Follow-Up Recommendations for Colon Cancer

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ABSTRACT

Recent evidence suggests that intensive follow-up after curative resection of colorectal cancer is associated with a small but significant improvement in survival. Regimens that employ cross-sectional imaging and carcinoembryonic antigen determination appear to have the greatest benefit. A risk-adapted approach to follow-up, intensively following patients at highest risk of recurrence, increases efficacy and cost-effectiveness. Ongoing improvements in risk stratification, disease detection, and treatment will increase the benefits of postoperative surveillance. Large randomized controlled trials are needed to determine the optimal surveillance regimen and must include an analysis of survival, quality of life, and cost-effectiveness to assess efficacy properly.

KEYWORDS: Colorectal neoplasm, neoplasm recurrence/detection, neoplasm metastasis/diagnosis, surveillance, follow-up, survival

Objectives: Upon completion of this article, the reader should be able to: (1) describe the primary and secondary goals of surveillance following curative resection of colorectal cancer; and (2) summarize the evidence in favor of intensive surveillance, recognizing its limitations and the issues that need additional clarification.

Although 80% of patients with a colorectal malignancy initially present with either local or locally advanced disease that is amenable to curative surgical resection, up to 40% suffer local, regional, or systemic recurrence.[1–6] Furthermore, these patients are at high risk for metachronous colorectal lesions as well as other cancers.[7,8] Thus, continued long-term surveillance or follow-up after the immediate postoperative period appears to be essential.

The optimal surveillance program has yet to be established, and there has been difficulty proving that intensive surveillance programs improve overall survival. Recurrences are often identified because of symptoms that occur between scheduled visits.[9–11] Although curative treatment remains primarily surgical, only a small percentage of patients are amenable to re-resection,[12–16] and an even smaller percentage realize a definitive cure.[7] In response, some authors advocate a minimalist approach.[17] Such an approach may not be justified as there is evidence to suggest that a small but recognizable subset of patients benefit from surveillance.[7,18–21]

In this article, we discuss the rationale behind postoperative follow-up and examine the best available evidence regarding the efficacy of postoperative follow-up, the most appropriate tests, and the optimal intensity of follow-up. We conclude with a discussion of secondary outcomes and a summary of surveillance strategies based on published practice guidelines.

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RATIONALE AND AIMS

The primary goal of surveillance following curative resection of colorectal cancer is to identify recurrent disease at an asymptomatic stage when it is amenable to re-resection and cure. This goal is not appropriate for all patients. Patients who cannot undergo further surgical resection because of comorbidities or patients with a low risk of recurrence require less intense protocols. A secondary goal of surveillance is the early identification of new polyps or cancers. All patients with a previous colorectal cancer are at increased risk for the development of metachronous colonic neoplasms.[22,23] Polyps can be identified and removed by colonoscopy, and a second cancer should be viewed as a failure of follow-up in this high-risk population. Regular surveillance can also lead to the identification of other health problems and provides a forum for discussion of new treatments, relevant changes in family history, and genetic issues. Additional benefits include the detection of postoperative problems (wound and stoma problems, sexual and/or urinary dysfunction), facilitation of audit for individual surgeons, the assurance of quality control for employers, and the provision of greater psychological support for the patient.[8,24,25] In general, patients derive a sense of well-being and reassurance with regular follow-up.[26,27] Should problems arise, there is clear recognition of whom to notify.

On the down side, some patients may experience anxiety prior to their visit. Furthermore, particularly with more intense surveillance regimens, there is a greater potential for false-positive test results that may provoke further anxiety and the costly use of additional resources. On the whole, however, studies have shown that patients are very willing to under go follow-up and experience no decrease in quality of life from frequent testing.[28] A pilot study by Stiggelbout et al suggested that regular follow-up visits were primarily reassuring and caused only minimal and manageable anxiety.[26] Kjeldsen et al examined quality of life and attitudes toward follow-up in a subset of 350 patients from a randomized trial comparing intensive follow-up with standard follow-up.[28] There was no difference between the two arms with respect to overall survival or recurrence. The quality of life and attitudes to follow-up were very similar between the intensive and standard arms, suggesting that the reassurance from frequent physician visits offset the inconvenience of additional tests for patients in the intensive group.

PRINCIPLES OF SURVEILLANCE

The terms screening and surveillance are often used interchangeably when discussing colorectal cancer; however, in practice they represent slightly different approaches. *Screening* refers to the use of a simple, nondefinitive test in an average-risk population to identify people at high risk for a specific disease. *Surveillance* refers to the use of a more definitive test in a previously identified high-risk population to identify disease.[29] Nonetheless, the primary goals of identification are the same: to allow intervention at an asymptomatic stage. In a broad sense, then, screening and surveillance are related. An abbreviated list of basic principles for effective disease screening is outlined in Table 1. For the purposes of discussion, we will use these as a framework to examine the suitability of recurrent colorectal cancer for surveillance.

Table 1 Criteria for Disease Screening*

1. The disease must be important and have important consequences.
2. A high-risk population must be identified.
3. There should be a detectable asymptomatic preclinical phase.
   a. The preclinical phase must be relatively long.
   b. Detection must be possible through reliable, valid, and practical tests.
4. Early detection should lead to more effective treatment and a more favorable prognosis.
   a. Effective treatment exists.
   b. Earlier intervention improves prognosis.

*Adapted from the World Health Organization criteria for disease screening. Available at: http://www.who.int/cancer/detection/en/

The Disease Must Be Important and Have Important Consequences

Colorectal cancer is the second leading cause of cancer death in North America and one of the leading causes of cancer death worldwide.[8] Up to 40% of all patients who undergo primary resection ultimately develop recurrent disease,[1–6] which is uniformly fatal if left untreated.

A High-Risk Population Must Be Identified

Patients who have had a resection for colorectal cancer are by definition a high-risk population and are at significant risk for developing a recurrence. However, within this population the risk for recurrence is not uniform. Identification of very high-risk subgroups where resources can be concentrated is essential to ensure that a surveillance program is efficient and cost effective. This underscores the need to base follow-up regimens on an individual's risk profile and explains why nonselective surveillance programs have failed to demonstrate significant survival benefits. Although many tumor variables conferring high risk have been identified (increasing T [tumor] or N [nodal] stage, lymphovascular invasion, poor differentiation),[30] several patients develop recurrence despite having what appear to be "good-risk"

tumors. It is not yet clear how to identify the latter subset of patients.

There Should Be a Detectable Asymptomatic Preclinical Phase

This principle centers around two major assumptions—the preclinical phase must be relatively long, and detection must be *possible* through reliable, valid, and practical tests. The preclinical phase for *primary* colorectal cancer is known to extend over several years as polyps grow into cancers. On the other hand, tumor doubling times in hepatic metastasis are known to be faster than those of the primary tumor.[31] In rapidly growing cancers, surveillance is unlikely to identify preclinical disease at a time when meaningful intervention can occur. This short "window of opportunity" may in part explain why many recurrences are diagnosed between scheduled visits. Colorectal cancers that progress more slowly may have a long preclinical phase and are more likely to be detected in a surveillance program because of length time bias.

The second assumption pertains to the availability of reliable (reproducible) and valid (sensitive and specific) tests for recurrence. At present, no single test is universally effective in identifying recurrent colorectal cancer; therefore, tests must be used in combination.[32] When they are used in parallel, sensitivity is increased but the specificity is decreased because of a greater number of false-positive results. When tests are used in series, sensitivity may be decreased while specificity is increased, as patients who are positive on sequential tests are more likely to have disease.[33] These theoretical constructs may also explain why so few recurrences are diagnosed at an asymptomatic stage.

Early Detection Should Lead to More Effective Treatment and a More Favorable Prognosis

This principle is also based on two major assumptions—that effective treatment exists and that "earlier" intervention improves prognosis. Surgery is the only potentially curative treatment and is effective only in cases of isolated organ-specific recurrence and locoregional recurrence within surgically resectable margins. At present, the percentage of patients with isolated, resectable liver or lung metastasis or pelvic recurrence remains small. The addition of neoadjuvant therapy holds promise, but it has demonstrated only a modest survival benefit at best.[34,35] The presumption that earlier intervention will improve survival seems intuitively obvious, but this may not be the case. Recurrence is essentially a persistence of primary disease. Patients with widespread metastases that are undetectable at the time of initial resection will not benefit from postoperative surveillance because of a short preclinical phase. Thus, our limited ability to detect microscopic disease makes "early intervention" difficult.

Given the variability in metastatic potential and temporal disease progression, our inability to detect microscopic disease, and limitations of surgical treatment, it is not surprising that it has been difficult to prove the value of surveillance following curative resection of colorectal cancer.

EVIDENCE FOR POSTOPERATIVE FOLLOW-UP

Unfortunately, post-treatment surveillance strategies have evolved unevenly and largely without appropriate clinical trials to demonstrate effectiveness.[36] Despite the results of early studies in favor of adopting aggressive follow-up regimes, a standardized intensive surveillance program has yet to be recommended by a major medical or surgical organization. Furthermore, the idea has not gained widespread acceptance by the surgical community at large. In a 1994 survey of members of the American Society of Colon and Rectal Surgeons (ASCRS), follow-up ranged from virtually none to intensive follow-up consisting of frequent monitoring with multiple blood tests and diagnostic imaging.[37] In the current era of evidence-based medicine and cost containment it is important to provide a rationale for such follow-up strategies to minimize the overuse of what have become limited medical resources and to protect against underuse and misuse of these resources.[36]

Until recently, the majority of studies that looked at postoperative surveillance following curative resection for colorectal cancer were retrospective with the inherent methodological problems of lead time and length time bias. To date, there have been six prospective randomized controlled trials (RCTs) specifically designed to answer the question of whether more intensive follow-up leads to an improvement in overall survival.[9,18,19,38–40] Four of the six trials compared intensive follow-up with minimal follow-up,[9,19,38,40] and two trials compared intensive follow-up to conventional follow-up.[18,39] Carcinoembryonic antigen (CEA) testing was used in five trials[9,18,19,34,35] and liver imaging in three trials.[18,19,35]

The inclusion criteria for all of the trials were similar. Three of the studies excluded patients based on advanced age and/or significant comorbidities that could either make follow-up difficult,[38] preclude further surgical resection,[9,38] or make 5-year survival unlikely.[40] Patients were observed for a minimum of 5 years or until their death in all six RCTs. Most of the recurrences occurred within the first 2 to 3 years of follow-up. The specific follow-up regimens (intensive and conventional or control) used for each trial are outlined in Table 2, along with some of the relevant outcomes.

Table 2 Summary of Prospective Randomized Trials of Postoperative Colorectal Cancer Surveillance: Strategies and Outcomes

RCT	N	Intensive Follow-up		Standard Follow-up		Time to First Recurrence (mo)	5-Year Survival (%)
Ohlsson et al[9] 1995	107	History & physical exam, Rigid proctosigmoidoscopy, CEA, LFT, FOBT, CXR	q3 mo × 2 yr then q6 mo × 2 yr then q12 mo	No organized follow-up Instructed to return if symptoms develop		20.4 vs. 24 (NS)	75 vs. 67 (NS)
		Colonoscopy	At 3, 15, 30, and 60 mo	Instructed to leave fecal samples	q3 mo × 2 yr then yearly		
		CT scan pelvis (APR)	3 & 6 mo then q6 mo × 24 mo				
Mäkelä et al[39] 1995	106	History & physical exam CBC, FOBT, CEA, CXR	q3 mo × 2 yr then q6 mo × 3 yr	History & physical exam, CBC, FOBT, CEA, CXR	q3 mo × 2 yr then q6 mo × 3 yr	10 vs. 15 ($P = 0.002$)	59 vs. 54 (NS)
		Flexible sigmoidoscopy	q3 mo	Rigid proctosigmoidoscopy (rectal and sigmoid cancer)	q3 mo × 2 yr then q6 mo × 3 yr		
		US liver	q6 mo				
		CT liver + surgical site	q12 mo	Barium enema	q12 mo		
		Colonoscopy	At 3 mo then q12 mo				
Kjeldsen et al[38] 1997	597	History & physical exam, DRE, gynecologic exam, FOBT, colonoscopy, CXR, CBC, ESR, LFT	q6 mo × 3 yr then yearly × 2 yr then at 10, 12.5, and 15 yr after resection	History & physical exam, DRE, gynecologic exam, FOBT, colonoscopy, CXR, CBC, ESR, LFT	At 5, 10, & 25 yr after resection	18 vs. 27 ($P < 0.001$)	70 vs. 68 (NS)
Pietra et al[18] 1998	207	History & physical exam, US liver, CEA	q3 mo × 2 yr then q6 mo × 3 yr then yearly	History & physical exam, US liver, CEA	q6 mo × 1 year then yearly	10.3 vs. 20.2 ($P < 0.0003$)	73.1 vs. 58.3 ($P < 0.02$)
		CXR, colonoscopy, CT scan	q12 mo	CXR, colonoscopy	q12 mo		
Schoemaker et al[40] 1998	325	History & physical exam, CBC, LFT, CEA, FOBT	q3 mo × 2 yr then q6 mo × 5 yr	History & physical exam, CBC, LFT, CEA, FOBT	q3 mo × 2 yr then q6 mo × 5 yr	Not stated	76 vs. 70 (NS)
		CXR, CT scan liver, colonoscopy	q12 mo	CXR, CT scan liver, colonoscopy	At 5 yr after resection		
Secco et al[19] 2002	358	*HIGH RISK (HR)**	q3 mo × 24 mo then q4 mo × 1 year then q6 mo × 2 yr	*LOW RISK (LR)**	q6 mo × 24 mo then yearly × 3 yr	*RISK-ADAPTED*	*RISK-ADAPTED*
		History & physical exam, CEA	q6 mo × 36 mo then yearly × 2 yr	History & physical exam, CEA	q6 mo × 2 yr then yearly	13.5 (HR) vs. 16 (LR)	50 (HR) vs. 80 (LR) ($P < 0.001$)
		US (abdomen and pelvis)	q1 yr × 5 yr	Rigid proctosigmoidoscopy (rectal ca)	q1 yr × 2 yr then q2 yr	*MINIMAL*	*MINIMAL*
		Rigid proctosigmoidoscopy (rectal ca)	q1 yr × 5 yr	CXR	q1 yr × 5 yr	8 (HR) vs. 14 (LR)	32 (HR) vs. 60 (LR) ($P < 0.01$)
		CXR					

*Patients stratified into high- or low-risk groups based on prognostic; randomized to risk-adapted follow-up (outlined earlier) or minimal surveillance (yearly clinical examination and q6mo phone check-ups). CXR, chest x-ray; CBC, complete blood count; FOBT, fecal occult blood test; LFT, liver function tests; CEA, carcinoembryonic antigen; ESR, erythrocyte sedimentation rate; DRE, digital rectal examination; CT, computed tomography; US, ultrasound; APR, abdominal perineal resection; NS, not significant.

Despite consistently finding fewer deaths in the intensive group of each study, the difference in 5-year survival between those in the intensive group and those in the control group did not reach statistical significance in four of the six studies.[9,38–40] Pietra and colleagues[18] were able to demonstrate a significant survival benefit for the patients who were more intensely observed. Of the patients who developed recurrent disease, a significantly higher proportion of those in the intensive group were asymptomatic at the time of diagnosis (58% versus 17%; $P < 0.05$) and had a shorter mean time to recurrence compared with the less intensive group, suggesting that more aggressive follow-up resulted in earlier detection. Curative re-resection was possible in significantly more patients in the intensive arm and appears to have translated into an increase in overall survival.

Unfortunately, the study by Pietra et al has several limitations. First, the sample size was small (207 patients in total). Second, many of the observed differences in outcome were limited to patients with rectal cancer, who were overrepresented in the trial. The authors concluded that the benefits of intensive follow-up may be limited to patients with rectal cancer because of more frequent detection of isolated local recurrences.[18] Although the probability of curative re-resection in these patients was greater, the reported survival benefit of 14.8% may be due to the exceedingly high rate of R0 re-resection (65%), which has led many to question the quality of the primary surgery.[41]

A novel concept that deserves further consideration and evaluation is a "risk-adapted" approach to follow-up. Such a strategy may save costs by searching for recurrent disease more aggressively in higher risk patients. Secco et al stratified patients with colorectal cancer treated by surgery alone into two groups using prognostic features to determine their risk of relapse (high or low).[19] Following stratification, patients were randomly assigned to either risk-adapted follow-up (intensive or less intensive depending on risk) or minimal follow-up.

High-risk patients experienced twice as many recurrences as low-risk patients, which validated the stratification. Patients in the risk-adapted follow-up program underwent significantly more curative reoperations whether they were categorized as high or low risk compared with the minimal surveillance group. There was a significant improvement in 5-year survival conferred to those undergoing risk-adapted follow-up regardless of risk (50% versus 80%; $P < 0.001$), which suggests that risk-adapted follow-up can improve the targeting of curative second surgeries and thereby improve survival independent of recurrence risk.[19]

Although the remaining four RCTs did not demonstrate a significant improvement in 5-year survival, their results must also be interpreted with caution, as sample sizes were small.[9,38–40] Although proper power calculations were performed in the two largest trials by Schoemaker et al[40] and Kjeldsen et al,[38] they were designed to detect large differences in survival (15% and 20%, respectively). Most authors would argue that this is an unrealistic survival difference to expect to gain by surveillance alone.

Three meta-analyses have been performed to overcome the lack of power in individual RCTs.[20,21,32] Two studies included the same five trials, and the third, published in 2003, included the most recent sixth trial. Renehan et al[20] found a significant improvement in overall survival associated with intensive surveillance, with an absolute reduction in mortality of 9% to 13%.[20] A subanalysis, including only the three trials in which computed tomography (CT) scan and frequent CEA monitoring were utilized in the intensive surveillance arm, demonstrated the largest effect. Diagnosis of disease recurrence in the intensive follow-up group was 8.5 months earlier and recurrences were more likely to be isolated. Jeffery et al[21] analyzed the same five trials and also found an improvement in overall survival (odds ratio 0.73; 95% confidence interval [CI] 0.58 to 0.92), earlier diagnosis of recurrences, and more frequent curative resection in patients subjected to intensive follow-up. Secondary analysis including only the three studies that used liver imaging in the intensive arm demonstrated a reduction in mortality (odds ratio 0.66; 95% CI 0.46 to 0.95). The third meta-analysis by Figueredo et al[32] was performed using all six RCTs and also found a significant improvement in overall survival with intensive follow-up (relative risk ratio 0.80; 95% CI 0.70 to 0.91). This corresponds to an absolute risk reduction of 7% at 5 years (95% CI 3% to 12%; $p = 0.002$). Again, separate analysis of only trials that used liver imaging and frequent CEA monitoring in the intensive arm of the study showed a significant improvement in overall survival and a significant increase in asymptomatic recurrences and reoperations for cure.

The combined evidence of these three meta-analyses suggests that there is a real survival benefit to be gained by the intensive follow-up of patients following curative resection of colorectal cancer. The absolute reduction in mortality is comparable to that realized by other interventions such as adjuvant chemotherapy. Meta-analyses are limited by the trials that are analyzed and their inherent problems. A criticism of these particular meta-analyses is that the RCTs they include are heterogeneous with respect to the follow-up protocols used. For example, what was defined as "intense" surveillance in one trial[9] was used in another trial as the less intense strategy.[18] For this reason, none of these meta-analyses can provide meaningful information regarding the optimal follow-up regimen, and what constitutes aggressive or intensive follow-up remains unclear.

EVIDENCE FOR INDIVIDUAL MODALITIES OF SURVEILLANCE

Although there is good evidence that follow-up in general is justified, there is insufficient proof to support the inclusion of all commonly used modalities of surveillance. In this section, the evidence pertaining to individual modalities is examined.

Clinical Assessment

History and physical examination form the mainstay of most surveillance strategies and are included in essentially every study that has addressed the issue of surveillance. However, there is no study that directly addresses the contribution of regular history and physical examination to survival, and therefore no hard data exist to either support or refute their use in follow-up. Indirect evidence from Schoemaker et al suggests that nearly 80% of recurrences are detected by abnormalities in CEA and only 20% are found by history and physical examination.[40]

Routine history and physical examination of asymptomatic patients rarely identify a resectable recurrence. Close to half of all recurrences within the first 3 years are discovered through investigation of symptoms that occur between scheduled follow-up visits.[9–11] Many patients wait until their next scheduled appointment before reporting symptoms,[8] enabling a period of time to elapse that could theoretically allow resectable disease to become unresectable. Even within RCTs, 16% to 66% of patients are symptomatic at the time of diagnosis—very few with resectable disease.[38,39]

Despite a lack of evidence, virtually all published evidence-based practice guidelines recommend the inclusion of routine history and physical examination in surveillance programs.[25,42–45] These recommendations are based on the additional theoretical benefits that may be gained, including the provision of reassurance and health care advice, discussions of preventative health care, colorectal cancer screening for relatives, and identification of metachronous neoplasms.[42]

Recommendations regarding the proper timing of office visits vary from one guideline to another because of insufficient evidence.[11,46–48] Increasing the frequency of office follow-up results in more recurrences being detected at routine visits,[49,50] and it is generally agreed that office visits should be scheduled more frequently in the first 2 years of follow-up, when the majority of recurrences appear.[39,51]

Routine Blood Tests

Although the test is commonly included in many follow-up strategies, recurrent disease is rarely identified by an isolated abnormality in serum hemoglobin. In a study by Graffner et al, none of the 47 recurrences that developed in their series of 190 were detected on the basis of an isolated abnormality in serum hemoglobin.[52] Similarly, very few recurrences are identified on the basis of abnormal liver function tests, which are typically a late finding occurring well after hepatic metastases have been discovered by another blood test or imaging study.[46] As the routine use of these tests does not lead to early detection of recurrent disease or improved survival, both the American Society of Clinical Oncology (ASCO) and ASCRS have recommended against the routine use of these tests for surveillance.[21,24,39]

Carcinoembryonic Antigen

There is good evidence that CEA should be part of colorectal cancer follow-up. CEA is the first abnormal test in 38% to 66% of patients who develop a recurrence, with an estimated lead time of 4 to 6 months when compared with other diagnostic modalities or the development of symptoms.[9,39,52–55] The sensitivity of CEA varies depending on the cutoff value used for a positive test result and also on the site of recurrence.[55] A CEA value greater than 5 ng/mL has a positive predictive value of 70% to 80% for recurrent disease.[39,52,55] Overall, CEA is more sensitive for detecting retroperitoneal and liver metastases than for peritoneal and pulmonary metastases or local recurrences.[52,54,55] Unfortunately up to 30% of primary colorectal cancers and their recurrences do not produce CEA,[56] particularly the tumors that are poorly differentiated,[42,56,57] leading to false-negative results. False-positive elevations are reported to occur in 7% to 16% of patients[55] and should be confirmed with a second test prior to embarking on a more intensive work-up.[25,42]

In the RCTs in which CEA monitoring was included in both follow-up arms, a rise in CEA was the most common method for identifying asymptomatic recurrences.[18,39] Unfortunately, this did not translate into an increase in the number of curative resections or improvement in survival. In the study by Mäkelä et al, only 2 of the 20 patients with CEA-identified recurrences could undergo complete resection.[39] Furthermore, no RCT in which CEA testing was used only in the intensive follow-up arm has demonstrated a survival advantage specifically attributable to the routine monitoring of CEA levels. In contrast, the three meta-analyses have all found frequent monitoring of CEA levels to be associated with a significant improvement in survival.[20,21,32] However, this effect was seen only in trials using frequent CEA testing and liver imaging together, and therefore the results may be due to the addition of liver imaging or the combination of both tests. The optimal interval for measuring CEA has yet to be properly addressed in a randomized trial.

Although elevations in CEA identify a subset of patients who require further investigation for recurrent

disease, second-look laparotomies solely on the basis of an elevated CEA without confirmatory preoperative imaging are not warranted as there is little benefit in terms of identifying resectable disease or enhancing survival.[58,59]

Chest Radiograph

Chest radiographs are relatively noninvasive, inexpensive, and have a low false-positive rate when used for the detection of lung metastases from colorectal cancer. Following curative resection, up to 22% of patients ultimately develop pulmonary metastases. Although the rate of disease isolated to the lungs is small, the reported 5-year survival rate after resection of isolated pulmonary metastases is 30% to 44%.[11,40,60,61]

Chest radiographs have been included in virtually all intensive follow-up schedules.

In the study by Schoemaker and colleagues,[40] yearly chest X-ray studies led to the discovery of seven asymptomatic lung metastases (4% of the intensive group), three of which were isolated recurrences amenable to resection. Only one patient remained alive and well at the conclusion of their study and was the only person in the intensive group to benefit from yearly chest radiography.[40,62]

Cross-Sectional Imaging

CT is considered the modality of choice for the detection of liver metastasis and other intra-abdominal or pelvic recurrences. However, studies have been unable to demonstrate that CT is better at identifying metastatic lesions amenable to curative resection.[11,44] In the RCT by Mäkelä and colleagues, five patients in the intensive arm were found to have liver metastases, none of which were detected by yearly CT scan (four detected by ultrasonography and one detected by an elevated CEA).[39] On the other hand, Schoemaker et al found that yearly CT scans significantly increased the detection rate of asymptomatic hepatic metastases in the intensive group.[40] Despite this difference, there was no significant improvement in the rate of resection or overall survival as only one patient with an asymptomatic liver metastasis discovered by CT experienced long-term survival.[40] One of the major criticisms of this trial is the relatively infrequent use of CT scans in the intensive follow-up arm. CT scans were performed yearly, and some authors feel that more frequent scanning, particularly in the first 2 years, may have led to an increase in the number of resectable recurrences.[36]

The meta-analysis by Figueredo et al[32] found that the significant improvement in survival associated with intensive surveillance was limited to trials that used some form of liver imaging. Both Renehan and Jeffery and their colleagues found similar results.[20,21] Renehan thought that this was due to earlier diagnosis of isolated liver metastases with liver imaging.[20] However, it is impossible to ascribe these results to liver imaging alone as it was coupled with frequent CEA determinations in the intensive arms.

To compound this discussion, technology is changing rapidly. The development of spiral and multidetector CT scanners with improved spatial resolution and multiplanar capability has enhanced both the sensitivity and specificity of this test.[63] Reevaluation in an RCT using current-generation CT scanners may provide patients with a survival benefit that previous studies have been unable to show. Identification of smaller asymptomatic liver lesions may make it possible to down-size isolated unresectable hepatic metastases substantially, so that they become amenable to curative surgery.[64,65]

A secondary analysis of a recent multicenter RCT comparing the efficacy of two different adjuvant therapies following curatively resected colorectal cancer examined the impact of surveillance with CEA and CT on the detection of recurrence and survival.[63] CEA levels were determined every 3 months for the first year, every 6 months for the second year, and annually thereafter. CT scans of the thorax, abdomen, and pelvis were performed at 12 and 24 months. Of the 155 patients who had relapse of disease, 58% were asymptomatic at the time of detection. Within the asymptomatic group of patients 39% were detected by CT alone, 35% by a rise in CEA, and 16% by a concomitant rise in CEA and abnormality on CT. Only 10% of asymptomatic recurrences were detected by means other than CT or CEA. The median time to recurrence was 6.8 months earlier in the asymptomatic group. When asymptomatic recurrence was detected by CT scan, the survival advantage for patients was twice as long (13.8 months) and patients had a better chance of curative resection and long-term survival compared with symptomatic patients. Although the authors suggest that the observed survival advantage was related to the ability of CT scan to identify patients with asymptomatic small-volume metastases amenable to resection, a large proportion of all recurrences (42%) were still symptomatic. These results warrant confirmation in a proper RCT.

At present, there is no evidence for the routine use of magnetic resonance imaging or positron emission tomography scanning in follow-up strategies. Their role should be relegated to investigation of symptoms or elevated CEA or confirmation of abnormal CT results.

Endoscopy

Colonoscopy has been evaluated for its ability to detect synchronous lesions, anastomotic or local recurrences, and metachronous lesions. It is generally accepted that complete colonoscopy should be performed in all

patients with colorectal cancer prior to surgical resection, to identify synchronous tumors and to remove adenomatous polyps. If factors preclude complete visualization of the colon prior to surgery, colonic evaluation should be performed within 6 months of surgery.[25,42,66]

Most local recurrences are the result of residual disease. Thus, they start extraluminally and cannot be detected endoscopically until they are very advanced.[25] It is generally agreed that the rate of anastomotic recurrence following resection for colon cancer is too low to justify routine visualization with colonoscopy during follow-up.[67] Only two small RCTs have considered the role of anastomotic visualization following curative resection of rectal cancer. Although they were unable to demonstrate an increase in the number of resectable recurrences, they were too small to be definitive.[9,39]

Approximately 5% to 10% of patients with a previously resected colorectal cancer develop a metachronous tumor at some point in their lives.[8] The risk of developing a second colorectal cancer is lifelong and is estimated to be 0.35% per year of follow-up.[68,69] In the four RCTs in which regular colonoscopy was included as part of intensive surveillance, less than 2% of patients developed neoplasms within the first 5 to 7 years of follow-up.[9,18,33,35] In the study by Schoemaker et al,[40] only 1 patient out of 167 in the intensive group had a metachronous lesion detected by yearly colonoscopy at a cost of performing an extra 505 colonoscopies. Patients in the standard follow-up group had colonoscopy performed at completion of follow-up (after 5 years) and no metachronous cancers were found. Schoemaker et al also reported two episodes of bleeding after colonoscopic polypectomy out of 731 colonoscopies (0.55%), comparable to the reported incidence in the literature.[40]

Although there is no direct RCT evidence for inclusion of colonoscopy in follow-up, there is indirect evidence from the National Polyp Study.[70] Colonoscopy performed at 3-year intervals was found to be as efficacious as that performed at yearly intervals in detecting new polyps following removal of an adenomatous polyp. Given that patients who have been treated for colorectal cancer represent a high-risk group for the development of polyps and metachronous cancers, it seems appropriate to extrapolate the data from the National Polyp Study to this group of patients.

SECONDARY OUTCOMES: QUALITY OF LIFE AND COST-EFFECTIVENESS

Improving long-term survival is only one of the potential benefits of follow-up. Other secondary endpoints include an increase in quality of life gained by early detection and treatment of relapse, the potential gain in survival time related to early palliative treatment of an asymptomatic recurrence, and the detection of secondary diseases.[41] Unfortunately, most of these secondary endpoints have not been thoroughly evaluated.

Cost-effectiveness analysis helps to determine whether a practice shown to be beneficial can be economically justified and, thus, whether it should become a standard of care.[71] The cost of surveillance is substantial.[72] With limited resources, routine practices such as surveillance require not only evidence of improved survival but also evidence that the cost of attaining this outcome is acceptable, often balancing an optimal follow-up regimen with the available resources.[73] This so-called cost acceptability differs from one society to another and depends on several factors, such as who pays for health care (public or private), the burden of disease on society, and the resources available within a particular society. In the case of publicly funded health care, the cost threshold refers to how much a society is willing to expend per year of additional life attributable to follow-up and varies depending on the society in question.[72] In wealthy nations it has been suggested that the number is probably about $50,000 to $100,000 per quality-adjusted life year.[72] Of course, this does not take into account the potential improvements in quality of life that may be gained.

A reliable estimate of cost-effectiveness is difficult when no standard follow-up regimen exists. Most of the published cost-effectiveness analyses are based on retrospective information and use survival as the primary endpoint. In a study by Virgo et al,[74] the average costs associated with 5-year follow-up of one colorectal cancer patient after curative treatment were calculated and compared for 11 separate follow-up strategies available in the literature at the time. The expensive strategies were those that used colonoscopy frequently, whereas the least expensive strategies consisted mainly of a combination of office visits, blood tests (including CEA), and chest radiography. There was a 28-fold difference in cost from the least intensive to most intensive strategy. Despite the large differences in cost between the two extremes of surveillance, there was no difference in efficacy. Several assumptions were made in their model; positive tests did not require additional work-up or confirmatory tests, each patient survived for 5 years, and the cost of treating new colon cancers, recurrences, and other conditions disclosed by surveillance was ignored. Nevertheless, this study effectively demonstrates the significant financial burden that intensive follow-up strategies may create socioeconomically. The variation in costs also highlights the need for a long-term RCT with the appropriate statistical power to determine whether higher costs are justified by increased quality and quantity of life.[75]

More recently, Renehan and colleagues[76] performed two cost-effectiveness analyses, the first based on the meta-analysis by Jeffery et al[21,75] that demonstrated an absolute reduction in mortality of 7% at 5 years

Table 3 Guidelines for Postoperative Screening Following Curative Resection of Colorectal Cancer: Recommendations by Major Organizations

	Recommendations			
Diagnostic Modalities	**ASCO 1999[42]**	**ESMO 2002[78]**	**NCCN 2003[45]**	**ASCRS 2004[25]**
History and physical examination	Every 3–6 mo × 3 years and then yearly	Every 6 mo × 2 years (distal cancers); all other cancers yearly × 3 years	Every 3 mo × 2 yr then every 6 months for total of 5 years	Routine office visits recommended at least three times per year for the first 2 years of follow-up
CEA	Every 2–3 mo in patients with stage II or III disease for ⩾ 2 years after diagnosis if candidate for resection of liver metastases	Against routine monitoring	Every 3 mo × 2 yr then every 6 mo for total of 5 years (for T2 or greater lesions if candidate for resection of liver metastases)	Check level a minimum of three times per year for the first 2 years of follow-up
CBC	No recommendation made	Against routine monitoring	No recommendation made	Against routine monitoring
Liver function tests	Against routine monitoring	Against routine monitoring	No recommendation made	Against routine monitoring
FOBT	Against routine monitoring	Against routine monitoring	No recommendation made	Against routine monitoring
Computed tomography	Against routine monitoring	Against routine monitoring; abdominal US yearly × 3 years	Only if indicated for certain clinical indications	Against routine monitoring
Chest x-ray	Against routine monitoring	Against routine monitoring	Only if indicated for certain clinical indications	Insufficient evidence for or against routine use
Colonoscopy	Pre- or postoperatively to document a cancer and polyp-free colon. Every 3–5 years to detect new cancers and polyps	Every 5 years	1 year postoperatively (or after 3–6 mo for obstructing lesions and unprepped bowel); if abnormal, repeat in 1 year or every 3–5 years if negative for polyps	Preoperative colonoscopy if practical; otherwise, within 6 months postoperatively Post-treatment colonoscopy every 3 years to detect new cancers and polyps
Flexible proctosigmoidoscopy	Periodic direct imaging of rectum in patients who had resection of rectal cancer who did not receive adjuvant chemoradiation therapy	Every 6 months for distal cancers × 2 years	No recommendation made	Periodic evaluation of anastomosis for patients who either had resection with anastomosis or local excision of rectal cancer

CBC, complete blood count; CEA, carcinoembryonic antigen; FOBT, fecal occult blood test.
ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology; ASCRS, American Society of Colon and Rectal Surgeons.

and the second based on outcome data from four RCTs in which surveillance was targeted to detect extraluminal recurrences with a pooled absolute reduction in mortality of 9%. This study included specific costs related to follow-up and to the treatment of recurrence incorporating three possible outcomes: inoperable disease requiring palliative care, salvage surgery with cure, and salvage with subsequent failure and palliative care. The primary outcome was the incremental cost-effectiveness ratio calculating the extra cost required for each change in life year as a result of intensive follow-up compared with conventional follow-up. Based on Jeffery's meta-analysis,[21] the cost for each life year gained by intensive follow-up was substantially lower than the £30,000 ($51,888) threshold of cost acceptability in the United Kingdom at the time. In the second analysis based on four RCTs, the cost was even lower, suggesting that surveillance targeted toward extraluminal recurrence is more cost effective. Unfortunately, the heterogeneity of the follow-up regimes in the RCTs does not allow determination of the cost-effectiveness of specific surveillance tools. In addition, indirect costs such as time lost from work and transportation charges were not factored into the analysis. Quality-of-life data were also absent. Although this study was published in 2004, the trials included in their analyses were conducted in the 1990s and did not include many aspects of contemporary practice that could affect costs and effectiveness.

Despite these results, some authors would argue that most schedules of intensive follow-up do not offer a worthwhile cost-benefit ratio for the small number of patients who demonstrate long-term survival after reoperation.[73] They argue that the resources and capital should be spent on prevention programs and screening of high-risk groups for primary cancer to benefit a larger proportion of the population. Although this may be true, the overall survival benefit estimated by meta-analyses is comparable to that expected from other costly adjuvant treatments with a higher risk-benefit ratio. Ideally, future estimates for cost-effectiveness of a follow-up program should come from RCTs that compare different follow-up strategies and include a quality-of-life assessment and prospective cost analyses.[71]

A risk-adapted follow-up in which the intensity varies according to the risk of recurrence[77] will increase the cost-effectiveness by concentrating resources on patients at very high risk. When this is combined with a regimen focused primarily to detect extraluminal recurrences, further cost reductions will be realized. Opponents of this approach have suggested that multiple follow-up strategies will be difficult and confusing to implement. However, this strategy is presently used in screening programs for primary colorectal cancer to improve cost-effectiveness and resource allocation.[66]

RECOMMENDATIONS

Despite the lack of consensus on the utility of intensive follow-up following curative resection of colorectal cancer, several groups in the United States,[25,42,45] Canada,[32,51] and Europe[8,78] have formulated practice guidelines based on the available evidence. The most current published evidence-based guidelines are listed in Table 3 for comparison. There is significant variability in the intensity of the different surveillance strategies with respect to the diagnostic modalities used to detect recurrence and the frequency with which they are applied.

CONCLUSIONS

Intensive surveillance following curative resection of colorectal cancer improves survival by a small but significant amount. Selective use of intensive follow-up regimens, excluding patients at very low risk for recurrence and patients who cannot tolerate further curative resection while concentrating on subpopulations of patients at very high risk, will increase the utility of such regimens and thus improve cost-effectiveness. The psychosocial benefits of surveillance, although hard to quantify, are real and to the individual patient are very important. In addition, follow-up gives the ability to compare different treatment regimens and outcomes.

Continued improvements in risk stratification (possibly through genetic markers), disease detection, and treatment will increase the benefits of postoperative surveillance. Large RCTs are needed to determine the optimal surveillance regimen and must include an analysis of survival, quality of life, and cost-effectiveness to assess efficacy properly.

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