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SPECIAL ARTICLE

Colonoscopy surveillance after colorectal cancer resection: recommendations of the US multi-society task force on colorectal cancer

Charles J. Kahi,[1,2] C. Richard Boland,[3] Jason A. Dominitz,[4,5] Francis M. Giardiello,[6] David A. Johnson,[7] Tonya Kaltenbach,[8,9] David Lieberman,[10] Theodore R. Levin,[11] Douglas J. Robertson,[12,13] Douglas K. Rex[2]

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The US Multi-Society Task Force has developed updated recommendations to guide health care providers with the surveillance of patients after colorectal cancer (CRC) resection with curative intent. This document is based on a critical review of the literature regarding the role of colonoscopy, flexible sigmoidoscopy, endoscopic ultrasound, fecal testing and CT colonography in this setting. The document addresses the effect of surveillance, with focus on colonoscopy, on patient survival after CRC resection, the appropriate use and timing of colonoscopy for perioperative clearing and for postoperative prevention of metachronous CRC, specific considerations for the detection of local recurrence in the case of rectal cancer, as well as the place of CT colonography and fecal tests in post-CRC surveillance.

In the United States, colorectal cancer (CRC) is the second leading cause of cancer deaths for men and women combined.[1] Of the estimated 132,700 new cases expected to be diagnosed in 2015,[1] 70%−80% will undergo surgical resection with curative intent[2,3] and up to 40% of patients with locoregional disease will develop recurrent cancer, of which 90% will occur within 5 years.[4] The postoperative surveillance of patients treated for CRC is intended to prolong survival by diagnosing recurrent and metachronous cancers at a curable stage, and to prevent metachronous cancer by detection and removal of precancerous polyps.

Surveillance strategies employ a combination of modalities, including history and physical examination, carcinoembryonic antigen (CEA), computed tomography (CT) scans, and endoluminal imaging, including colonoscopy, sigmoidoscopy, endoscopic ultrasound (EUS), and CT colonography (CTC). Although the optimal surveillance strategy is still not clearly defined, the role of colonoscopy is primarily to clear the colon of synchronous cancers and polyps and prevent metachronous neoplasms.

In 2006, the US Multi-Society Task Force (USMSTF) published a consensus guideline to address the use of endoscopy for patients after CRC resection.[5] This updated document focuses on the role of colonoscopy in patients after CRC resection. Additionally, based on a comprehensive literature review updated from the 2006 recommendations, we review the possible adjunctive roles of fecal testing (eg, fecal immunochemical testing for hemoglobin) and CTC. The use of CEA, CT scans of the liver, as well as chest radiographs are beyond the scope of this document and are not reviewed. The goal of this consensus document is to provide a critical review of the literature and recommendations regarding the role of colonoscopy, flexible sigmoidoscopy, EUS, fecal testing, and CTC in surveillance after surgical resection of CRC.

METHODOLOGY

Literature review

The English-language medical literature was searched using MEDLINE (2005 to September 30, 2015), EMBASE (2005 to September 30, 2015), the Database of Abstracts of Reviews and Effects (2005 to October 7, 2015), and the Cochrane Database of Systematic Reviews (2005 to October 7, 2015). In MEDLINE, subject headings for colorectal neoplasms were combined with the subheading for surgery, resection, postoperative, colectomy, curative, survivor, survival, neoplasm recurrence, second primary neoplasms, and treatment outcome. The resulting set was combined with subject and keywords for colonoscopy or follow-up studies. Similar searches were performed in EMBASE, the Database of Abstracts of Reviews and Effects, and the Cochrane Database of Systematic Reviews. Case reports and studies performed in patients with inflammatory bowel disease, prior CRC, or hereditary CRC syndromes were

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TABLE 1. Grading of recommendations assessment, development, and evaluation ratings of evidence

Rating of evidence	Definition
A: High quality	Further research is very unlikely to change our confidence in the estimate of effect
B: Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
C: Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
D: Very low quality	Any estimate of effect is very uncertain

excluded. Review papers, meta-analyses, gastroenterology textbooks, and editorials were searched manually for additional references. Data from studies with no explicit documentation that perioperative colonoscopic clearing had been performed were not included in the overall summary tables, but some of these studies are referred to in the discussion of the evidence. The review includes studies published since 2005, but also incorporates older evidence used to draft the 2006 guidelines.[5] Evidence-based recommendations are provided with supporting discussion to help guide clinicians in the management of these patients.

Definitions

The review focused on the use of colonoscopy after surgical resection in patients with TNM stages I–III (or Dukes A–C) CRC, and selected patients with resected stage IV cancer.[6] When available, we included studies with specific reporting of overall and cancer-specific survival, and rates of second primary (metachronous) cancers and anastomotic recurrences. Although significant variability exists in the terminology of the reviewed studies, the following general definitions were employed: metachronous cancer refers to CRC diagnosed as a second primary after surgical resection and perioperative clearing, and anastomotic recurrence includes CRC which recurs intraluminally at or within close proximity of the surgical anastomosis.

Rectal cancer is generally associated with a higher risk of local recurrence than cancer in other segments of the colon, and requires additional considerations for surveillance, which are discussed in more detail in a separate section.

Throughout the document, reference is made to "high-quality" colonoscopy for perioperative clearing and surveillance for metachronous neoplasms. A high-quality colonoscopy assumes completeness (cecum or anastomosis is reached), adequate bowel preparation, and meticulous examination by appropriately trained operators who meet adenoma detection benchmarks (ie, frequency of conventional adenoma detection of $\geq$25% in average-risk screening colonoscopies).[7,8]

Process and levels of evidence

The USMSTF includes gastroenterology experts with specific interest in CRC. These members represent the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy. Summary tables and a draft document were circulated to members of the Task Force, and final guidelines were developed by consensus during a joint teleconference. The document underwent committee review and governing board approval by all 3 societies. The USMSTF grades the quality of evidence and strength of recommendations using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[9] The GRADE process categorizes the quality of the evidence as high, moderate, low, or very low (Table 1). This categorization is based on an assessment of the study design (eg, randomized controlled trial or observational study), study limitations, inconsistency of results, indirectness of evidence, imprecision, and publication bias. The USMSTF members conduct literature searches to identify published papers that address the key issues discussed within these recommendations. These publications are supplemented both by review of citations from the identified papers as well as other key references elicited from the subject matter experts on the Task Force. The GRADE process involves the collection of literature, analysis, summary (often as meta-analysis), and a separate review of the quality of evidence and strength of recommendations. The USMSTF members employ a modified, qualitative approach for this assessment based on exhaustive and critical review of evidence, without a traditional meta-analysis. The GRADE process separates evaluation of the quality of the evidence to support a recommendation from the strength of that recommendation. This is done in recognition of the fact that, although the quality of the evidence impacts the strength of the recommendation, other factors can influence a recommendation, such as side effects, patient preferences, values, and cost. Strong recommendations mean that most informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly. Weak recommendations mean that patients' choices will vary according to their values and preferences, and clinicians must ensure that patients' care is in keeping with their values and preferences.[9] Weaker recommendations are indicated by phrases such as "we suggest," whereas stronger recommendations are stated as "we recommend."

RESULTS OF LITERATURE REVIEW

Effect of surveillance colonoscopy on survival

Observational studies utilizing large administrative databases[10-12] and meta-analysis of randomized controlled trials (RCTs)[13,14] show that patients who receive surveillance colonoscopy after CRC resection have lower overall,[10-14] but not disease-specific[11,14] mortality. Cancer-specific mortality is considered the most important outcome in cancer trials.[15] Possible explanations for the discrepancies between all-cause and CRC-specific mortality are unmeasured comorbidity leading physicians to select healthier patients for colonoscopic surveillance, cancer survivors tending to be more closely scrutinized and receiving more non-oncologic medical care, and inaccurate adjudication of cause of death.[3,16]

Colonoscopy is one of several modalities used in the surveillance of CRC patients after curative-intent surgical resection, and the impact of colonoscopy on patient outcomes cannot be discussed without considering the broader context of other co-interventions. The modalities used for surveillance include a combination of medical examinations, CEA measurements, radiologic imaging, and colonoscopy. To date, 11 RCTs that enrolled >4000 patients have compared different surveillance regimens.[17-27] The surveillance strategies (test selection and frequency of administration) used in these RCTs were heterogeneous, complicating the drawing of definitive conclusions regarding the optimal use of individual tests and their effect on patient outcomes.[28,29] Furthermore, some the findings may be less relevant to contemporary surveillance recommendations because several of the RCTs enrolled patients in the 1980s and 1990s. Since then, there have been important improvements in surgical technique (such as total mesorectal excision for rectal cancer), CT imaging technology to detect recurrences earlier, and the use of chemotherapy (for stage III and certain stage II patients, and to downstage patients with previously unresectable disease).[30,31] Three ongoing RCTs[27,32,33] should better clarify the impact of CRC surveillance regimens on patient outcomes (Table 2).

Despite these limitations, meta-analyses and systematic reviews[13,14,34-36] incorporating evidence from the RCTs have been conducted. A Cochrane review showed that patients undergoing more intensive follow-up (variably defined between studies) had reduced all-cause 5-year mortality (odds ratio [OR] = 0.73; 95% confidence interval [CI]: 0.59−0.91), and reduced mean time until recurrence (−6.75 months, 95% CI: −11.06 to −2.44 months).[35] A meta-analysis that included 7 RCTs[17-23] and preliminary results of an ongoing RCT[27] reported comparable findings.[13] This analysis also found that colonoscopy (vs no colonoscopy) was associated with improved overall survival; however, the frequency of colonoscopy had no significant effect on survival.[13] The most recent meta-analysis[14] included 11 RCTs and reported that patients undergoing more intensive follow-up had reduced overall mortality (hazard ratio = 0.75; 95% CI: 0.66−0.86), higher probability of detection of asymptomatic recurrences (RR = 2.59; 95% CI: 1.66−4.06), curative surgery attempted at recurrences (RR = 1.98; 95% CI: 1.51−2.60), survival after recurrences (RR = 2.13; 95% CI: 1.24−3.69), and a shorter time to detecting recurrences (mean difference, −5.23 months; 95% CI: −9.58 to −0.88 months). There was, however, no significant difference in cancer-specific mortality. It is important to note that although intensive multimodality surveillance is associated with increased overall survival and earlier detection of cancer recurrence, these benefits are most apparent in studies using frequent CEA measurements to detect recurrent disease.[13,14,34-36] The performance of radiologic imaging (such as CT to detect liver metastases) has been associated with improved overall mortality when compared with no imaging in most,[14,34-36] but not all,[13] analyses. The recently published FACS (Follow Up After Colorectal Surgery)[25] RCT reported that intensive imaging with CT of the chest, abdomen, and pelvis, and CEA measurement were each associated with increased rates of surgical resection of recurrences with curative intent, but not improved survival compared with minimal follow-up. Conversely, annual or more frequent surveillance colonoscopy has not been shown to improve survival.[13,22,26,36] This is not surprising because the rates of intraluminal or anastomotic recurrences are low, particularly for cancer proximal to the rectum, and usually associated with extraluminal disease that is not amenable to curative surgical resection. Increasing the intensity of surveillance colonoscopy solely to detect intraluminal disease is unlikely beneficial.[5,36]

A recently published RCT conducted in China provides additional information regarding colonoscopy surveillance after CRC resection.[26] In this trial, 326 patients undergoing surgery for CRC were randomized to either intensive colonoscopic surveillance (ie, colonoscopy at 3-month intervals for 1 year, at 6-month intervals for the next 2 years, and once a year subsequently), or routine colonoscopic surveillance (ie, colonoscopy at 6, 30, and 60 months postoperatively). All patients underwent preoperative colonoscopy (or within 6 months postoperatively), and similar non-colonoscopic surveillance (ie, medical history and examination, CEA, chest x-ray, and CT or ultrasound of the liver), and were followed until the date of last visit or death. There were no differences in overall 5-year survival rates (77% in the intensive colonoscopic surveillance group vs 72% in the routine colonoscopic surveillance group; $P = .25$). Although the authors stated that intensive colonoscopic surveillance improved the prognosis of patients with symptomatic postoperative CRC, others have suggested lead-time bias as explanation.[37] Furthermore, the higher rate of reoperation has been observed in other studies comparing intensity of surveillance strategies; this might be due to intervention bias, which can occur when clinicians not blinded to randomization arm make decisions regarding the selection of patients for reoperation.[16] Of note, there were 3 complications in the intensive

TABLE 2. Ongoing randomized controlled trials of surveillance after colorectal cancer resection

Trial (NCT identifier)	Setting	Subjects	Intensive group	Control group
Assessment of Frequency of Surveillance after Curative Resection in Patients with Stage II and III Colorectal Cancer (COLOFOL) (NCT00225641)	Centers in Denmark, Sweden, Poland, Hungary, the Netherlands	2500 with Dukes stage B–C	CT or MR of the liver, CEA, CT or X-ray of the lungs at 6, 12, 18, 24, and 36 months	CT or MR of the liver, CEA, CT or X-ray of the lungs at 12 and 36 months
Gruppo Italiano di Lavaro per la Diagnosi Anticipata (GILDA) (NCT02409472)	Italy	1500 with Dukes stage B2–C	Office visit, blood tests (CEA, CBC, liver tests, CA19-9) every 4 months for 2 years, then every 6 months for 2 years then at 5 years Colonoscopy and chest X-ray every year for 5 years Liver ultrasound at 4, 8, 12, 16, 24, 36, 48, and 60 months	Office visit, CEA, every 4 months for 2 years, then every 6 months for 2 years then at 5 years Colonoscopy at 1 year and at 4 years Liver ultrasound at 8 and 20 months
Federation Francophone de Cancerologie Digestive (FFCD) PRODIGE 13 (NCT00995202)	France	1750 with stage II or III[a]	Clinical assessments every 3 months until year 3 and every 6 months until year 5, then at least yearly thereafter Alternating assessments every 3 months comprising thoraco-abdomino-pelvic CT scan or abdominal ultrasound until year 3 and then every 6 months until year 5 Colonoscopy at 3 years after surgery then every 3 to 6 years thereafter	Clinical assessments every 3 months until year 3 and every 6 months until year 5, then at least yearly thereafter Abdominal ultrasound every 3 months until year 3 and then every 6 months until year 5; chest x-ray every 6 months until year 3 and then annually until year 5; and colonoscopy at 3 years after surgery then every 3 to 6 years thereafter

[a]In addition to primary randomization, patients also undergo a second randomization at the beginning of the study based on CEA measurement (measurement of CEA levels every 3 months until year 3, every 6 months until year 5, and at least yearly thereafter vs no CEA measurement).

colonoscopic surveillance group (2 cases of hemorrhage requiring hospitalization and 1 perforation requiring laparotomy) and none in the routine colonoscopic surveillance group. These rates are similar to those reported in an older RCT.[22] Thus, increased intensity of surveillance colonoscopy after curative resection of CRC[38] does not produce better outcomes, and might increase harm to some patients.

In summary, the evidence shows that although postoperative colonoscopy is associated with improved overall survival, there is no effect on cancer-specific death, and no survival benefit associated with frequent performance of surveillance colonoscopy. The role of postoperative colonoscopy is confined primarily to perioperative clearing and prevention of metachronous colon cancer, which are discussed in the following sections. The possible role of intraluminal imaging and EUS in improving survival from rectal cancer are discussed.

COLONOSCOPY AND PERIOPERATIVE CLEARING IN PATIENTS WITH CANCER OF THE COLON OR RECTUM

The critical importance of a complete high-quality colonoscopy to exclude synchronous tumors and find and resect polyps in patients with CRC cannot be overemphasized. In patients with CRC, the prevalence of synchronous cancers ranges from 0.7% % to about 7%.[39-48] Colonoscopy is preferably performed preoperatively[49]; however, it can be deferred for 3 to 6 months postoperatively if colonoscopy is incomplete due to malignant obstruction. The 3-month lower limit is intended to provide patients with sufficient time for postoperative recovery. Intraoperative colonoscopy has been proposed as an alternative approach,[50] although not commonly practiced.

Available evidence indicates that perioperative colonoscopy should be meticulous, with the goal of detecting both synchronous cancers and precancerous lesions. Finding and resecting synchronous precancerous polyps in patients with CRC to prevent metachronous neoplasia is highly relevant. Considerable evidence indicates that significant neoplastic lesions can be missed during colonoscopy. The quality of the baseline examination, measured by the adenoma detection rate, is directly associated with the risk of development of, and death from, interval CRC.[51,52] Variable colonoscopy quality has also been demonstrated with respect to the completeness of polypectomy.[53] In fact, the great majority of interval CRC cases are attributed to missed lesions or incomplete polyp resection.[54] The issues regarding variability in colonoscopy quality, and the negative impact of this variability on protection from CRC described in average-risk cohorts, are potentially even more relevant in the higher-risk CRC patients. A large population-based study utilizing the Netherlands Cancer

Registry employed an adjudication algorithm to ascribe likely etiology for metachronous CRC in a cohort of 5157 patients with CRC.[47] There were 93 (1.8%) metachronous cancers diagnosed between 7 and 356 months after the initial CRC diagnosis (40.8% diagnosed within 36 months), and these were attributed to missed lesions in 43%, nonadherence to surveillance recommendations in 43%, and incomplete resection in 5.4%; de novo cancers accounted for only 5.4%. Several studies show that patients with CRC and synchronous adenomas or advanced adenomas have a higher risk of developing metachronous adenomas[12,40,42,46,55-59] and advanced neoplasms, including cancer[40,56-61] after surgery, underscoring the importance of adequate perioperative colonoscopy. The role of CTC in the perioperative setting is discussed in the section "Alternatives and Adjuncts to Colonoscopy," but the case of obstructive CRC precluding preoperative colonoscopy and perioperative clearing done by CTC deserves additional comment. In this context, choosing colonoscopy instead of CTC for the first postoperative examination is prudent because synchronous diminutive and flat neoplastic lesions, which might be missed or not reported by CTC, are potentially highly relevant in a patient with CRC. Recently, serrated polyposis syndrome (SPS) has been recognized as the most common polyp syndrome, and is associated with an increased risk of CRC in both the right and left colon. In patients with SPS and CRC, SPS has usually been recognized at the colonoscopy that diagnosed CRC or during surveillance after CRC resection.[62] Because patients with SPS should undergo colonoscopy at more frequent intervals,[63,64] this underscores the importance of colonoscopist awareness of SPS and consideration of SPS diagnosis in patients with multiple and/or large serrated lesions.

Recommendation: We recommend that patients with CRC undergo high-quality perioperative clearing with colonoscopy. The procedure should be performed preoperatively, or within a 3- to 6-month interval after surgery in the case of obstructive CRC. The goals of perioperative clearing colonoscopy are detection of synchronous cancer and detection and complete resection of precancerous polyps.

Strong recommendation, low-quality evidence

COLONOSCOPY AND PREVENTION OF METACHRONOUS CANCER AFTER SURGERY FOR COLON AND FOR RECTAL CANCER

Colonoscopy is the procedure of choice for the detection of intraluminal metachronous CRCs. Pooled data from studies selected for this review (Supplementary Tables 1 and 2, available online at www.giejournal.org) show that approximately two-thirds of metachronous cancers are asymptomatic, TNM stage I or II (or Dukes stage A or B), and reoperated with curative intent. Data from population-based registries suggest that metachronous CRCs are being diagnosed at earlier stages, possibly reflecting the effect of increased surveillance.[48,65] The cumulative incidence of metachronous cancers of the colon and rectum is estimated to be about 0.3%−0.35% per year,[5,60,66] presenting at any time, even decades after the index malignancy.[4,18-20,39,41-43,45,55,66-80] All colorectal segments are at increased risk for a metachronous cancer, although some studies suggest that among older survivors, the risk remains elevated only in the proximal colon.[81] Thus, postoperative colonoscopic surveillance in CRC patients is indicated long term, or until the benefit is outweighed by decreased life expectancy due to age and/or competing comorbidity.

The optimal intervals of surveillance colonoscopy after CRC resection are not established by RCTs. However, several studies report an increased incidence of cancers diagnosed within the first few years after surgery, despite seemingly adequate perioperative colonoscopic clearance. In the post-CRC resection studies included in this review, there were 253 (1.6%) metachronous cancers in 15,803 patients; when timing could be determined, about 30% were detected within 2 years of resection of the index malignancy (Supplementary Table 2, available online at www.giejournal.org). Several of these studies did not explicitly identify patients with Lynch syndrome, and inclusion of these patients could have inflated some of the estimates of the rates of early metachronous cancers.[60,82] The USMSTF recently recommended that all CRCs be studied for evidence of Lynch syndrome.[83] The impact of not accounting for these patients is uncertain (a similar concern exists for unrecognized SPS); however, when the analysis was restricted to studies stating that patients with Lynch syndrome were excluded,[26,42,46,71,76] the rate of metachronous cancers diagnosed within 3 years of surgery was about 33%. Recently published, large, population-based cancer registry studies, including ones that specifically excluded patients with Lynch syndrome,[47,66] report a high incidence of metachronous CRC within the first few years after surgery.[47,66,81,84] The most plausible explanation is that many early, apparently metachronous cancers are actually due to prevalent cancers or advanced adenomas missed at the time of the primary malignancy diagnosis. The factors involved in the occurrence of interval CRC are presumably the same in the case of missed synchronous cancers and missed synchronous advanced adenomas, and are likely related to the quality of the baseline clearing examination. The consensus 2006 USMSTF guidelines recommended colonoscopy at 1 year after surgery (or after the perioperative clearing colonoscopy), in addition to high-quality perioperative clearing to exclude synchronous neoplasia.[5] Studies published since 2005 show that the 1-year examination is high-yield and cost-effective.[85] In a study conducted in a large health maintenance organization, 652 patients with curative resection for CRC and at least 1 colonoscopy were evaluated. Of

those, 20 patients (3.1%) were diagnosed with a second primary CRC, including 9 cancers that were detected within 18 months of the initial cancer diagnosis.[12] In the 5-year follow-up of the VA Cooperative Study 380, 5 cancers were detected in patients who had CRC diagnosed at baseline (n = 23), and 4 of 5 were found within 18 months.[86] One study[87] challenged the concept of performing a colonoscopy at the 1-year interval: A review of a subgroup of 155 CRC patients in a cancer registry with both a complete preoperative and at least one complete postoperative colonoscopy (performed at mean of 478 ± 283 days) revealed no metachronous CRC cases. However, there were 3 anastomotic recurrences and 24 patients with 28 adenomatous polyps; 5 of which were ≥1 cm. In the RCT published by Wang et al,[26] 5 of 9 metachronous cancers were diagnosed within 3 years after surgery. This study provides additional evidence that even with appropriate perioperative clearing of the colon, some patients present a short time after surgery with a second primary cancer, strengthening the recommendation to perform colonoscopy 1 year after surgical resection of CRC.

The timing of subsequent surveillance examinations is supported by weaker evidence, and is based largely on the approach to post-polypectomy surveillance of patients with high-risk adenomas.[63] If the 1-year examination reveals no neoplasia, colonoscopy should be performed after 3 years (4 years from CRC diagnosis or perioperative colonoscopy) and if this examination finds no neoplasia, 5 years later (9 years from CRC diagnosis or perioperative colonoscopy). Subsequent surveillance intervals should not exceed 5 years. If polyps are found during any of the examinations, then the interval for the next colonoscopy can be shortened, based on guidelines for post-polypectomy surveillance.[63] Patients with known or suspected Lynch syndrome due to tumor testing, age at diagnosis, family history, and/or tumor characteristics should be distinguished from patients with sporadic CRC and referred for genetic counseling and appropriate surveillance based on USMSTF recommendations.[88]

Recommendation: We recommend that patients who have undergone curative resection of either colon or rectal cancer receive their first surveillance colonoscopy 1 year after surgery (or 1 year after the clearing perioperative colonoscopy). Additional surveillance recommendations apply to patients with rectal cancer (see "Additional Considerations in Surveillance of Rectal Cancer").

Strong recommendation, low-quality evidence

Recommendation: We recommend that, after the 1-year colonoscopy, the interval to the next colonoscopy should be 3 years (ie, 4 years after surgery or perioperative colonoscopy) and then 5 years (ie, 9 years after surgery or perioperative colonoscopy). Subsequent colonoscopies should occur at 5-year intervals until the benefit of continued surveillance is outweighed by diminishing life expectancy. If neoplastic polyps are detected, the intervals between colonoscopies should be in accordance with published guidelines for polyp surveillance intervals. These intervals do not apply to patients with Lynch syndrome.

Strong recommendation, low-quality evidence

ADDITIONAL CONSIDERATIONS IN SURVEILLANCE OF RECTAL CANCER

An important distinction is made between colon and rectal cancer because of the latter's higher propensity for local recurrence. In the studies compiled for this review that reported on colon and rectal cancer separately, >80% of anastomotic recurrences involved patients with cancer of the rectum or distal colon.[18,20,26,39-41,44,76,89] In the RCT by Wang et al,[26] recurrent cancers diagnosed in the colon had higher resectability than rectal malignancies. The local recurrence rate of rectal cancer depends on accurate preoperative staging, neoadjuvant chemoradiation for locally advanced disease, and surgical technique. Rectal cancer recurrence is decreased by total mesorectal excision in which the rectum and mesorectal fascia are resected en bloc by precise sharp dissection.[90] Excision of the rectum and mesorectum, via the low anterior abdominoperineal approach, has historically been the preferred surgical approach to low rectal cancer. Concerns about increased mortality and morbidity and decreased quality of life postoperatively have spurred interest in less invasive local excision options for early rectal cancer (T1 and some T2 tumors), such as transanal excision or transanal endoscopic microsurgery, however, these techniques are associated with higher local recurrence rate than radical surgery.[91-96] Endoscopic submucosal dissection is used in some centers as definitive treatment of selected rectal cancers with superficial submucosal invasion.[97-99] In cases where total mesorectal excision is not performed (including transanal excision methods), there is a rationale for periodic examination of the rectum using sigmoidoscopy or endoscopic ultrasound. Presently, it is unclear which of these 2 modalities is better, or what the ideal surveillance intervals should be, although EUS has the potential for detection of extraluminal recurrence before development of intraluminal endoscopic findings. The use of EUS allows for sampling of suspicious subepithelial lesions or lymph nodes and detects recurrences at earlier stages. Some studies also report that approximately 10% of rectal cancer recurrences are diagnosed by EUS only, and missed by other modalities, including proctoscopy.[100,101] However, there are no controlled trials evaluating whether intensive EUS improves the survival of patients with rectal cancer. The optimal approach to luminal surveillance in an individual patient with resected rectal cancer requires a multidisciplinary collaboration between gastroenterologist, colorectal surgeon, and oncologist. The 2006 USMSTF guidelines suggested sigmoidoscopy or rectal EUS every 3 to 6 months for the first 2 or 3 years after surgery, in addition to colonoscopic surveillance for metachronous neoplasms, and this suggestion is maintained in the current document.

Recommendation: Patients with localized rectal cancer who have undergone surgery without total mesorectal excision, those who have undergone transanal local excision (ie, transanal excision or transanal endoscopic microsurgery), or endoscopic submucosal dissection, and those with locally advanced rectal cancer who did not receive neoadjuvant chemoradiation and then surgery using total mesorectal excision techniques, are at increased risk for local recurrence. In these situations, we suggest local surveillance with flexible sigmoidoscopy or EUS every 3−6 months for the first 2−3 years after surgery. These surveillance measures are in addition to recommended colonoscopic surveillance for metachronous neoplasia.

Weak recommendation, low-quality evidence

Alternatives and adjuncts to colonoscopy

Computed tomographic colonography. CTC is a USMSTF guideline-endorsed option for CRC screening,[102] and its role in patients with CRC is evolving. CTC is an appropriate option in patients with obstructing CRC in whom preoperative colonoscopy to examine the colon proximal to the obstruction is not feasible. One large case series included 284 patients with obstructing CRC and reported sensitivity of 88.6% and negative predictive value of 97.4% for synchronous advanced neoplasia (including advanced adenomas and cancer) proximal to the obstructing cancer.[103] The use of CTC with intravenous contrast can be considered preoperatively to exclude both synchronous neoplasia and distant metastases, although caution is advised in cases with complete colonic obstruction due to increased perforation risk associated with gas insufflation. In unselected patients, CTC outperforms double-contrast barium enema at all polyp size ranges.[104,105] A large multicenter UK study[106] randomized 3838 patients with symptoms suggestive of CRC to barium enema or CTC. The detection rate of CRC or large polyps was significantly higher in the CTC group (7.3% vs 5.6%; RR = 1.31; 95% CI: 1.01−1.68; P = .039), and CTC missed 3 of 45 CRC, while barium enema missed 12 of 85. Thus, CTC is preferred over barium enema for preoperative patients with obstructing cancers; however, barium enema remains an option if local resources and expertise do not allow CTC.

CTC has been proposed for postoperative surveillance because it combines contrast abdominopelvic CT, which is already part of standard post-CRC surveillance, with the ability to detect intraluminal lesions. Thus, CTC could be a one-step assessment for metachronous lesions, local recurrence, and distant metastases.[107] In the largest cohort to date,[108] 742 patients without clinical or laboratory evidence of recurrence underwent contrast-enhanced CTC after curative-intent CRC surgery. Six metachronous cancers and one anastomotic recurrence were found by CTC, with sensitivity of 100% for cancer and 81.8% for advanced neoplasia (using colonoscopy with pathologic confirmation as the reference standard). All intraluminal cancers were amenable to additional curative treatment; an additional 11 patients were found to have extracolonic recurrences. In patients who have undergone CRC resection, CTC requires expertise to differentiate normal postoperative findings (such as inflammatory changes at the anastomosis) from true recurrences.[109] Also, using CTC for extraluminal surveillance requires use of intravenous contrast. Other issues are important to consider: CTC has relatively low sensitivity for the detection of flat and diminutive (≤5 mm) colonic lesions,[110] and sensitivity for nonadenomatous lesions (such as sessile serrated polyps), although not well-studied, is lower than for adenomas at comparable size thresholds.[111,112] Diminutive polyps have extremely low prevalence of advanced histology in average-risk patients; however, this might not apply to patients with CRC in whom even diminutive lesions could be clinically significant. There are no longitudinal studies examining the consequences of missing or nonreporting of diminutive flat lesions and nonadenomatous lesions in patients with CRC. In conclusion, although CTC has good diagnostic accuracy for cancer, the optimal timing of CTC in post-CRC resection surveillance and how it is best used in conjunction with other modalities remain undefined.[109]

Recommendation: In patients with obstructive CRC precluding complete colonoscopy, we recommend CTC as the best alternative to exclude synchronous neoplasms. Double-contrast barium enema is an acceptable alternative if CTC is not available.

Strong recommendation, moderate-quality evidence

Fecal tests. Older guaiac-based fecal occult blood tests are inferior to fecal immunochemical tests (FIT) for CRC screening.[113] Limited data exist on the role of FIT for surveillance after CRC resection. One study[114] included 1736 patients with a personal or family history of colorectal neoplasia (24% had a personal history of CRC) who had undergone at least 2 colonoscopies and were offered an annual FIT. The diagnosis of CRC and advanced adenomas was made at a median of nearly 2 years earlier in patients with a positive FIT compared with those without testing, although it was unclear whether this applied to the subgroup of patients with personal history of CRC. The quality of the baseline examinations in this study was unknown; thus, it is possible that the interval cancers were lesions missed or incompletely resected, rather than metachronous lesions detected by FIT.[115] Nevertheless, these data call for additional investigation to determine the role of FIT in post-CRC resection surveillance.

Fecal DNA testing[116] has emerged as an option for CRC screening. Available data[117,118] suggest that DNA abnormalities clear from stool after resection of colorectal neoplasms; however, the role of fecal DNA testing in surveillance programs after CRC resection is yet to be investigated.

Recommendation: There is insufficient evidence to recommend routine use of FIT or fecal DNA for surveillance after CRC resection.

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Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; CRC, colorectal cancer; CT, computed tomography; CTC, computed tomographic colonography; EUS, endoscopic ultrasound; FIT, fecal immunochemical test; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SPS, serrated polyposis syndrome; USMSTF, US Multi-Society Task Force.

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Current affiliations: Richard L. Roudebush VA Medical Center, Indianapolis, IN (1); Indiana University School of Medicine, Indianapolis, Indiana (2); Baylor University Medical Center at Dallas, Dallas, Texas (3); VA Puget Sound Health Care System, Seattle, Washington (4); University of Washington School of Medicine, Seattle, Washington (5); Johns Hopkins University School of Medicine, Baltimore, Maryland (6); Eastern VA Medical School, Norfolk Virginia (7); Veterans Affairs Palo Alto, Palo Alto, California (8); Stanford University School of Medicine, Palo Alto, California (9); Oregon Health and Science University, Portland, Oregon (10); Kaiser Permanente Medical Center, Walnut Creek, California (11); VA Medical Center, White River Junction, Vermont (12); and Geisel School of Medicine at Dartmouth, Hanover, NH (13)

Reprint requests: Charles J. Kahi, MD, MSc, FACP, FACG, AGAF, FASGE, Indiana University School of Medicine, Richard L. Roudebush VA Medical Center, 1481 W 10th Street, 111G, Indianapolis, Indiana 46202. fax: (317) 988-5313. E-mail: ckahi2@iu.edu.

APPENDIX. Summary of recommendations

We recommend that patients with CRC undergo high-quality perioperative clearing with colonoscopy. The procedure should be performed preoperatively or within a 3- to 6-month interval after surgery in the case of obstructive CRC. The goals of perioperative clearing colonoscopy are detection of synchronous cancer and detection and complete resection of precancerous polyps.
We recommend that patients who have undergone curative resection of either colon or rectal cancer receive their first surveillance colonoscopy 1 year after surgery (or 1 year after the clearing perioperative colonoscopy). Additional surveillance recommendations apply to patients with rectal cancer (see "Additional Considerations in Surveillance of Rectal Cancer").
We recommend that, after the 1-year colonoscopy, the interval to the next colonoscopy should be 3 years (ie, 4 years after surgery or perioperative colonoscopy), and then 5 years (ie, 9 years after surgery or perioperative colonoscopy). Subsequent colonoscopies should occur at 5-year intervals, until the benefit of continued surveillance is outweighed by diminishing life expectancy. If neoplastic polyps are detected, the intervals between colonoscopies should be in accordance with the published guidelines for polyp surveillance intervals. These intervals do not apply to patients with Lynch syndrome.
Patients with localized rectal cancer who have undergone surgery without total mesorectal excision, those who have undergone transanal local excision (transanal excision or transanal endoscopic microsurgery) or endoscopic submucosal dissection, and those with locally advanced rectal cancer who did not receive neoadjuvant chemoradiation and then surgery using total mesorectal excision techniques are at increased risk for local recurrence. In these situations, we suggest local surveillance with flexible sigmoidoscopy or EUS every 3–6 months for the first 2–3 years after surgery. These surveillance measures are in addition to recommended colonoscopic surveillance for metachronous neoplasia.
In patients with obstructive CRC precluding complete colonoscopy, we recommend CTC as the best alternative to exclude synchronous neoplasms. Double-contrast barium enema is an acceptable alternative if CTC is not available.
There is insufficient evidence to recommend the routine use of FIT or fecal DNA for surveillance after CRC resection.

SUPPLEMENTARY TABLE 1. Post cancer resection surveillance colonoscopy studies: qualitative aspects

First author, year	Setting/sampling frame	Design	No. of subjects (no. of colonoscopies)	Perioperative clearing	Endoscopic follow-up schedule	Definition metachronous CRC	Definition anastomotic recurrence
Barillari, 1996[39]	Italy/1980−1990	Retrospective	481	Preoperative colonoscopy	Group 1: First colonoscopy at 12 mo, then at mean intervals of 12 mo Group 2: First colonoscopy at 12 mo, then at mean intervals of 24 mo	Neoplasm arising >5 cm from anastomosis and more than 1 y after surgery	Intraluminal lesion within 5 cm from surgical anastomosis
Barrier, 1998[40]	France/ 1986−1992	Retrospective	61[a]	Preoperative colonoscopy on subgroup of 61 patients	First colonoscopy: 12 ± 6 mo Second colonoscopy: 30 ± 12 mo Third colonoscopy: 54 ±12 mo		Intraluminal lesion within 5 cm from surgical anastomosis
Battersby, 2014[77]	United Kingdom/ 1995−2012	Retrospective	538 (613)	Preoperative colonoscopy or within 3 mo after surgery if obstructive CRC	In accordance with 1997 AGA and ACS guidelines		
Castells, 1998[80]	Spain/1987−1990	Prospective	199	Preoperative colonoscopy, or barium enema and flexible sigmoidoscopy if stenosis If inadequate preoperative clearing, repeat endoscopy within 3 mo postop	Annual colonoscopy		"Locoregional": restricted to anastomosis or region of primary operation
Chen, 1994[55]	Australia/ 1972−1990	Prospective	231	Preoperative colonoscopy and/or colonoscopy at 1 y postop	Colonoscopy at first year postop, then every 3 y If adenomas, annual colonoscopy until clear	Not present at time of preop or first postop colonoscopy, then developed elsewhere in colon	
Cone, 2013[83]	United States/ 2002−2010	Retrospective	155 (155)	Preoperative colonoscopy	First postoperative colonoscopy		
Couch, 2013[78]	United Kingdom/ 2001−2003 and 2006−2007	Retrospective	86 in first cohort 100 in second cohort	Preoperative "luminal imaging"	Variable, 5-y follow up for first cohort, 2-y for second cohort		
Eckardt, 1994[68]	Germany/1978 −1987	Prospective	212	Preoperative colonoscopy, or barium enema and flexible sigmoidoscopy if stenosis If inadequate preoperative clearing, repeat endoscopy within 3 mo postop	Annual colonoscopy for 5 y, then every 3 y		Local recurrence

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

First author, year	Setting/sampling frame	Design	No. of subjects (no. of colonoscopies)	Perioperative clearing	Endoscopic follow-up schedule	Definition metachronous CRC	Definition anastomotic recurrence
Freeman, 2013[69]	Canada/ 1980–2005	Retrospective	128 (all T1N0M0 CRC, 80% treated surgically, 20% by polypectomy) (941)	Preoperative colonoscopy or within 6 mo of resection	Annual colonoscopy for 5 y, then every 3 y if no polyps detected If neoplasia found at 5-y exam, colonoscopy annually until no neoplasia, then every 3 y	Any subsequent cancer during follow-up period	
Granqvist, 1992[41]	Sweden/ 1981–1990	Retrospective	390 (600)	Preoperative colonoscopy or within 6 mo postop	Colonoscopy at 2 y postop, then every fourth year If adenomas, annual colonoscopy until clear		
Green, 2002[60]	United States/ 1989–1993	Historical cohort	3278	Colonoscopy or barium enema and flexible sigmoidoscopy at diagnosis	Colonoscopy at 6, 12, 18 mo then annually (study guidelines), or at 6 mo then every 18–24 mo (physician discretion)	Arising from a preexisting polyp or found at a site distant from primary tumor (not at anastomosis), without evidence of penetration from bowel serosa	
Hassan, 2006[42]	Italy/1999–2004	Prospective	318	Preoperative colonoscopy	Colonoscopy at 1-, 3-, and 5-y intervals postop		
Juhl, 1990[43]	United States/ 1978–1985	Prospective	133[b] (316)	Colonoscopy and barium enema perioperatively	Annual colonoscopy for 6 y		
Khoury, 1996[70]	United States/ 1984–1994	Retrospective	389 (3889)	Perioperative colonoscopy	Variable, median interval between procedures 13 mo	At least 1 y postop	
Kjeldsen, 1997[4]	Denmark/ 1983–1994	RCT	597 (intensive subgroup: 290)	Complete colonoscopy or incomplete colonoscopy plus barium enema	Intensive: colonoscopy at 6, 12, 18, 24, 30, 36, 48, 60, 120, 150, 180 mo Control: colonoscopy at 60, 120, 180 mo	At least 12 mo after primary cancer	Local recurrence: tumor growth in the region of the primary radical operation, including surgical wound
Lan, 2005[71]	Taiwan/ 1981–2001	Retrospective	3846	Preoperative colonoscopy or at 6 mo postop	Colonoscopy at 1 year If negative or 1 polyp <5 mm, then 2–3 y later If 1 polyp >5 mm, or ≥2 polyps, then 1 y after polypectomy If 2 negative colonoscopies, then 5-y intervals	Arising from the mucosa at a site other than anastomosis line, after at least 12 mo from initial resection and/or at least a negative postoperative colonoscopic surveillance	
Lee, 2014[46]	Korea/ 2004–2007	Retrospective	1049	Preoperative or within 6 mo after surgery if obstructive CRC or poor bowel preparation	Colonoscopy every 1–2 y	At least 6 mo after resection, and at least 4 cm from anastomosis	

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SUPPLEMENTARY TABLE 1. Continued

First author, year	Setting/sampling frame	Design	No. of subjects (no. of colonoscopies)	Perioperative clearing	Endoscopic follow-up schedule	Definition metachronous CRC	Definition anastomotic recurrence
Makela, 1995[18]	Finland/ 1988–1990	RCT	106 (intensive subgroup: 52)	Preoperative colonoscopy or at 3 mo postop (intensive subgroup)	Intensive: Colonoscopy once a year, plus flexible sigmoidoscopy every 3 mo for rectal/sigmoid cancers Control: barium enema at 12 mo then once a year If rectal/sigmoid cancer, rigid sigmoidoscopy every 3 mo for 2 y, then every 6 mo for 3 y		"Local recurrence": restricted to the anastomosis and its surroundings
Mathew, 2006[73]	United Kingdom/ 1998–2003	Retrospective	105 (140)	Preoperative colonoscopy or postop in emergency cases (up to 1 y after surgery)	Colonoscopy at 2 and 5 y postop		
McFarland, 1991[79]	United Kingdom/ 1980–1991	Prospective	74 (237)	Colonoscopy as close as possible to time of resection	Annual colonoscopy for 5 y, then every 2 y		
Obrand, 1997[44]	Canada/ 1976–1992	Retrospective	444	Perioperative colonoscopy	Colonoscopy every 3 y		"Local": Endoluminal at anastomosis site
Ohlsson, 1995[19]	Sweden/ 1983–1986	RCT	107 (intensive subgroup: 53)	Preoperative barium enema, then colonoscopy and barium enema within 3 mo postop	Intensive: colonoscopy at 3, 15, 30, 60 mo, plus endoscopic control of anastomosis (flexible sigmoidoscopy or colonoscopy) at 9, 21, and 42 mo		Intraluminal recurrence within 5 cm of anastomosis
Patchett, 1993[74]	Ireland/ 1983–1988	Prospective	132	Colonoscopy after operation	Colonoscopy at 6, 12, 18, 30, 48 mo		
Pietra, 1998[20]	Italy/1987–1990	RCT	207 (intensive subgroup: 104)	Preoperative colonoscopy or at 3 mo postop	Annual colonoscopy		"Intraluminal local recurrence": Involves only suture or staple line of bowel anastomosis
Platell, 2005[85]	Australia/ 1996–2002	Prospective	253 (227)	Preoperative colonoscopy or at 3 mo postop	Colonoscopy at 12 mo or every 3 y		
Rodriguez-Moranta, 2006[21]	Spain/1997–2001	RCT	259 (intensive subgroup: 127)	Preoperative colonoscopy or postoperative if preoperative colonoscopy could not be performed	Intensive: annual colonoscopy for 5 y Control: colonoscopy at first and third year if family history of HNPCC or synchronous neoplasms, otherwise only if symptoms or abnormal labs		"Locoregional": Restricted to anastomosis or region of primary operation

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SUPPLEMENTARY TABLE 1. Continued

First author, year	Setting/sampling frame	Design	No. of subjects (no. of colonoscopies)	Perioperative clearing	Endoscopic follow-up schedule	Definition metachronous CRC	Definition anastomotic recurrence
Shoemaker, 1998[22]	Australia/ 1984–1990	RCT	325 (intensive subgroup: 167) (733)	Perioperative colonoscopy	Intensive: Annual colonoscopy for 5 y Control: colonoscopy only if clinical or screening test abnormality, and after 5 y of follow-up		
Skaife, 2003[75]	Singapore	Prospective	611 (609)	Colonoscopy at time of cancer resection	Annual colonoscopy until no polyps, then every 3–5 y	Remote from anastomosis	Located at, or adjacent to, anastomotic line
Stigliano, 2000[76]	Italy/ 1970–1988	Retrospective	322	"Clean colon before surgery"	Annual colonoscopy or on request for first 5 y, then every 2 y	At least 2 y after surgery	
Togashi, 2000[45]	Japan/ 1992–1995	Retrospective	341 (1569)[c]	Preoperative colonoscopy or barium enema If stenosis, barium enema	Variable	All cases detected after surgery	
Wang, 2009[26]	China/ 1995–2001	RCT	326 (intensive subgroup: 165) (1561)	Preoperative colonoscopy or within 6 mo postop	Intensive colonoscopy: every 3 mo for a year, then every 6 mo for the next 2 y, then annually for the next 2 y Routine colonoscopy: At 6, 30, and 60 mo postop	Second primary CRC after exclusion of synchronous cancer by complete colon evaluation preoperatively or within 6 mo postop	Intraluminal recurrence within 5 cm of the anastomosis. Local recurrence included anastomotic and extraluminal recurrence

NOTE. Adapted with permission from Wiley-Blackwell.[119]

AGA, American Gastroenterological Association; *ACS*, American Cancer Society; *HPNCC*, hereditary nonpolyposis colorectal cancer.

[a]Subgroup that underwent complete preoperative colonoscopy (total patients, n = 175).

[b]Subgroup excludes patients with rectal cancer treated by abdominoperineal resection (total patients, n = 174).

[c]Mean number of procedures per patient reported as 4.6 (range, 2–15).

SUPPLEMENTARY TABLE 2. Post cancer resection surveillance colonoscopy studies: results and outcomes

Author, year	Synchronous CRC	Time to CRC diagnosis	Metachronous CRC	Anastomotic CRC	Metachronous adenomas	Outcomes	Comments
Barillari, 1996[39]	3.3%	Median 25 mo (range, 10–73 mo)	12 Dukes A or B: 9 Reoperated[a]: 7	34 All rectal Intraluminal only: 10 Reoperated: 10		5-y survival: Metachronous CRC: 50% Anastomotic: 45.4% Asymptomatic recurrence: 41% Symptomatic recurrence: 12.5%	Second CRC within 24 mo: 24 of 46 (52%)[b] Asymptomatic: 22 of 46 (48%)[b]; 81% of rectal recurrences detected within 18 mo
Barrier, 1998[40]	6.6%	Mean, 14 mo (range, 7–26 mo)	0	4 All distal colon/ upper rectum All within 26 mo All asymptomatic Reoperated: 73%[c]	9 TA All <10 mm		
Battersby, 2014[77]		Median, 7 y and 6 mo (range, 2–14 y)	15 Early: 0 AJCC stage I or II: 12 Reoperated: 13 Asymptomatic: 9				
Castells, 1998[80]		Compliant patients: 13 ± 21 mo Noncompliant: 15 ± 9		42 Locoregional Asymptomatic: 5 Reoperated: 13		5-y survival: Compliant: 63% Noncompliant: 37%	Systematic postoperative surveillance increases rate of tumor recurrence amenable to curative-intent surgery, and improves overall and cancer-related survival
Chen, 1994[55]		Mean, 7.75 y (range, 3–17 y)	4 Early[d]: 0 Reoperated: 4 Asymptomatic: 4		130 TA	Metachronous CRC incidence: 1 per 324.5 patient-year of follow-up	
Cone, 2013[83]			0	3	24 patients, 5 with polyps ≥1 cm		2 of 3 anastomotic recurrences were found in the rectum after LAR
Couch, 2013[78]		1–5 y	4	3	27	All 4 CRC found within 2 y underwent re-resection for cure	In group with complete preop imaging in both cohorts (n = 186), there were 7 CRCs, 5 of 7 found within 2 y
Eckardt, 1994[68]			26[e] Reoperated: 7 Asymptomatic: 13	[e]		5-y survival: Compliant: 80% Noncompliant: 59% Asymptomatic recurrence: 42% Symptomatic recurrence: 8%	Postop endoscopic surveillance leads to early tumor detection and improves survival

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SUPPLEMENTARY TABLE 2. Continued

Author, year	Synchronous CRC	Time to CRC diagnosis	Metachronous CRC	Anastomotic CRC	Metachronous adenomas	Outcomes	Comments
Freeman, 2013[69]	0.8%	7–13 y	6[f] Dukes A or B: 6 Early: 0 Reoperated: 6 Asymptomatic: 6		217 adenomas, of which 33 (15%) were advanced		
Granqvist, 1992[41]	2.8%	0.5–7 y	12 Early: 7 Reoperated: 10	14 Rectal/Sigmoid: 9 Early: 14 Reoperated: 8	106 ≥10 mm: 24 HGD: 11	Metachronous: 7 of 10 reoperated alive after 1-5 y Anastomotic: 6 of 8 reoperated alive after 0.5 y	Asymptomatic: 14 of 26 (7 Dukes A or B)[b] Symptomatic: 12 of 26 (3 Dukes A or B)[b]
Green, 2002[60]		Median, 18.4 mo (range, 3.4–70.1 mo)	42 Dukes A or B: 23 Early: 24			14 of 42 (33%) died within study period CRC incidence: 274/100,000 patient-years; cumulative incidence 1.5% at 5 y	More than half of patients did not adhere to surveillance protocol
Hassan, 2006[42]	1.6%	1–5 y	10 At 1 y: 4 At 3 y: 5 At 5 y: 1		104 nonadvanced adenomas 19 advanced adenomas	Cumulative incidence CRC and advanced adenomas (excluding 1-y lesions): 3 y: 2.9% 5 y: 5.6% (2.2/100 patient-years)	
Juhl, 1990[43]	1.7%	Metachronous: >2 y Anastomotic: 12–30 mo	4 Dukes A or B: 4 Early: 0 Reoperated: 4 Asymptomatic: 4	9 All LAR Reoperated: 5 for palliation (4 inoperable) All symptomatic	<1 cm: 123 >1 cm: 37 (7 villous polyps)		
Khoury, 1996[70]		13–56 mo[g]	1	2	240 neoplastic polyps >10 mm: 4 (all at first colonoscopy)		
Kjeldsen, 1997[4]		Intensive: 18 mo Control: 27 mo	10 Reoperated: 8 Asymptomatic: 8	91[h] Reoperated: 14 Asymptomatic: 16		5-y survival: Intensive: 70% Control: 68% (P = NS)	Intensive follow-up led to earlier diagnosis of recurrence (by 9 mo) and more reoperations, but no improvement in survival
Lan, 2005[71]		Mean 71 ± 47 mo (range, 14–240 mo)	43 Early (20-mo interval): 5 Dukes A or B: 31 Reoperated: 35			Metachronous CRC group: 5-y survival: 90% 10-y survival: 71% Annual incidence: 0.18%	

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SUPPLEMENTARY TABLE 2. Continued

Author, year	Synchronous CRC	Time to CRC diagnosis	Metachronous CRC	Anastomotic CRC	Metachronous adenomas	Outcomes	Comments
Lee, 2014[46]	3.7%	12–41 mo	6 Early: 5 6/6 stage II or III		454 (43.3%) of patients developed metachronous adenomas, including 46 (4.4%) with advanced adenoma or CRC		Older age, synchronous adenoma, and diabetes mellitus associated with risk of metachronous neoplasia
Makela, 1995[18]		Intensive: 10 ± 5 mo Control: 15 ± 10 mo	1 Reoperated: 1	3 Rectal/sigmoid: 2 Dukes B: 1 Dukes C:2 Reoperated: 3 Asymptomatic: 2	13 TA 4 TVA (including 2 polyps with HGD)	5-y survival: Intensive: 59% Control: 54% (P = NS)	Intensive follow-up led to earlier detection of recurrence, but not significantly increased reresectability or improved 5-y survival
Mathew, 2006[73]		Metachronous: 2 and 5 y Recurrence: 2 y	2	3	TA in 24 patients (5 patients with advanced adenomas)		
McFarland, 1991[79]		At 2 y	0	2 Reoperated: 2	31 TA ≥1 cm: 12		
Obrand, 1997[44]	4%	Mean, 16.2 mo	0	44 Rectal: 29 Reoperated: 20		47% of re-resected patients alive at mean of 80 mo	Anastomotic recurrence higher for rectal than colon cancer (20.3% vs 6.2%, P = .001)
Ohlsson, 1995[19]		Median 1.7 y (range, 0.3–7.6 y)	0[i]	2[i] Reoperated: 2 Asymptomatic: 1 Re-recurrence: 2	6 patients with "adenomas with varying degrees of atypia"	5-y survival: Intensive: 75% Control: 67% (P > .05)	Intensive follow-up did not prolong survival
Patchett, 1993[74]		Range, 7–43 mo	2 Asymptomatic: 0	6 Asymptomatic: 0	22 TA		Rectal: 4 of 8[b] Reoperated: 4 of 8[b] Dukes B: 5 of 8[b] Dukes C: 5 of 8[b]
Pietra, 1998[20]		Intensive: 10.3 ± 2.7 mo Control: 20.2 ± 6.1 mo	1	2 Rectal: 1	21 patients with adenomas	5-y survival: Intensive: 73.1% Control: 58.3 % (P < .02)	Intensive follow-up led to improved survival, primarily because local recurrences are more resectable when detected early
Platell, 2005[85]		12 mo	0	3 All rectal All metastatic	62 TA (≥1 cm: 6) 9 TVA 10 VA Overall prevalence advanced adenomas: 7.9%		65% of preoperative colonoscopies performed outside study center and reports not available to authors

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SUPPLEMENTARY TABLE 2. Continued

Author, year	Synchronous CRC	Time to CRC diagnosis	Metachronous CRC	Anastomotic CRC	Metachronous adenomas	Outcomes	Comments
Rodriguez-Moranta, 2006[21]		Intensive: 39 ± 21 mo Control: 38 ± 19 mo	6	24		After median follow-up of 48 mo, no difference in probability of overall survival (HR = 0.87, 95% CI: 0.49−1.54; P = .62)	Intensive follow-up associated with higher survival in patients with stage II tumors (HR = 0.34, 95% CI: 0.12−0.98; P = .045) and those with rectal lesions (HR = 0.09; 95% CI: 0.01−0.81; P = .03), due to higher rate of re-resectability Colonoscopy responsible for detection of highest proportion (44%) of resectable recurrences in intensive arm
Shoemaker, 1998[22]		7−42 mo	5	3	18 TA 39 TVA 1 VA	5-y survival: Intensive: 75% Control: 70 % (P = .2)	8 metachronous or locally recurrent tumors detected by colonoscopy[b] Early: 5 Dukes A or B: 5 Asymptomatic: 1
Skaife, 2003[75]		Median 36 mo (range, 6−67)	5 Early: 1 5 with no "extracolonic disease"	4 Early: 1 2 with no "extracolonic disease"			
Stigliano, 2000[76]		3rd or 8th y	5 Early: 0 Dukes A: 5	22 All rectal/distal sigmoid Early: 20 Reoperated: 16	24 patients with adenomas (all <1 cm)	Overall 5-y survival: 65% (Rectal: 57%, colon: 71%)	
Togashi, 2000[45]	6.7%[j]	<4 mo: 9 25−60 mo: 9 >61 mo: 4	22[k] Early: 9 Dukes A or B: 10 Reoperated: 22[k]				

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SUPPLEMENTARY TABLE 2. Continued

Author, year	Synchronous CRC	Time to CRC diagnosis	Metachronous CRC	Anastomotic CRC	Metachronous adenomas	Outcomes	Comments
Wang, 2009[26]		Intensive: 22.0 ± 17.6 mo Routine: 35.0 ± 23.9 mo	9 Early: 1 (5 if including 1st 3 y)	22 Early: 9		Patients in intensive colonoscopy group more likely to be asymptomatic, undergo reoperation with curative intent, and survive longer (69.9 vs 24.4 mo, $P = .03$)[l]	76.5 % of patients with asymptomatic recurrence able to undergo repeat surgery, vs 35.7% of symptomatic patients Patients with asymptomatic recurrence survived longer (71.6 vs 18.6 mo, $P = .005$) 3 complications in the intensive colonoscopy group: 2 hemorrhages requiring hospitalizations, 1 perforation requiring laparotomy

NOTE. Adapted with permission from Wiley-Blackwell.[119]

HGD, High-grade dysplasia; *HR*, hazard ratio; *LAR*, low anterior resection; *TA*, tubular adenoma; *TVA*, tubulovillous adenoma; *VA*, villous adenoma.

[a]Reoperations with curative intent, unless otherwise specified.

[b]Combined metachronous CRCs and local recurrences.

[c]Eight of 11 (73%) total anastomotic recurrences in both patient subgroups (with and without preoperative colonoscopy).

[d]"Early": Within 24 mo of primary curative-intent resection, unless otherwise specified.

[e]All tumor recurrences (separate data for metachronous and anastomotic not presented).

[f]One metachronous poorly differentiated neuroendocrine carcinoma of the colon not included.

[g]Median time from preceding colonoscopy. Metachronous cancer found at first colonoscopy (median, 13 mo from surgery), anastomotic recurrences found at second colonoscopy (median, 15 mo from first colonoscopy) and fourth colonoscopy (median, 14 mo from third colonoscopy).

[h]Local recurrence with or without distant spread (local recurrence without distant spread: 74 patients).

[i]Intensive follow-up group undergoing scheduled endoscopic surveillance (n = 53). One symptomatic metachronous cancer occurred after 3 y and 2 anastomotic recurrences in the control group (n = 54).

[j]Excluding synchronous stage 0 (Tis) cancers.

[k]Twenty-two metachronous cancers, including 12 stage 0 (Tis) cancers confined to the mucosa. Nine of 12 Tis cancers treated by endoscopic resection (3 of 12 required colectomy).

[l]Data for all postoperative cancers, including metachronous and local recurrences.