy for detection of high-risk sessile serrated polyps. *Am J Gastroenterol*. 2016;111(4):516-522.
51. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med*. 2014;370(14):1298-1306.
52. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med*. 2010;362(19):1795-1803.
53. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc*. 2015;81(1):31-53.
54. Johnson DA, Barkun AN, Cohen LB, et al; US Multi-Society Task Force on Colorectal Cancer. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US multi-society task force on colorectal cancer. *Gastroenterology*. 2014;147(4):903-924.
55. Siddiki HA, Fath AR, Ravi S, Ramirez FC, Crowell MD, Gurudu S. Comparison of ADR and SSP detection rate (SSP-DR) between small volume split dose preparation (SDP) and large volume SDP [DDW abstract 553]. *Gastrointest Endosc*. 2017;85(5 suppl).
56. Horton N, Garber A, Hasson H, Lopez R, Burke CA. Impact of single vs. split dose low volume bowel preparations on bowel movement kinetics, patient inconvenience, and polyp detection: a prospective trial. *Am J Gastroenterol*. 2016;111(9):1330-1337.
57. Jrebi NY, Hefty M, Jalouta T, et al. High-definition colonoscopy increases adenoma detection rate. *Surg Endosc*. 2017;31(1):78-84.
58. Hashimoto K, Higaki S, Nishiahi M, Fujiwara K, Gondo T, Sakaida I. Does chromoendoscopy improve the colonoscopic adenoma detection rate? *Hepatogastroenterology*. 2010;57(104):1399-1404.
59. Dinesen L, Chua TJ, Kaffes AJ. Meta-analysis of narrow-band imaging versus conventional colonoscopy for adenoma detection. *Gastrointest Endosc*. 2012;75(3):604-611.
60. Chung SJ, Kim D, Song JH, et al. Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates. *Gastrointest Endosc*. 2010;72(1):136-142.
61. Rex DK, Chadalawada V, Helper DJ. Wide angle colonoscopy with a prototype instrument: impact on miss rates and efficiency as determined by back-to-back colonoscopies. *Am J Gastroenterol*. 2003;98(9):2000-2005.
62. Adler A, Aminalai A, Aschenbeck J, et al. Latest generation, wide-angle, high-definition colonoscopes increase adenoma detection rate. *Clin Gastroenterol Hepatol*. 2012;10(2):155-159.
63. Halpern Z, Gross SA, Gralnek IM, et al. Comparison of adenoma detection and miss rates between a novel balloon colonoscope and standard colonoscopy: a randomized tandem study. *Endoscopy*. 2015;47(3):238-244.
64. Leufkens AM, DeMarco DC, Rastogi A, et al; Third Eye Retroscope Randomized Clinical Evaluation [TERRACE] Study Group. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. *Gastrointest Endosc*. 2011;73(3):480-489.
65. Pohl H, Bensen SP, Toor A, et al. Cap-assisted colonoscopy and detection of Adenomatous Polyps (CAP) study: a randomized trial. *Endoscopy*. 2015;47(10):891-897.
66. Brand EC, Dik VK, van Oijen MGH, Siersema PD. Missed adenomas with behind-folds visualizing colonoscopy technologies compared with standard colonoscopy: a pooled analysis of 3 randomized back-to-back tandem colonoscopy studies. *Gastrointest Endosc*. 2017;86(2):376-385.e2.
67. Chin M, Karnes W, Jamal MM, et al. Use of the Endocuff during routine colonoscopy examination improves adenoma detection: a meta-analysis. *World J Gastroenterol*. 2016;22(43):9642-9649.
68. Hafner S, Zolk K, Radaelli F, Otte J, Rabenstein T, Zolk O. Water infusion versus air insufflation for colonoscopy. *Cochrane Database Syst Rev*. 2015;(5):CD009863.
69. Cohen J, Grunwald D, Grossberg LB, Sawhney MS. The effect of right colon retroflexion on adenoma detection: a systematic review and meta-analysis [published online September 28, 2016]. *J Clin Gastroenterol*. doi:10.1097/MCG.0000000000000695.

Categorization of Gastrointestinal Polyps and Endoscopic Removal Techniques

Vivek Kaul, MD, FACG, FASGE, AGAF

Segal-Watson Professor of Medicine
Chief, Division of Gastroenterology & Hepatology
Center for Advanced Therapeutic Endoscopy
University of Rochester Medical Center
Rochester, New York

The Paris classification divides polyps into many types based on morphology (Table 1).[1] It serves as a reference point for polyp definition, as well as endoscopic resection. This system, however, is not routinely used on a daily basis in either private practice or academic settings.

Clinical Decisions on Patient Management

During colonoscopy, several factors determine whether a polyp is best suited for endoscopic removal vs surgical removal. Size is important when considering endoscopic resection feasibility and recurrence risk (Figure 6). However, large size alone is no longer a contraindication for endoscopic removal given the advanced techniques and devices available today. It is now routine to remove very large colon polyps, up to 8 to 10 cm in size, using advanced techniques like endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).

Table 1. The Paris Classification

Endoscopic Appearance	Paris Class	Description
Protruded lesions	Ip	Pedunculated polyps
	Ips	Subpedunculated polyps
	Is	Sessile polyps
Flat elevated lesions	IIa	Flat elevation of the mucosa
	IIa/IIc	Flat elevation with central depression
Flat lesions	IIb	Flat mucosal change
	IIc	Mucosal depression
	IIc/IIa	Mucosal depression with raised edge

Adapted from Endoscopic Classification Review Group. *Endoscopy*. 2005;37(6):570-578.[1]

Endoscopists vary, however, in their perceptions of "how big is too big" for endoscopic removal. The decision is based primarily on their training, expertise, experience, and, ultimately, their overall comfort level in managing a particular lesion. The endoscopist's own assessment of his or her ability to manage any potential complications (eg, bleeding, perforation) and the available surgical back-up weighs heavily into this decision-making process.

Several other factors impact the polyp removal decisions and technique. An appearance of central ulceration or infiltration may indicate deeper invasion of the lesion. In determining the resectability of a polyp, the endoscopist should estimate the relative mobility of the lesion vs fixity to the colon wall. Does the lesion appear fixed to the colon wall? Is the endoscopic appearance more suggestive of an advanced malignancy rather than a mucosal-based lesion? It can be helpful to gently probe the lesion with biopsy forceps to obtain a sense of how firm it is relative to the wall. A submucosal saline injection can be used to check if there is adequate and appropriate "lifting" of the polyp or lesion, which would then indicate safe resectability. A "non-lifting" sign (the surrounding mucosa elevates, the

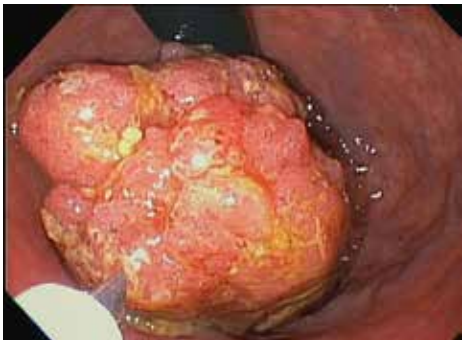

Figure 6. The size and location of the polyp are important when considering endoscopic resection feasibility and recurrence risk.

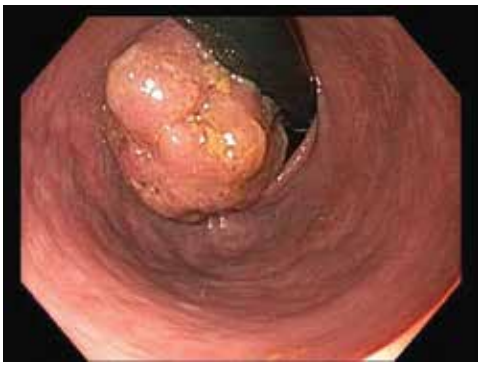

Figure 7. A retroflexed view of a large polyp prior to initiation of resection.

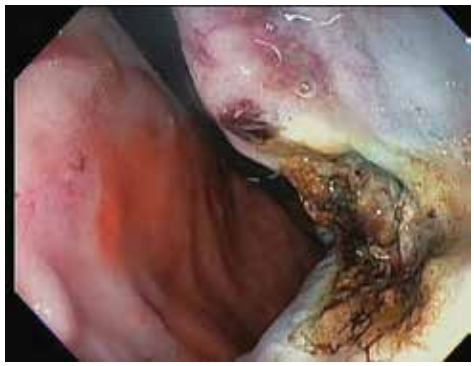

Figure 8. An endoscopic mucosal resection site after argon plasma ablation of the edges around the site.

polyp does not) is suggestive of invasive pathology and infiltration deeper into the colonic wall, which precludes safe and complete endoscopic resection. The non-lifting sign may also be seen when significant scarring is present in and around the base of the lesion, as may be seen in the setting of prior (incomplete) resection attempts, extensive prior biopsies, and tattooing close to or within the lesion.

In certain locations, for example, in the rectum and possibly in the sigmoid colon, it is possible to assess the polyp's depth of invasion with endoscopic ultrasound using a dedicated echoendoscope. This technique is often used for large rectal polyps, which may harbor high-grade dysplasia or carcinoma, and if there is concern for invasion. The limitation of endoscopic ultrasound is that it cannot be used to examine more proximal lesions in the colon, at least using the echoendoscopes. The echoendoscopes typically cannot reach the proximal left colon, the transverse colon, the right colon, or the cecum. The mini-probe ultrasound is relatively limited in its assessment, although it can be used in certain cases to clarify the nature of a lesion.

Other factors that impact endoscopic resectability are colonic anatomy, polyp location, colon preparation quality, and coagulopathy. It can be difficult to safely and completely remove large, laterally spreading lesions around the hepatic and splenic flexures, as well as those lesions that involve the appendiceal orifice and the ileocecal valve. Special techniques like cap-assisted colonoscopy EMR and resection in the "retroflexed" colonoscope position may be needed to effectively enable such resections (Figures 7 and 8). Cap-assisted colonoscopy may make insertion of the instrument difficult in patients with narrow, spastic sigmoid colons, especially when severe diverticulosis is present. Poor bowel preparation impairs safe and complete resection for obvious reasons, and carries the theoretical risk for intraluminal explosion with cautery use. The importance of an optimal bowel preparation cannot be overemphasized when embarking on EMR/ESD of colonic lesions. Finally, the presence of coagulopathy (liver disease) or the use of antithrombotic/antiplatelet agents may impact the resection approach as well. As far as possible, the coagulation status needs to be optimized prior to resection, the bleeding risk discussed in detail, and any anticoagulation withheld for an appropriate, recommended period of time. In addition, the endoscopist may plan to prophylactically close the EMR/ESD defect with endoclips (Figure 9) and/or sutures in very high-risk patients, especially those with minimal cardiopulmonary reserve who may not tolerate significant postpolypectomy bleeding well. All of the above factors must be considered when planning a colon polyp EMR/ESD.

Nearly all patients who are referred for endoscopic resection have colon polyps that are suitable for EMR/ESD removal. Nowadays, surgical resection is recommended only for the rare patient who has a clearly infiltrative, advanced lesion that is not amenable to endoscopic resection as determined through a detailed examination by an experienced endoscopist.

Traditional Submucosal Injection Agents

In the United States, the use of a submucosal injection agent (Figure 10) is generally preferred when a polyp is 1.5 cm to 2 cm or larger, particularly when it is located in the proximal colon, where the colonic wall is thinner. The purpose of the submucosal injection is to lift the mucosal-based lesion away from the muscularis propria, thereby reducing the risk of colonic perforation and postpolypectomy (serosal burn) syndrome. Traditionally, the most common injectate used is normal saline. Over the years, however, several other agents have been introduced to achieve submucosal lift, thus enabling safe and effective EMR/ESD, as mentioned below.

The Injection Technique

It is important for the injection needle to approach the target lesion at an angle, with the aim of entering the

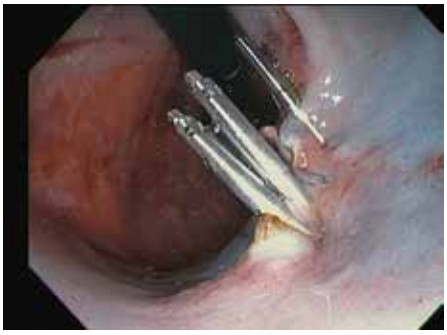

Figure 9. An endoscopic mucosal resection site closed prophylactically with endoclips.

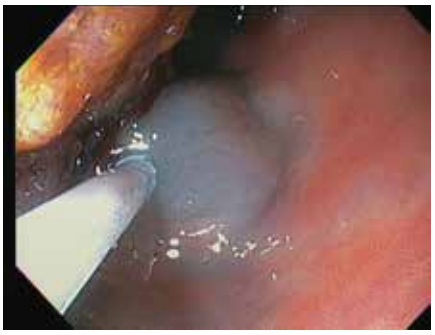

Figure 10. Use of a submucosal injection.

submucosal plane. A deeper, more perpendicularly oriented injection typically will find the muscle layer, and will not achieve an adequate lift. One of 2 basic techniques may be used for submucosal injection:

(1) The needle is brought into view in the endoscopic field and then inserted into the lesion or in the mucosa immediately adjacent to the lesion in a quick, "harpoon-like" fashion, followed by initiation of injection. Slight withdrawal of the needle catheter may be needed to find the correct submucosal plane, as evidenced by a visible lift.

(2) Once the needle is brought into the endoscopic field, the injection begins in the lumen, and then the needle is injected into the lesion. With this approach, the submucosal plane is found relatively immediately as the actively injecting needle enters the lesion.

Traditionally, earlier use of EMR and ESD for colon polyps involved the use of saline injection. Saline is available ubiquitously and is relatively inexpensive.[2] It can be used without any restrictions or concern for chemical or allergic reactions or interactions. However, there are at least 2 main disadvantages. Saline dissipates quickly, and large volumes with frequent injections may be needed for complex, large polyp resections, which increases the procedure time. The submucosal cushion that saline creates typically does not last long, especially when several injections are made into the mucosa and the submucosa, which create multiple "leak" sites. Saline injection can be used to help remove small lesions. The vast majority of patients who are now referred for endoscopic polyp removal tend to have larger lesions, which require different types of injection solutions with enhanced characteristics, such as those described below.

Newer Submucosal Injection Agents

As the field of EMR and ESD has evolved and become more established over the past 2 decades, several novel submucosal injection agents have emerged. They include hyaluronic acid, hetastarch, dextrose water, hypertonic saline, and hydroxypropyl methylcellulose. Even the patient's own blood has been used as a submucosal cushioning agent. However, for the first time, there is now a premixed, dedicated novel solution for submucosal lifting known as Eleview. This premixed solution obviates the need for nurses or technicians to mix a variety of different agents in order to prepare an injectable solution for EMR/ESD. Eleview contains methylene blue, water for injection, medium-chain triglycerides, poloxamer 188 (the bulking/cushioning agent), polyoxyl-15-hydroxystearate, and sodium chloride in a premixed state. Methylene blue provides the light blue coloring that is important for maintaining good vision/definition of the submucosal plane. Initial animal studies of Eleview suggested that a single injection results in a submucosal lift that lasts at least 45 minutes.[3] Equally importantly, the submucosal lift was shown to decline at a much slower rate than that seen with saline and other solutions. The substantial submucosal lift allows for a relatively easier resection of larger lesions, without the need for repeated, frequent injections, while maintaining a reassuring safety cushion to proceed with the resection. This approach represents a major advance in the field of submucosal lifting agents for EMR/ESD.

At the 2017 DDW, Rex and colleagues presented interim results of a randomized, double-blind trial of Eleview for EMR of colonic polyps larger than 2 cm.[4] The trial excluded patients with macroscopic or pit pattern features suggestive of invasive cancer, those who had undergone previous endoscopic attempts at resection, and those with coagulation disorders. The primary efficacy endpoints were:

- Total injected volume needed to complete the EMR procedure.
- Total injected volume per lesion size.
- Time to resect the lesion completely.

Table 2. Total Injected Volume Used to Complete the EMR Procedure in a Trial of Eleview vs Saline

Endpoint	Statistics	Eleview (n=102)	Saline (n=109)
Total injected volume to complete the EMR procedure (mL)	Mean (±SD)	16.1 (±9.8)	31.6 (±32.1)
	Range	3.0-41.0	4.0-248.0
	P value	<.001	

EMR, endoscopic mucosal resection; SD, standard deviation.

Data from Rex D et al. DDW abstract 689. *Gastrointest Endosc.* 2017;85(5 suppl).[4]

Table 3. Time to Resect the Lesion in a Trial of Eleview vs Saline

Endpoint	Statistics	Eleview (n=102)	Saline (n=109)
Time to resect the lesion (minutes)	Mean (±SD)	19.15 (±16.80)	29.70 (±69.18)
	Range	1-100	2-687
	P value	.326	

SD, standard deviation.

Data from Rex D et al. DDW abstract 689. *Gastrointest Endosc.* 2017;85(5 suppl).[4]

Secondary endpoints included the Sydney Resection Quotient (calculated by dividing the lesion size [in mm] by the number of resections required to remove the lesion), the number of reinjections, the proportion of subjects with en bloc resection, the number of resection pieces, and the ease of use (rated on a 5-point scale). A total of 226 patients were enrolled as of April 21, 2017. The primary analysis provided data for the 211 patients in the per protocol group.

Compared with saline, Eleview required a lower mean total injection volume to complete the EMR procedure (16.1 ±9.8 mL vs 31.6 ±32.1 mL; *P*<.001; Table 2).[4] Eleview was associated with a shorter mean time to resect the lesion (19.15 ±16.80 minutes vs 29.70 ±69.18 minutes; *P*=.326 [Table 3]). With Eleview, the lesion was removed in fewer resected pieces (mean, 5.70 ±6.0 vs 6.47 ±5.0; *P*=.052 [Table 4]). Although more patients were able to achieve an en bloc resection with Eleview compared with saline, the difference was not statistically significant (18.6% vs 11.0%; *P*=.125). Eleview was associated with a superior mean Sydney Resection Quotient (10.3 ±8.1 vs 8.0 ±5.7; *P*=.044). Most endoscopists ranked Eleview as either neutral, easy, or very easy to use (80.3%). The rate of complications was similar with Eleview vs saline (15.0% vs 15.2%), and there was no significant increase in the risk for bleeding complications.

These data from this initial study comparing Eleview with saline are significant because for the first time, a novel, premixed, ready-to-use submucosal injection solution was shown to reduce procedure time, enable higher en bloc resection rates, lead to fewer pieces per resection, and allow a lower volume of injectate to be used, when compared with saline. These technical parameters are of great importance to the endoscopist and the team involved with these procedures, and suggest that Eleview may positively impact the overall efficiency of EMR/ESD procedures. Studies with larger populations may bear out statistically significant differences among the variables that were shown to trend favorably in this study for Eleview.

Table 4. Secondary Endpoints in the Efficacy Analysis of a Trial of Eleview vs Saline

Endpoint	Statistics	Eleview (n=102)	Saline (n=109)
Sydney Resection Quotient	Mean (±SD)	10.3 (±8.1)	8.0 (±5.7)
	P value	.044	
Number of resection pieces	Mean (±SD)	5.70 (±6.0)	6.47 (±5.0)
	P value	.052	
Injected volume to provide initial lift (mL)	Mean (±SD)	10.4 (±7.0)	15.3 (±11.7)
	P value	<.001	
Proportion of subjects with en bloc resections	n (%)	19 (18.6%)	12 (11.0%)
	P value	.125	

SD, standard deviation.

Data from Rex D et al. DDW abstract 689. *Gastrointest Endosc.* 2017;85(5 suppl).[4]

Polyp Removal

Once the submucosal lift is achieved, a relatively smaller polyp (2-4 cm) in a good location may be suitable for an en bloc resection, which means the entire lesion is removed in one piece by EMR or ESD. There are obvious advantages to removing the lesion in a single piece: it provides the best sample for accurate pathologic assessment of deep and lateral margins, and the procedure is quicker than with piecemeal resection, more likely to be a complete resection, and utilizes fewer injections and injectate. The pathologist is able to definitively look at the margins, both lateral margins and deep margins, and

is able to provide a more confident pathologic diagnosis in terms of invasion.

When the polyp sizes are larger (>4 cm) and/or in relatively difficult locations that may not be suitable for safe and easy en bloc resection, then piecemeal resection is performed. This approach entails making submucosal injections starting at one edge of the polyp or lesion and then proceeding with piecemeal resection of sizable areas, moving from one end of the lesion to the other, until the resection is complete. Piecemeal resection takes longer, requires multiple injections, and may end up providing a fragmented pathologic specimen more difficult to interpret for the pathologist. When a more advanced pathology is suspected, it is important to properly orient the pieces of the specimen on a foam board upon presentation to the pathologist, to ensure a more reliable diagnosis in terms of the lesion's depth and lateral margin assessment.

EMR and ESD are both well-established techniques for polyp removal. After an adequate submucosal lift is achieved, the intent of the ESD resection is to dissect or carve out the entire lesion circumferentially in 1 piece. This approach affords the significant advantage of providing a single specimen to the pathologist, almost like a surgical specimen, except that it is performed endoscopically from within the lumen of the colon. ESD for colonic polyps is now a well-established procedure. However, compared with EMR, it is still primarily performed by a smaller percentage of clinicians who have training and expertise in this technique. ESD involves a steeper learning curve, and it requires different specialty instruments (eg, ESD "knives"). For most practitioners, the ESD procedure takes somewhat longer than colonic EMR. ESD may carry a slightly higher rate of complications, particularly perforation. As experience has evolved, however, the more-experienced practitioners are reporting relatively fewer complications and more efficient procedure times.

Improving Polypectomy Techniques

The basic techniques in colonoscopy and polypectomy must be mastered before a clinician attempts large or complex colonic EMRs or ESDs. Such mastery includes the ability to remove smaller lesions with cold snares and to remove intermediate-size lesions (1-2 cm) with the EMR technique or with en bloc resection without submucosal injection, when deemed appropriate. The important factors here are to properly assess the size and extent of the lesion, especially for serrated adenomas that can be subtle in endoscopic appearance. These lesions are usually covered by a "mucus cap," and adequate bowel preparation and meticulous examination in high-definition white-light and narrow-band imaging (NBI) are necessary to examine these lesions. It is important to completely assess the nature, size, and extent of a lesion and plan the resection strategy before proceeding with the intervention. The endoscopist should be prepared to manage any complications that may arise and/or have surgical or interventional radiology backup in place.

As mentioned before, it might be necessary to remove some lesions in a retroflexed endoscope position, which is difficult but can allow very efficient and complete lesion removal. The anterograde and retrograde endoscope positions might need to be used in combination during the same procedure to achieve the best results. After visualization of the entire lesion, a plan for the resection should be made that encompasses the appropriate snares for a given lesion as well as the type and volume of submucosal injectate needed.

After performance of a piecemeal EMR, there should be a low threshold for performing argon-plasma coagulation around the edges of the EMR site. Studies have shown that argon-plasma coagulation decreases the potential for residual adenoma at the EMR site and significantly reduces rates of adenoma recurrence. Follow-up interval colonoscopy is typically performed at 6 to 12 months to confirm that no recurrent or residual adenoma exists at the prior EMR site and to document complete resection. Recurrences can almost always be managed endoscopically. Surveillance should continue indefinitely at recommended intervals in these high-risk patients.

Disclosure

Dr Kaul is a consultant/speaker for Aries Pharmaceuticals.

References

1. Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. *Endoscopy*. 2005;37(6):570-578.
2. Uraoka T, Saito Y, Yamamoto K, Fujii T. Submucosal injection solution for gastrointestinal tract endoscopic mucosal resection and endoscopic submucosal dissection. *Drug Des Devel Ther*. 2009;2:131-138.
3. Repici A, Maselli R, Carrara S, Anderloni A, Enderle M, Hassan C. Standard needle versus needleless injection modality: animal study on different fluids for submucosal elevation. *Gastrointest Endosc*. 2017;86(3):553-558.
4. Rex D, Wallace MB, Sharma P, Lollo G, Maselli R, Repici A. A randomized, double-blind trial of a new injectable solution (Sic 8000) for endoscopic resection of colonic polyps larger than 2 cm: an interim report [DDW abstract 689]. *Gastrointest Endosc*. 2017;85(5 suppl).

Advances in the Resection of Gastrointestinal Polyps

Heiko Pohl, MD

Associate Professor of Medicine
Geisel School of Medicine at Dartmouth
Hanover, New Hampshire
Department of Gastroenterology, Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Department of Gastroenterology, VA Medical Center
White River Junction, Vermont

As previously discussed, the aim of CRC screening is to decrease cancer incidence and CRC-related mortality. With most CRC screening tests, these goals are achieved through the detection and removal of neoplastic precancerous polyps. In other words, just the detection of these polyps is not enough—they must also be effectively removed.

Unfortunately, it has become increasingly apparent in recent years that polyp resection has not been completely effective in clinical practice. Polyps can recur and subsequently progress to CRC. Although the majority of interval CRCs are attributed to missed or de novo polyps, 10% to 27% are attributed to incomplete resection.[1-3] In a prospective study at 2 academic medical centers, the incomplete resection rate was determined by assessing for the presence of neoplastic tissue in postpolypectomy biopsies.[4] The study identified 346 polyps, ranging in size from 5 to 20 mm, from 269 patients. They had been removed by 11 different gastroenterologists. The rate of incomplete resection was 10.1%. The rate of incomplete resection grew with increased polyp size (17.3% vs 6.8% for large [10-20 mm] vs small [5-9 mm] lesions). Sessile serrated polyps were notably more difficult to remove in their entirety compared with adenomas. The rates of incomplete resection were 31.0% for sessile serrated polyps vs 7.2% for adenomas.

Techniques to Resect Large Polyps

Larger polyps are more likely to become cancerous. They are typically removed by EMR or ESD. ESD is performed primarily in Asian countries, whereas EMR is more common in Western countries.[5] Both of these techniques require submucosal injection to lift the lesion off the muscularis propria to provide a submucosal safety cushion. With EMR, the lifted polyp is then ensnared and removed, mostly in piecemeal fashion, using electrocautery. In contrast, ESD requires a circumferential incision and then a careful dissection of the submucosal plane to remove the entire lesion in a single piece.

There remains a great deal of controversy regarding when EMR vs ESD should be used. Proponents of ESD argue that it should be used for all colorectal lesions because it ensures an en bloc resection. ESD achieves complete resection for almost all lesions, and recurrence is very low overall (1-2%).[6,7] Furthermore, ESD may achieve en bloc resection and complete removal of superficial submucosal cancer. Because the risk of systemic or lymph node invasion is very low for these cancers (<2%),[8] this technique can be considered curative,[9] and surgical colectomy may be avoided for some patients. However, ESD is associated with a higher complication rate (including a perforation rate of up to 5%), and the procedure requires more time and greater skill.[7]

In Western countries, most colorectal lesions are removed by EMR because of the low overall risk of cancer in these regions. EMR has a high recurrence rate (approximately 15% at first surveillance colonoscopy).[6,7] Endoscopic removal of recurrent tissue is typically achieved for most patients, and at second surveillance colonoscopy, the recurrence rate approaches that of ESD, at approximately 2%.[10,11] EMR is easier to perform, as it requires less skill and less time. The perforation rate is less than 1%.[6] However, EMR may remove submucosal cancers piecemeal, and in that situation, a cancer cannot be adequately assessed for free margins, and surgery is still required.

At the 2017 DDW, Rex presented an overview of EMR and ESD techniques and preferences.[11] Among the issues discussed were the identification of lesions with submucosal invasion, which allows them to be selected

for ESD, and how to remove lesions without submucosal invasion by EMR. An interesting abstract by Bahin and colleagues provided a cost-effectiveness analysis comparing universal ESD (as performed in some Asian countries) vs the selection of ESD for lesions with a higher risk of cancer.[12] A third strategy of universal EMR for all lesions was also included in the assessment. High risk was defined as lesions with a Kudo class V pit pattern, a Paris classification of 0 to IIc (indicating a depressed lesion), or a nonlifting sign.[12] Patients with these lesions were assigned either selective or universal ESD and were followed for up to 18 months. The main outcome of interest was the requirement for surgery. Surgery would be required for all low-risk cancers removed by EMR, for all high-risk cancers (defined as those with deeper submucosal invasion or with features such as poor differentiation or lymphovascular invasion), and for perforation that would not be amenable to endoscopic management.

The investigators found that selective ESD was the most cost-effective strategy.[12] It was more effective than EMR and slightly less effective than universal ESD. Compared with universal ESD, selective ESD of high-risk lesions was associated with an incremental cost-effectiveness of $146,312 Australian dollars (approximately $115,800 US) per surgery avoided. When the procedure was performed in the rectum, this cost-effectiveness advantage was decreased to $50,344 Australian dollars (approximately $39,850 US). Overall, the study appears to support selection of the resection technique based on the underlying risk of invasive cancer.

Endoscopic Mucosal Resection

Most recent studies evaluating EMR for polyp resection have originated from the Australian Colonic Endoscopic (ACE) resection study group, which started collecting prospective data in 2008. Through the years, the study has enrolled more than 2000 patients with more than 2300 nonpedunculated colorectal lesions 20 mm or larger.[13]

There are 2 clinically important challenges associated with EMR. The first is a higher risk of delayed bleeding, referred to as post-EMR bleeding, which occurs in approximately 5% to 10% of cases.[6,14-16] Typically, within a week of the procedure, patients present with hematochezia that may require hospitalization, blood transfusion, and repeat colonoscopy. The second challenge is a significant recurrence rate of approximately 15% (ranging from approximately 6% to 30% across studies) at the first surveillance colonoscopy.[17]

To increase resection efficacy and reduce the risk of recurrence, several attempts have been made to improve the EMR technique. To truly produce improvements, however, it is important to understand which characteristics of a polyp make it more difficult to resect or confer a higher risk of recurrence. Tate and colleagues presented an abstract on this issue at the 2016 DDW.[18] The Sydney EMR Recurrence Tool (SERT) is a strategy to stratify the risk of recurrence. It provides a score that considers 4 aspects: polyp size, colonic location (either left side or right side), polyp morphology (pedunculated, sessile, or flat), and how the endoscopist subjectively judged the EMR (easy or difficult). The resulting score, ranging from 4 points to 12 points, is then grouped into stratification categories for risk of recurrence. The lowest SERT scores corresponded to polyps that were smaller, located on the left side, had a pedunculated or sessile morphology, and were thought to be easily resectable. A lower SERT score was associated with successful EMR. Interestingly, low SERT scores were also associated with decreased risks of intraprocedural bleeding and delayed bleeding. The SERT score was also found to successfully identify those patients at greatest risk for recurrence. For example, after 6 months post-EMR, the cumulative risk of recurrence was 5.6% for SERT 0 lesions compared with 14.8% for SERT 1 through 4 lesions (P<.001). This pattern continued and remained significant at 12 months (7.8% vs 25.3%; P<.001), 18 months (8.5% vs 31.8%; P<.001), and 36 months (16.8% vs 46.6%; P<.001) of post-EMR follow-up. One potential use of SERT in clinical practice would be to refer patients with high-scoring polyps to an expert with greater skill.

Another interesting aspect of EMR is the question of whether electrocautery is needed for successful resection. It has long been known that diminutive polyps (<5 mm) can be removed without electrocautery. In recent years, an increasing number of cohort studies have investigated the use of cold snare resection for slightly larger polyps (<10 mm). Initial results suggest that cold snare resection for polyps smaller than 10 mm is at least as effective, and likely safer, than hot snare resection.[19] Because the risk of delayed bleeding complications appears very low with this technique, it has been evaluated for use with increasingly larger polyps. One recent case series of more than 73 patients (56 completing follow-up) showed that large nonpedunculated polyps larger than 1 cm could be safely and completely removed by cold snare resection, with no postprocedure bleeding.[20] Cold snare resection requires piecemeal removal of the polyp, and therefore takes longer to accomplish. Additionally, this piecemeal removal may increase the risk for recurrence.

At the 2017 DDW, a prospective observational study was presented by Tutticci and Hewett on the role of cold piecemeal EMR for large, sessile serrated colonic polyps.[21] The study enrolled patients who had at least 1 sessile serrated polyp that was 10 mm or larger. A total of 163 polyps from 99 patients were identified and resected using

cold piecemeal resection with submucosal injection. The mean size of the resected polyps was 17 mm (range, 10-40 mm), and 38% of polyps were 20 mm or larger. Nearly all polyps (98%) were located in the proximal colon. All but 2 polyps (1%) were completely removed, based on biopsy from the resection margin. There was only 1 case of residual (or recurrent) serrated neoplasia at surveillance colonoscopy, which was performed a median of 154 days after EMR (81% completion rate). Intraprocedural bleeding that was controlled with a clip was reported in 1 patient. One patient required admission for abdominal pain postprocedure, and no delayed bleeding occurred. The study suggests that cold piecemeal resection for sessile serrated polyps 10 mm or larger is safe and effective, with low overall bleeding complications and very low recurrence rates.

As mentioned previously, the risk of recurrence is a primary concern with EMR. Over the past few years, different groups have investigated whether biopsies are needed to prove recurrence. Results from a German study suggested that a risk for recurrence remains even if the biopsies are negative at the time of the second colonoscopy.[22] Separately, another group from the Mayo Clinic in Jacksonville, Florida, demonstrated that biopsies could be avoided if NBI is used in conjunction with confocal lesion microscopy.[23]

At the 2017 DDW, Kandel and colleagues reported on an evaluation of the diagnostic accuracy of high-definition white light and NBI with and without near-focus mode in the optical detection of residual neoplasia after EMR in real-time.[24] This ongoing, prospective, double-blind, observational study included patients with EMR scars from an initial polyp that was 20 mm or larger. Endoscopists predicted recurrence (and indicated their level of confidence) based on visual assessment of the previous EMR site using 4 imaging modalities: high-definition white-light colonoscopy, high-definition white-light colonoscopy with near-focus, NBI, and NBI with near-focus. Subsequently, all images were presented in a random order 3 to 6 months after the index procedure to 5 experienced EMR physicians to check interobserver agreement across the modalities.

A total of 161 post-EMR scars in 154 patients were included. The median follow-up was 8 months. The prevalence of recurrence was 28.0%, corresponding to 45 lesions. Most of the recurrent lesions were located in the proximal colon (87%). The median original polyp size was 30 mm (range, 20-140 mm). All 45 lesions had been removed piecemeal. Using NBI with near-focus imaging, 80% of the EMR lesions were accurately diagnosed with high confidence. This rate decreased to 77% with NBI alone, and was even lower with white light alone (62%) and white light with near-focus (68%). The interobserver agreement for NBI with near-focus was substantial (kappa, 0.81; 95% CI, 0.68-0.94). NBI with near-focus imaging was found to have a high sensitivity and negative predictive value, together with a good positive predictive value. These results strongly suggest that biopsies may be avoided at the first follow-up colonoscopy, thus lending insight into an important aspect of follow-up after EMR resection of large polyps.

Endoscopic Submucosal Dissection

An important question raised in the past few years is how to select polyps for endoscopic resection vs surgical resection. Traditionally, there was an argument that polyps perhaps should not be removed if located in the ileocecal valve, at the anal canal, or in the appendiceal orifice. Previously, the ACE study group showed that large lesions extending into the ileocecal valve or at the anorectal junction could indeed be removed by EMR very effectively.[25,26]

At the 2017 DDW, a study presented by Boda and colleagues from Japan evaluated the resection of large, nonpedunculated lesions in the cecum.[27] This retrospective analysis identified 78 consecutive patients with cecal lesions (29 patients had lesions that extended into the appendiceal orifice; lesions in the remaining 49 patients did not extend into the appendiceal orifice). Data were evaluated for patients with lesions in which a distal margin could be seen and was still accessible. The study found that lesions that extended to the appendiceal orifice took longer to remove and had significantly more submucosal fibrosis (48% vs 24%; $P<.05$). The rate of en bloc resection using ESD was 90% among patients whose lesions extended into the appendiceal orifice vs 96% in patients whose lesions did not extend into that region. Perforations occurred in 2 of the 29 patients with extension into the appendiceal orifice and in 1 of the 49 patients in the comparison group. The authors concluded that ESD is an effective and safe technique for resection of polyps that extend into the appendiceal orifice. The study is limited by its small size, retrospective design, and lack of patient matching. However, the data suggest that ESD can be used to remove large lesions, even those that extend into the appendiceal orifice.

Areas of Future Research

We have gained a great deal of experience with EMR and ESD over recent years. As exemplified by some of the presentations at the 2017 DDW, large polyp resection must be performed by an endoscopist who is not only experienced in EMR or ESD, but who is also an expert at "reading" polyps and understanding characteristics of

higher risk. Endoscopists must be able to apply the Paris classification system as well as identify the Kudo pit pattern and surface features, such as granular or nongranular appearance.

The guiding principle for endoscopic resection is to select the best approach, determine whether a lesion should be removed by EMR or ESD, and understand which adjunctive strategies might help ensure completeness of resection. These adjunctive approaches include assuring an optimal position, using retroflexion as appropriate, using a cap to optimize position of the scope in front of the lesion, and using gravity. It is also vital to recognize complications, such as the target sign, which suggests a deep mural injury with an impending perforation and requires closure of the mucosal defect.[28]

Cold snare resection will likely have an important role in future research, as it has the potential to confer a lower risk of complications. Larger, comparative studies must be performed for confirmation. Another approach is to better understand whether closing a mucosal defect with clips after resection will help reduce bleeding complications. Finally, because of the high skill level required for ESD, a simpler approach using advancements in endoscopic equipment technology could prove useful.

Disclosure

Dr Pohl is a consultant for Interscope Inc and Aries Pharmaceuticals. He had received grants from Boston Scientific and US Endoscopy. The contents of this article do not represent the views of the Department of Veterans Affairs or the United States Government.

References

1. Leung K, Pinsky P, Laiyemo AO, Lanza E, Schatzkin A, Schoen RE. Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. *Gastrointest Endosc*. 2010;71(1):111-117.
2. Farrar WD, Sawhney MS, Nelson DB, Lederle FA, Bond JH. Colorectal cancers found after a complete colonoscopy. *Clin Gastroenterol Hepatol*. 2006;4(10):1259-1264.
3. Robertson DJ, Lieberman DA, Winawer SJ, et al. Interval cancer after total colonoscopy: results from a pooled analysis of eight studies [AGA abstract 795]. *Gastroenterology*. 2008;134(suppl 1).
4. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy—results of the complete adenoma resection (CARE) study. *Gastroenterology*. 2013;144(1):74-80.e1.
5. Burgess NG, Bourke MJ. Endoscopic resection of colorectal lesions: the narrowing divide between East and West. *Dig Endosc*. 2016;28(3):296-305.
6. Hassan C, Repici A, Sharma P, et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. *Gut*. 2016;65(5):806-820.
7. Fujiya M, Tanaka K, Dokoshi T, et al. Efficacy and adverse events of EMR and endoscopic submucosal dissection for the treatment of colon neoplasms: a meta-analysis of studies comparing EMR and endoscopic submucosal dissection. *Gastrointest Endosc*. 2015;81(3):583-595.
8. Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal ID. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. *Endoscopy*. 2013;45(10):827-834.
9. Backes Y, de Vos Tot Nederveen Cappel WH, van Bergeijk J, et al. Risk for incomplete resection after macroscopic radical endoscopic resection of T1 colorectal cancer: a multicenter cohort study. *Am J Gastroenterol*. 2017;112(5):785-796.
10. Moss A, Williams SJ, Hourigan LF, et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut*. 2015;64(1):57-65.
11. Rex DK. Does every big polyp need EMR? General Session presentation at: the 2017 Digestive Disease Week; May 6-9, 2017; Chicago, IL. Session Sp66.
12. Bahin FF, Heitman SJ, Rasouli KN, Lee EY, Williams SJ, Bourke MJ. Wide-field endoscopic mucosal resection versus endoscopic submucosal dissection for laterally spreading colorectal lesions: a cost-effectiveness analysis [DDW abstract 47]. *Gastrointest Endosc*. 2017;85(5 suppl).
13. ClinicalTrials.gov. The Australian Colonic Advanced Mucosal Neoplasia and Endoscopic Resection Study (ACER/AMN). https://clinicaltrials.gov/ct2/show/NCT02000141. Identifier: NCT02000141. Accessed August 17, 2017.
14. Metz AJ, Bourke MJ, Moss A, Williams SJ, Swan MP, Byth K. Factors that predict bleeding following endoscopic mucosal resection of large colonic lesions. *Endoscopy*. 2011;43(6):506-511.
15. Albéniz E, Fraile M, Ibáñez B, et al; Endoscopic Mucosal Resection Endoscopic Spanish Society Group. A scoring system to determine risk of delayed bleeding after endoscopic mucosal resection of large colorectal lesions. *Clin Gastroenterol Hepatol*. 2016;14(8):1140-1147.
16. Burgess NG, Metz AJ, Williams SJ, et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. *Clin Gastroenterol Hepatol*. 2014;12(4):651-661.
17. Ortiz AM, Bhargavi P, Zuckerman MJ, Othman MO. Endoscopic mucosal resection recurrence rate for colorectal lesions. *South Med J*. 2014;107(10):615-621.
18. Tate DJ, Klein A, Desomer L, et al. Predicting adenoma recurrence after colonic endoscopic mucosal resection; the Sydney EMR Recurrence Tool (SERT) [DDW abstract 391]. *Gastrointest Endosc*. 2016;83(5 suppl).
19. Repici A, Hassan C, Vitetta E, et al. Safety of cold polypectomy for <10mm polyps at colonoscopy: a prospective multicenter study. *Endoscopy*. 2012;44(1):27-31.
20. Piraka C, Saeed A, Waljee AK, Pillai A, Stidham R, Elmunzer BJ. Cold snare polypectomy for non-pedunculated colon polyps greater than 1 cm. *Endosc Int Open*. 2017;5(3):E184-E189.
21. Tutticci NJ, Hewett DG. Cold piecemeal endoscopic mucosal resection (EMR) for large sessile serrated colonic polyps [DDW abstract 693]. *Gastrointest Endosc*. 2017;85(5 suppl).
22. Knabe M, Pohl J, Gerges C, Ell C, Neuhaus H, Schumacher B. Standardized long-term follow-up after endoscopic resection of large, nonpedunculated colorectal lesions: a prospective two-center study. *Am J Gastroenterol*. 2014;109(2):183-189.
23. Shahid MW, Buchner AM, Coron E, et al. Diagnostic accuracy of probe-based confocal laser endomicroscopy in detecting residual colorectal neoplasia after EMR: a prospective study. *Gastrointest Endosc*. 2012;75(3):525-533.
24. Kandel P, Brand EC, Chen WC, et al. Diagnostic accuracy of optical detection of colorectal neoplasia after endoscopic mucosal resection: prospective double blind comparison of high definition white light, narrow band imaging and near focus [DDW abstract 690]. *Gastrointest Endosc*. 2017;85(5 suppl).
25. Nanda KS, Tutticci N, Burgess NG, Sonson R, Williams SJ, Bourke MJ. Endoscopic mucosal resection of laterally spreading lesions involving the ileocecal valve: technique, risk factors for failure, and outcomes. *Endoscopy*. 2015;47(8):710-718.
26. Holt BA, Bassan MS, Sexton A, Williams SJ, Bourke MJ. Advanced mucosal neoplasia of the anorectal junction: endoscopic resection technique and outcomes (with videos). *Gastrointest Endosc*. 2014;79(1):119-126.
27. Boda K, Tanaka S, Oka S, et al. Endoscopic submucosal dissection for superficial colorectal tumors with extension into the appendiceal orifice [DDW abstract 50]. *Gastrointest Endosc*. 2017;85(5 suppl).
28. Burgess NG, Bassan MS, McLeod D, Williams SJ, Byth K, Bourke MJ. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors [published online July 27, 2016]. *Gut*. doi:10.1136/gutjnl-2015-309848.

Polyp Resection and Removal Procedures: Further Observations

Vivek Kaul, MD, FACG, FASGE, AGAF
Segal-Watson Professor of Medicine
Chief, Division of Gastroenterology & Hepatology
Center for Advanced Therapeutic Endoscopy
University of Rochester Medical Center
Rochester, New York

Carol Burke, MD, FACG, AGAF, FASGE, FACP
Vice Chair, Department of Gastroenterology and Hepatology
Director of the Center for Colon Polyp and Cancer Prevention
Cleveland Clinic
Cleveland, Ohio

Heiko Pohl, MD
Associate Professor of Medicine
Geisel School of Medicine at Dartmouth
Hanover, New Hampshire
Department of Gastroenterology, Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Department of Gastroenterology, VA Medical Center
White River Junction, Vermont

Vivek Kaul, MD There are 3 points that we have become familiar with as endoscopists. The first point is that extensive biopsies of these lesions during the first colonoscopy procedure can sometimes create fibrosis that may then interfere with future EMR/ESD procedures. Biopsies performed at the edge of the lesion are preferable. The second point concerns tattooing of these lesions by the referring physician. A tattoo should not be made into or near the lesion or the lesion base; it should be made away from the lesion. The tattoo itself creates fibrosis and may also make subsequent EMR or ESD more tedious. The third point is that endoscopists should not attempt an endoscopic resection if they are not confident of (or committed to) completing the resection, especially if the lesion is too large and/or in a difficult location anatomically. Such partial attempts at resection, especially using cautery, create significant fibrosis that tethers the polyp significantly to the colonic wall, making subsequent resection not only more difficult, but also increases the potential for perforation due to the adherence of the wall layers and inability to lift the lesion optimally using submucosal injection.

Carol Burke, MD Most practitioners are seeing patients with reasonably sized polyps, smaller than 10 mm. It is becoming less common to see very large polyps. Is there a best approach for diminutive and small polyps?

Heiko Pohl, MD There have been many studies of diminutive polyps. It is concerning to see how common they are, and their rate of incomplete resection. It is clear that diminutive polyps should not be removed with forceps. The incomplete resection rate is very high with forceps, and it increases with the size of the polyp. Instead, a snare should be used. Comparative studies have shown that a snare achieves a higher rate of complete resection compared with forceps.

Cold snare resection has increasingly been applied for medium-sized polyps up to 10 mm. A cold snare resection appears to be safe, with a low rate of concerning adverse events. Recent guidelines from the European Society of Gastrointestinal Endoscopy recommend cold snare for all polyps smaller than 10 mm. This approach is not widely practiced throughout the United States.

A study from Japan compared standard snares with dedicated cold snares, which tend to be more stiff.[1] The study found that the dedicated cold snare had a lower

incomplete resection rate than the standard snare. Both rates of incomplete resection were high, at 20% and 10%, but it seems that a dedicated cold snare might be better. In a way, this finding makes sense. A stiff snare seems to grab the healthy margins a little better. It is still unclear which snares require a particular technique. The gentle "push-close-cut" technique with cold snare removal, as opposed to the "close-and-lift" technique with hot snare resection, may be less familiar to clinicians. It can be difficult to cut through a lesion with a snare. Tissue remnants recognized as fibrous tissue are typically not neoplastic tissue. There is a learning curve that accompanies the use of cold snares for larger polyps. It is unclear what the upper size limit is for a cold snare.

It appears that submucosal injection may facilitate cold snare resection. In Asian and European countries, endoscopists are more likely to use submucosal injection for smaller polyps than in the United States. It appears that US endoscopists reserve submucosal injection for polyps that are larger. Perhaps we should have a lower threshold for using submucosal injectate to ensure a better margin and for complete removal. Studies of this question would be an important contribution to the field.

Carol Burke, MD In clinical practice, it seems obvious that submucosal injection with some contrast agents can define the borders of a serrated neoplasm much better than just fluid. Are there studies of indigo carmine or methylene blue?

Heiko Pohl, MD In general, I am not aware of any comparative studies between indigo carmine and methylene blue. Some endoscopists do have a preference for one or the other. Methylene blue is often used in a very diluted fashion. As you said, the margins may be more contrasted by the injection dye. A study by Pellise and colleagues found a recurrence rate for sessile serrated polyps of 7% as compared with 18% for adenomatous polyps.[2] Lifting the lesion and using methylene blue injectate may improve the complete resection rate by contrasting the lesion with the normal surrounding mucosa. With respect to injectates, those that are more viscous (eg, artificial tears, hetastarch, hydroxyethyl starch, or succinylated gelatine) provide a longer lasting cushion, and are therefore often preferred over normal saline. At the 2017 DDW, Rex and colleagues presented the results of a randomized, controlled trial that compared normal saline vs Eleview, which is a viscous fluid that includes medium-chain triglycerides and methylene blue as a contrast agent.[3] Lesions in the Eleview group required less injection volume, and were removed in a shorter time, supporting the use of Eleview as a submucosal injectate.

Disclosures

Dr Kaul is a consultant/speaker for Aries Pharmaceuticals. Dr Burke has received research support from Cancer Prevention Pharmaceuticals and Ferring Pharmaceuticals. Dr Pohl is a consultant for Interscope Inc and Aries Pharmaceuticals. He had received grants from Boston Scientific and US Endoscopy. His comments do not represent the views of the Department of Veterans Affairs or the United States Government.

References

1. Horiuchi A, Hosoi K, Kajiyama M, Tanaka N, Sano K, Graham DY. Prospective, randomized comparison of 2 methods of cold snare polypectomy for small colorectal polyps. *Gastrointest Endosc*. 2015;82(4):686-692.
2. Pellise M, Burgess NG, Tutticci N, et al. Endoscopic mucosal resection for large serrated lesions in comparison with adenomas: a prospective multicentre study of 2000 lesions. *Gut*. 2017;66(4):644-653.
3. Rex D, Wallace MB, Sharma P, Lollo G, Maselli R, Repici A. A randomized, double-blind trial of a new injectable solution (Sic 8000) for endoscopic resection of colonic polyps larger than 2 cm: an interim report [DDW abstract 689]. *Gastrointest Endosc*. 2017;85(5 suppl).

Slide Library

Colorectal Cancer

- The second-leading cause of cancer-related deaths in men and the third in women[1]
- An estimated 50,260 deaths will be attributed to CRC in the United States in 2017[2]
- When CRC is diagnosed at a localized stage (confined to the colon or rectum), the 5-year relative survival rate reaches 89.9%
- However, only 39% of all patients with CRC are diagnosed at a curable stage, and most are diagnosed after CRC has spread to regional lymph nodes (35%) or metastasized to distant organs (21%), when it is associated with a 5-year survival of 13.9%

CRC, colorectal cancer. 1. American Cancer Society. Cancer Facts and Figures 2017. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf. 2. National Cancer Institute. Cancer Stat Facts: Colon and Rectum Cancer, 2017. https://seer.cancer.gov/statfacts/html/colorect.html

Most Common Methods for CRC Screening

- Colonoscopy
- Fecal occult blood test
- Stool DNA test
- Virtual (CT) colonoscopy
- Sigmoidoscopy

CT, computed tomography.

Screening Colonoscopy

- Screening colonoscopy is very effective, and it is associated with durable protection from CRC
- Multiple cohort and case-control studies have demonstrated the efficacy of screening colonoscopy for decreasing CRC incidence and preventing CRC-related mortality
- The durability of protection of a negative screening colonoscopy lasts up to 10 years

Adenoma Detection Rate

- The ADR is considered a premier colonoscopy quality benchmark
- It inversely correlates with the incidence and mortality of interval CRCs
- For every 1% increase in the ADR, there is a 3% decrease in CRC incidence and a 5% decrease in CRC-related mortality[1]
- Physicians who had an ADR of 20% or better had a substantially reduced rate of interval cancers compared with physicians who had an ADR under 20%[2]

ADR, adenoma detection rate. 1. Corley DA et al. *N Engl J Med*. 2014;370(14):1298-1306. 2. Kaminski MF et al. *N Engl J Med*. 2010;362(19):1795-1803.

Strategies to Enhance Adenoma Detection

- High-definition colonoscopy has been shown to increase ADR compared with standard white-light colonoscopy in physicians with a low ADR[1]
- Reports have suggested that chromoendoscopy may increase ADR vs standard white-light colonoscopy, but data are not conclusive[2]
- Technology that allows visualization behind colonic folds—such as wide-angle colonoscopy, a retrograde viewing device, a ring attachment on the scope tip, and a balloon colonoscope—has been associated with lower miss rates of adenomas smaller than 10 mm compared with standard colonoscopy[3-6]

1. Ahlenius NY et al. *Surg Endosc*. 2017;31(1):79-84. 2. Hashimoto K et al. *Hepatogastroenterology*. 2010;57(104):1399-1404. 3. Rex DK et al. *Am J Gastroenterol*. 2003;98(9):2000-2005. 4. Adler A et al. *Clin Gastroenterol Hepatol*. 2012;10(2):155-159. 5. Halphen Z et al. *Endoscopy*. 2015;47(3):238-244. 6. Leufkens AM et al. *Gastrointest Endosc*. 2011;73(3):480-489.

Polyp Resection

- The completeness of polyp resection in clinical practice is dependent on several factors: endoscopist experience, technique, and expertise; polyp size and morphology; polyp location; colonic anatomy; and quality of the bowel prep
- Larger polyps are more likely to harbor advanced pathology, and they are typically removed by EMR or ESD techniques
- Surgical resection is recommended only for those patients who have a clearly infiltrative (invasive), advanced lesion that is not amenable to safe and complete endoscopic resection

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

Endoscopic Mucosal Resection vs Endoscopic Submucosal Dissection

- EMR has a relatively high recurrence rate of approximately 15% at first surveillance colonoscopy[1,2]
- Endoscopic removal of recurrent adenoma is typically achieved for most patients, and at second surveillance colonoscopy, the recurrence rate approaches that of ESD (approximately 2%)[3,4]
- EMR is easier to perform, as it requires less skill and less time, and it uses less expensive devices
- However, EMR may lead to piecemeal resection, making assessment of deep and lateral margins difficult, especially in the setting of advanced pathology

1. Hassan C et al. Gut. 2010;59(3):309-315. 2. Fujiya M et al. Gastrointest Endosc. 2013;81(3):583-595. 3. Moss A et al. Gut. 2010;59(1):57-65. 4. Rex D et al. DDW abstract 689. Gastrointest Endosc. 2017;85(5 suppl).

Submucosal Injection

- In the United States, the use of submucosal injection is preferred when a polyp is 1.5 cm to 2 cm or larger, particularly when it is located in the proximal colon, where the colon wall is thinner
- Submucosal injection decreases the risk of thermal injury and perforation if a hot snare is used
- The traditional medium, saline, dissipates quickly, and the submucosal cushion it creates typically does not last long

A Novel Premixed Solution for Submucosal Lifting

- Eleview contains methylene blue, water for injection, medium-chain triglycerides, poloxamer 188 (the bulking/cushioning agent), polyoxyl-15-hydroxystearate, and sodium chloride (premixed for injection)
- At the 2017 DDW, Rex and colleagues presented interim results of a randomized, double-blind trial of Eleview for EMR of colonic polyps >2 cm[1]
- Compared with saline, Eleview required a lower mean total injection volume to complete the EMR procedure (16.1 ±9.8 mL vs 31.6 ±32.1 mL; *P*<.001)
- Eleview was associated with a shorter mean time to resect the lesion (19.15 ±16.80 min vs 29.70 ±69.18 min; *P*=.326). With Eleview, the lesion was removed in fewer resected pieces (mean, 5.70 ±6.0 vs 6.47 ±5.0; *P*=.052)

DDW, Digestive Disease Week; EMR, endoscopic mucosal resection. 1. Rex D et al. DDW abstract 689. Gastrointest Endosc. 2017;85(5 suppl).

En Bloc Resection

- Once the submucosal lift is achieved, a smaller polyp (2 to 4 cm) in a good location may be suitable for an en bloc resection, which means the entire lesion is removed in 1 piece by EMR or ESD
- There are obvious advantages to removing the lesion in a single piece: it provides the best sample for accurate pathologic assessment of deep and lateral margins, and the procedure is quicker than with piecemeal resection, more likely to be a complete resection, and utilizes fewer injections and injectate
- The pathologist is able to definitively look at the margins, both lateral margins and deep margins, and is able to provide a more confident pathologic diagnosis in terms of invasion (or lack of invasion)

For a free electronic download of these slides, please direct your browser to the following web address:

http://www.gastroenterologyandhepatology.net


G&H