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Management of the malignant colorectal polyp

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Introduction

The term "malignant polyp" refers to any polyp of the colon or rectum harboring malignancy that invades through the muscularis mucosa. Management of these polyps has progressively become both a more common and more complex subject facing surgeons and endoscopists. The use of screening colonoscopy has increased and therefore more malignant polyps are being detected. Simultaneously, a variety of new endoluminal devices and advanced endoscopic techniques have become available. These approaches have opened new avenues to minimally invasive polyp removal but have complicated the decision-making process for surgeons. In this monograph, we review the principles, and literature surrounding the management of malignant colorectal polyps.

Epidemiology

Colorectal cancer is the fourth most commonly diagnosed cancer in the United States, and for men and women it is the third most common cause of cancer related mortality.[1] In 2018, colorectal cancer was expected to account for 8.1% of all new colorectal cancer diagnoses.[2] Malignant polyps comprised roughly 12% of all colorectal polyps in a recent series.[3] The increasing incidence of colorectal cancer has coincided with increasing utilization of screening colonoscopy. In a large, multicenter prospective study from 2000-2011, the utilization of screening colonoscopy increased 3-fold over the past decade.[4] Along with the increased discovery of malignant polyps, patients undergoing screening are increasingly more likely to undergo surgical resection.[5] In the United States, the incidence of surgery for non–malignant polyps and for colorectal cancer has almost doubled from 2000 to 2014.[6]

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Reported incidence rates of malignant polyps vary widely. As few as 0.4% and as many as 10% of all endoscopically removed polyps have been found to be malignant depending upon the series.[7–10] This discrepancy is likely in part due to the different time periods in which these series were performed, as well as the unique patient populations from which they were drawn. There are few recent large series available and it is therefore difficult to make inferences regarding the true incidence of malignant polyps. However, since 85%-95% of colorectal cancers are felt to arise from adenomatous polyps, it is likely that the incidence of malignant polyps mirrors that of colorectal cancer more generally.[11,12] Recently there are concerning increases in colorectal cancer incidence especially in young people. Although population level data are lacking, it can be expected that the incidence of malignant polyps in this patient population will continue to increase as well.[13,14]

Risk factors

Patient-related risk factors for the development of malignant polyps are the same as those for the development of advanced adenomas and colorectal cancer. Age is closely related with risk for adenoma and colon cancer development.[15–17] In particular, the rate of adenoma development is known to increase after 50 years of age, which has guided screening recommendations.[18] However, clinicians should be cognizant of the increasing incidence of colorectal cancer in patients less than 50 years old.[19]They should also be aware that the prevalence of adenomas in adults 40-49 years old is similar to that in adults 50-59 years old, although fewer of these adenomas are clinically advanced at the time of detection.[20]

Sex, as well as race and ethnicity, also play a role in adenoma and cancer risk. Compared to their White counterparts, the Black population at a similar age has a higher risk of advanced adenoma development, and those of Hispanic ethnicity have a slightly lower risk of advanced adenoma development. Overall, women have a lower risk of advanced adenoma development compared to men, regardless of race.[21] When the risk factors of age, race and/or ethnicity, and sex are combined, similar levels of risk are seen in 50 to 54 tear old White men, 65 to 69 year old White women, 55 to 59 year old Black women, 50 to 54 year old Black men, 55 to 59 year old Hispanic men, and 70 to 74 year old Hispanic women.[22]

Many other patient-related risk factors for colorectal cancer risk have been identified. These risk factors include a personal or family history of colorectal cancer or advanced adenoma, cigarette smoking, alcohol consumption, obesity, sedentary lifestyle, and red meat consumption.[23–25] Protective factors against the development of colorectal cancer include exercise, fruit and vegetable consumption, aspirin use, and hormone replacement therapy.[26,27] Several important hereditary polyposis and colorectal cancer syndromes exist.

Pathology

Malignant polyps are defined as those polyps which harbor adenocarcinoma that invades through the muscularis mucosa and into the submucosa. These lesions are categorized as T1 lesions in the TNM staging system.[28] Subsequent management is heavily reliant on several key histopathologic features. These features include size, gross morphology, depth of invasion, polypectomy margin, architecture, lymphovascular invasion, and differentiation. Other pathologic entities, such as carcinoma in situ, high grade dysplasia, and pseudo-invasion are distinct from the malignant polyp.

Malignant polyp formation is theorized to take place in 2 separate phases: tumor initiation and the tumor progression. Tumor initiation is the time at which the adenoma first forms within the lumen of the colon or rectum. The *APC* gene found in epithelial cells is believed to be responsible for most, if not all, of adenoma formation. This malignant transformation occurs via the 2-hit hypothesis in which both *APC* alleles mutate and thus lose function. This may happen either via a germline mutation inherited from an affected parent, as in familial adenomatosis

polyposis (FAP), or by somatic mutation whereby the *APC* is either lost or mutated in situ to initiate the carcinogenic cascade. Tumor progression encompasses the cascade of genetic mutations that then follow. K-Ras, DCC, and p53 are involved in this process, leading to the development of malignant and metastatic properties.

Malignant polyps can also arise from defects in DNA mismatch repair. This is seen most notably in hereditary non–polyposis colon cancer (HNPCC). Mismatch repair proteins normally are responsible for recognizing and correcting the errors that normally occur during DNA replication. When mismatch repair enzymes are deficient, errors in DNA accumulate. Indirect evidence of these errors can be detected as changes in the length of short repeats of DNA, termed microsatellites. Microsatellite instability is therefore associated with deficient mismatch repair and subsequent cancer development.[29,30] Microsatellite instability is observable in 15% of sporadic colon cancers and 85% of HNPCC-associated colon cancers.[31]

Size and morphology

At the time of index endoscopy, polyps are classified grossly as either pedunculated or sessile. Pedunculated polyps are attached to the surrounding colonic epithelium via a stalk. Sessile polyps form in a broad, flat morphology. This gross morphology has implications for removal. Sessile polyps lack the protective stalk of pedunculated polyps and are more likely to harbor lymphatic invasion as well as lymph node metastases at the time of identification.[32–34] Sessile polyps can also be more technically demanding to remove. This is especially true for endoscopic snare polypectomy, which may be straightforward for a pedunculated polyp, but challenging or even impossible for a similarly-sized sessile polyp.

Polyp size and the likelihood of harboring malignancy are closely linked, with small polyps being much less likely to contain invasive adenocarcinoma. In one series of more than 5000 polyps less than 5 mm in diameter, none contained malignant properties.[35] However, as size increases, so, too, does the risk of malignancy. In the same large series, polyps between 2.6 cm and 3.5 cm contained malignancy in 42.7% of cases, whereas polyps larger than 3.5 cm were found to contain malignancy in 75.8% of cases. Both size as well as morphology should therefore be considered when estimating the risk of underlying malignancy in a polyp.

There are several additional distinct polyp morphologies that are indicative of potential submucosal invasion. Elevated lesions with a depressed center, described as type IIa and IIc lesions by the Paris classification, are at increased risk.[36] Similarly, irregular contours, a short or immobile stalk, or inability to elevate a sessile polyp are qualities concerning for invasion.[37]

Depth of invasion

The radial spread of carcinoma from the epithelium into deeper layers of the bowel wall is referred to as depth of invasion. The Haggitt classification has been used to describe the level of invasion in greater detail for both pedunculated and sessile polyps (Fig 1).[38] Lesions at level 0 in the Haggitt system are confined to the mucosa and do not penetrate the muscularis mucosa. Levels I-III only apply to pedunculated polyps and refer to submucosal invasion in the head, neck, or stalk of the polyp, respectively. Level IV can be used to describe either sessile or pedunculated polyps, and refers to invasion into the submucosa, at the level of surrounding epithelium. Any sessile polyp with some degree of submucosal invasion is therefore automatically considered to be at least Haggitt level IV. Level IV is also the only clinically relevant Haggitt level, as it portends an increased risk of lymph node metastasis.[33] Although the risk of lymph node metastasis related to a Haggitt level 0-III lesion is less than 1%, the risk of a lymph node metastasis in Haggitt 4 lesions can be up to 25%.[1]

For sessile polyps, the degree of submucosal invasion has been further subcategorized into 3 levels.[39,40] Invasion confined to the superficial third of the submucosa is referred to as Sm1, and invasion into the middle and deep thirds, Sm2 and Sm3, respectively.[41] Deeper penetration

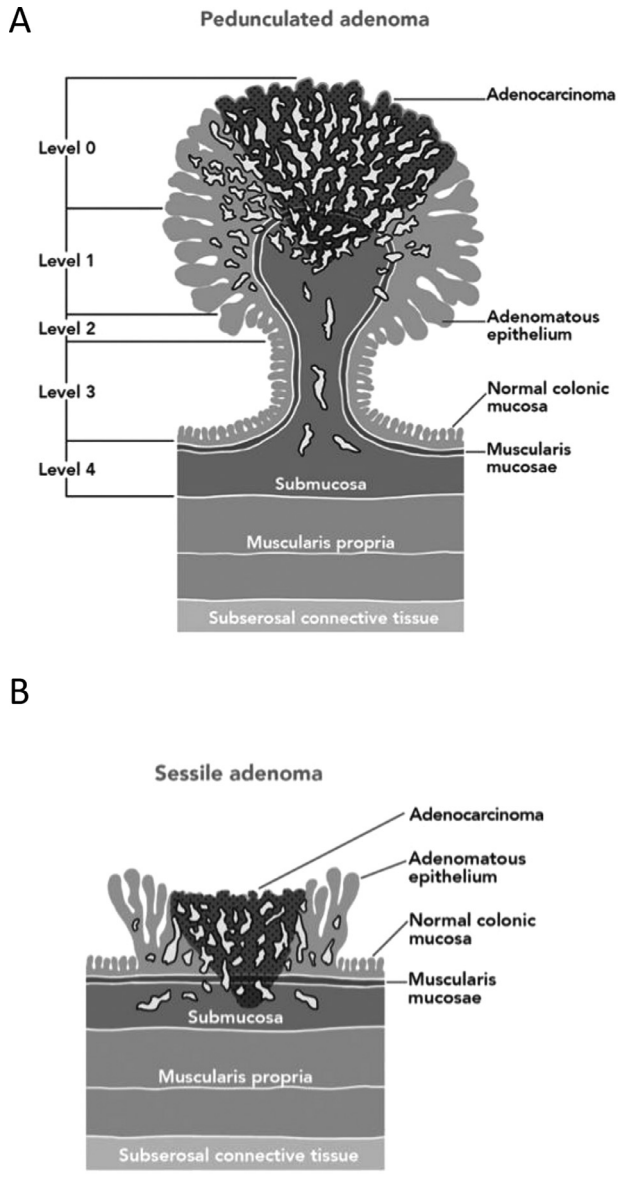

Fig. 1. (A) Haggitt classification of pedunculated polyps and (B) Kikuchi classification of sessile polyps.

into the submucosa is associated with greater likelihood of lymph node metastases, particularly in Sm3 lesions.[42,43] A major drawback of this classification scheme is that it requires either the specimen to contain a portion of the muscularis propria, or for the pathologist to estimate where this margin might have been, which also puts the patient at a greater risk of perforation.[44] Others have suggested that invasion of more than 1 mm into the submucosa is associated with lymph node metastasis.[45–47] Using 1 mm of submucosal invasion as a cutoff limits some of the subjective assessment required with other methods, while potentially still identifying patients who are adequately treated with polypectomy.

Resection margin

Polypectomy specimens must be removed with sufficient margin to ensure adequate local clearance of malignant cells. The size of the margin required is debated, but most evidence favors a margin of 1 mm or greater for malignant polypectomy specimens. In a series by Butte and colleagues (48), none of the patients with a polypectomy margin ≥1 mm had residual disease in the specimen obtained during subsequent colectomy. This finding was confirmed by Kim and colleagues[49] who performed a similar retrospective review of 148 patients who had undergone colectomy after malignant polypectomy. They also found that none of the 67 patients with a negative polypectomy margin (≥1 mm) had residual disease. These studies support prior series, which found no statistically significant improvement in the rate of adverse outcomes for specimens with a wider resection margin.[32] Several other large case series have used 2 mm as a cutoff for positive margin.[50,51] Current National Comprehensive Cancer Network (NCCN) guidelines do not favor a specific margin for malignant polyp excision and note the lack of consensus on an acceptable margin.[52]

Polyp architecture

There are 3 main architectural variants of adenomatous polyps: tubular, villous, and tubulovillous. Malignant potential is correlated directly with the degree of villous histology. Villous polyps have the highest association with underlying malignancy (10%-18%), more so than tubulovillous (6%-8%), and tubular polyps (2%-3%).[53]

Tumor budding, or epithelial-mesenchymal transition, is a newly described phenomenon observed in colorectal, gastric, and oral polyps. The finding is typified by tumor cells extending and dissociating from the tumor margin into the desmoplastic stroma. Early research has shown worse prognosis in patients with this histopathologic finding. A meta-analysis of tumor budding found a strong adverse prognostic impact on lymph node metastases, tumor recurrence, and cancer related death at 5 years.[54] For pT1 disease in particular, tumor budding has also been found to correlate with nodal metastases.[55]

Lymphovascular invasion

Invasion of the malignant polyp into the submucosa opens the possibility of metastasis into the lymphatic or vascular systems. Several case series have explored this issue in patients undergoing malignant polypectomy followed by subsequent colectomy. Lymphovascular invasion has been consistently and independently associated with a risk of lymph node metastasis in these retrospective series.[37,48,56] For this reason, the presence or absence of lymphovascular invasion is an important pathologic feature of malignant polyps, and an important factor when choosing a management strategy.

Differentiation

Histologic tumor grade categorizes colorectal neoplasms as well, intermediate, or poorly differentiated, based on the percentage of glandular formation within the tumor.[57] The area of least differentiation is used to define the tumor as a whole. For the purposes of characterizing malignant polyps, poor differentiation is an important determinant in clinical decision making as it is associated with increased mortality.[37] However, compared to other clinicopathologic features, poor differentiation is a relatively weak risk factor. This is perhaps in part due to the fact that there is only moderate inter-rater reliability in differentiation grading by pathologists.[58] Additionally, poor differentiation is a relatively rare finding in malignant polyps, with less than 10% of malignant polyps being categorized as poor differentiation.[33]

Pseudoinvasion

Pseudoinvasion or pseudocarcinomatous invasion, first described by Muto and colleagues,[59] refers to the prolapse of the adenomatous epithelium into the polyp stalk which may mimic invasive adenocarcinoma. This pathologic finding is likely a result of trauma or ischemia which results in disruption of the polyp and rupture of glands into the stalk. Pseudoinvasion is most commonly found in Peutz-Jeghers syndrome.[60] Distinguishing pseudoinvasion from malignant polyps remains a difficult task for both the endoscopist as well as the pathologist. Histologically, markers such as MMP-1, p5, collagen IV, and E-cadherin can aid in distinction.[61]

Pathology and management

Taken together the histopathologic features of the polyp are paramount in guiding management.[32,62] Polypectomy may be insufficient treatment in several scenarios: (1) when carcinoma is present at or within 1 mm of the polyp resection margin; (2) when there is poorly differentiated carcinoma present; (3) when there is evidence of lymphovascular invasion; or[4] when there is invasion of the submucosa. Invasion of the submucosa that would contraindicate polypectomy includes any Haggitt level IV pedunculated lesion and for sessile lesions, invasion beyond the superficial two-thirds of the submucosa or more than 1 mm.

Interdisciplinary care

Recently there has been a proliferation in the use of interdisciplinary teams, most often employed as a disease-specific conference, to guide the management of complex oncologic care.[63] These teams leverage the expertise of a range of specialists to improve management decisions.[64,65] Interdisciplinary teams work to standardize decision making, improve guideline adherence, accelerate communication between specialists, and synchronize care.[66] Interdisciplinary care has led to well established improvements in the quality of care provided to patients in a variety of cancer treatments.[67]

Multidisciplinary teams are particularly salient to the management of patients with malignant or difficult polyps. A wide range of potential therapies exist, and these therapies require the involvement of endoscopists, surgeons, gastrointestinal (GI) pathologists, radiologists, and medical oncologists. Contributions from other specialists such as palliative care practitioners, nursing specialists, and enterostomal therapists may also add valuable input. Integration of patient preferences into this process is important but can be challenging.[68]

There is limited evidence in the use of multidisciplinary teams in the management of complex or difficulty polyps specifically; nevertheless wider evidence for colorectal cancer patients applies more broadly. For example, in rectal cancer the use of a multidisciplinary conference has been associated with improved circumferential resection margin.[69] In one series, discussion at a multidisciplinary conference led to changes in treatment plans for 29% of patients with rectal cancer.[70] For patients with colon cancer, the implementation of a multidisciplinary conference has also been associated with improved survival compared to historical controls.[71]

A critical component of a multidisciplinary team is the involvement of a pathologist. Treatment decisions in the management of malignant polyps to a large degree are dictated by pathologic findings. This requires a high degree of accuracy on the part of the pathologist. Several studies have compared the accuracy and interrater reliability of blinded pathology review of polyp specimens.[72,73] Invasive carcinoma was identified correctly in only 91% and 93% of specimens in 2 small series.[74,75] Whether a dedicated GI pathologist can improve the accuracy of diagnosis in colonoscopy biopsy specimens remains controversial.[76] However, there is some evidence that expert GI pathologists have a higher degree of inter-rater reliability in regard to T stage.[58] Involvement of the interpreting pathologist is therefore a critical component of the discussion of a malignant polyp in a multidisciplinary conference.

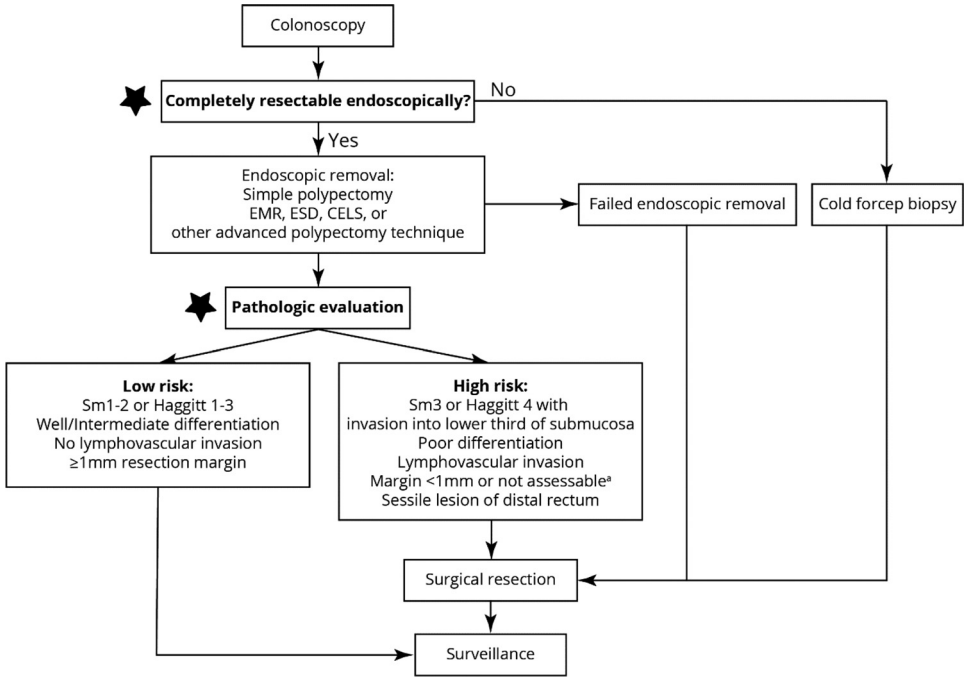

Fig. 2. Malignant polyp management algorithm. Stars (*) indicate key decision points. (A) Some authors advocate for a minimum margin of 2 mm. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; CELS, combined endoscopic and laparoscopic surgery.

Principles in management

There are 2 key decision points in the management of malignant polyps which frequently occur (Fig 2). The first decision point is at the time of colonoscopy, when the endoscopist must decide whether a suspicious polyp can be safely endoscopically resected. The second decision point is after pathologic examination of a polypectomy specimen, when a decision must be made about attempted endoscopic re-excision, surgical resection, or surveillance.

There is no single treatment approach that can be universally applied for patients with a malignant polyp. Instead, these management decisions should be guided by a few core principles. Care should optimize oncologic safety, while maintaining sensitivity to patient-specific risk factors, and informed patient preferences.

Oncologic safety

Oncologic safety refers to the likelihood that a given treatment will result in cure. Procedures with less oncologic safety are more likely to result in residual disease being left behind. This manifests as positive margins, local recurrence, and lymph node or distant metastases. When treating malignant or difficult polyps a range of options are available, and each is associated with a distinct profile of oncologic safety. The treating physician should strive to maximize oncologic safety whenever it is feasible to do so. However, oncologic safety is also frequently correlated with the extent of resection, with formal surgical resection generally having the highest oncologic safety, but also carrying with it more potential morbidity. Endoscopic therapies may have a lower oncologic safety in some situations, while a watch-and-wait approach generally has

the highest risk of persistence or recurrence of disease. Oncologic safety must be balanced with other considerations such as the risk of recurrence, patient selection, and patient preferences.

Patient selection

The success of a given treatment is, in part, reliant on appropriate patient selection. Ability to tolerate general anesthesia, age, and degree of comorbidity should be considered. For extremely infirm or comorbid patients, the reduced immediate morbidity of endoscopic or minimally invasive resection must be balanced with the likelihood of technical success as well as the potential consequences of later recurrence. For example, a patient electing to pursue endoscopic polypectomy must be willing to undergo the associated post-procedure surveillance protocol. The consequences of potential complications such as endoscopic perforation during surveillance or re-intervention must also be considered.

Patient preference

Patient preference plays an important role in guiding selection of a treatment approach. For example, some patients may be unwilling to tolerate the need for surveillance endoscopy after polypectomy. Others may strongly desire a minimally invasive endoscopic approach, even if this comes at a cost of reduced oncologic safety. Providers should elicit patient preferences when offering treatment options.

Informed consent

Patient comprehension and ability to recall surgical options presented to them during informed consent is generally poor.[77] It can be particularly challenging for patients to make an informed decision when a number of complex treatment options are available, as is frequently the case with malignant polyps. This may be partly addressed by involvement of family or friends during decision making, utilization of a checklist, and use of plain language in consent forms and patient literature.[78–81] Tools such as the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Universal Risk Calculator can also be useful in apprising patients of postoperative risks, particularly for well-defined procedures such as colectomy.[82] A visual description of the best and worst case scenarios, along with the most likely outcome can also be helpful when multiple different treatment choices are available.[83] Regardless of the approach that is taken, patient involvement in the decision making process is paramount.

Diagnosis

The management of malignant polyps starts with detection during colonoscopy. Colonoscopy is one of the most commonly performed procedures annually, with 11.5 million colonoscopies completed in the United Stated in 2009 alone.[84] Complete colonoscopy is necessary to rule out synchronous lesions which would alter management as well as to evaluate the lesion for endoscopic resectability. Although modalities such as flexible sigmoidoscopy, fecal testing, or computed tomography (CT) colonography are potentially useful for screening, a positive screen using one of these adjuncts must be followed by complete colonoscopy.

A complete mechanical bowel preparation is essential for accurate colonoscopic examination as well as subsequent endoscopic treatment. Several preparation formulas and regimens are available. Our preference is for a clear liquid diet followed by polyethylene glycol diluted with the patient's beverage of choice. Adequate preparation rates are superior with this technique.

The American Society of Gastrointestinal Endoscopy (ASGE) has established a set of quality indicators in order that operators meet a minimum requirement of use (Table 1).[85]

Table 1
American Society of Gastrointestinal Endoscopy (ASGE) quality indicators.

1. Cecal intubation rate for screening with photo documentation ≥95%.
2. ≥30% adenoma detection rate in men, ≥20% adenoma detection rate in women, and ≥25% overall.
3. Colonoscopy withdrawal time ≥6 min on average.
4. <1% post-polypectomy bleeding.
5. <1:1000 incidence of perforation during screening colonoscopy.

Despite improvements in screening colonoscopy techniques, equipment, and user knowledge, there is still a significant miss rate for both polyps, and cancer reported in the literature. A systematic review published in 2006 reported a miss rate of 13% for polyps 5-10 mm and 2.1% for polyps 10 mm or larger with the use of screening colonoscopy.[86]

Tattoo

It is essential to localize small lesions prior to surgery, as it can be difficult to identify them intraoperatively.[87] This is particularly true of lesions that were partially removed at the time of diagnosis, and may be hard to identify again endoscopically. Endoscopic tattooing is the primary means by which reidentification is achieved. Most recent studies recommend tattooing of any suspicious lesions on colonoscopy without any reference to size. The endoscopist therefore must make a subjective assessment of the need for future localization based on the appearance of the lesion.[88]

Theoretically, direct injection of the dye near or through neoplastic lesions may lead to tumor seeding. Tattooing should therefore be performed submucosally in the colonic wall away from the lesion to avoid this risk.[89] Tattooing is performed in a 2-step fashion. First, a bleb is created by submucosal injection of 1 mL of sterile saline, followed by injection of the dye agent.[90,91] Performing the saline injection first leads to 98% accurate visualization compared to 80% with a single-step injection.[87] Care must be taken to avoid accidental transmural dye injection, which may obscure the location of the lesion to nearby loops of bowel.

Indocyanine green and methylene blue are 2 dyes used to stain the bowel serosa. However due to their rapid absorption and diffusion through the bowel tissue, they are inappropriate for localization.[92,93] India ink is preferred, as it lacks diffusion through mesentery, and can persist for years.[94,95] A carbon-based product with similar properties is also available.[96]

Sigmoidoscopy

Flexible sigmoidoscopy is a diagnostic endoscopic procedure used to examine the lower portion of the colon. It can be performed with an array of endoscopic instruments, including the standard 60 cm sigmoidoscope, an adult or pediatric colonoscope, or an esophagogastroduodenoscope. The ACS and United States Preventive Services Task Force (USPSTF) both recommend screening of the colon every 5 years in average risk patients. The ACS recommends screening from age 45 to age 75 for healthy patients, while patients at increased risk of cancer should be screening for an additional 10 years to age 85 depending on the mutual decision made between patient, and provider.

The greatest advantage of sigmoidoscopy is its ability to be performed in the clinic without sedation.[97] Patients may only require the use of 1 or 2 enemas in order to evacuate the sigmoid rather than the full colonic preparation reserved for colonoscopy. Despite its ease of patient experience, the main limitation of sigmoidoscopy is that it can only examine the rectum, sigmoid, and descending colon under optimal conditions.[97] Wang and colleagues[98] queried the Surveillance, Epidemiology and End Results (SEER) database and found that patients 67 years or older had a 3-fold higher miss rate for left sided colorectal cancers with sigmoidoscopy compared to colonoscopy. This finding has been recapitulated in several other studies; 15%-25% of patients

will have neoplastic lesions in the proximal colon at colonoscopy after having negative flexible sigmoidoscopy, and negative guaiac fecal occult blood test (gFOBT).[99–103]

For these reasons, there has been a recent decline in the use of flexible sigmoidoscopy in the United States, while colonoscopy rates continue to rise. A study between 1993 and 2002 showed that there was a 54% decrease in sigmoidoscopy utilization while colonoscopy increased 6-fold over that same time period.[104]

Fecal tests

Guaiac fecal occult blood test

Stool based testing is an alternative screening technique that is less invasive than structural exams. The gFOBT was the original screening modality, introduced more than 30 years ago for the detection of colon cancer.[105] It remains the most commonly used stool-based test for colorectal cancer screening despite its poor positive predictive value. It works by identifying the enzyme peroxidase found in intact hemoglobin and free heme molecules in stool samples. The presence of peroxidase implies the presence of colorectal cancer or colorectal polyps larger than 1 cm as these lesions are highly vascularized and often lead to occult bleeding.

The routine protocol consists of collecting 2 samples from each of 3 consecutive bowel movements at home every 2 years.[97] Prior to testing, the patient is asked to avoid vitamin C, red meat, poultry, fish, aspirin and other nonsteroidal anti–inflammatory drugs (NSAIDs) because these may alter the test results, through occult bleeding of healthy tissue as well as the misidentification of peroxidase found in these products, thereby increasing the false-positive results of the test.[106] There are major limitations to gFOBT. Bleeding from larger polyps may be intermittent and multiple specimen collections are necessary to mitigate against false-negative tests. Requiring patients to bring multiple stool specimens into clinic has major obstacles and limits the willingness of patients to participate. Specimen procurement more commonly is performed in the physician's office with only a single-panel test followed by digital rectal examination which severely limits its efficacy.[107] The sensitivity of a single gFOBT varies markedly. A cohort study of 8104 asymptomatic adults undergoing screening reported sensitivity of gFOBT for cancer ranging from 37.1%-79.4% depending on the type oftest.[108] However, the T-stage of incident cancers in the cohort was not reported. Findings from the same cohort found slightly lower sensitivity for the detection of polyps $\geq$1 cm in size, ranging from 30.8%-68.6%.

Fecal immunochemical test (FIT)

FIT testing is a stool test that utilizes monoclonal or polyclonal antibodies targeted to the globin moiety of human hemoglobin. This is more specific than the aforementioned gFOBT which identifies the presence of peroxidase.[97,109] FIT is more specific for lower GI bleeding, in particular, because globin degraded in the upper GI tract by digestive enzymes will be detected by gFOBT as free heme molecules but not by FIT. Finally, FIT sampling is less cumbersome than gFOBT because it requires fewer samples and less handling of feces.[97] In 2014, a meta-analysis showed that FIT has 79% sensitivity, 94% specificity, and 95% overall accuracy.[110] Unfortunately, the sensitivity of FIT for early-stage cancers is lower than that for higher stage disease. In a review of more than 18,000 patients screened at a Taiwanese center, the sensitivity of FIT for in situ or T1 lesions was 67%, compared to 100% for T2-T4 lesions. In the same study, the sensitivities of FIT for non–advanced and advanced adenomas were only 11% and 28%, respectively, highlighting the difficulty in using FIT as a screening modality for malignant polyps.[111]

Stool DNA assays

The use of gFOBT and FIT for cancer screening is predicated on the assumption that occult bleeding is due to carcinoma, which is not always the case. However, adenomas and carcinomas continuously shed epithelial cells into the bowel lumen with the passage of stool. These abnormal epithelial cells may provide a key avenue for the noninvasive detection of cancer.[112]

Stool DNA testing is a multi-target DNA assay which identifies point mutations in APC, K-Ras, P53, and other genes that contribute to the malignant transformation of colorectal cancer.[97] A

cross-sectional cohort study of almost 10,000 patients found the sensitivity of a stool DNA assay to be 92.3% for any colorectal cancer. Encouragingly, there was no decrement in sensitivity with lower T stage. The sensitivity for detecting advanced precancerous lesions ≥1 cm was only 42.4%, but this compared favorably to the sensitivity of FIT for precancerous lesions in the same cohort of 23.8%.[113] Although these results are encouraging, the specificity for such tests remains too low for them to be adopted exclusively in the diagnosis of colorectal cancer, and for malignant polyps in particular.

CT colonography

CT colonography has been touted as an alternative screening modality for colorectal malignancy detection. This less invasive alternative, also known as "virtual colonoscopy," has acceptable sensitivity, and specificity for polyps larger than 10 mm.[114] However, the accuracy of CT colonography in the detection small polyps is still limited. One recent meta-analysis reported 82% sensitivity to detect tumors larger than 10 mm (95% CI, 76%-88%) and 56% sensitivity to detect tumors smaller than 5 mm (95% CI, 42%-70%).[115] This raises concerns for screening because, as Kulling and colleagues[116] reported in a retrospective review of a polyp registry, 8.5% of polyps smaller than 5 mm, and 15.5% of polyps smaller than 10 mm, have either a villous component or severe dysplastic component concerning for advanced disease. Although the sensitivity of CT colonography will likely improve in the future, it remains exclusively a diagnostic procedure, without the potential benefit of therapeutic intervention as with colonoscopy.

Management

A variety of avenues are available to the surgeon and endoscopist treating malignant polyps. When selecting a resection technique, the risk of lymphatic spread should be assessed. The operator may then choose from among several options.

Simple polypectomy

Endoscopic polypectomy alone may be an appropriate first step for polyps without high-risk features. It is critical that the endoscopist perform a full resection without residual tumor as well as localize the polyp's location in the colon with a permanent marker such as India ink. The majority of malignant pedunculated polyps are considered low risk and can be managed with polypectomy alone either via endoscopic forceps or snare cautery.[117] Subsequent surgical resection is necessary when the lesion has poor histologic differentiation, vascular or lymphatic involvement, or positive margins on pathology. Patients without these risk factors have traditionally been considered low risk for post-polypectomy residual tumor or lymph node metastases.[43,118] However, a recent SEER retrospective study evaluated the utility of endoscopic resection vs formal oncologic resection for pT1 malignant polyps. The study found that the cohort undergoing surgical resection had higher rates of survival compared to endoscopic resection at 1 year (92% vs 88%) and 5 years (75% vs 62%) with a hazard ratio of 1.15. However, after patient stratification for risk factors such as age, comorbidities, and histology, there was no statistical difference between the 2 groups.[119] These findings suggest that polypectomy alone is a safe and effective therapeutic option for select pT1 polyps.

Sessile polyps, due to their morphology, remain a challenge to resect because of the technical difficulties, and the high complication rate. Since sessile polyps are imbedded within the mucosa of the bowel wall without a protective stalk, there is greater concern for residual malignancy at the resection margin. A review of 105 malignant polyps unsurprisingly found that incompletely removed sessile malignant polyps had the highest likelihood of lymph node metastases. However, in the same series a sessile morphology alone was also associated with 6.7 times higher odds of lymph node metastases.[34] A small series of 16 patients with sessile malignant polyps undergoing endoscopic resection by an expert endoscopist noted the technical feasibility of this

approach. However, there were 2 patients that developed recurrence, and distant metastases in long-term follow-up.[120] The approach to sessile polyps therefore remains somewhat controversial. The British Society of Gastroenterology position statement on the resection of sessile polyps notes that endoscopic resection is possible, but should be undertaken by an appropriately skilled endoscopist.[121]

Whenever possible, endoscopic polypectomy should be performed for all adenomatous appearing tissue during colonoscopy. Polypectomy can be performed with a number of through-the-scope devices. Biopsy forceps, with or without electrocautery, are the most commonly used, although the addition of electrocautery can distort the histology of the specimen, making pathologic interpretation challenging. Snare polypectomy is also available and commonly used, particularly for pedunculated lesions. The target lesion is centered near the 6-o'clock position of the scope, the snare is placed around the lesion, and then the scope is tented away from the bowel wall as cautery is applied and the snare is closed. The risk of perforation or bleeding during snare polypectomy is small and many series comparing cold and hot snare polypectomy did not observe any bleeding or perforation events.[122,123] In a meta-analysis of 6 trials and 1031 lesions, the overall adverse event rates for cold and hot snare polypectomy were 2.5% and 3.6%, respectively.[124]

Lesions which have an endoscopic appearance of penetration beyond the submucosa are not amenable to polypectomy. This is further suggested by lesions which do not elevate with submucosal injection, have central umbilication, or ulceration. Especially large lesions may not be amenable to polypectomy, and a more advanced technique is preferred in these cases.

Piecemeal polypectomy

Inevitably, larger lesions undergoing endoscopic polypectomy with traditional techniques may be removed in pieces rather than en bloc. Regardless of the approach, care should be taken to remove all adenomatous tissue. Piecemeal polypectomy presents additional challenges to both the endoscopist and the pathologist. Minor bleeding after the initial attempt at polypectomy may obscure remnant adenomatous tissue in the mucosa. Recurrence or persistence of polyps after piecemeal polypectomy is relatively common, occurring in as many as 24% of patients in one series, although most of these recurrences are amenable to further endoscopic therapy.[125] Incomplete polypectomy can also make future attempts at advanced endoscopic removal more technically challenging. Piecemeal polypectomy particularly of malignant polyps can also pose a formidable challenge to the pathologist, as this may preclude an accurate assessment of margins and therefore mandate surgical resection.

Recurrence rates for malignant polyps after endoscopic piecemeal mucosal resection (EPMR) in the literature are inconclusive, with variable parameters for size, and length of follow-up reported. Seo and colleagues[126] found a 33.3% rate of overall recurrence for malignant polyps removed by EPMR compared to only 3% in benign lesions. Given this finding, the current literature recommends follow-up colonoscopy at 3-6 months, followed by additional colonoscopy 1 year later.[127]

The colorectal surgeon commonly encounters patient referrals for management of an incompletely resected malignant polyp. Several factors help to determine whether a repeated endoscopic attempt should be made prior to definitive surgical intervention. First, it must be determined whether the initial biopsy found malignant or adenomatous tissue. Repeated endoscopic attempts are reasonable for experienced endosocopists, with as many as 58% of such patients undergoing subsequent complete endoscopic resection, and avoiding colectomy.[128] However, attempts at repeated endoscopic removal are unlikely to have significant benefit when the patient is referred by an experienced endoscopist with a malignant polyp.[129] Fortunately, attempts at endoscopic resection do not appear to impact the subsequent perioperative morbidity or oncologic outcomes in those patients who ultimately require surgical resection.[130]

Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) is an adaptation of snare polypectomy for the removal of larger or more challenging polyps. A tumescent solution is first injected into the submucosa to raise the lesion. Normal saline is inexpensive and widely available, but it is rapidly absorbed, requiring repeated injections during longer procedures. Alternative tumescent solutions are available which persist longer in the tissue. These solutions consist of albumin, dextrose, glycerol, hyaluronic acid, or a number of other commercially available preparations. Once the mucosa has been raised, a snare is then passed around the polyp. A cap-assisted technique is also possible, with the use of a suction cap to aid visualization. EMR is indicated for malignant polyps confined to the superficial submucosa, and those not amenable to simple snare polypectomy. In one prospective observational cohort of Australian patients undergoing EMR for colonic lesions, EMR was found to dramatically reduce the number of lesions referred for surgical resection, allowing 83.7% of patients to avoid surgery. EMR was associated with low rates of perforation (1.3%) and post-procedural bleeding (2.9%). Piecemeal resection was common, however, and recurrent or residual adenoma occurred in 20% of patients.[131] Importantly for malignant polyps, pathologic examination of EMR specimens is limited by the lack of submucosa included with the specimen.

Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) is an advanced endoscopic technique for the removal of large or challenging polyps. ESD provides a deeper submucosal plane of dissection, permitting en bloc removal of a large or malignant polyp, and subsequent accurate histologic examination. This technique is particularly useful for polyps that are unable to be lifted during EMR, intramucosal malignant polyps, and those with carcinoma confined to the superficial submucosa.

ESD was developed and originally performed for gastric tumors and was repurposed for the resection of colorectal polyps. Like EMR, ESD begins with elevation of the lesion with a tumescent solution of either normal saline or sodium hyaluronate. The resection margin should then be marked out with electrocautery. A submucosal plane is then developed, lifting the lesion upward. Endoscopic electrocautery knives with a protected tip are used to develop this plane and coagulate small vessels. Due to the more extensive dissection, ESD has higher perforation rates (7.4% in 1 series), and longer procedure times but lower recurrence rates with less residual tumor compared to polypectomy alone.[132,133]

Both bleeding and perforation during ESD are usually amenable to treatment with endoscopic clips once the polypectomy has been completed. The application of clips prior to the completion of polypectomy should be avoided, however, as they may obscure the field of view for further dissection. Due to the increased depth of the resection, ESD in the thin wall of the cecum and right colon should be undertaken selectively and cautiously.[134]

ESD can be technically challenging, time consuming, and resource intensive. Several studies have examined the learning curve for colorectal ESD, noting that as many as 40 cases may need to be performed before proficiency is established.[135,136] A major challenge in the performance of ESD is that the operator must use a single arm to simultaneously view the dissection plane, retract, and dissect. Several techniques and devices have been developed to overcome this limitation. For example, an additional biopsy forcep can be passed alongside the scope to aid with retraction. The bowel lumen can also be filled with water to help stabilize the colon, minimize the interference of smoke, and limit thermal spread from the electrocautery.[137]

A double-balloon over-the-scope device is also available which stabilizes the scope within the colon and permits introduction of separate endoscopic tools through working channels. These working channels can be operated independent of the scope, permitting fine retraction, better visualization, and more controlled dissection.[138]

Additional over-the-scope devices are available to retract large lesions into a cap, resecting the lesion while simultaneously deploying a large over-the-scope clip to close the defect. Full thickness colonic biopsies can then be taken, allowing complete pathologic evaluation of the

depth of the lesion.[139] As these devices are relatively new, their role in the treatment of colorectal neoplasia is not yet well defined. Despite these advances and given the technical challenges involved and time required to become proficient, ESD remains a relatively uncommon procedure.[140]

Although ESD and EMR are discussed separately, a hybrid technique can be used for some polyps. For example, the polyp can be lifted with tumescent solution and EMR tools used to mark out the polypectomy border. After the mucosa has been incised, the configuration of the polyp may make it more amenable to snare polypectomy than it had been previously. A snare can then be deployed rather than completing the submucosal dissection with ESD tools. This hybrid technique avoids the additional time and expertise needed for traditional ESD, and in a small randomized controlled trial was associated with similar rates of complete polypectomy and adverse events such as perforation.[1]

Combined endoscopic and laparoscopic surgery

Novel methods for minimally invasive resection are increasingly being used to increase patient safety and minimize procedure associated risks. A combined endoscopic and laparoscopic surgery (CELS) is one such approach.[141] Also referred to as laparoscopic endoscopic cooperative surgery (LECS), the procedure begins with colonoscopy, and lesion identification. If the polyp appears amenable to a combined approach, laparoscopic abdominal access is established. Laparoscopic instruments may then be used to manipulate the bowel wall toward the scope, aiding polypectomy. The abdominal team can also assist in navigating around flexures or angulations in the colon. If a perforation occurs, the operator is positioned to easily repair or convert to formal colectomy during the same operation. A recent randomized controlled trial showed similar complication rates but shorter overall hospital stays with CELS compared to formal colectomy.[142]

Polyps particularly amenable to CELS are those which may be hidden behind haustra or those difficult to reach endoscopically due to a tortuous colon. CELS is also especially advantageous for lesions in the right colon for which perforation is a serious concern. Damage to the serosa can be identified and treated immediately.

There are several drawbacks of CELS to bear in mind. Insufflation of carbon dioxide during colonoscopy distends both the large and small bowel unless care is taken to laparoscopically occlude the bowel proximal to the lesion. Regardless, there is frequently some loss of the laparoscopic visualization. Additionally, lesions located on the mesenteric side of the bowel wall or in a retroperitoneal or extraperitoneal location may be challenging to manipulate or monitor closely laparoscopically.

Rectal lesions

Rectal lesions deserve special consideration. The management of rectal cancer is a multidisciplinary process that requires complex decisions about the provision, timing, and sequence of chemotherapy, radiation, and surgery. In locally advanced rectal cancer, outcomes are optimized when chemoradiation is used in the neoadjuvant rather than adjuvant setting.[143] Due to these considerations, a complete staging evaluation should be performed before intervening on a suspected malignant rectal polyp. Dedicated rectal protocol magnetic resonance imaging (MRI) should be performed to identify any suspicious locoregional nodes. Before proceeding with endoluminal resection, consideration should also be given to whether the patient would be appropriate for a watch-and-wait approach.[144] Removal of the primary lesion may make it challenging or impossible to subsequently follow the clinical response of a patient undergoing neoadjuvant treatment.

Another feature that may alter treatment algorithms of some rectal polyps is their propensity for early lymphatic spread. In one series of 353 patients with sessile T1 rectal lesions that underwent resection, 34% of those arising in the distal one third of the rectum were found to have

lymph node metastases. For this reason, sessile lesions of the distal rectum should be considered for either surgical resection with lymphadenectomy, or trans anal full thickness excision.

Although there are multiple technical approaches available for rectal malignant polyps, careful patient selection is paramount. In one review of early-stage rectal lesions undergoing local excision, 18% of pT1 lesions were noted to have recurrence within 10 years.[145] Additionally, local excision after neoadjuvant therapy in rectal cancer is associated with high rates of morbidity from impaired wound healing.[146]

Transanalmicrosurgery (TEM) and transanalminimally invasive surgery (TAMIS) are 2 similar approaches to malignant rectal polyps with several common technical features. Pneumorectum is established via an insufflation device and either a reusable metal sheath or a flexible single incision laparoscopic surgery (SILS) port. In the case of suspected neoplasia, laparoscopic instruments are then introduced transanally to create a full thickness resection of the rectal wall. The defect is closed transversely to minimize luminal narrowing, and the colon is desufflated. Data on functional outcomes after TEM or TAMIS are controversial. A recent systemic review of functional outcomes noted that manometric scores deteriorated, but patient reported outcomes of quality of life and incontinence were not severely impacted.[1]

Conventional trans anal excision (TAE) may be the best approach for rectal polyps that are too distal for the placement of a TEM or TAMIS platform. Stay sutures or a retractor device are placed to evert the dentate line and rectal mucosa. Dissection around the lesion is then performed with electrocautery to create a full thickness en bloc resection, taking care to avoid, and preserve the sphincter muscle complex. The defect can then be closed transversely.

Surgical resection

Lesions which have high risk of lymphatic spread should undergo surgical resection. These features, which include invasion into the deep third of the submucosa, sessile lesions of the distal rectum, poorly differentiated lesions, or those with lymphovascular invasion, are summarized in Figure 2. Piecemeal resection is a relative indication for resection, as margins typically cannot be assessed in that setting. Adequate margin is debated, but should be at least 1 mm, with some authors advocating for 2 mm margins. Despite the proliferation of novel endoscopic techniques, surgical resection remains the standard of care whenever the oncologic safety of other approaches cannot be guaranteed. Minimally invasive approaches and enhanced recovery pathways can minimize morbidity and speed recovery, and should be utilized whenever possible.[147]

Surveillance

Screening and surveillance colonoscopy are based on the principle that defined interval examinations prevent and reduce the morbidity and mortality related to colorectal cancer through early intervention. Patients found to have an adenoma on initial colonoscopy have a 30%-50% probability of having additional adenomas at the time of detection and 30% probability of detection at a later date.[148]

After removal of a malignant polyp, routine surveillance is recommended to assess for residual polyp as well as later recurrence. Malignant polyps are frequently excluded from surveillance guidelines.[149] However, an early repeat colonoscopy should be performed at 3 to 6 months, particularly in the case of piecemeal polypectomy.[53] If findings are negative at early follow-up, colonoscopy should be repeated at regular intervals based on baseline risk stratification, as well as prior polyp pathology and number.[127] This is largely based off the landmark National Polyp Study which showed that only 3.3% of patients at 3-year follow-up colonoscopy had advanced adenomas.[150] Our group typically performs surveillance at 2-3 months and then at 6 months for the first 2 years depending on subsequent findings.

There are no data to support or refute post-polypectomy surveillance with cross-sectional imaging (either CT or MRI). These modalities are insufficiently sensitive to identify early luminal

recurrence, but may be able to detect suspicious lymphadenopathy. Other modalities such as colonoscopic high-frequency ultrasound have been proposed as a method to evaluate residual disease and lymph node involvement after polypectomy.[151] However, such screening is highly operator dependent and resource intensive, and low sensitivity has been reported elsewhere for nodal metastases.[152]

Special cases

Hereditary syndromes

GI cancer syndromes also pose a significant threat to affected patients. Therefore, diagnosis should be made early, surveillance colonoscopies should be performed frequently, and treatment should be definitive. Documented or suspected malignancy, multiple large adenomas, or an inability to surveil the colon completely are all indications for colectomy in patients with hereditary GI cancer syndromes. For these reasons, malignant polyps should not be managed endoscopically in most patients with hereditary GI cancer syndromes.[153]

Inflammatory bowel disease

The management of malignant polyps in patients with Crohn's colitis or ulcerative colitis differs from that of patients with otherwise healthy colon. In a series of 50 patients with Crohn's colitis undergoing colectomy, dysplasia was multifocal in 44% and of those with a cancer, 40% had dysplasia remote from the cancer site.[1]In ulcerative colitis, high grade dysplasia or a malignant polyp should prompt surgical resection.

Conclusions

Malignant polyps are those colorectal polyps which harbor a focus of invasive adenocarcinoma. These polyps are increasingly encountered by clinicians as the use of colonoscopy becomes more widespread. Before deciding on a management strategy, multidisciplinary assessment should be undertaken with accurate staging and review of pathology by a dedicated GI pathologist whenever possible.

Key management principles to consider include oncologic safety of the proposed operation, adequate resection margin, and careful patient selection. Based on these factors, an approach can be selected ranging from watch-and-wait, to endoscopic resection, to formal surgical resection.

For lesions with favorable pathologic features, endoscopic resection may be a feasible option. A number of advances have been made to aid polypectomy including high-definition scopes, novel energy devices, and over-the-scope systems. In experienced hands, these devices should increase the number of polyps amenable to endoscopic resection. This has the potential to reduce the morbidity incurred by segmental surgical resection.

Regardless of the treatment strategy selected, patients should be surveilled after treatment for both local, and distant recurrence. Post-treatment surveillance should aim to detect any recurrence as soon as possible, permitting early restaging and intervention.

The most efficacious treatment strategy for malignant polyps remains an active area of research. Future work should focus on the rates of local and distant recurrence after polypectomy alone.

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References

1. Cancer Facts & Figures. American Cancer Society https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2019.html (2019).
2. National Cancer Institute. SEER cancer stat facts: colorectal cancer [Internet]. Accessed at: March 5, 2018. Accessed from: https://seer.cancer.gov/statfacts/html/colorect.html.
3. Bujanda L, Cosme A, Gil I, Arenas-Mirave JI. Malignant colorectal polyps. *World J Gastroenterol*. 2010;16:3103–3111.
4. Lieberman DA, Williams JL, Holub JL, et al. Colonoscopy utilization and outcomes 2000 to 2011. *Gastrointest Endosc*. 2014;80:133–143.
5. Reggiani-Bonetti L, Di Gregorio C, Pedroni M, et al. Incidence trend of malignant polyps through the data of a specialized colorectal cancer registry: clinical features and effect of screening. *Sc and J Gastroenterol*. 2013;48:1294–1301.
6. Peery AF, Cools KS, Strassle PD, et al. Increasing rates of surgery for patients with nonmalignant colorectal polyps in the united states. *Gastroenterology*. 2018;154:1352–1360 e3.
7. Netzer P, Forster C, Biral R, et al. Risk factor assessment of endoscopically removed malignant colorectal polyps. *Gut*. 1998;43:669–674.
8. Hackelsberger A, Frühmorgen P, Weiler H, Heller T, Seeliger H, Junghanns K. Endoscopic polypectomy and management of colorectal adenomas with invasive carcinoma. *Endoscopy*. 1995;27:153–158.
9. Hermanek P, Frühmorgen P, Guggenmoos-Holzmann I, Altendorf A, Matek W. The malignant potential of colorectal polyps–a new statistical approach. *Endoscopy*. 1983;15:16–20.
10. Hancke E, Remmele W. Colorectal polyps. Pathologico-anatomical and statistical studies on 3037 polyps. *Chirurg*. 1978;49:757–768.
11. Strum WB. Colorectal adenomas. *N Engl J Med*. 2016;374:1065–1075.
12. Bond JH. Clinical evidence for the adenoma-carcinoma sequence, and the management of patients with colorectal adenomas. *Semin Gastrointest Dis*. 2000;11:176–184.
13. Austin H, Henley SJ, King J, Richardson LC, Eheman C. Changes in colorectal cancer incidence rates in young and older adults in the United States: what does it tell us about screening. *Cancer Causes Control*. 2014;25:191–201.
14. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, Ahmedin J. Colorectal Cancer Incidence Patterns in the United States, 1974–2013. *JNCI: Journal of the National Cancer Institute*. 2017;109(8):djw322. doi:10.1093/jnci/djw322.
15. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med*. 2013;369:1095–1105.
16. Hassan C, Pooler BD, Kim DH, Rinaldi A, Repici A, Pickhardt PJ. Computed tomographic colonography for colorectal cancer screening: risk factors for the detection of advanced neoplasia. *Cancer*. 2013;119:2549–2554.
17. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med*. 2014;370:1298–1306.
18. Pendergrass CJ, Edelstein DL, Hylind LM, et al. Occurrence of colorectal adenomas in younger adults: an epidemiologic necropsy study. *Clin Gastroenterol Hepatol*. 2008;6:1011–1015.
19. Murphy CC, Lund JL, Sandler RS. Young-onset colorectal cancer: earlier diagnoses or increasing disease burden? *Gastroenterology*. 2017;152:1809–1812 e3.
20. Rundle AG, Lebwohl B, Vogel R, Levine S, Neugut AI. Colonoscopic screening in average-risk individuals ages 40 to 49 vs 50 to 59 years. *Gastroenterology*. 2008;134:1311–1315.
21. Lieberman DA, Holub JL, Moravec MD, Eisen GM, Peters D, Morris CD. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic black and white patients. *JAMA*. 2008;300:1417–1422.
22. Lieberman DA, Williams JL, Holub JL, et al. Race, ethnicity, and sex affect risk for polyps >9 mm in average-risk individuals. *Gastroenterology*. 2014;147:351–358.
23. Tao S, Hoffmeister M, Brenner H. Development and validation of a scoring system to identify individuals at high risk for advanced colorectal neoplasms who should undergo colonoscopy screening. *Clin Gastroenterol Hepatol*. 2014;12:478–485.
24. Imperiale TF, Monahan PO, Stump TE, Glowinski EA, Ransohoff DF. Derivation and validation of a scoring system to stratify risk for advanced colorectal neoplasia in asymptomatic adults: a cross-sectional study. *Ann Intern Med*. 2015;163:339–346.
25. Giovannucci E. Modifiable risk factors for colon cancer. *Gastroenterol Clin North Am*. 2002;31:925–943.
26. Lee DH, Keum N, Giovannucci EL. Colorectal cancer epidemiology in the nurses' health study. *Am J Public Health*. 2016;106:1599–1607.
27. Symer MM, Wong NZ, Abelson JS, Milsom JW, Yeo HL. Hormone replacement therapy and colorectal cancer incidence and mortality in the prostate, lung, colorectal, and ovarian cancer screening trial. *Clin Colorectal Cancer*. 2018;17:e281–e288.
28. Amin MB. *American Joint Committee On Cancer, Society AC. Ajcc Cancer Staging Manual*. 8th ed. Chicago, IL: Springer; 2017.
29. Carethers JM, Stoffel EM. Lynch syndrome and Lynch syndrome mimics: The growing complex landscape of hereditary colon cancer. *World J Gastroenterol*. 2015;21:9253–9261.

30. Grady WM, Carethers JM. Genomic and epigenetic instability in colorectal cancer pathogenesis. *Gastroenterology*. 2008;135:1079–1099.
31. Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology*. 2010;138:2073–2087.e3.
32. Murakami T, Mitomi H, Yao T, et al. Distinct histopathological characteristics in colorectal submucosal invasive carcinoma arising in sessile serrated adenoma/polyp and conventional tubular adenoma. *Virchows Arch*. 2017;472:383–393.
33. Nivatvongs S, Rojanasakul A, Reiman HM, et al. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. *Dis Colon Rectum*. 1991;34:323–328.
34. Boenicke L, Fein M, Sailer M, Isbert C, Germer C-T, Thalheimer A. The concurrence of histologically positive resection margins and sessile morphology is an important risk factor for lymph node metastasis after complete endoscopic removal of malignant colorectal polyps. *Int J Colorectal Dis*. 2010;25:433–438.
35. Nusko G, Mansmann U, Partzsch U, et al. Invasive carcinoma in colorectal adenomas: multivariate analysis of patient and adenoma characteristics. *Endoscopy*. 1997;29:626–631.
36. Participants in the Paris WorkshopThe Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon. *Gastrointest Endosc*. 2003;58:S3–S43.
37. Hassan C, Zullo A, Risio M, Rossini FP, Morini S. Histologic risk factors and clinical outcome in colorectal malignant polyp: a pooled-data analysis. *Dis Colon Rectum*. 2005;48:1588–1596.
38. Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology*. 1985;89:328–336.
39. Kudo S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. *Endoscopy*. 1993;25:455–461.
40. Kikuchi R, Takano M, Takagi K, et al. Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. *Dis Colon Rectum*. 1995;38:1286–1295.
41. Nivatvongs S. Surgical management of malignant colorectal polyps. *Surg Clin North Am*. 2002;82:959–966.
42. Yamamoto S, Watanabe M, Hasegawa H, et al. The risk of lymph node metastasis in T1 colorectal carcinoma. *Hepatogastroenterology*. 2004;51:998–1000.
43. Okabe S, Shia J, Nash G, et al. Lymph node metastasis in T1 adenocarcinoma of the colon and rectum. *J Gastrointest Surg*. 2004;8:1032–1039.
44. Kouyama Y, Kudo S-E, Miyachi H, et al. Practical problems of measuring depth of submucosal invasion in T1 colorectal carcinomas. *Int J Colorectal Dis*. 2016;31:137–146.
45. Kitajima K, Fujimori T, Fujii S, et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J Gastroenterol*. 2004;39:534–543.
46. Beaton C, Twine CP, Williams GL, Radcliffe AG. Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. *Colorectal Dis*. 2013;15:788–797.
47. Tominaga K, Nakanishi Y, Nimura S, Yoshimura K, Sakai Y, Shimoda T. Predictive histopathologic factors for lymph node metastasis in patients with nonpedunculated submucosal invasive colorectal carcinoma. *Dis Colon Rectum*. 2005;48:92–100.
48. Butte JM, Tang P, Gonen M, et al. Rate of residual disease after complete endoscopic resection of malignant colonic polyp. *Dis Colon Rectum*. 2012;55:122–127.
49. Kim KJ, Lee HS, Jeon SW, Jin S, Lee SW. Association of poor differentiation or positive vertical margin with residual disease in patients with subsequent colectomy after complete macroscopic endoscopic resection of early colorectal cancer. *Gastroenterol Res Pract*. 2017;2017:7129626.
50. Seitz U, Bohnacker S, Seewald S, et al. Is endoscopic polypectomy an adequate therapy for malignant colorectal adenomas? Presentation of 114 patients and review of the literature. *Dis Colon Rectum*. 2004;47:1789–1796.
51. Volk EE, Goldblum JR, Petras RE, Carey WD, Fazio VW. Management and outcome of patients with invasive carcinoma arising in colorectal polyps. *Gastroenterology*. 1995;109:1801–1807.
52. National Comprehensive Cancer Network. NCCN clinical practice guideline in oncology: rectal cancer. NCCN https://www.nccn.org/guidelines/guidelines-detail (2020).
53. Williams JG, Pullan RD, Hill J, et al. Management of the malignant colorectal polyp: ACPGBI position statement. *Colorectal Dis*. 2013;15(Suppl 2):1–38.
54. Rogers AC, Winter DC, Heeney A, et al. Systematic review and meta-analysis of the impact of tumour budding in colorectal cancer. *Br J Cancer*. 2016;115:831–840.
55. Cappellesso R, Luchini C, Veronese N, et al. Tumor budding as a risk factor for nodal metastasis in pT1 colorectal cancers: a meta-analysis. *Hum Pathol*. 2017;65:62–70.
56. Tateishi Y, Nakanishi Y, Taniguchi H, Shimoda T, Umemura S. Pathological prognostic factors predicting lymph node metastasis in submucosal invasive (T1) colorectal carcinoma. *Mod Pathol*. 2010;23:1068–1072.
57. The International Agency For Research On Cancer. WHO classification of tumours of the digestive system (medicine). 4th ed. Lyon: World Health Organization; 2010.
58. Komuta K, Batts K, Jessurun J, et al. Interobserver variability in the pathological assessment of malignant colorectal polyps. *Br J Surg*. 2004;91:1479–1484.
59. Muto T, Bussey HJ, Morson BC. Pseudo-carcinomatous invasion in adenomatous polyps of the colon and rectum. *J Clin Pathol*. 1973;26:25–31.
60. Westerman AM, van Velthuysen ML, Bac DJ, Schouten WR, Wilson JH. Malignancy in Peutz-Jeghers syndrome? The pitfall of pseudo-invasion. *J Clin Gastroenterol*. 1997;25:387–390.
61. Yantiss RK, Bosenberg MW, Antonioli DA, Odze RD. Utility of MMP-1, p53, E-cadherin, and collagen IV immunohistochemical stains in the differential diagnosis of adenomas with misplaced epithelium versus adenomas with invasive adenocarcinoma. *Am J Surg Pathol*. 2002;26:206–215.
62. Choi JY, Jung S-A, Shim K-N, et al. Meta-analysis of predictive clinicopathologic factors for lymph node metastasis in patients with early colorectal carcinoma. *J Korean Med Sci*. 2015;30:398–406.
63. Expert Advisory Group on Cancer to the Chief Medical Offices of England and Wales. A policy framework

for commissioning cancer services. 1995 Accessed from: January 3, 2018; Available from: http://webarchive.nationalarchives.gov.uk.
64. Sievers CK, Kratz JD, Zurbriggen LD, et al. The multidisciplinary management of colorectal cancer: present and future paradigms. *Clin Colon Rectal Surg*. 2016;29:232–238.
65. Fleissig A, Jenkins V, Catt S, Fallowfield L. Multidisciplinary teams in cancer care: are they effective in the UK? *Lancet Oncol*. 2006;7:935–943.
66. Lamb BW, Taylor C, Lamb JN, et al. Facilitators and barriers to teamworking and patient centeredness in multidisciplinary cancer teams: findings of a national study. *Ann Surg Oncol*. 2013;20:1408–1416.
67. Valicenti RK, Gomella LG, El-Gabry EA, et al. The multidisciplinary clinic approach to prostate cancer counseling and treatment. *Semin Urol Oncol*. 2000;18:188–191.
68. Taylor C, Finnegan-John J, Green JSA. No decision about me without me" in the context of cancer multidisciplinary team meetings: a qualitative interview study. *BMC Health Serv Res*. 2014;14:488.
69. Burton S, Brown G, Daniels IR, et al. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? *Br J Cancer*. 2006;94:351–357.
70. Snelgrove RC, Subendran J, Jhaveri K, et al. Effect of multidisciplinary cancer conference on treatment plan for patients with primary rectal cancer. *Dis Colon Rectum*. 2015;58:653–658.
71. MacDermid E, Hooton G, MacDonald M, et al. Improving patient survival with the colorectal cancer multi-disciplinary team. *Colorectal Dis*. 2009;11:291–295.
72. Demers RY, Neale AV, Budev H, Schade WJ. Pathologist agreement in the interpretation of colorectal polyps. *Am J Gastroenterol*. 1990;85:417–421.
73. Lasisi F, Mouchli A, Riddell R, et al. Agreement in interpreting villous elements and dysplasia in adenomas less than one centimetre in size. *Dig Liver Dis*. 2013;45:1049–1055.
74. Rex DK, Alikhan M, Cummings O, Ulbright TM. Accuracy of pathologic interpretation of colorectal polyps by general pathologists in community practice. *Gastrointest Endosc*. 1999;50:468–474.
75. Costantini M, Sciallero S, Giannini A, et al. Interobserver agreement in the histologic diagnosis of colorectal polyps. the experience of the multicenter adenoma colorectal study (SMAC). *J Clin Epidemiol*. 2003;56:209–214.
76. Eaden J, Abrams K, McKay H, Denley H, Mayberry J. Inter-observer variation between general and specialist gastrointestinal pathologists when grading dysplasia in ulcerative colitis. *J Pathol*. 2001;194:152–157.
77. Sherlock A, Brownie S. Patients' recollection and understanding of informed consent: a literature review. *ANZ J Surg*. 2014;84:207–210.
78. Jefford M, Moore R. Improvement of informed consent and the quality of consent documents. *Lancet Oncol*. 2008;9:485–493.
79. Schenker Y, Fernandez A, Sudore R, Schillinger D. Interventions to improve patient comprehension in informed consent for medical and surgical procedures: a systematic review. *Med Decis Making*. 2011;31:151–173.
80. Ripley BA, Tiffany D, Lehmann LS, Silverman SG. Improving the informed consent conversation: a standardized checklist that is patient centered, quality driven, and legally sound. *J Vasc Interv Radiol*. 2015;26:1639–1646.
81. Kinnersley P, Phillips K, Savage K, et al. Interventions to promote informed consent for patients undergoing surgical and other invasive healthcare procedures. *Cochrane Database Syst Rev*. 2013;6:CD009445.
82. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg*. 2013;217 833–42.e1.
83. Taylor LJ, Nabozny MJ, Steffens NM, et al. A framework to improve surgeon communication in high-stakes surgical decisions: best case/worst case. *JAMA Surg*. 2017;152:531–538.
84. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012;143:1179–1187.e3.
85. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Am J Gastroenterol*. 2015;110:72–90.
86. Van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol*. 2006;101:343–350.
87. Yeung JMC, Maxwell-Armstrong C, Acheson AG. Colonic tattooing in laparoscopic surgery - making the mark? *Colorectal Dis*. 2009;11:527–530.
88. Zafar A, Mustafa M, Chapman M. Colorectal polyps: when should we tattoo? *Surg Endosc*. 2012;26:3264–3266.
89. Kang H-J, Lee B-I, Kim B-W, et al. Potential cancer cell inoculation of tattoo site through use of a contaminated needle. *Gastrointest Endosc*. 2006;63:884–886.
90. Park JW, Sohn DK, Hong CW, et al. The usefulness of preoperative colonoscopic tattooing using a saline test injection method with prepackaged sterile India ink for localization in laparoscopic colorectal surgery. *Surg Endosc*. 2008;22:501–505.
91. Sawaki A, Nakamura T, Suzuki T, et al. A two-step method for marking polypectomy sites in the colon and rectum. *Gastrointest Endosc*. 2003;57:735–737.
92. Ovid: endoscopic tattoo agents in the colon: tissue responses and clinical implications. [Internet]. Accessed at: January 21, 2018. Accessed from: http://ovidsp.tx.ovid.com.ezproxy.med.cornell.edu/sp-3.27.2b/ovidweb.cgi?&S=AEEDFPJNLIDDKJJMNCFKNBFBGPLJAA00&Link+Set=S.sh.22%7c1%7csl_10.
93. Miyoshi N, Ohue M, Noura S, et al. Surgical usefulness of indocyanine green as an alternative to India ink for endoscopic marking. *Surg Endosc*. 2009;23:347–351.
94. Fu KI, Fujii T, Kato S, et al. A new endoscopic tattooing technique for identifying the location of colonic lesions during laparoscopic surgery: a comparison with the conventional technique. *Endoscopy*. 2001;33:687–691.
95. Feingold DL, Addona T, Forde KA, et al. Safety and reliability of tattooing colorectal neoplasms prior to laparoscopic resection. *J Gastrointest Surg*. 2004;8:543–546.
96. Askin MP, Waye JD, Fiedler L, Harpaz N. Tattoo of colonic neoplasms in 113 patients with a new sterile carbon compound. *Gastrointest Endosc*. 2002;56:339–342.
97. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer

and adenomatous polyps, 2008: a joint guideline from the American cancer society, the US multi-society task force on colorectal cancer, and the American college of radiology. *CA Cancer J Clin*. 2008;58:130–160.
98. Wang YR, Cangemi JR, Loftus EV, Picco MF. Increased odds of interval left-sided colorectal cancer after flexible sigmoidoscopy compared with colonoscopy in older patients in the United States: a population-based analysis of the SEER-Medicare linked database, 2001-2005. *Mayo Clin Proc*. 2013;88:471–478.
99. Lieberman DA, Smith FW. Screening for colon malignancy with colonoscopy. *Am J Gastroenterol*. 1991;86:946–951.
100. Achkar E, Carey W. Small polyps found during fiberoptic sigmoidoscopy in asymptomatic patients. *Ann Intern Med*. 1988;109:880–883.
101. Brady PG, Straker RJ, McClave SA, Nord HJ, Pinkas M, Robinson BE. Are hyperplastic rectosigmoid polyps associated with an increased risk of proximal colonic neoplasms? *Gastrointest Endosc*. 1993;39:481–485.
102. Rex DK, Smith JJ, Ulbright TM, Lehman GA. Distal colonic hyperplastic polyps do not predict proximal adenomas in asymptomatic average-risk subjects. *Gastroenterology*. 1992;102:317–319.
103. Mehran A, Jaffe P, Efron J, Vernava A, Liberman A. Screening colonoscopy in the asymptomatic 50- to 59-year-old population. *Surg Endosc*. 2003;17:1974–1977.
104. Gross CP, Andersen MS, Krumholz HM, McAvay GJ, Proctor D, Tinetti ME. Relation between Medicare screening reimbursement and stage at diagnosis for older patients with colon cancer. *JAMA*. 2006;296:2815–2822.
105. Greegor DH. Diagnosis of large-bowel cancer in the asymptomatic patient. *JAMA*. 1967;201:943–945.
106. Ransohoff DF, Lang CA. Screening for colorectal cancer with the fecal occult blood test: a background paper. American college of physicians. *Ann Intern Med*. 1997;126:811–822.
107. Nadel MR, Shapiro JA, Klabunde CN, et al. A national survey of primary care physicians' methods for screening for fecal occult blood. *Ann Intern Med*. 2005;142:86–94.
108. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med*. 1996;334:155–159.
109. Caligiore P, Macrae FA, St John DJ, Rayner LJ, Legge JW. Peroxidase levels in food: relevance to colorectal cancer screening. *Am J Clin Nutr*. 1982;35:1487–1489.
110. 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;160:171.
111. Chiu H-M, Lee Y-C, Tu C-H, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. *Clin Gastroenterol Hepatol*. 2013;11 832–8.e1.
112. Sidransky D, Tokino T, Hamilton SR, et al. Identification of ras oncogene mutations in the stool of patients with curable colorectal tumors. *Science*. 1992;256:102–105.
113. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. 2014;370:1287–1297.
114. Kay CL, Kulling D, Hawes RH, Young JW, Cotton PB. Virtual endoscopy–comparison with colonoscopy in the detection of space-occupying lesions of the colon. *Endoscopy*. 2000;32:226–232.
115. Rosman AS, Korsten MA. Meta-analysis comparing CT colonography, air contrast barium enema, and colonoscopy. *Am J Med*. 2007;120:203–210.e4.
116. Külling D, Christ AD, Karaaslan N, Fried M, Bauerfeind P. Is histological investigation of polyps always necessary? *Endoscopy*. 2001;33:428–432.
117. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med*. 2012;366:687–696.
118. Christie JP. Polypectomy or colectomy? Management of 106 consecutively encountered colorectal polyps. *Am Surg*. 1988;54:93–99.
119. Cooper GS, Xu F, Barnholtz Sloan JS, Koroukian SM, Schluchter MD. Management of malignant colonic polyps: a population-based analysis of colonoscopic polypectomy versus surgery. *Cancer*. 2012;118:651–659.
120. Wu X, Liang J, Church JM. Management of sessile malignant polyps: is colonoscopic polypectomy enough? *Surg Endosc*. 2015;29:2947–2952.
121. East JE, Atkin WS, Bateman AC, et al. British society of gastroenterology position statement on serrated polyps in the colon and rectum. *Gut*.. 2017;66:1181–1196.
122. Paspatis GA, Tribonias G, Konstantinidis K, et al. A prospective randomized comparison of cold vs hot snare polypectomy in the occurrence of postpolypectomy bleeding in small colonic polyps. *Colorectal Dis*. 2011;13:e345–e348.
123. Ichise Y, Horiuchi A, Nakayama Y, Tanaka N. Prospective randomized comparison of cold snare polypectomy and conventional polypectomy for small colorectal polyps. *Digestion*. 2011;84:78–81.
124. Fujiya M, Sato H, Ueno N, et al. Efficacy and adverse events of cold vs hot polypectomy: a meta-analysis. *World J Gastroenterol*. 2016;22:5436–5444.
125. Maguire LH, Shellito PC. Endoscopic piecemeal resection of large colorectal polyps with long-term followup. *Surg Endosc*. 2014;28:2641–2648.
126. Seo M, Song EM, Kim GU, et al. Local recurrence and subsequent endoscopic treatment after endoscopic piecemeal mucosal resection with or without precutting in the colorectum. *Intest Res*. 2017;15:502–510.
127. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US multi-society task force on colorectal cancer and the American cancer society. *CA Cancer J Clin*. 2006;56:143–159.
128. Voloyiannis T, Snyder MJ, Bailey RR, Pidala M. Management of the difficult colon polyp referred for resection: resect or rescope? *Dis Colon Rectum*. 2008;51:292–295.
129. Lipof T, Bartus C, Sardella W, Johnson K, Vignati P, Cohen J. Preoperative colonoscopy decreases the need for laparoscopic management of colonic polyps. *Dis Colon Rectum*. 2005;48:1076–1080.
130. Rickert A, Aliyev R, Belle S, Post S, Kienle P, Kähler G. Oncologic colorectal resection after endoscopic treatment of malignant polyps: does endoscopy have an adverse effect on oncologic and surgical outcomes? *Gastrointest Endosc*. 2014;79:951–960.

131. Moss A, Bourke MJ, Williams SJ, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. *Gastroenterology*. 2011;140:1909–1918.
132. Lee E-J, Lee JB, Choi YS, et al. Clinical risk factors for perforation during endoscopic submucosal dissection (ESD) for large-sized, nonpedunculated colorectal tumors. *Surg Endosc*. 2012;26:1587–1594.
133. Saito Y, Yamada M, So E, et al. Colorectal endoscopic submucosal dissection: Technical advantages compared to endoscopic mucosal resection and minimally invasive surgery. *Dig Endosc*. 2014;26(Suppl 1):52–61.
134. Tanaka S, Kashida H, Saito Y, et al. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc*. 2019;27(4):417–434.
135. Hotta K, Oyama T, Shinohara T, et al. Learning curve for endoscopic submucosal dissection of large colorectal tumors. *Dig Endosc*. 2010;22:302–306.
136. Shiga H, Ohba R, Matsuhashi T, et al. Feasibility of colorectal endoscopic submucosal dissection (ESD) carried out by endoscopists with no or little experience in gastric ESD. *Dig Endosc*. 2017;29(Suppl 2):58–65.
137. Yoshii S, Akasaka T, Hayashi Y, et al. Underwater" endoscopic submucosal dissection: a novel method for resection in saline with a bipolar needle knife for colorectal epithelial neoplasia. *Surg Endosc*. 2018;32:5031–5036.
138. Sharma SK, Hiratsuka T, Hara H, Milsom JW. Antigravity ESD - double-balloon-assisted underwater with traction hybrid technique. *Endosc Int Open*. 2018;6:E739–E744.
139. Meier B, Albrecht H, Wiedbrauck T, Schmidt A, Caca K. Full-thickness resection of neuroendocrine tumors in the rectum. *Endoscopy*. 2020;52(1):68–72.
140. Draganov PV, Wang AY, Othman MO, Fukami N. AGA institute clinical practice update: endoscopic submucosal dissection in the United States. *Clin Gastroenterol Hepatol*. 2019;17:16–25.e1.
141. Garrett KA, Lee SW. Combined endoscopic and laparoscopic surgery. *Clin Colon Rectal Surg*. 2015;28:140–145.
142. Lascarides C, Buscaglia JM, Denoya PI, Nagula S, Bucobo JC, Bergamaschi R. Laparoscopic right colectomy vs laparoscopic-assisted colonoscopic polypectomy for endoscopically unresectable polyps: a randomized controlled trial. *Colorectal Dis*. 2016;18:1050–1056.
143. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351:1731–1740.
144. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA Oncol*. 2019;5:e185896.
145. Oh BY, Yun H-R, Kim SH, et al. Features of late recurrence following transanal local excision for early rectal cancer. *Dis Colon Rectum*. 2015;58:1041–1047.
146. Hallam S, Messenger DE, Thomas MG. A systematic review of local excision after neoadjuvant therapy for rectal cancer: are ypT0 tumors the limit? *Dis Colon Rectum*. 2016;59:984–997.
147. Yeo HL, Isaacs AJ, Abelson JS, Milsom JW, Sedrakyan A. Comparison of open, laparoscopic, and robotic colectomies using a large national database: outcomes and trends related to surgery center volume. *Dis Colon Rectum*. 2016;59:535–542.
148. Winawer SJ, O'Brien MJ, Waye JD, et al. Risk and surveillance of individuals with colorectal polyps. Who collaborating centre for the prevention of colorectal cancer. *Bull World Health Organ*. 1990;68:789–795.
149. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US multi-society task force on colorectal cancer. *Gastroenterology*. 2012;143:844–857.
150. O'Brien MJ, Winawer SJ, Zauber AG, et al. The National Polyp Study. Patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. *Gastroenterology*. 1990;98:371–379.
151. Haji A, Ryan S, Bjarnason I, Papagrigoriadis S. High-frequency mini-probe ultrasound as a useful adjunct in the management of patients with malignant colorectal polyps. *Colorectal Dis*. 2013;15:304–308.
152. Akasu T, Kondo H, Moriya Y, et al. Endorectal ultrasonography and treatment of early stage rectal cancer. *World J Surg*. 2000;24:1061–1068.
153. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol*. 2015;110:223–262.