The Role of Postoperative Surveillance in Colorectal Cancer

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ABSTRACT

Postoperative surveillance for recurrent and/or metachronous disease is an important component of the treatment of patients with colorectal cancer. The optimal schedule of follow-up investigations remains controversial. Several randomized trials have suggested a moderate improvement in 5-year survival and earlier detection of cancer recurrence with the implementation of intensive surveillance protocols. Whether these protocols are cost-effective has yet to be determined. Current guidelines from the American Society of Colon and Rectal Surgeons recommend periodic patient follow-up with office visits, carcinoembryonic antigen (CEA) measurement, and endoscopy following potentially curative resection of colorectal cancer.

KEYWORDS: Colorectal cancer, cancer surveillance

Objectives: Upon completion of this article, the reader should: (1) understand the rationale for colorectal cancer surveillance; (2) recognize the various diagnostic modalities employed in the follow-up of colorectal cancer patients; and (3) be familiar with major societal guidelines for colorectal cancer surveillance.

Colorectal cancer remains the third most common cause of cancer death in the United States, with an estimated 41,930 new cases of rectal cancer diagnosed annually.[1] Despite advances in surgical and adjuvant therapeutic modalities, disease recurrence occurs in up to 40% of patients following primary therapy.

Many diagnostic modalities are currently employed in the postoperative surveillance of patients with rectal cancer. In this review, we will discuss the rationale for postoperative surveillance, the available diagnostic methods for detection of disease recurrence, and the current recommendations for the role of surveillance from major medical and surgical societies.

RATIONALE FOR POSTOPERATIVE SURVEILLANCE

The primary objectives of surveillance following surgical resection for rectal cancer are to detect disease recurrence (local and metastatic) and to screen for metachronous colorectal lesions and primary cancers in other organ systems. Although most clinicians agree with the necessity of rectal cancer surveillance, no strong consensus exists regarding the scheduling and utility of various diagnostic modalities.[2]

Between 60 to 80% of rectal cancer recurrences occur within 24 months following primary treatment, and 90% occur within 4 years.[2–4] Improved clinical outcomes have been demonstrated when recurrent cancer is treated at an early stage.[3–8] Therefore,

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most proposed surveillance protocols emphasize initial follow-up at shorter intervals.

METHODS FOR DETECTION OF RECURRENT OR METACHRONOUS DISEASE

History and Physical Examination

Multiple diagnostic modalities are available for combined use in the surveillance of patients with colorectal cancer. The simplest of these is the history and physical examination. Symptoms suggestive of locoregional or distant disease recurrence include coughing, abdominal or pelvic pain, change in bowel habits, rectal bleeding, and fatigue.[3] A thorough physical examination, including digital rectal exam, palpation of inguinal nodes, and pelvic examination in female patients should also be performed. Recurrent disease is rarely diagnosed on the basis of the history and physical exam (H&P) alone,[9] and studies have indicated that symptomatic disease recurrences are less likely to be resected for cure.[3,9–11] Positive clinical findings are an indication for further diagnostic investigation. Other advantages of routine postoperative clinical assessment include patient education and reassurance and detection of disease in other organ systems.

Laboratory Studies

Various laboratory tests, including serum hemoglobin, hepatic enzymes, and carcinoembryonic antigen (CEA) levels, have been extensively studied as markers of colorectal cancer recurrence. Serum hemoglobin and liver function tests have not been demonstrated to be effective indicators of disease recurrence and are not recommended for use in routine surveillance.[3,9,12,13]

CEA, an oncofetal protein associated with colorectal and various other cancers, lacks both sensitivity and specificity and is therefore not a useful screening tool for colorectal cancer. However, in patients with an established history of colorectal cancer, an abnormal CEA is often the first indication of disease recurrence.[3–6,12–16] Because false positive CEA elevations are common (7 to 16%), a second level should be obtained to confirm the elevation prior to embarking upon an extensive diagnostic workup.[12,15]

Radiographic Imaging

Disease recurrence at distant sites, most commonly lung and liver metastases, can be detected with abdominal computer tomography (CT) imaging and chest radiography. Resection of isolated pulmonary metastases is associated with a 5-year survival rate between 30 to 40%.[9,11] Chest radiography is a relatively inexpensive, noninvasive method by which asymptomatic pulmonary metastases may be detected.

The use of routine abdominal CT imaging for the detection of resectable hepatic metastases is controversial. Several studies have demonstrated the utility of routine CT imaging for detecting asymptomatic hepatic recurrences. However, few of these recurrences were resected for cure.[10–12,17]

The role of positive emission tomography (PET) scanning in routine surveillance has not been extensively studied. This modality can be effective for the detection of disease recurrence in patients found to have persistent CEA elevations.[12]

Endorectal ultrasound (EUS) is emerging as a useful adjunct in the surveillance of patients with previously resected rectal cancer.[16,18,19] Using this technique, the rectal wall and perirectal tissue can be examined for evidence of local recurrence of disease. However, results are operator-dependent, and this modality is not at this time recommended in standard surveillance protocols.

Endoscopy

Complete endoscopic evaluation of the colon for synchronous lesions should be performed prior to surgical resection of rectal cancer. If this is not possible, colonic evaluation should be performed within 6 months following surgery. Because the risk of metachronous cancer is 1.5 to 3 times greater in patients with an established history of colorectal cancer, lifelong endoscopic surveillance is mandatory. Flexible sigmoidoscopy, which can be performed with minimal preparation in an office setting, is a useful method for visualizing rectal anastomoses for evidence of recurrence.

SURVEILLANCE SCHEDULES: IS INTENSIVE FOLLOW-UP BENEFICIAL?

Several randomized trials[4,6,10,11,16] and meta-analyses have examined the theoretical benefit of intensive surveillance following potentially curative resection of colorectal cancer. None of these studies specifically addressed primary rectal cancer. Furthermore, there is considerable variability between these studies in the modalities included in "intensive" or "standard" follow-up.

In a 1995 study, Ohlsson et al[4] reported a randomized study in which 53 patients were enrolled in an intensive postoperative surveillance program. This program required physical examination, rigid proctosigmoidoscopy, serum CEA, liver function tests (LFTs), fecal occult blood testing, and chest x-rays at 3 month intervals, with complete colonoscopy performed at 3, 15, 30, and 60 months postoperatively. CT of the pelvis was performed at 3, 6, 12, 18, and 24 months in patients who

underwent abdominoperineal resection. Compared with a control group of patients ($n = 54$) who underwent no scheduled follow-up studies, no significant difference in time to disease recurrence or overall 5-year survival was demonstrated.

A prospective, randomized trial by Makela et al[10] compared postsurgical patients who underwent standard follow-up with those who underwent intensive follow-up. The intensive schedule included annual CT imaging of the abdomen and pelvis, hepatic ultrasound every 6 months, and colonoscopy at 3 months and then annually. Barium contrast enemas were performed instead of colonoscopy in the standard follow-up arm. The time to first disease recurrence was significantly decreased (10 versus 15 months) in the intensive follow-up group. There was no difference in 5-year survival. Similar results were reported in a larger study by Kjeldsen et al in 1997,[18] in which the control arm underwent minimal follow-up postoperatively.

In the only major randomized prospective study to demonstrate an increase in survival with intensive follow-up, Pietra et al[16] compared conventional follow-up ($n = 103$) to intense follow-up ($n = 104$). Cancer recurrence was detected significantly earlier (10.3 versus

Table 1 Intensive versus Standard Surveillance: Results of Five Prospective Randomized Trials

	N		First Recurrence (Months)		5-Year Survival (%)	
	Intensive	Standard	Intensive	Standard	Intensive	Standard
Ohlsson et al[4]	53	54	20.4	24 (NS)	75	67 (NS)
Intensive protocol: –H&P with CBC, FOBT, CEA, cxr every 3 mo x 2 y, then every 6 mo –Annual colonoscopy and computed tomography –Hepatic ultrasound every 6 mo –Sigmoidoscopy every 3 mo for rectal and sigmoid cancers Standard protocol: –H&P with CBC, FOBT, CEA, cxr every 3 mo x 2 y, then every 6 mo –Annual barium enema –Sigmoidoscopy every 3 mo for rectal cancers						
Makela et al[10]						
Intensive protocol: –H&P with CBC, FOBT, CEA, cxr every 3 mo x 2 y, then every 6 mo –Colonoscopy at 3,15,30, & 60 mo –Computed tomography after APR at 3,6,12,18, & 24 mo Standard protocol: –No scheduled follow-up –FOBT samples delivered to clinic every 3 mo x 2 y, then annually	52	54	10	15 ($p = 0.002$)	59	54 (NS)
Schoemaker et al[11]	167	158	Not	evaluated	76	70 (NS)
Intensive protocol: –H&P with CBC, FOBT, LFTs,CEA every 3 mo x 2 y, then every 6 mo –Colonoscopy annually –Computed tomography and cxr annually Standard protocol: –H&P with CBC, FOBT, LFTs,CEA every 3 mo x 2 y, then every 6 mo						
Pietra et al[16]	104	103	10.3	20.2 ($p < 0.0003$)	73.1	58.3 ($p < 0.02$)
Intensive protocol: –H&P with CEA and hepatic ultrasound every 3 mo x 2 y, then every 6 mo –Annual colonoscopy, cxr and computed tomography Standard protocol: –H&P with CEA and hepatic ultrasound every 6 mo x 1 year, then annually –Annual colonoscopy and cxr						
Kjeldsen et al[18]						
Intensive protocol: –H&P with CBC, FOBT, ESR, LFTs, colonoscopy and cxr every 6 mo x 3 y, every 12 mo x 2 y, then every 5 y Standard protocol: –H&P with CBC, FOBT, ESR, LFTs, colonoscopy and cxr at 5 and 10 y	290	307	18	27 ($p < 0.001$)	70	68 (NS)

H&P, history and physical examination; CBC, complete blood count; FOBT, fecal occult blood test; CEA, carcinoembryonic antigen; APR, abdominoperineal resection; LFTs, liver function tests; cxr, chest x-ray; ESR, erythrocyte sedimentation rate; NS, not significant.

Table 2 Summary of Recommended Surveillance Protocols

Test/Procedure	ASCRS[12]	NCCN[23]	ASCO[24]
History and physical exam	Minimum of 3 times/year for the first 2 y	Every 3–6 mo for 2 y, then every 6 mo for 5 y	Every 3–6 mo for 3 y, every 6 mo years 4 & 5, then physician discretion
Fecal occult blood test	Not recommended	Not addressed	Not addressed
Complete blood count	Not recommended	Not addressed	Not recommended
Liver function tests	Not recommended	Not addressed	Not recommended
Carcinoembryonic antigen	Minimum of 3 times/year for the first 2 years	Every 3–6 mo for 2 y, then every 6 mo for 5 y for T2 or greater	Every 3 mo for 3 y or longer
Chest radiography	Not recommended	Not recommended	Not recommended
Flexible sigmoidoscopy/ proctoscopy, endoscopic ultrasound	Periodic anastomotic evaluation recommended (patients who have undergone resection/ anastomosis or local excision of rectal cancer)	Consider proctoscopy every 6 mo × 5 y	Flexible proctoscope/sigmoidoscopy every 6 mo × 5 y for patients who have not received pelvic irradiation
Colonoscopy	Every 3 years following primary therapy	1 y after primary therapy, then at 3 y & every 5 y (repeat in 1 y if abnormal)	At 3 y, then every 5 y if normal
Computed tomography of chest/abdomen/pelvis	Not recommended	Annually × 3 y for patients at higher risk of recurrence (lymphovascular invasion, poor differentiation)	Annually × 3 y for patients at higher risk recurrence (lymphovascular invasion, poor differentiation)
Abdominal ultrasound	Not recommended	Not addressed	Not addressed

ASCRS, Standards Practice Task Force of the American Society of Colon and Rectal Surgeons; NCCN, National Cancer Care Network; ASCO, the American Society of Clinical Oncology.

20.2 months) in the intense follow-up group. These patients underwent surveillance every 3 months for the first 2 years, every 6 months for years 3 through 5, and annually thereafter. Five-year survival rates were 73.1 for the intense follow-up group and 58.3 for the standard follow-up group ($p < 0.02$).

A recent meta-analysis of the five major randomized comparisons of intensive and standard colorectal cancer surveillance protocols demonstrated a significant reduction in all-cause mortality ($p = 0.007$), earlier detection of all cancer recurrences ($p < 0.001$), and an increased detection rate for local cancer recurrences ($p < 0.011$).[20] Improvement in overall survival rates were most pronounced in studies that incorporated frequent CEA evaluation and computed tomography in intensive follow-up schedules. A brief synopsis of these studies is displayed in Table 1.

COST ANALYSIS

In today's health care environment, surveillance protocols must be cost-effective to gain widespread acceptance. In a cost-analysis of 11 surveillance protocols by Virgo et al,[21] 1992 Medicare-allowed charges varied from a low of $561 for an annual barium-enema only to a high of $16,492 for patients enrolled in the intensive surveillance protocol of Makela et al.[10] They concluded that higher-cost strategies did not appear to increase survival or quality of life.

Graham et al[14] focused on the cost–benefit ratio of periodic physical examination, CEA analysis, chest x-ray, and colonoscopy in 421 patients with recurrent rectal cancer. The estimated mean cost of each test was evaluated in a subset of patients found to have recurrent disease amenable to surgical resection ($n = 96$). Despite a cumulative cost of $418,615 for office visits, no resectable recurrences were diagnosed on routine physical examination. The detection rate for chest X-ray was 0.9%, with a total cost of $120,934 (cost per resectable recurrence = $10,078). One percent of resectable recurrences were detected by colonoscopy, with a cumulative cost of $641,344 (cost per resectable recurrence = $45,810). Analysis of CEA was the most cost-effective test in detecting potentially curable recurrent disease, with a 2.2% detection rate and cost per recurrence of $5,696 (cumulative cost $170,880).

In a 2001 Dutch study of similar design,[22] 42 of 496 patients were found to have resectable disease recurrence. Of this group, 22 were diagnosed based on hepatic ultrasound, colonoscopy, or CT, with a cost of $11,790 per patient. Routine physical examination, chest radiography, and CEA measurement were indications of recurrence in 6 patients, with an average cost per patient of $19,850. They concluded that these later three modalities are not cost-effective for use in standard surveillance.

Based on these disparate findings, it is evident that further investigation is warranted to determine the most cost-effective strategy to detect recurrent disease in patients with an established history of colorectal cancer.

CURRENT SURVEILLANCE GUIDELINES

In 2004, the Standards Practice Task Force of the American Society of Colon and Rectal Surgeons (ASCRS) proposed practice parameters for follow-up of patients with colon and rectal cancer based on the current literature related to surveillance efficacy.[12] They determined that follow-up for patients with completely resected colorectal cancer is justified, and should include routine office visits, CEA evaluation, periodic anastomotic evaluation in rectal cancer patients, and colonoscopy. Serum hemoglobin, fecal occult blood testing, liver function studies and routine hepatic imaging were not recommended as components of the standard follow-up schedule.

A summary of the current ASCRS guidelines and those proposed by the National Cancer Care Network (NCCN) and the American Society of Clinical Oncology (ASCO) is included in Table 2.[12,23,24]

CONCLUSIONS

Surveillance following potentially curative resection of colorectal cancer is well supported by the current literature. However, controversy remains concerning the utility and cost-effectiveness of specific diagnostic modalities. Further investigation is necessary to determine an optimal schedule for postoperative follow-up of colorectal cancer patients.

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