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Colorectal Neoplasms: Screening and Surveillance After Polypectomy

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Key Concepts

- Screening can reduce colorectal mortality.
- Screening recommendations are based upon risk for polyp/cancer development (family history of cancer or polyps, personal history cancer/polyps, genetic syndromes (FAP, MYH, and HNPCC), and inflammatory bowel disease).
- Surveillance after polypectomy depends on the histology of polyp and the completeness of its resection.
- The decision to perform colectomy for a polyp that contains cancer depends on the extent of invasion (Haggitt staging for pedunculated polyp and Kikuchi classification for sessile polyp).

Introduction

Colorectal cancer is the second leading cause of cancer-related deaths in the United States in men and women combined [1]. In 2014, the National Cancer Institute (NCI) estimated 96,000 new colon cancer and 40,000 new rectal cancer cases, and the estimated number of deaths for both colon and rectal cancer combined was 50,310. The fortunate news is that the death rate from colorectal cancer has been decreasing over the last 20 years. This reduction in the number of new cancer cases and cancer-related deaths is a consequence of current screening programs [2, 3]. The rationale for the above is that adenomatous polyps are considered precursors to cancer, and through their early endoscopic removal, carcinoma can be prevented. In addition to the therapeutic roles of colonoscopy, it also allows for the identification of individuals at higher risk for accelerated carcinogenesis (e.g., multiple polyps, unfavorable histology, dysplasia, and large polyps (≥1.0 cm)), who may benefit from more frequent screening.

Of further interest and consideration is that upon following current routine screening recommendations, the potential to identify large groups of patients with adenomatous polyps also exists. This creates a huge burden on the healthcare system (costs, risks, and resources) in terms of surveillance of these patients.

Recommended Screening Guidelines

Guidelines from the American Cancer Society (ACS), the American Society of Colon and Rectal Surgeons (ASCRS), and the American Gastroenterological Association (AGA) all recommend that colorectal cancer screening begin at the age of 50 for both men and women with average risk (i.e., no family history of colorectal cancer, no personal history of inflammatory bowel disease, and asymptomatic) [4–6]. These accepted guidelines are based on joint efforts set forth in 2008 by the ACS, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology (ACR) [7]. Screening regimens can be divided into two categories: fecal testing and structural examinations. While structural examinations are designed to detect both polyps and cancer, fecal testing primarily detects already established cancers or possibly advanced adenomas. It is the opinion of the above organizations that the goal of colorectal cancer screening should be that of prevention. There are various screening options for asymptomatic individuals. The recommended time intervals are listed below and will be further evaluated in this section [7].

Screening Options and Timing for Average-Risk Individuals

- Colonoscopy every 10 years
- CT colonography (virtual colonoscopy) every 5 years
- Flexible sigmoidoscopy every 5 years
- Double-contrast barium enema every 5 years
- Guaiac-based fecal occult blood test (gFOBT) every year
- Fecal immunochemical test (FIT) every year
- Stool DNA (sDNA) test every 3 years

S.R. Steele et al. (eds.), *The ASCRS Textbook of Colon and Rectal Surgery*, DOI 10.1007/978-3-319-25970-3_24

It is important to note that in order for the above to be effective, each of these screening regimens should be performed at regular intervals. In addition, if any of the non-colonoscopy screening tests listed are abnormal, a full colonoscopy is warranted, and the patient should be made aware of this possibility prior to initiation of screening.

Screening Guidelines for Individuals at an Increased Risk Based on Family History

1. If there is a history of colorectal cancer or adenomatous polyps in a first-degree relative before age 60, or in two or more first-degree relatives at any age (non-hereditary syndrome), then screening should begin at age 40 or 10 years prior to the youngest case, whichever is earlier. A colonoscopy is the recommended test in this instance, with screening every 5 years.
2. If there is a history of colorectal cancer or adenomatous polyps in a first-degree relative aged 60 or older, or in at least two or more second-degree relatives at any age, then screening should begin at age 40. Any of the screening options for average-risk individuals may be recommended along with the same screening intervals [8].

Screening Guidelines for Individuals Considered at High Risk Based on Genetics

1. If there is positive genetic testing for familial adenomatous polyposis (FAP) or suspected FAP without testing, then screening should begin at age 10–12 years. Screening should include yearly flexible sigmoidoscopy and consideration for genetic testing if not yet performed. Consideration for colectomy is recommended when testing is positive.
2. If there is a genetic or clinical diagnosis of Lynch syndrome or an individual at increased risk for Lynch, screening should begin at age 20–25 years or 10 years prior to the youngest case. This should include colonoscopy every 1–2 years and genetic testing if not yet performed. In addition, genetic testing should be offered to all first-degree relatives if a Lynch mutation is identified.
3. Individuals with inflammatory bowel disease (chronic ulcerative colitis or Crohn's disease) should begin screening 8 years after the onset of pan colitis or 12–15 years after the onset of left-sided colitis. Screening should be performed by colonoscopy every 1–2 years with biopsies assessing for dysplasia [8].

Screening Cessation

The US Preventive Services Task Force recommends screening up to the age of 75. Screening should be discontinued in individuals aged 76–85 years, if they have had routine screening. However, screening may be considered in this age group if never screened previously and according to each individual's health status and risk. Screening should not be performed in individuals after the age of 85 years [9].

Methods of Screening

Colonoscopy

The use of colonoscopy as a screening and therapeutic modality has become widespread since its initial undertaking by Wolf and Shinya in 1969 [10]. In 2009, there were 11.5 million colonoscopies performed in the United States [11]. In fact, colonoscopy has become one of the most commonly performed medical procedures performed today. The major advantages for colonoscopy as a screening regimen are that it allows visualization of the entire colon, along with the identification, biopsy, or removal of encountered polyps or cancer. Although colonoscopy is widely utilized in the United States for colorectal cancer screening, there are no prospective, randomized trials demonstrating a reduction in the incidence of, or the mortality from, colorectal cancer as a result of colonoscopy. However, as other screening modalities result in subsequent therapeutic colonoscopy after polyp detection, there is indirect evidence suggesting that colonoscopy is beneficial in reducing cancer incidence. This is evident from the Minnesota Colon Cancer Control Study, a randomized, controlled trial which demonstrated a 20 % reduction in colon cancer incidence after subsequent colonoscopy and follow-up based on FOBT screening [12]. Furthermore, studies evaluating cancer incidence after initial complete colonoscopy with polypectomy also demonstrate significant reductions in the incidence of colorectal cancer, ranging from 76 to 90 % depending on the reference population [2, 13]. More recently, subsequent follow-up of the National Polyp Study with a median surveillance period of 15.8 years after colonoscopic polypectomy also demonstrated a 53 % reduction in colorectal cancer-related mortality [14]. It is therefore evident that colonoscopy has the ability to effectively screen and remove adenomatous polyps, thereby reducing the risk of colorectal cancer development and mortality.

Although the use of colonoscopy as a screening modality has major benefits in risk reduction, there are also associated drawbacks with this procedure. Colonoscopy is usually done with sedation and thus requires a chaperone to accompany the patient for transportation. In addition, a complete bowel preparation is required and is often the most difficult part of the process for the patient. However, it is also one of the most important components to completing the procedure successfully and is critical in terms of quality. Rex et al. published an update of several quality indicators set forth by the American Society for Gastrointestinal Endoscopy (ASGE) and American College of Gastroenterology (ACG) Task Force on Quality in Endoscopy [15]. In this update, proposed quality indicators and performance targets are summarized for colonoscopy examinations in the pre-procedure, intra-procedure, and post-procedure periods (Table 24-1). It is imperative that each individual endoscopist be familiar with these targets and utilize them for guidance when screening.

TABLE 24-1. Proposed quality indicators in colonoscopy

Quality indicator	Grade of recommendation	Measure type	Performance target (%)
Pre-procedure			
1. Frequency with colonoscopy is performed for an indication that is included in a published standard list of appropriate indications, and the indication is documented	IC+	Process	>80
2. Frequency with which informed consent is obtained, including specific discussion of risks associated with colonoscopy, and fully documented	IC	Process	>98
3. Frequency with which colonoscopies follow recommended post-polypectomy and post-cancer resection surveillance intervals and 10-year intervals between screening colonoscopies in average-risk patients who have negative examination results and adequate bowel cleansing (priority indicator)	IA	Process	≥90
4. Frequency with which ulcerative colitis and Crohn's colitis surveillance is recommended with proper intervals	2C	Process	≥90
Intraprocedure			
5. Frequency with which the procedure note documents the quality of preparation	3	Process	>98
6. Frequency with which bowel preparation is adequate to allow the use of recommended surveillance or screening intervals	3	Process	≥85 of outpatient exams
7. Frequency with which visualization of the cecum by notation of landmarks and photodocumentation of landmarks is documented in every procedure (priority indicator)	1C	Process	
Cecal intubation rate with photography (all examinations)			≥90
Cecal intubation rate with photography (screening)			≥95
8. Frequency with which adenomas are detected in asymptomatic average-risk individuals (screening) (priority indicator)	1C	Outcome	
Adenoma detection rate for male/female population			≥25
Adenoma detection rate for male patients			≥30
Adenoma detection rate for female patients			≥20
9a. Frequency with which withdrawal time is measured	2C	Process	>98
9b. Average withdrawal time in negative-result screening colonoscopies	2C	Process	≥6 min
10. Frequency with which biopsy specimens are obtained when colonoscopy is performed for indication of chronic diarrhea	2C	Process	>98
11. Frequency of recommended tissue sampling when colonoscopy is performed for surveillance in ulcerative colitis and Crohn's colitis	1C	Process	>98
12. Frequency with which endoscopic removal of pedunculated polyps and sessile polyps <2 cm is attempted before surgical referral	3	Outcome	>98
13. Indication of perforation by procedure type (all indications vs. colorectal cancer screening/polyp surveillance) and post-polypectomy bleeding	1C	Outcome	
Incidence of perforation—all examinations			<1:500
Incidence of perforation—screening			<1:10,000
Incidence of post-polypectomy bleeding			<1 %
14. Frequency with which post-polypectomy bleeding is managed without surgery	1C	Outcome	≥90
15. Frequency with which appropriate recommendation for timing of repeat colonoscopy is documented and provided to the patient after histologic findings are reviewed	1A	Process	≥90

This list of potential quality indicators is meant to be a comprehensive listing of measurable end points. It is not the intention of the task force that all end points be measured in every practice setting. In most cases, validation may be required before a given end point may be adopted universally

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Selected important target areas include: (1) cecal intubation rates for screening with photodocumentation of ≥95 %, (2) an overall adenoma detection rate of ≥25 % (≥30 % for males, ≥20 % for females), (3) average scope withdrawal time of ≥6 min, (4) incidence of perforation during screening of <1:1000, (5) incidence of post-polypectomy bleeding of <1 %, and (6) the frequency with which appropriate recommendations for timing of repeat colonoscopy are documented and provided to the patient of ≥90 %. Furthermore, an adequate bowel preparation is also necessary in this context and is also listed as a pre-procedure quality indicator. The target recommendation for the frequency for which bowel preparation is adequate should be ≥85 %. Sherer et al. reported that in cases where poor bowel preparation was recorded, the detection rate of advanced histology was significantly affected as compared with adequate preparation [16].

Unfortunately, despite best efforts, there are reported miss rates for both polyps and cancers with the use of colonoscopy. A systematic review evaluating miss rates by same-day colonoscopy revealed a miss of 2.1 % for polyps ≥10 mm and 13 % for polyps 5–10 mm in size [17]. Higher miss rates were noted when concomitant CT colonography was utilized

rather than tandem colonoscopy. With this approach, a miss rate of 11.8 % was noted for polyps ≥10 mm in size [18]. Similarly, potential miss rates for cancer are reported to be 3.4 %, especially lesions within the proximal colon (5.9 %), based upon evaluation of patients who have received a screening colonoscopy within 3 years of diagnosis [19]. While there may be several reasons for failure of neoplasia detection, it only further stresses the importance of adequate bowel preparation and adherence to evaluation guidelines in order to minimize miss rates.

It also appears that miss rates may be somewhat dependent on location within the colon in that the proximal colon may not be as reliably or consistently evaluated. Again, Bressler et al. noted that most cancer misses occurred within the right colon compared to the left side (5.9 % vs. 2.3 % in the sigmoid or rectum) [19]. Similarly, Baxter et al. revealed that colonoscopy screening reduced the number of deaths due to left-sided colorectal cancer, but not right-sided, suggesting that screening colonoscopy for right-sided lesions may be less effective [20]. This finding was not evident with the use of CT colonography; however, Pickhardt et al. revealed that misses can occur throughout the colon, usually behind the proximal aspect of a fold and even within 10 cm of the anal verge [18]. In any event, it is apparent that even with our best screening modality, the ability to screen reliably is not without error.

Incomplete Colonoscopy

As noted in Table 24-1, recommended rates of incomplete colonoscopy (without cecal intubation) should be <5 % during screening and <10 % overall. Unfortunately, there are no apparent guidelines or consensus as to the best management strategies in cases of incomplete colonoscopy. Advanced neoplasia is noted in 4 % of these cases within the non-visualized portion of the colon [21]. When colonoscopy is incomplete, options include repeat colonoscopy, use of other endoscopic modalities (i.e., smaller endoscope, double balloon endoscopy), CT colonography, or barium enema. The decision of which modality is best suited is dependent on both the reasons for the incomplete exam and the institution-specific resources available [22].

Adjuncts to Colonoscopy

In an effort to improve colonoscopy screening, more recent technical developments in colonoscopic imaging have targeted advancements in polyp detection. These advances have included (1) techniques applied to current colonoscopy methods, including high-definition monitors, chromoendoscopy, or cap-assisted colonoscopy (CAC), and (2) colonoscope enhancements to current imaging, such as narrow band imaging (NBI), autofluorescence imaging (AFI), and Fujinon intelligent color enhancement (FICE).

The addition of high-definition white light (HDWL) and high-definition monitors to standard colonoscopy may optimize mucosal visualization. A meta-analysis evaluating five studies comparing high-definition to conventional colonoscopy revealed a slight improvement (3.5 %) in adenoma detection rates [23].

Pan-colonic chromoendoscopy (PCC) involves the topical spray application of a dye, usually 0.4 % indigo carmine via the colonoscope. The dye is not absorbed but rather highlights irregular, flat, or small lesions that may be less obvious. Possible advantages to this technology are noted in two prospective, randomized trials comparing chromoendoscopy to either standard or HDWL colonoscopy. While a marginal, though not significant, improvement in overall adenoma detection rate was noted when compared to HDWL, there were improvements in flat adenoma detection [24]. In contrast, compared to standard colonoscopy, Pohl et al. found improvements in both flat and overall adenoma detection rates. However, PCC required more time to complete the procedure as well [25].

CAC attaches a clear cap to the tip of the colonoscope. This allows for deflection of mucosal folds without obscuring visualization, potentially improving detection in these locations. However, the findings of randomized, controlled trials are mixed as to whether CAC offers improvements in adenoma detection rates over conventional colonoscopy [26, 27].

A virtual chromoendoscopy technique, NBI, involves the placement of narrow band filters behind the light source to remove red light and thus increase blue and green wavelengths. This enhances mucosal surface vascularity and therefore polyp visualization. A meta-analysis comparing NBI with standard colonoscopy demonstrated no improvements in adenoma detection with the addition of NBI [28]. Similarly, systematic comparisons between high-definition NBI and HDWL colonoscopy also failed to show improvements in adenoma detection [29]. However, there is a suggestion that high-definition NBI may have an advantage over standard colonoscopy with respect to minimizing polyp and adenoma miss rates [30].

Other virtual techniques include AFI which utilizes a blue filter to create an autofluorescent image from the tissue. Neoplastic tissue will take on a red-green fluorescence in contrast to surrounding normal mucosa [31]. Similarly, FICE utilizes a computed spectral estimation technology that narrows light bandwidth without the use of filters and allows for visualization at various wavelengths. In particular, this allows for enhancement of mucosal vascular and pit patterns [32]. In a randomized study of over 1600 subjects, neither NBI nor FICE increased the adenoma detection rate when compared with standard colonoscopy [33]. A meta-analysis of 42 studies assessed each of the previously discussed colonoscopy enhancement modalities, including each of the virtual capabilities in their ability to improve adenoma detection rates over standard high-definition/white light colonos-

copy. In doing so, only chromoendoscopy with indigo carmine demonstrated potential improvement [34].

Complications

Complications related to colonoscopy have included cardiopulmonary events, bleeding, perforation, diverticulitis, and post-polypectomy syndrome. The risk of unplanned cardiopulmonary events after colonoscopy is 1.1 % and is usually related to the effects of conscious sedation [35]. In a review by Rutter et al., the overall 30-day risk of serious adverse events after colonoscopy was 4.7 per 1000 screening colonoscopies and 6.8 per 1000 follow-up colonoscopies. The risk of perforation was 0.04 % for screening (0.07 % with polypectomy) and 0.12 % after follow-up. Most related bleeding occurs after polypectomy, with a rate of 0.27 % for screening and 0.50 % after polypectomy. Post-polypectomy bleeding can be immediate or delayed. Older age was associated with higher rates of perforation or bleeding [36]. Post-polypectomy syndrome is related to an electrocautery full-thickness burn resulting in localized peritonitis. In a review by Ko et al., the risk of post-polypectomy syndrome ranged from 0.003 to 0.1 %, while the risk of diverticulitis ranged from 0.04 to 0.08 % and the overall risk of death from 0 to 0.09 % [37]. Overall, there is a 1.17 % admission rate after colonoscopy for the above complications.

CT Colonography or Virtual Colonoscopy

CT colonography (CTC) or virtual colonoscopy is a minimally invasive, radiographic option for colorectal cancer screening. It utilizes computed tomography to generate two-dimensional (2D) images that allow for further three-dimensional (3D) reconstruction with the assistance of software technology. Together, evaluation of both 2D and 3D images allows for accurate neoplasia detection. Figure 24-1a–d demonstrates 2D and 3D imaging of a pedunculated sigmoid polyp and subsequent colonoscopic identification.

CTC still requires adequate bowel preparation and must have gaseous distension of the colon to allow for adequate examination. This entails insertion of a rectal catheter to allow for manual or automated inflation with carbon dioxide, infused continuously as images are acquired. Tagging of residual stool contents with an oral delivery of dilute barium (2 %) and residual fluid tagging with water-soluble iodinated contrast (diatrizoate) have further increased sensitivity [38]. As with optical colonoscopy, meeting appropriate quality parameters is also important in CTC. These parameters as recommended by the ACR should include (1) adequate colon cleansing and distension, (2) complete anatomic coverage of the colon and rectum, (3) visualization of each colonic segment in at least one position, (4) appropriate physician training for CTC performance and interpretation, and (5) proper documentation and communication of clinical findings [39].

CTC does not require sedation, and the exam can be performed rather quickly. However, in cases where polyps are detected, subsequent therapeutic colonoscopy is required. Ideally, this should be performed on the same day since bowel preparation is already complete. This requires program coordination between gastroenterology and radiology departments. In cases where polyps are detected, findings of one or more polyps ≥10 mm or three or more polyps ≥6 mm should be referred for subsequent colonoscopy and polypectomy. Though somewhat controversial, isolated polyps in the 6–9 mm range may also be referred for therapeutic intervention [38, 40]. Since very small polyps (≤5 mm) carry low clinical risk, reporting and referral for these isolated lesions are currently not recommended [39, 41]. A further advantage of CTC is that it allows for a limited evaluation for extracolonic findings as well [42]. Of these potential findings, it was noted that 7.4 % were clinically relevant with 2.1 % gaining clinical benefit from detection [43].

Complications related to CTC are very rare. A survey of a virtual colonoscopy working group reported no perforations in more than 11,000 CTC screening examinations, and two perforations in more than 10,000 exams for diagnostic indications (0.02 %), only one of which was symptomatic [44]. Although often discussed, the radiation exposure associated with CTC is also quite low, reportedly around 5 mSv for screening purposes [45]. This is well below the 100 mSv threshold often considered when attempting to address associated health risk [46].

In an early assessment of over 1200 asymptomatic subjects undergoing same-day CTC and optical colonoscopy, a 94 % sensitivity for the detection of adenomas greater than 1 cm was noted and 89 % for adenomas ≥6 mm [47]. More recently, the American College of Radiology Imaging Network (ACRIN) national, multicenter CTC trial assessed over 2500 patients. The per-patient sensitivity for the detection of polyps or cancer ≥10 mm was 90 % and 78 % for polyps ≥6 mm [48]. Furthermore, when considering detection rates for cancer only, meta-analysis conferred a 96 % sensitivity for the detection by CTC with a prevalence of 3.6 % [49]. These findings compare favorably to optical colonoscopy. In a parallel screening program utilizing both colonoscopy and CTC in over 3100 patients, similar detection rates for advanced neoplasia (polyps and cancer) were noted (3.4 % and 3.2 %, respectively). There were many more polypectomies performed in the optical colonoscopy group and also more procedure-related complications [50]. Upon assessing the outcomes in over 1000 cases where screening CTC exams were negative, one interval cancer and 11 large adenomas were noted after a mean follow-up of 4.7 years [51]. Together, these studies suggest that CTC is an

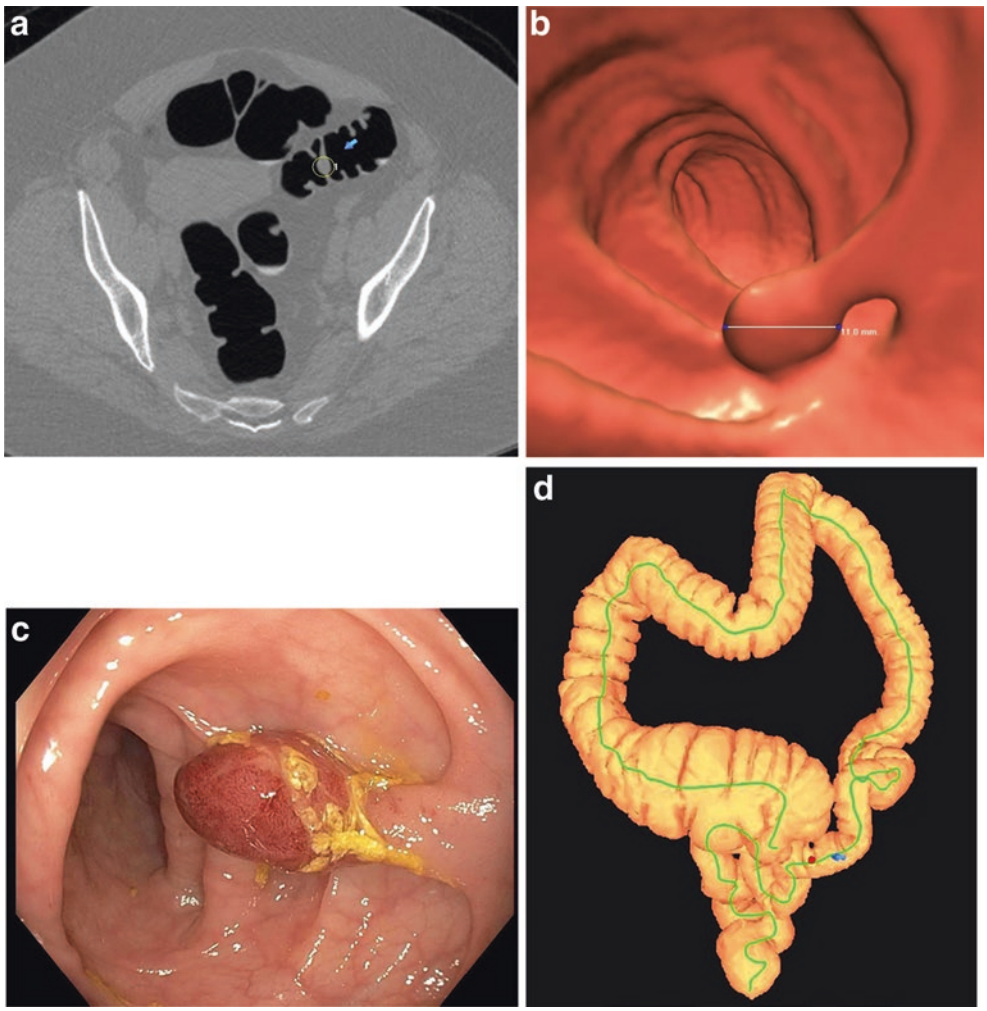

FIGURE 24-1. CT colonography images demonstrate both (**a**) 2D and (**b**) 3D imaging of a pedunculated sigmoid polyp, and subsequent (**c**) colonoscopic identification (**d**) demonstrates the virtual location of the polyp by CT imaging.

acceptable alternative to optical colonoscopy and that current 5-year screening intervals are appropriate.

Flexible Sigmoidoscopy

Flexible sigmoidoscopy may be useful as a component of the screening regimen for colorectal cancer. The standard sigmoidoscope is 60 cm in length. To be effective as a screening modality, the quality of the evaluation must be adequate. Therefore, it has been recommended that the scope be advanced to a minimum of 40 cm in order to minimize the risk of missing a distal colorectal cancer [52]. In addition, if distal pathology is identified, it must be properly biopsied in order to best determine the need for further evaluation. With adenoma detection, the risk of harboring concomitant disease more proximally is at least twofold and thus requires formal colonoscopy [53]. The advantages of flexible sigmoidoscopy lie in the ability to perform the procedure without sedation (although with some potential patient discomfort), by a variety of healthcare professionals and after only minimal bowel preparation.

The major problem with sigmoidoscopy lies in its inability to evaluate the more proximal colon. Despite this, meta-analyses have demonstrated a beneficial reduction in the incidence of colorectal cancer and long-term mortality when compared with no screening [54]. When considering only intention to treat analyses, a reduction in the incidence of distal colorectal cancer and mortality was reported as 31 % and 46 %, respectively [55]. Results of a large randomized, clinical trial demonstrated a 21 % reduction in colorectal cancer incidence and a 26 % reduction in mortality. However, mortality from proximal colorectal cancer was not affected, with a mortality reduction of 50 % when considering only distal colorectal cancer [56]. Finally, a more recently published randomized, controlled trial compared the use of flexible sigmoidoscopy alone or in combination with fecal occult blood testing (FOBT) as a one-time screening regimen in age groups beginning at both 50 and 55 years of age. Patients with positive findings with either test were then offered a colonoscopy. This study revealed a 63 % rate of adherence to screening and a 28 % reduction in the incidence of colorectal cancer and a 12 % reduction in mortality. Interestingly, there

was no difference noted between groups receiving flexible sigmoidoscopy alone or in combination with FOBT [57].

Complications

The risk of GI complications including perforation with flexible sigmoidoscopy is extremely low, reported to be 0.02 % [58]. Gatto et al. reported an incidence of perforation after flexible sigmoidoscopy of 0.88 per 1000 procedures for patients aged 65 or older [59].

Fecal Occult Blood Testing/Fecal Immunochemical Testing

FOBT is aimed at detecting subtle blood loss in the gastrointestinal tract. Based on randomized, controlled trials, annual screening for FOB is recommended for detecting cancer and precancerous polyps in average-risked patients starting at the age of 50. There are two general types of FOBT based on the analyte detected: guaiac versus immunochemical. With positive testing, the patient will then need to undergo appropriate diagnostic testing (colonoscopy or flexible sigmoidoscopy) within a year of the abnormal result. Previous reports demonstrated that only 25–59 % of patients with a positive FOBT receive diagnostic evaluation after a positive test [60].

A stool guaiac test (gFOBT) is done by smearing feces onto an absorbent paper that has been chemically treated. Hydrogen peroxide is then placed onto the paper, and if a trace amount of blood is present, the color will change. The color change is due to the fact that heme has peroxidase-like activities that breakdown hydrogen peroxide. Optimal use depends on following strict dietary adjustments prior to collecting the stool sample. This test requires at least 2 mL of blood loss a day to become positive. There have been several randomized, controlled trials that demonstrate a benefit of FOBT in reducing mortality from CRC (about 15 % reduction) [61, 62].

FIT utilizes specific antibodies to detect globin. FIT has replaced most gFOBT tests in that it is both cheap and quantitative. There is evidence that FIT has higher sensitivity and specificity over gFOBT (13–25 % vs. 81 %). FIT can pick up as little as 0.3 mL of blood in the stool, and patients are not required to follow any dietary restrictions prior to testing. A recent systematic review demonstrated an overall accuracy of 95 % for CRC detection with 79 % sensitivity and 94 % specificity [63]. However, it does have a lower sensitivity in terms of adenoma detection (only 28 %) [64].

Stool DNA Testing

Perhaps the most recent advancement in colorectal cancer screening involves the use of DNA testing of stool samples. Tumor cells and their associated DNA are continuously passed into the stool. Tumor DNA constitutes a very small amount of the fecal content; therefore, a large stool sample is needed for analysis. This assay tests for DNA mutations and methylations of common genes associated with colorectal cancer (i.e., KRAS mutations). These tests also assay for human hemoglobin similar to FIT. This test concomitantly tests for beta-actin to allow for an estimation of the total amount of human DNA present. The results of the assay allow for a composite score that is compared to a standardized value in order to determine a positive or negative test result. There are no dietary restrictions with this test. In a recent study in asymptomatic patients, stool DNA testing detected significantly more cancers than did FIT but also had more false positives [65]. In screening and surveillance, polyps greater than 1 cm can be detected with stool DNA testing, unlike FIT testing [66]. Its sensitivity for polyps greater than 1 cm is 57 %, for greater than 2 cm is 73 %, and for greater than 3 cm is 83 % (the same rate for detecting polyps with high-grade dysplasia) [67].

Double-Contrast Barium Enema

With the more widespread use of the previously described screening entities, the use of contrast enema has diminished as a screening modality. However, it may still be utilized in regions where other screening modalities are not available. Double-contrast barium enema (DCBE) involves coating the colonic mucosal surface with barium followed by distension with air through a rectally placed catheter. Fluoroscopic and standard radiographic imaging is utilized during various positional changes to assess the entire colon. Prior bowel preparation is also required to allow for removal of adherent fecal content.

A small number of studies utilized both colonoscopy and DCBE to assess neoplasia detection. Winawer et al. reported the sensitivity of DCBE to detect polyps ≤5 mm, 6–10 mm, and >10 mm as 32 %, 53 %, and 48 %, respectively [68]. Similarly, Rockey et al. noted sensitivities of 48 % for lesions ≥10 mm and 35 % for lesions 6–9 mm [69]. Furthermore, a meta-analysis comparing DCBE and CTC demonstrated lower sensitivities for detecting polyps ≥6 mm with DCBE [70]. When considering only colorectal cancer detection, the sensitivity of DCBE increases to 85 % [71]; however, the rate of new or missed cancers following DCBE has also been reported as high as 22 % [72]. These findings suggest that DCBE may be inferior to other methods of screening. In addition, the use of DCBE may be less attractive to both patient and radiologist, due to the nature and labor intensiveness of the exam [7].

Screening Reality

Although there are several modalities available for colorectal cancer screening, the ACS reports that in 2012 only 59 % of Americans over the age of 50 were screened according to current guidelines. Furthermore, there appears to be a wide variability in screening patterns by state of residence [73].

Surveillance

Guidelines for Surveillance After Polypectomy

History

In the 1970s, the follow-up recommendations for post-polypectomy included a repeat colonoscopy on an annual basis. In 1997, guidelines were published by the gastrointestinal consortium, based on the results of the 1993 National Polyp Study [2], which recommended that the first follow-up examination after polypectomy occur at 3 years. These guidelines were then updated in 2003 based on risk stratification into low-risk and higher-risk adenomas, the goal of which was to identify predictors of future advanced adenomas and cancers to create risk stratification for patients. Higher-risk patients are categorized as those with ≥3 adenomas, high-grade dysplasia, villous features, or an adenoma ≥1 cm. Lower-risk patients are those with 1–2 adenomas with no high-grade dysplasia. With this stratification system, the secondary goals were to decrease the surveillance burden on the system and to decrease the risks to the patients by tailoring follow-up based on risk. It is important to note that the current guidelines for surveillance are to be applied only after high-quality baseline colonoscopy with complete removal of all detected lesions. If either of these two criteria is not met, then repeat examination should be planned. Also, discontinuation of surveillance should be considered in patients with serious comorbidities with less than a 10-year life expectancy. Finally, these guidelines apply only to asymptomatic individuals; new symptoms need diagnostic workup.

Surveillance Based on Pathology of Polyp

Hyperplastic and Serrated Polyps

Serrated lesions of the colon and rectum are classified by the World Health Organization (WHO) into three general categories based on cytological features, architectural features, and location. The categories include hyperplastic polyps, sessile serrated adenoma/polyps, and traditional serrated adenomas (Figure 24-2a, b). These lesions are usually located proximally, sessile or flat in morphology, and pale in color, with indistinct borders, and usually have a mucus cap. Due to their indistinct appearance, there is a high rate of incomplete resection. NBI and chromoendoscopy techniques can be used to facilitate identification and delineation of borders. Given that incomplete resection rates are high in serrated adenomas greater than 1 cm, it seems reasonable to tattoo these lesions so that they can be identified on repeat endoscopy in 3–6 months [74].

Most international post-polypectomy surveillance guidelines do not recommend surveillance for serrated polyps. However, there is increasing awareness that these lesions may be major precursor lesions to cancer development in about 1/3 of colorectal cancer cases. The US Multi-Society Task Force guidelines for post-polypectomy surveillance are 1–5 years depending on the number, size, and presence of dysplasia. Recent reviews on the management of serrated lesions recommended complete removal of all lesions except for ≤5 mm in the sigmoid or rectum. Those small lesions should be randomly biopsied for histology.

Those patients with small rectal hyperplastic polyps are considered to have normal colonoscopies and therefore should be screened every 10 years. The exceptions to this are those patients who have hyperplastic polyposis syndromes (HPS). HPS is a rare syndrome characterized by multiple hyperplastic and/or serrated adenomas. Patients with this syndrome have a lifetime risk of colorectal cancer of up to 50 % [75]. The WHO criteria for HPS are defined as meeting one of the following criteria: having five or greater serrated lesions proximal to the sigmoid colon (with two being greater than 1.0 cm) or more than 30 serrated lesions throughout the colon. There are no evidence-based guidelines for surveillance for these patients, but most physicians are screening them annually or biennially [76]. First-degree relatives of patients with HPS should undergo colonoscopy at the age of 40 or 10 years before the age of diagnosis of HPS. With regard to patients with serrated adenomas that do not have HPS, there are limited observational studies to make strong recommendations for surveillance. However, there are consensus recommenda-

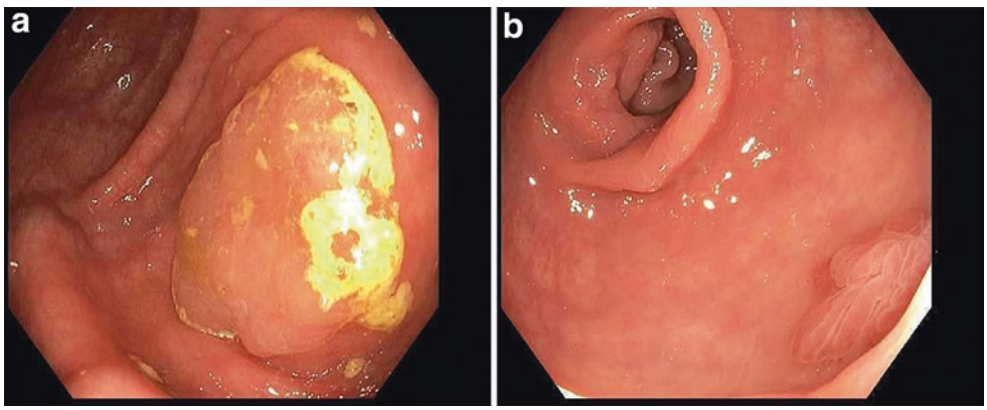

FIGURE 24-2. Endoscopic views of two different types of serrated polyps. (**a**) Sessile serrated adenoma/polyp in the cecum and (**b**) a traditional serrated adenoma of the rectum.

TABLE 24-2. Recommendations for screening intervals based on consensus guidelines for patients with serrated polyps based on histology, number, location, and size[a]

Histology	Size (mm)	Number	Location	Interval in years
HP	<10	Any number[b,c]	Rectosigmoid	10
HP	≤5	≤3	Proximal to sigmoid	10
HP	Any	≥4	Proximal to sigmoid	5
HP	>5	≥1	Proximal to sigmoid	5
SSA/P or TSA	<10	<3	Any	5
SSA/P or TSA	≥10	1	Any	3
SSA/P or TSA	<10	≥3	Any	3
SSA/P	≥10	≤2	Any	1–3[d]
SSA/P w/dysplasia	Any	Any		1–3[e]

[a]The interval recommendations presented here represent consensus opinion based on low-quality or very low-quality evidence. They are likely to change as higher quality evidence becomes available, and alternatives may be equally reasonable

[b]Patients with >20 HPs in the rectosigmoid meet the World Health Organization definition of serrated polyposis if there are additional serrated lesions proximal to the sigmoid

[c]Some panel members follow a policy of 5 years if there are multiple HPs 6–9 mm in size in the rectosigmoid

[d]Patients with two or more serrated polyps ≥10 mm in the proximal colon meet the World Health Organization criteria for serrated polyps if three additional serrated lesions of any size are proximal to the sigmoid are identified

[e]SSA/P with cytological dysplasia is a more advanced lesion than SSA/P. Depending on the size of the lesion, the confidence in complete endoscopic resection and other associated lesions, intervals shorter than 3 years may be appropriate

Note 1: Patients with both significant serrated findings and concurrent adenomas may be at a more advanced stage in the progression toward cancer. Closer follow-up may be indicated in some cases based on clinical judgment

Note 2: In general, these recommendations for surveillance are for the first follow-up. For findings with short follow-up recommendations, a longer subsequent follow-up interval may be appropriately applied when a follow-up exam shows improvement in findings, i.e., reduction in the number, size, and/or histologic severity of lesions

Note 3: Because of interobserver variation in the pathologic differentiation of HP from SSA/P, proximal colon serrated lesions >10 mm in size that are designated HP may be considered to be SSA/P by clinicians

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tions that were made in 2012 where surveillance intervals were made based on histology (HP, SSA/P, or TSA), size, number, and location (Table 24-2) [77].

Adenoma

Adenomas can be classified histologically as tubular, villous, or tubulovillous. According to the World Health Organization criteria, tubular adenomas have less than 25 % villous component, tubulovillous 25–75 %, and villous greater than 75 % [78]. Tubular adenomas are the most common type of adenoma found followed by tubulovillous and then villous. Tubular adenomas have <5 % of harboring cancer, while the risk of tubulovillous is 20–25 % and villous adenomas is 35–40 % [79]. Screening series have reported an adenoma prevalence rate of 15–30 %. With the addition of high-definition colonoscopy, this number has been quoted as high as 50 % [80].

The recommendations for post-polypectomy surveillance in patients with one or two small polyps that are less than 1 cm in size range from 3 to 10 years post-polypectomy, depending on which recommendation is followed. The ASGE and the Polyp Guidelines from the ACG recommend follow-up in 5 years. The ACS recommends follow-up in 3–6 years. The Multi-Society Task Force and the Joint ACS and Multi-Society Task Force recommend follow-up in 5–10 years [81]. If low-grade dysplasia is identified on pathology for these patients, the surveillance guidelines do not change.

Patients with 3–10 adenomas, any adenoma ≥1 cm, any adenoma with villous features, or high-grade dysplasia should have their next colonoscopy in 3 years provided the entire polyp was removed in a non-piecemeal fashion (Figure 24-3).

Those patients with sessile adenomas that were removed in piecemeal should be reexamined in 2–6 months to confirm complete removal. If on follow-up colonoscopy there are only 1–2 tubular adenomas, the interval to screening is increased to 5 years. A meta-analysis evaluated the safety and efficacy of endoscopic resection specifically for large polyps (greater than 2 cm). They found a recurrence rate of 14 % with the majority of recurrences being amenable to further endoscopic therapy. It was noted that endoscopic submucosal dissection appeared to reduce the risk of recurrence, while invasive cancer on histology was the main reason for endoscopic failure [82].

Those patients with >10 adenomas at one examination should have follow-up in less than 3 years and should be referred for consultation with a genetic counselor.

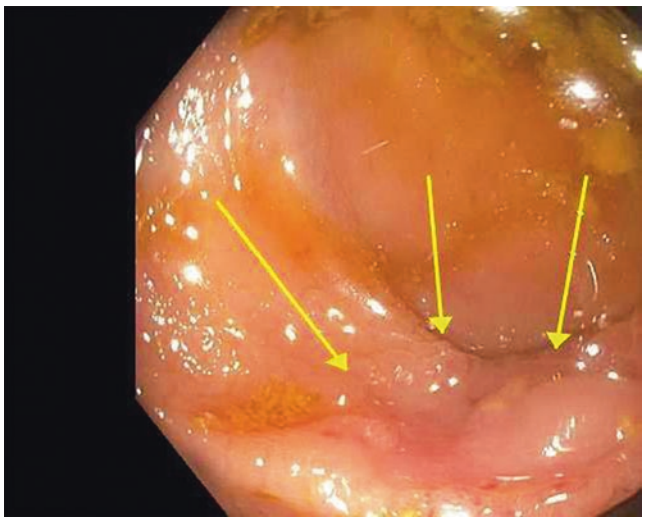

FIGURE 24-3. Endoscopic view of a cecal ulceration which pathology after biopsy demonstrated colonic mucosa with adenomatous change and focal high-grade dysplasia.

Inflammatory Polyps

Inflammatory polyps include benign lymphoid polyps and pseudopolyps (such as those seen in ulcerative colitis). Benign lymphoid polyps are composed of the normal lymphoid tissue and therefore do not require any surveillance if this is seen on pathology. Pseudopolyps are discussed below in the inflammatory disease section.

Hamartomatous Polyps

Hamartomatous of the colon and rectum include juvenile polyps and polyps seen in Peutz-Jeghers disease. Juvenile polyps, as the name suggests, occur in children. These are not frequently seen after 15 years of age. In 70 % of cases, there is only one polyp identified. Juvenile polyposis syndrome (JPS) is a disorder of multiple juvenile polyps. These polyps may cause bleeding, abdominal pain, or obstruction. The diagnosis is made when there is any one of the following: (1) more than five juvenile polyps of the colon or rectum, (2) juvenile polyps in other parts of the gastrointestinal tract, and (3) any number of juvenile polyps and one or more affected family members. Three different types of JPS have been described based on the signs and symptoms of the disease. Most juvenile polyps are benign. It is estimated that people with JPS have a 10–50 % risk of developing cancer of the gastrointestinal tract (most commonly colon and rectal cancer). This disorder is associated with mutations in the BMPR1A and SMAD4 genes. It is inherited in an autosomal dominant fashion. Treatment depends on size and number of polyps found. When there are only a few polyps identified and the polyps are small enough, they can be removed endoscopically. Polyps that are too large or too numerous to be removed this way may require an operative resection. If a polyp is seen on endoscopy, it should be removed, and screening should be done yearly until no polyps are found. Thereafter, patients with juvenile polyps should be screened every 3 years if endoscopies are negative [83].

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by intestinal hamartomatous polyps along with a distinct pattern of skin and mucosal melanin deposition. These patients have a 15-fold increased risk of developing intestinal cancers compared to the general population. The genetic mutation identified with this syndrome is in the STK11 gene (also known as LKB1). A clinical diagnosis of PJS requires the presence of one of the following: (1) two or more histologically confirmed PJ polyps, (2) any number of PJ polyps detected in a patient with a family history, (3) characteristic mucocutaneous pigmentation in an individual who has family history of PJS, and (4) any number of PJ polyps in an individual who has the characteristic mucocutaneous pigmentation. Those patients that met clinical criteria should undergo genetic testing for a germline mutation. In terms of surveillance, these patients should undergo a colonoscopy every 2–3 years starting in late adolescence. They should also have upper endoscopies every 2–3 years. Small bowel interrogation (CT enterography) should also occur every 2–3 years [84].

Inflammatory Bowel Disease

In patients with inflammatory bowel disease (IBD), the presence of chronic inflammation puts them at an increased risk for dysplasia and cancer. Polyps detected in patients with IBD are referred to as a dysplasia-associated lesion or mass (DALM). DALM lesions are then divided into three categories based on endoscopic appearance and location: (1) It is a sporadic adenoma if the polyp resembles an adenoma both endoscopically and histologically and is located outside an area of histologically proven colitis. Complete polypectomy with routine surveillance is adequate with these lesions. (2) It is an IBD-associated adenoma-like polypoid dysplasia if

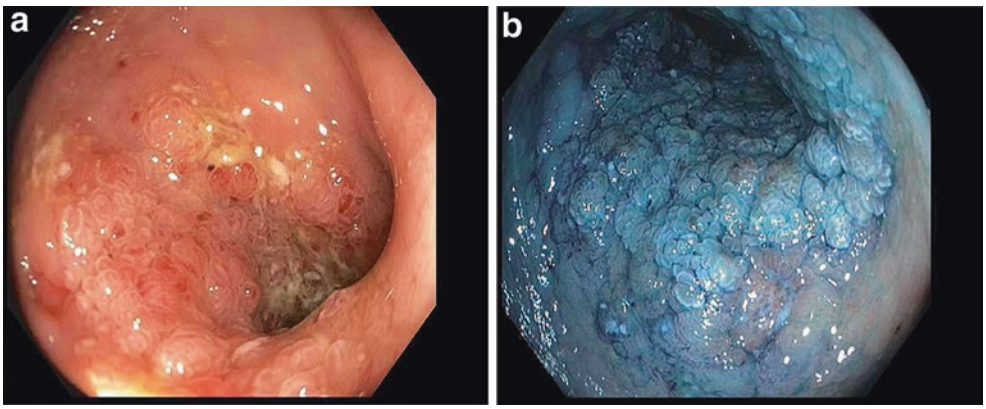

FIGURE 24-4. (**a**) Endoscopic view of a polyp in the sigmoid colon of a patient with ulcerative colitis. (**b**) The use of chromoendoscopy in 4 Ballows for better visualization of the borders of the polyp compared to the images without indigo carmine in 4A.

the lesion resembles an adenoma endoscopically and histologically and is located in an area of colitis. For these lesions, if they are not associated with flat dysplasia or carcinoma, polypectomy with surveillance at a shortened interval is recommended. (3) Finally, IBD-associated non-adenoma-like dysplasia, which is considered a true DALM, is a lesion that is irregular and broadly based and is located in an area of colitis. These lesions are at high risk for associated carcinoma and should be treated with colectomy after the diagnosis of dysplasia is confirmed by an experienced pathologist (Figure 24-4a, b) [85].

Surveillance with Cancer Resection

Patients who are undergoing curative resection for colon cancer are recommended to obtain a colonoscopy 1 year after resection. If the examination at 1 year is normal, then the interval should be extended to 3 years. If that subsequent one is normal, then the interval is again increased to 5 years.

For those patients who are undergoing resection for rectal cancer then there should be periodic examinations to identify early recurrence. This usually entails proctoscopic examination every 3–6 months for the first 2–3 years.

Early Cancer (T1) Within Polyp

There are two classification systems that are established for the identification of cancer within a polyp. The first is Haggitt classification which is utilized for quantifying the extent of invasion in pedunculated polyps. The second is the Kikuchi classification for sessile polyps.

Haggitt Classification

- Haggitt level 0: Noninvasive.
- Haggitt level 1: Cancer invades into the submucosa but limited to the head of the polyp.
- Haggitt level 2: Cancer invades into the neck of the polyp.
- Haggitt level 3: Cancer invades the stalk of the polyp.
- Haggitt level 4: Cancer invades the submucosa of the bowel wall below the stalk.

The risk of spread to the lymph nodes is less than 1 % for levels 1–3. For Haggitt level 4, the risk of lymph node disease ranges from 12 to 25 % [86, 87].

Kikuchi classification of the submucosa is divided into three levels:

- SM1 is invasion of the upper one-third.
- SM2 is invasion of the middle third.
- SM3 is invasion into the lower one-third.

Haggitt levels 1–3 are equivalent to SM1 and Haggitt level 4 can be SM1, SM2, or SM3. There have been several factors identified that increase the risk of lymph node metastases. These factors include lymphovascular invasion, poor differentiation, gender, extensive budding, and SM3 invasion [88].

For low-risk cancers, Haggitt levels 1–3, Kikuchi SM1, or no evidence of poor differentiation or angioinvasion, where the lesion has been completely resected in one piece with negative margins, endoscopic or local excision is regarded as adequate treatment. However, patients should be made aware that although the risk of nodal metastases is very low, it is not zero and that there is no effective surveillance that will reliably detect nodal metastases prior to distant metastatic spread. Although surveillance colonoscopy is recommended at frequent intervals (e.g., yearly), the risk of tumor growth is in the nodes, not in the lumen, calling into question the value of frequent colonoscopy. Surveillance is usually continued for 5 years. There has been some debate on this matter, however, in that there are studies that demonstrate that the risk for recurrence extends past 5 years post-polypectomy [89]. Formal surgical resection is indicated for high-risk cancers (Haggitt level 4, Kikuchi SM3, lymphovascular invasion, poor differentiation, or positive resection margin, cancer in sessile lesions removed in piecemeal fashion).

When to Tattoo an Area After Polypectomy

Current guidelines strongly recommend tattooing of suspicious lesions during colonoscopy. Given that the risk of cancer arising from a polyp in the National Bowel Cancer Screening Program increased significantly when the polyp was greater than 1 cm in size, most would recommend tattoo of all polyps greater than 1 cm (Figure 24-5a, b). In addition, when sessile lesions are removed in piecemeal fashion, the risk of recurrence is high. Tattoo at the site of polypectomy should be considered to help identify the area at subsequent colonoscopy.

Benefits of Surveillance

There have been several studies that have examined the benefits of post-polypectomy surveillance in terms of cancer prevention [90, 91]. These studies identified the risk of colorectal cancer after adenoma resection that depended not only upon the characteristics of the adenoma (advanced or non-advanced) but also colonoscopy surveillance practices. None of these studies are randomized, controlled trials, so there is no direct evidence on the exact benefit that is obtained through surveillance. Most of these studies emphasize the importance of surveillance especially in high-risk adenomas, but there is evidence of the importance of surveillance in low-risk lesions. A recent meta-analysis found that patients with low-risk adenomas had a relative risk of 1.8 (95 % CI: 1.3–2.6) for a metachronous advanced neoplasm compared to those without adenomas, though the absolute risk noted in both groups was low [92].

Reality of Surveillance

Surveys demonstrated that 50 % of endoscopists are not following the guidelines for post-polypectomy surveillance [93]. Levin indicated that failure to follow these guidelines was due to uncertainty, fear of malpractice, and financial incentives [94].

Chemoprevention

A variety of oral agents have been evaluated as possible chemopreventive strategies for both adenoma and carcinoma formation. These agents have included nonsteroidal anti-inflammatory agents, folic acid, calcium, and various antioxidants. A systematic review identified several randomized, controlled trials evaluating for the potential benefits of these agents [95]. They concluded that the use of aspirin (81–325 mg/day) in individuals with a history of adenomas or colorectal cancer (CRC) resulted in a 21 % reduction in adenoma recurrence. Though not evident until after a prolonged follow-up period (23 years), a 26 % reduction in CRC incidence was noted in the general population in studies evaluating a larger aspirin dose (300–1500 mg/day). Furthermore, nonaspirin anti-inflammatory medications such as celecoxib (400 mg/day) have also demonstrated benefit in patients with a history of adenomas, revealing a 34 % reduction in adenoma recurrence.

Though the use of folic acid failed to show benefit with respect to adenoma recurrence, calcium intake (1200–2000 mg/day) was found beneficial with an 18 % risk reduction after a history of prior adenomas. Finally, there was no significant benefit toward adenoma recurrence noted with antioxidant ingestion (vitamins A, C, and E, beta-carotene, or selenium) after a history of adenoma removal.

Conclusion

Proper screening recommendations are based on age and risk, which can be based on personal or family history. Screening for colorectal cancer now has several options, though colonoscopy currently remains most common. CT colonography, although not therapeutic, is an ideal alternative to colonoscopy. It also has the potential to reveal extracolonic lesions. Surveillance after colonoscopic polypectomy is dependent on polyp type, size, and number. When an occult cancer is encountered within a polyp after colonoscopic excision, management considerations should be based

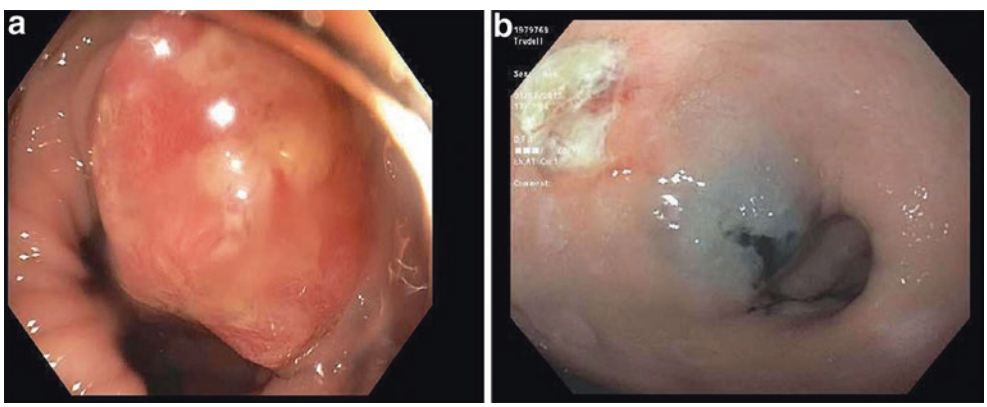

FIGURE 24-5. (**a**) A 2 cm rectal polyp noted endoscopically. (**b**) Polyp was resected and tattooed based on size criteria. Final pathology demonstrated moderately differentiated invasive colonic adenocarcinoma with mucinous features arising from tubulovillous adenoma. Carcinoma was present at cauterized margins.

on histology and polyp morphology (sessile vs. pedunculated). Adherence to recommended guidelines and monitoring of published quality indicators may improve outcomes and minimize polyp miss rates during colonoscopy.

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