Follow-up of Patients with Curatively Resected Colorectal Cancer

Members of the Gastrointestinal Cancer Disease Site Group

This Evidence-based Series (EBS) was put in the Education and Information section in March 2012 by the Gastrointestinal Cancer DSG.

This Education and Information EBS guideline provides one piece of evidence for the more current EBS 26-2 Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer. Please refer to EBS 26-2 for the most current recommendations on this subject. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

The EBS contains the original Summary and Full Report dated January 2004 and is available on the CCO website (http://www.cancercare.on.ca) PEBC Gastrointestinal Cancer Disease Site Group page at: http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/gastro-ebss/.

Release Date: March 20, 2012

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Follow-up of Patients with Curatively Resected Colorectal Cancer Practice Guideline Report #2-9


This Evidence-based Series (EBS) was put in the Education and Information section in March 2012 by the Gastrointestinal Cancer DSG. This Education and Information EBS guideline provides one piece of evidence for the more current EBS 26-2 Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer. Please refer to EBS 26-2 for the most current recommendations on this subject.

Guideline Question
Does follow-up of patients after curative resection of colorectal cancer improve survival?

Target Population
These recommendations apply to adult patients with curatively resected colorectal cancer, defined as patients who have had all apparent disease removed by surgery.

Recommendations
- Patients with curatively resected colorectal cancer should be alerted to the future risk of disease recurrence, which is related to tumour stage, and to the development of a second colorectal cancer.
- There is evidence from one randomized trial and a meta-analysis of six randomized trials of a small survival benefit with more intensive follow-up compared to less intensive follow-up. This benefit is due to the early diagnosis and resection of limited recurrent disease in the liver, lungs, or local sites. It is not known at this time whether this diagnosis of resectable recurrences is due to the early assessment of symptoms or to the use of screening tests.
(blood carcinoembryonic antigen, chest-x-ray, liver ultrasound, or colonoscopy). There is insufficient evidence on which to base a recommendation for specific screening tests.

- In light of the uncertainty of the schedule of visits and screening tests to be recommended, and based on the rate of recurrent disease and second neoplasms, and on current practices, we advise:
  1. In patients who are at high risk of relapse (stages IIb and III disease) and who are fit and willing to undergo investigations and treatment:
     - Prompt assessment for symptoms of potential disease relapse (see Appendix 1)
     
     **Update:**
     - For patients at high-risk of recurrence (stages IIb and III), clinical assessment is recommended when symptoms occur or at least every six months the first three years and yearly for at least five years, instead of for at least three years as recommended in the original guideline.
     - During those visits patients may have blood carcinoembryonic antigen, chest x-rays, and liver ultrasound;
     - When recurrences of disease are detected, patients should be assessed by a multi-disciplinary oncology team including surgical, radiation, and medical oncologists to determine the best treatment options.

  2. In patients at high risk of relapse but who have co-morbidities that may interfere with prescribed tests or potential treatment for recurrence, or who are unwilling to undergo prescribed tests or potential treatment for recurrence:
     - Clinical assessments yearly or for suggestive symptoms of relapse.

  3. In all patients with resected colorectal cancer (stages I, II, and III) and based on the U.S. Polyp Study:
     - Colonoscopy postoperatively if not yet done;
       - if polyps are present, excise as they are potential precursors of colorectal cancer; repeat colonoscopy yearly as long as polyps are found.
       - if there are no polyps, repeat colonoscopy in three to five years. (see Appendix 2).

   - Patients should be encouraged to participate in clinical trials investigating screening tests added on to their clinical assessment. These trials of follow-up need to target patients with resectable recurrent disease who are fit for required surgery.

   **Update**
   - For patients at lower risk of recurrence (stages I and Ia) or those with co-morbidities impairing future surgery, only visits yearly or when symptoms occur are recommended. All patients should have a colonoscopy before or within six months of initial surgery, repeated yearly if villous or tubular adenomas >1 cm are found; otherwise, repeat every three to five years.

**Methods**
Entries to MEDLINE (1966 through January (week 1) 2004), CANCERLIT (1983 through October 2002), EMBASE (1996 through week 52 2003), and the Cochrane Library (2003, Issue 3) databases and abstracts published in the 1997 to 2003 proceedings of the annual meeting of the American Society of Clinical Oncology were systematically searched for evidence relevant to this practice guideline report. In addition, the Physician Data Query clinical trials database on the Internet was searched for reports of new or ongoing trials. The reference lists from retrieved papers were searched for additional trials.

Evidence was selected and reviewed by one member of the Practice Guideline
Initiative’s Gastrointestinal Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Gastrointestinal Cancer Disease Site Group, which comprises medical oncologists, radiation oncologists, surgical oncologists, an anatomical pathologist, a gastroenterologist, a hematologist, and two patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence
- Of six randomized trials comparing one follow-up program to a more intense program, only two individual trials detected a statistically significant survival benefit favouring the more intense follow-up program. Pooling of all six randomized trials demonstrated a significant improvement in survival favouring more intense follow-up (relative risk ratio 0.80; 95% confidence interval, 0.70 to 0.91; p=0.0008). Although the rate of recurrence was similar in both of the follow-up groups compared, asymptomatic recurrences and re-operations for cure of recurrences were more common in patients with more intensive follow-up. Trials including blood carcinoembryonic antigen monitoring and liver imaging also had significant results, whereas trials not including these tests did not.

For further information about this practice guideline report, please contact Dr. Jean Maroun, Chair, Gastrointestinal Cancer Disease Site Group, Ottawa Regional Cancer Centre, General Division, 503 Smyth Road, Ottawa, Ontario, K1H 1C4; TEL (613) 737-7700, ext. 6708; FAX (613) 247-3511.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle. The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:


For the most current versions of the guideline reports and information about the PEBC, please visit the CCO Web site at:
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I. QUESTION

Does follow-up of patients after curative resection of colorectal cancer improve survival?

II. CHOICE OF TOPIC AND RATIONALE

Colorectal cancer is one of the most common malignancies, with an estimated age-adjusted annual incidence in North America of 75 cases per 100,000 population (1-3). About 75% of newly diagnosed cases have the tumour confined to a portion of the bowel and regional lymph nodes. Complete removal of the tumour en bloc with a portion of normal bowel along with mesenteric and regional lymph nodes is considered a curative resection. In spite of this curative resection, approximately half the patients develop recurrent disease, and their median survival does not exceed two years (1-4). Most of these recurrences occur in patients who at initial staging had a tumour invading across the bowel wall causing perforation of the bowel, adhesion, invasion of neighbouring organs (stage IIb disease), or lymph node metastases (stage III disease). Besides disease recurrence, patients with colorectal cancer are considered to be at a higher risk for developing a second or metachronous bowel cancer (5,6).

The principal aim of follow-up programs after curative resection of colorectal cancer is to improve survival. To achieve this goal, patients are screened for early recurrent disease and a second colorectal cancer, with the intent of a second curative surgery. Common sites of recurrence and the screening tests used to detect early disease in those sites are shown in Table 1. As no single screening test is best for all sites of recurrent disease and second colorectal cancer, a combination or package of tests is commonly used. The screening tests are directed to areas of potential disease and conducted at pre-established intervals. Since the incidence of recurrent disease occurs at an exponential rate over the first three to four years after surgery but then reaches a plateau (1-3), the screening tests for recurrent disease are conducted frequently during the first three years and infrequently afterwards. Screening tests for second colorectal cancer, on the other hand, must be done at equally spaced intervals for life because the incidence of second colorectal cancer occurs at a constant cumulative rate of 3% every six years (5,6).

Early screening programs, based on clinical assessment, blood counts, liver enzymes, fecal occult blood (FOB), some x-rays of the chest and abdomen, and rigid endoscopy, failed to uncover resectable disease. During the 1950s, with knowledge that relapses occurred most frequently in the abdomen and within three years of the initial surgery (4), Wangesteen et al developed the concept of a "second-look laparotomy". Asymptomatic patients at high risk for recurrence underwent a direct inspection of the abdominal cavity with resection of all apparent disease. This invasive approach was associated with high mortality and few curative resections (7).

The introduction of the carcinoembryonic antigen (CEA) as a screening test for colorectal cancer, as well as the development of improved imaging methods and surgical techniques, refocused the "second-look" approach to cases of early recurrences (8,9). This led to recommendations for intensive screening programs of follow-up (7-16). A 1994 survey of members of the American Society of Colon and Rectal Surgeons (10) showed that most patients are assessed every three months for three years and every six to twelve months thereafter. During those visits, patients have clinical assessment, blood tests including CEA, x-rays of the chest and abdomen, and colorectal endoscopy.

A debate has developed as to the effectiveness, expense1 and possible harm that may result from such

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1 A program of colorectal cancer follow-up similar to those described by Vernava et al (10), and using U.S. costs per test given by Nelson (17), would have an approximate five-year cost per patient of $10,000, half of this amount due to colonoscopy. This cost does not include surgical procedures ($8,000 per operation) for asymptomatic disease, most of which cannot be curatively resected. Several other investigators have also emphasized
intensive follow-up programs (11-14). The purpose of the present systematic overview is to critically evaluate the literature regarding the impact of colorectal cancer follow-up on patient survival and to develop appropriate recommendations.

### Table 1. Sites of recurrent disease and screening tests for colorectal cancer.

<table>
<thead>
<tr>
<th>Site of Recurrence</th>
<th>Percent of Patients with Recurrence at 5 Years by Site of Initial Tumour</th>
<th>Screening Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colon</td>
<td>Rectum</td>
</tr>
<tr>
<td>Liver</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Lung</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>15</td>
<td>5†</td>
</tr>
<tr>
<td>Peripheral Lymph Nodes</td>
<td>2</td>
<td>7†</td>
</tr>
<tr>
<td>Other (brain, bones)</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Loco-regional</td>
<td>15</td>
<td>35†</td>
</tr>
<tr>
<td>Second or metachronous colon cancer</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: ?, questionable test; CEA, carcinoembryonic antigen; CT, computerized tomography; FOB, fecal occult blood; RIS, radioimmunoscintigraphy; Sx, symptoms; US, ultrasound.

† Data modified from Galandiuk et al (4). The median time to recurrence is significantly shorter for stage C versus B and for lesions that originally had perforation or adhesion/invasion of surrounding structures (p<0.01).

Update

During the publication peer-review process, many changes were made in this section of the practice guideline (PG). Due to their no longer meeting the inclusion criteria, the non-randomized controlled trial data found in references 7-9, and 15 were removed. A listing of the removed citations may be found at the end of the References section.

Additional evidence supporting the statement from the original practice guideline that, "besides disease recurrence, patients with colorectal cancer are considered to be at a higher risk for developing a second or metachronous bowel cancer" was found (1u-4u). Two reports noted that this is even more important if patients are 60 years of age or younger (2u,3u).

In addition to the two reports included in the original practice guideline (10,17), two papers (5u,6u) were obtained that detailed the high economic cost of intensive follow-up programs.

### III. METHODS

**Guideline Development**

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care, using the methods of the Practice Guidelines Development Cycle (18). Evidence was selected and reviewed by three members of the PGI’s Gastrointestinal Cancer Disease Site Group (DSG) and methodologists. Members of the Gastrointestinal Cancer DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on follow-up of patients with curatively resected colorectal cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the
recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy
MEDLINE (1966 to September 2001), CANCERLIT (1983 to August 2001) and the Cochrane Library (2001, Issue 3) were searched with no language restrictions. “Colonic neoplasms” (Medical subject heading [MeSH]), “rectal neoplasms” (MeSH) and “colorectal neoplasms” (MeSH) were combined with “recurrence” (MeSH), “prognosis” (MeSH), “compliance” (MeSH), “survival analysis” (MeSH) and the following phrases used as text words: “follow-up” and “surveillance”. These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, systematic reviews or meta-analyses, randomized controlled trials, cohort studies, and retrospective studies. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://nci.nih.gov/search/clinical_trials/) and the conference proceedings of the 1997 to 2001 annual meetings of the American Society of Clinical Oncology (ASCO) were searched for reports of new or ongoing trials. The reference lists from retrieved papers were searched for additional trials.

Update
The literature search was updated in January 2004 using the MEDLINE (1966 to January (week 1) 2004), EMBASE (1996 to week 52 2003), and Cochrane Library (2003, issue 3) databases, and the 2003 ASCO proceedings. The PDQ clinical trials database was also searched for relevant trials.

Inclusion Criteria
Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of:
1. Randomized or non-randomized studies and systematic reviews comparing groups of patients receiving different follow-up programs after curative resection of colorectal cancer, and overall patient survival was reported.
2. Cohort studies that investigated compliance with follow-up programs after curative resection of colorectal cancer, and overall patient survival was reported.

Update
The inclusion criteria for updates to this practice guideline have been revised to:
1. Randomized trials comparing groups of patients receiving different follow-up programs after curative resection of colorectal cancer, and reporting overall patient survival.
2. Meta-analyses of these randomized trials.

Although survival was the main outcome of interest, results of trials were also searched for recurrence rates, time to recurrence, asymptomatic recurrences, re-operation rates for recurrences, complications, and compliance with follow-up programs.

While not considered for inclusion in any analysis where randomized trials were available, some cohort studies were retained for discussion.

Synthesizing the Evidence
Due to the multiple factors that can affect survival results (e.g., variety and frequency of screening tests, compliance with tests and interventions, co-morbidity), both clinical and statistical heterogeneity among study results was expected. Prior to the estimation of risk reduction, each study was appraised individually, the mortality rates for both groups were assessed for heterogeneity using scatter plots (19), and visual impressions were confirmed by calculating heterogeneity coefficients with significance levels set at 0.10 as recommended in the statistical literature (19,20). Mortality rates were pooled using Review Manager 4.1 (Metaview© Update Software), which is available through the Cochrane Collaboration. The numbers used for data pooling were those reported or those calculated from tables or survival curves in published reports of study results. Results were reported as mortality Odds Ratios (OR) with 95% confidence intervals (CI) obtained by the random effects model of DerSimonian and Laird (21). An OR less than one favours the more intense follow-up and an OR greater than one favours less intense follow-up.
It was planned, a priori, to conduct a subgroup analysis to examine the pooled results of all studies by intensity of follow-up programs compared and by inclusion of blood CEA testing. This decision was based on the proposed hypothesis that increasing the frequency of assessments and the number of tests would result in earlier diagnosis of recurrences and lead potentially to improved patient survival (15). Blood CEA testing was considered important in previous studies (8,9,15,22). To conduct the analyses by intensity of follow-up, the studies were divided into two subgroups: those that compared regular follow-up (i.e., assessments at least once a year) versus minimal follow-up, and those that compared intensive follow-up (i.e., regular follow-up added with more frequent assessments and/or other tests) versus regular follow-up. As the direction of expected effect in these subgroup analyses were stated a priori, the p-values provided are one-sided only.

Mortality rates from the randomized trials were pooled, and the results were used to develop recommendations for follow-up after curatively resected colorectal cancer. Mortality rates from the non-randomized studies were combined in a separate analysis because it was considered inappropriate to combine results of randomized and non-randomized studies. In addition, results of cohort studies of compliance were pooled separately to examine the impact of patient compliance with follow-up on their survival.

Update
Only published data from randomized trials, or from meta-analyses of randomized trials, have been used in any analyses for this update. A quality analysis of the eligible trials, not performed in the original PG, was undertaken individually by two authors (AF, BR), using the methodology described in Detsky et al (7u), and is reported in the Update section. Summary statistics, expressed as OR in the approved PG, are reported as Relative Risk Ratios (RR) with 95% CI for all meta-analyses in both the published and updated version. An RR less than one favours the more intense follow-up and an RR more than one favours less intense follow-up. Survival rates from the randomized trials were pooled, and the results were used to develop recommendations for follow-up programs.

IV. RESULTS

Literature Search Results
The literature search identified two published meta-analyses (22,23), one position paper and one guideline that included a systematic literature review (24,25), six randomized trials (26-31), eight non-randomized comparative cohort studies (32-39), and three cohort studies of compliance with follow-up (40-42). The randomized trials and non-randomized comparative cohort studies included in this practice guideline were classified according to the trial design, the intensity of follow-up programs compared, and use of blood CEA testing (Table 2). The literature search identified studies that compared regular follow-up versus minimal follow-up (26,28,30), and those that compared intensive follow-up versus regular follow-up (27,29,31).

Update
Twelve additional papers were obtained during updating (8u-19u). The updated literature search, using the updated inclusion criteria, identified two published meta-analyses of randomized trials (8u,9u), and two additional randomized trials (11u,12u). The trial by Barillari et al (12u) combined results of randomized with non-randomized patients, and was excluded from the analysis.

A quality of life study (10u), a report providing additional evidence that computed tomography (CT) is more sensitive than ultrasound (US) in detecting liver metastases (13u), a study showing the benefit of adding CEA testing to CT and US in detecting liver metastases (14u), a report detailing the incidence of lung metastases after resection (15u), a paper detailing subsequent surgery for colon cancer recurrence (16u), and a paper detailing the possible complications from colonoscopy were obtained (17u).

An update (18u) of the Gruppo Italiano di Lavoro per la Diagnosi Anticipata (GILDA) trial, included in the Ongoing Trials section of the original practice guideline report (47) was obtained. An update of the Polyp Surveillance Study performed in the United States, and discussed in the original guideline (48), was obtained (19u).
Table 2. Classification of randomized trials of colorectal cancer follow-up

<table>
<thead>
<tr>
<th>Trials [Reference]</th>
<th>Follow-up programs compared</th>
<th>CEA testing used</th>
<th>Liver Imaging testing used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makela [27]</td>
<td>Intense vs. Conventional</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ohlsson [26]</td>
<td>Intense vs. Minimal</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Kjeldsen [30]</td>
<td>Intense vs. Minimal</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Schoemaker [28]</td>
<td>Intense vs. Minimal</td>
<td>No*</td>
<td>Yes</td>
</tr>
<tr>
<td>Pietra [31]</td>
<td>Intense vs. Conventional</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Secco [11u]</td>
<td>Intense vs. Minimal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Isolated increase in CEA levels did not trigger further investigations.

Update

Quality of trial reporting

While a formal quality analysis of included trials was not done for the original practice guideline, one was performed for this update. The Detsky instrument (7u), which assesses five quality domains (randomization, outcome measures, patient eligibility, treatments, and statistics) and provides a score between one (adequate) and zero (inadequate), was used for evaluation. Partial marks (0.5) were given for partial adequate criteria. Study quality evaluation detected significant deficits in the reporting of trial design and performance. Although all trials randomized patients after surgery, the description of the randomization process and stratification for prognostic factors was rarely mentioned (28). It was impossible to assess bias in assignment except for the trial by Schoemaker et al (28). Criteria for patient inclusion and exclusion were described but co-morbidity was not mentioned. Criteria to measure outcomes were described and seemed objective, but blind assessment was mentioned in only the trial by Schoemaker et al (28); radiologists unaware of follow-up assignment. Except for the Schoemaker et al study (28), it is not known how many patients were excluded from randomization due to refusal, co-morbidity, or other factors. The follow-up regimens were well described. The statistical analysis was appropriate. Sample size justification and confidence intervals for negative trials were mentioned in only two trials (28,30). Overall Detsky scores ranged from 0.57 to 0.86, median 0.67.

Compliance with the programs of follow-up were described in three trials (26,28,8u). The description was about drop-outs in all three and compliance with testing in two (26,28). Most patients were followed for five years except in one study that reported only 52% of patients doing so (30) and another that reported only median follow-up time (8u).

In all randomized trials, the study population was patients who underwent curative resection for colorectal cancer. There were 1679 patients, with a male to female ratio of 1.17, a median age in the mid-sixties, and an age range of 30 to 87 years; one trial had a cut-off age of 76. Tumours involved the colon (n=837) and rectum (n=505). All trials included patients with Dukes’ or modified Dukes’ stages A, B, and C. Patients with stage Dukes’ C comprised only 33% of the populations studied. Only one trial had a risk-adapted follow-up for patients at higher and lower risk of recurrence (11u). Patient characteristics were reported in tabular form and appeared comparable. Formal statistical tests were rarely performed.

Outcomes

Meta-analyses

A meta-analysis was reported by Bruinvels et al in 1994 (22). Pooling of four non-randomized studies which reported the actual number of deaths (32,33,36,40) detected a non-significant 12.4% (95% CI, -5.4% to 30.1%; p-value not reported) absolute difference in five-year survival favouring intensive follow-up compared with minimal or no follow-up. There was evidence of heterogeneity (p-value not reported). Three non-randomized studies involved blood CEA monitoring in an intensive follow-up program (34,36,40). Pooling of these three studies detected a significant 9.1% (95% CI, 2.2% to 16.0%; p-value not reported) survival benefit for intensive follow-up with blood CEA monitoring compared with minimal or no follow-up, and there was no
evidence of heterogeneity (p-value not reported). After discussing the multiple potential biases affecting non-randomized studies, Bruinvels et al concluded that no definite answers could be obtained but that the available data suggested that follow-up programs should include CEA testing.

In 1998, Rosen et al (23) published a meta-analysis that included two randomized trials (26,27) and three non-randomized comparative cohort studies (36-38) of intensive follow-up compared with traditional follow-up. Intensive follow-up involved history, physical examination, and CEA testing at least three times a year for at least two years. Traditional follow-up was defined as no routine follow-up and physician response to changes in symptoms only. Pooling of these five studies detected a significant survival benefit (RR, 1.15; 95% CI, 1.12 to 1.75; p=0.003) favouring intensive follow-up compared with traditional follow-up. This improvement in survival was correlated with a higher rate of curative resection of recurrences (p=0.00001) and a higher survival rate after recurrence (p=0.00004). Tests for heterogeneity were not reported. The non-randomized comparative cohort studies were combined with the randomized trials in the pooled analysis because of the paucity of randomized trials.

**Update**

Updating procedures obtained two published meta-analyses of randomized trials (8u,9u). Both meta-analyses are of excellent methodological quality with a clear description of bibliographical search, inclusion/exclusion criteria, standardized collection of data, consideration of the quality of trial reporting, concerns with the possibility of biases in publication and reporting, and high level statistical management of the data. In both meta-analyses, further details not reported in the published trials were obtained by contacting investigators involved with the trials; however, which data were acquired in this manner is not reported.

Both meta-analyses examined the same five randomized trials (26-28,30,31). The meta-analysis by Renehan et al (8u) found a significant improvement in overall survival, with a larger effect in four trials using abdominal CT scans and frequent CEA determinations. In attempting to explain the survival benefits, the authors note the similar recurrence rates regardless of follow-up plan but the earlier diagnosis (by 8.5 months; 95% CI, 7.6 to 9.4) and the more frequent finding of isolated local recurrences with the more intense follow-up. The meta-analysis by Jeffery et al (9u) had similar findings: improved survival, no difference in recurrence rates, earlier diagnosis of recurrences, and more frequent curative resection on patients undergoing more intense follow-up. Further, these findings occurred because of performing more tests, especially liver imaging. These latter results, when expressed as risk differences, were not significant. Both studies noted the low rate of metachronous cancer, which was not different for the compared follow-up programs. Also noted in these overviews are the paucity of data on complications and quality of life: only the colonoscopy complication rate by Schoemaker et al (28) and the limited quality of life study by Kjeldsen et al (10u). The conclusions of these meta-analyses are that intensifying programs of follow-up improves survival but there is no data to recommend tests or frequency of visits.

**Position Paper**

In 1997, the Canadian Society of Surgical Oncology and the Canadian Society of Colon and Rectal Surgeons published a position paper (24) on the follow-up of patients after resection of colorectal cancer. Three randomized trials (26,27,30), three non-randomized comparative cohort studies (32,33,36), and two cohort studies of compliance (40,41) were appraised using the Canadian Task Force on the Periodic Health Examination methodology. Following the assessment of the studies, the authors concluded that there was insufficient evidence to make a recommendation on the benefit of postoperative surveillance in colorectal cancer patients and that further randomized trials were needed to clarify the role of postoperative follow-up.

**Guideline**

ASCO recently published evidence-based guidelines for the postoperative surveillance of colorectal cancer (25). An expert panel conducted a qualitative review of the evidence, including three randomized trials (26-28), and developed recommendations for follow-up. These included clinical assessments every three to six months for the first three years and annually thereafter, adding CEA testing every two to three months for more than two years if resection of liver metastases was contemplated, and colonoscopy perioperatively and every three to five years.
**Randomized Trials**

Our literature search uncovered six randomized trials (26-31) comparing the survival of patients who received different follow-up programs (Table 3). For three randomized trials (26,28,30), regular follow-up (intervention) was compared with minimal follow-up (control); of these, one trial (26) included CEA testing. For the other three randomized trials (27,29,31), intensive follow-up (intervention) was compared with regular follow-up (control); all of these trials included CEA testing.

In all randomized trials, the study population was patients who underwent curative resection for colorectal cancer. Data on age, sex, tumour stage, and tumour site were provided for all randomized trials except for the trial by Lennon et al (29). Authors of two trials (28,31) reported that baseline characteristics were similar between the two follow-up programs, although p-values were not reported. Ohlsson et al (26) reported that patient compliance with follow-up was 98% in the regular follow-up group, whereas 19% of patients in the minimal follow-up group did not return after randomization. In the trial by Schoemaker et al (28), 10 (6%) patients in the regular follow-up group and eight (5%) patients in the minimal follow-up (control) group withdrew or were lost to follow-up after randomization. Data on patient compliance and the number of patients lost to follow-up were not reported for the other randomized trials. Authors of two trials reported sample size calculations (28,30). In the trial by Schoemaker (28), a minimum of 312 patients were required with at least 85 deaths observed to detect an improvement in survival of 15% (power 90%, p<0.05, one-tail log rank test). Six hundred patients were required in the trials by Kjeldsen (30) to be able to detect a 20% improvement in survival (power 80%, p<0.05).

Results of the randomized trials are presented in Table 4. Recurrence rates were similar in both groups for the four randomized trials that reported this outcome (26,27,30,31). Three of these trials found that recurrences were diagnosed significantly earlier for patients in the more intense follow-up group. Makela et al (27) found that the mean time to recurrence was ten months for the intense follow-up group compared with 15 months for patients who received the standard follow-up program (p=0.002), although the rate of radical resection of recurrences was similar in both groups. Kjeldsen et al (30) reported that relapses occurred nine months earlier and curative resections were more common (22% versus 7%, p=0.15) in the most frequently screened group. Similarly, Pietra et al (31) found that local recurrences were diagnosed earlier (10.3 versus 20.2 months, p<0.0003) and more patients were asymptomatic and completely resected in the group screened more intensely.

Results of the survival analysis of the six randomized trials favoured more intensive follow-up, but only one trial (31) detected a statistically significant survival benefit (p<0.02). Of note, results were preliminary in the trial by Northover et al (29), who planned to screen 1500 patients for elevated level of blood CEA and, once a consistent elevation was demonstrated, randomize these patients to disclosure or no disclosure of the elevated CEA to the clinicians. Patients with disclosed elevation of CEA were also to be investigated aggressively for recurrent disease, including a second-look laparotomy. Among 1447 screened patients, 216 with elevated CEA level were evenly randomized to an aggressive or a conventional approach, and there was no difference in survival between the groups (RR, 1.16; 95% CI, 0.87 to 1.38; p=0.25) (29). The trial was stopped early because it was highly unlikely that any survival advantage would be demonstrated for patients undergoing second-look surgery (43).

Pooled results of all randomized trials revealed no statistically significant heterogeneity (X^2=4.89; p=0.10) and a significant decrease in mortality favouring the more intensive programs of follow-up (OR, 0.76; 95% CI, 0.62 to 0.95; p=0.015) (Figure 1). Subgroup analysis was undertaken to determine whether type of follow-up or use of CEA testing had an impact on survival. Thus, the pooled results of three trials comparing regular follow-up (assessments at least once a year) with minimal follow-up (26,28,30) were analyzed separately from three trials comparing intensive versus regular follow-up (27,29,31). The OR for the regular versus minimal follow-up group was 0.78 (one-sided p=0.031). The OR for the intensive versus regular follow-up group was 0.75 (one-sided p=0.115). Although the ORs favoured improved survival for the more intensive follow-up groups in both comparisons, the results were statistically significant only for the comparison of regular versus minimal follow-up. The OR for the pooled results of the four trials using CEA monitoring (26,27,29,31) was 0.71 (one-sided p=0.032). The pooled results of the four tests using CEA monitoring detected no heterogeneity (X^2=3.36; p=0.10). The OR of pooled results of two trials not using CEA monitoring was 0.80 (one-sided p=0.08), demonstrating no impact on survival. It must be noted that those comparisons that detected statistical significance using a one-sided test would not have detected significance had a two-sided test been used, as
the CI included 1.0 indicating no difference between the two groups. One-sided tests were used in these comparisons since the expected direction of effect was stated a priori.

**Update**

**Randomized Trials**
The six randomized trials (26-28,30,31,11u) reported the survival of patients who received different follow-up programs following curative surgery. Four trials compared intensive follow-up (intervention) to minimal follow-up (control) [and two trials compared intensive follow-up (intervention) to conventional follow-up (control)] (Table 2). Blood CEA testing was used in the management of patients in four trials (26,27,31,11u), and liver imaging was used in four trials (27,28,31,11u) (Table 2). The trial by Barillari et al (12u) combined results of randomized with non-randomized patients and was excluded from the analysis.

The follow-up programs for each of the trials are shown in Table 3. Results of individual trials are presented in Table 4.

Overall survival is significantly improved for patients in the more intensive programs of follow-up. This improvement amounts to a risk difference of 7% (95% CI, 3% to 12%; p=0.002) in five year survival. The number of all recurrences was similar in programs of more and less intense follow-up. The incidence of asymptomatic recurrences was, however, significantly more common in patients undergoing more intense follow-up. The latter may explain the more common re-operation for cure of recurrences in the group of patients undergoing the more intense follow-up.

Overall survival was also investigated for the group of trials according to the use of CEA and liver imaging screening. Trials using blood CEA screening demonstrate a significant impact on survival whereas those not using CEA do not (Figure 2). A similar finding is that whereas trials using liver imaging show a significant improvement in survival, trials not using liver imaging do not (Figure 3).

Pooled results of all randomized trials revealed no statistically significant heterogeneity ($X^2=3.95; p>0.10$).

**Table 3. Description of randomized trials of follow-up of colorectal cancer after resection.**

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Location (Years)</th>
<th>Control [Minimal (n=54)]:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohlsson (26)</td>
<td>Sweden (1983-86)</td>
<td>FOB every 3 months for 2 years, then yearly, and to consult for a list of symptoms.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention [Regular (n=53)]: Clinical assessments, blood CEA and liver enzyme, chest x-ray, FOB, and rigid sigmoidoscopy every 3 months for 2 years, then every 6 months; endoscopy control of anastomosis by flexible endoscopy at 9, 21, and 42 months; complete colonoscopy at 3, 15, 30, and 60 months; CT of pelvis (if they had abdominoperineal resection) at 3, 6, 12, 18, and 24 months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Location (Years)</th>
<th>Control [Regular (n=54)]:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makela (27)</td>
<td>Finland (1988-90)</td>
<td>Clinical assessment, blood counts and CEA, chest x-ray, and fecal occult blood (FOB) every 3 months for 2 years, then every 6 months for next 3 years; rigid sigmoidoscopy for rectosigmoid tumours at each visit; and yearly barium enema for all patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention [Intensive (n=52)]: Clinical assessment, blood counts and CEA, chest x-ray, and FOB as in regular follow-up program. In addition, colonoscopy at 3 months if not performed preoperatively and then yearly thereafter on all patients, flexible sigmoidoscopy for rectosigmoid tumors every 3 months, liver ultrasound every 6 months, and yearly CT of liver and site of operation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Location (Years)</th>
<th>Control [Minimal (n=158)]:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoemaker (28)</td>
<td>Australia (1984-90)</td>
<td>Clinical assessment, blood counts, CEA, liver function tests, and FOB every 3 months for 2 years, then every 6 months for 5 years; chest x-rays, liver CT scan, and colonoscopy at 5 years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention [Regular (n=167)]: Clinical assessment, blood counts, CEA, liver function tests, and FOB as in regular follow-up program. In addition, chest x-rays, liver CT scan, and colonoscopy annually. Isolated increase in CEA levels did not trigger further investigations.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Location (Years)</th>
<th>Control [Minimal (n=307)]:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kjeldsen (30)</td>
<td>Denmark (1985-94)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical assessment, blood hemoglobin, sedimentation rate and liver enzymes, chest x-ray, FOB, and colonoscopy (if incomplete, double contrast barium enema) at 5, 10, and 15 years.

**Intervention** [Regular (n=290)]:
Same tests as minimal follow-up program, but tests were conducted every 6 months for 3 years, and then at 4, 5, 7.5, 10, 12.5, and 15 years.

**Study (Reference):** Pietra (31)  
**Location (Years):** Italy (1987-90)

**Control** [Regular (n=103)]
Clinical assessment, CEA, and liver ultrasound every 6 months for one year, then yearly; chest x-ray and colonoscopy yearly.

**Intervention** [Intensive (n=104)]
Clinical assessment, CEA, and liver ultrasound as regular follow-up program but tests conducted every 3 months for 2 years, then every 6 months for 3 years, and yearly thereafter. In addition, chest x-ray, abdominal CT, and colonoscopy yearly.

**Study (Reference):** Secco (11u)  
**Location (Years):** Italy (1988-96)

**Control** [Minimal (n=145)]
Patients to phone the surgical team every 6 months. Clinical assessment by family physician at least once a year or when suggestive symptoms of recurrence occurred.

**Intervention** [Intensive (n=192)]
High Risk Patients: Clinical assessment and CEA every 3 months for 2 years, every 4 months in the third year, and every 6 months in years 4 and 5. Abdominal and pelvic ultrasound performed every 6 months the first 3 years and yearly in years 4 and 5. Rigid rectosigmoidoscopy and chest x-ray yearly for patients with rectal cancer.

Low Risk Patients: Clinical assessment and CEA every 6 months for 2 years, then yearly; abdominal and pelvic ultrasound every 6 months for 2 years, then once a year. Rigid recto-sigmoidoscopy for rectal cancer yearly twice, then every 2 years and chest x-ray yearly.

Note: CEA, carcinoembryonic antigen; FOB, fecal occult blood; CT, computerized tomography.

### Table 4. Results of randomized trials of follow-up after resection of colorectal cancer.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Follow-up Program intensity</th>
<th>Number of Patients Randomized</th>
<th>Median Observation (months)</th>
<th>Overall Recurrence Rate (%)</th>
<th>Number of Second Bowel Cancers</th>
<th>Radical Reoperation Rate (%)</th>
<th>5-year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohlsson 1995 (26)</td>
<td>Less</td>
<td>54</td>
<td>82</td>
<td>33</td>
<td>NR</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>More</td>
<td>53</td>
<td></td>
<td>32</td>
<td></td>
<td>29</td>
<td>75</td>
</tr>
<tr>
<td>Makela 1995 (27)</td>
<td>Less</td>
<td>54</td>
<td>&gt;60</td>
<td>39</td>
<td>NR</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>More</td>
<td>52</td>
<td></td>
<td>42</td>
<td></td>
<td>23</td>
<td>59</td>
</tr>
<tr>
<td>Schoemaker 1998 (28)</td>
<td>Less</td>
<td>158</td>
<td>&gt;60</td>
<td>NR</td>
<td>5</td>
<td>NR</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>More</td>
<td>167</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>76</td>
</tr>
<tr>
<td>Kjeldsen 1997 (30)</td>
<td>Less</td>
<td>307</td>
<td>&gt;60</td>
<td>26</td>
<td>3</td>
<td>NR</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>More</td>
<td>290</td>
<td></td>
<td>26</td>
<td>7</td>
<td>NR</td>
<td>70</td>
</tr>
<tr>
<td>Pietra 1998 (31)</td>
<td>Less</td>
<td>103</td>
<td>&gt;60</td>
<td>19</td>
<td>1</td>
<td>10</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>More</td>
<td>104</td>
<td></td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>73†</td>
</tr>
<tr>
<td>Secco 2002 (11u)</td>
<td>Less</td>
<td>145</td>
<td>&gt;60</td>
<td>53</td>
<td>NR</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>More</td>
<td>192</td>
<td></td>
<td>57</td>
<td></td>
<td>16</td>
<td>63</td>
</tr>
</tbody>
</table>

Note: NR, not reported.  
* p<0.01  
† p<0.05
Figure 1. Pooled results of randomized trials: overall mortality at five years.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehta [36]</td>
<td>21/52</td>
<td>25/54</td>
<td></td>
<td>9.28</td>
<td>0.83 [0.66, 1.05]</td>
<td>1996</td>
</tr>
<tr>
<td>Ormiston [37]</td>
<td>10/53</td>
<td>10/54</td>
<td></td>
<td>4.04</td>
<td>0.74 [0.40, 1.35]</td>
<td>1995</td>
</tr>
<tr>
<td>Karlsen [38]</td>
<td>87/250</td>
<td>98/250</td>
<td></td>
<td>30.70</td>
<td>0.94 [0.74, 1.23]</td>
<td>1997</td>
</tr>
<tr>
<td>Schoemakers [39]</td>
<td>40/147</td>
<td>47/158</td>
<td></td>
<td>13.55</td>
<td>0.81 [0.66, 1.01]</td>
<td>1998</td>
</tr>
<tr>
<td>Peeters [40]</td>
<td>28/104</td>
<td>43/103</td>
<td></td>
<td>11.61</td>
<td>0.84 [0.44, 0.85]</td>
<td>1998</td>
</tr>
<tr>
<td>Seco [11a]</td>
<td>71/192</td>
<td>75/193</td>
<td></td>
<td>30.06</td>
<td>0.71 [0.56, 0.89]</td>
<td>2002</td>
</tr>
<tr>
<td>Total (85% CI)</td>
<td>866</td>
<td>621</td>
<td></td>
<td>100.00</td>
<td>0.80 [0.70, 0.91]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 201 (Treatment), 300 (Control)
Test for heterogeneity: Chi² = 3.35, df = 5 (p = 0.50), p = 0.9%
Test for overall effect: Z = 3.36 (p = 0.0008)

Overall relative risk ratio = 0.80 (95% CI, 0.70 to 0.91; p=0.0008)

Figure 2. Pooled results of randomized trials: overall survival sub-group analysis. [No CEA testing; CEA testing]

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL no CEA testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holdean [38]</td>
<td>97/250</td>
<td>99/257</td>
<td></td>
<td>23.37</td>
<td>0.94 [0.74, 1.19]</td>
<td>1997</td>
</tr>
<tr>
<td>Schoemakers [39]</td>
<td>40/167</td>
<td>47/180</td>
<td></td>
<td>10.63</td>
<td>0.81 [0.66, 1.16]</td>
<td>1998</td>
</tr>
<tr>
<td>Suntra (95% CI)</td>
<td>457</td>
<td>465</td>
<td></td>
<td>100.00</td>
<td>0.80 [0.73, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Total events: 127 (Treatment), 145 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Test for heterogeneity: Chi² = 0.49, df = 1 (p = 0.48), p = 0.0%
Test for overall effect: Z = 1.00 (p = 0.28)

DL CEA testing

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehta [36]</td>
<td>21/50</td>
<td>25/54</td>
<td></td>
<td>16.08</td>
<td>0.78 [0.59, 1.02]</td>
<td>1995</td>
</tr>
<tr>
<td>Ormiston [37]</td>
<td>10/50</td>
<td>10/54</td>
<td></td>
<td>0.74</td>
<td>0.74 [0.40, 1.05]</td>
<td>1995</td>
</tr>
<tr>
<td>Peeters [40]</td>
<td>28/104</td>
<td>43/109</td>
<td></td>
<td>20.96</td>
<td>0.82 [0.46, 0.95]</td>
<td>1998</td>
</tr>
<tr>
<td>Seco [11a]</td>
<td>71/192</td>
<td>75/193</td>
<td></td>
<td>84.27</td>
<td>0.71 [0.56, 0.88]</td>
<td>2002</td>
</tr>
<tr>
<td>Total events: 133 (Treatment), 151 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Test for heterogeneity: Chi² = 0.43, df = 3 (p = 0.93), p = 0.0%
Test for overall effect: Z = 5.73 (p = 0.0002)

Overall relative risk ratio, no CEA testing = 0.90 (95% CI, 0.73 to 1.09; p=0.28)
Overall relative risk ratio, CEA testing = 0.71 (95% CI, 0.60 to 0.85; p=0.0002)
**Non-randomized Comparative Cohort Studies**

Eight non-randomized comparative cohort studies compared the results of prospectively assessed patients on programs of follow-up with the results of patients from the same institutions who did not receive follow-up (32-39). Four studies compared regular follow-up (intervention) with minimal follow-up (control) (32,35,36,38) and three studies compared intensive follow-up (intervention) with regular follow-up (control) (33,34,37,39). The control group for these studies was either a concurrent (36,38) or a historic (32-35,37,39) cohort of patients. Only one study (37) reported a significant survival benefit for the group of patients who received more intense follow-up compared with a historic control (63% versus 45% at five years; p<0.05; personal communication).

Pooled results from these eight studies (Figure 2) revealed significant heterogeneity ($X^2 = 18.23; p=0.011$). When the studies were separated according to the type of control patients, those studies with concurrent controls (36,38) demonstrated no significant heterogeneity and a significant reduction in mortality (OR, 0.71; 95% CI, 0.57 to 0.90; p=0.0048) favouring more intense follow-up compared with less intense follow-up. Pooling of studies with historic controls revealed significant heterogeneity of results.

**Single Cohort Studies of Compliance with Follow-up**

Three single cohort studies investigated retrospectively whether compliance with follow-up affected outcomes (40-42). Two of the studies (41,42) found improved survival for compliant versus non-compliant patients. Pooled results of the three studies demonstrated a significant decrease in mortality for the compliant patients (OR, 0.51; 95% CI, 0.29 to 0.91; p=0.024) but there was significant heterogeneity among the pooled results ($X^2 = 5.09; p<0.10$).

**V. INTERPRETIVE SUMMARY**

We must start by acknowledging that results of individual studies generally showed no statistically significant benefit for organized programs of follow-up of patients with curatively resected colorectal cancer. However, some of these studies (26,27) lacked the power to detect statistically significant differences in survival associated with two follow-up programs of different intensities. Meta-analysis, by pooling the results of under-powered studies, may detect small but clinically significant differences. Indeed, meta-analyses by Bruinvels et al (22) and Rosen et al (23) had shown significant improvements in survival for patients on more intense follow-up. The results obtained in our pooled results of the six randomized trials comparing two intensities of follow-up also demonstrated that patients on more intensive programs of follow-up have decreased mortality compared with patients on minimal or no follow-up (mortality OR, 0.76; 95% CI, 0.62 to 0.95; p=0.0015).

The finding of decreased mortality with more intensive follow-up does not permit us to recommend a
specific program of follow-up. To be more specific, the studies were divided into two sub-groups, those of regular follow-up compared with minimal follow-up and those of regular follow-up compared with more intensive follow-up. Pooled results within the sub-groups of randomized trials comparing regular versus minimal follow-up as well as those comparing the more intense follow-up versus regular follow-up showed a trend towards decreased mortality in the more intense follow-up, but the results did not achieve statistical significance. Therefore, no definite conclusions can be drawn other than that more tests and assessments are more likely to improve survival. These conclusions are consistent with the original hypothesis of intensive follow-up for the early discovery and treatment of recurrences.

Another question posed by our systematic review was the role of CEA monitoring. Our results are inconclusive but again show a non-significant trend towards improved survival if CEA is performed regularly. The meta-analysis by Bruinvels et al (22) suggested that CEA was an important follow-up test: However, this conclusion was based on the pooling of two non-randomized comparative cohort studies and one cohort study of compliance. On the other hand, Northover et al (29) performed a randomized trial to investigate the effect of CEA monitoring, and an aggressive approach to diagnosis of recurrence, on patient survival. The investigators hypothesized that earlier diagnosis of asymptomatic recurrence would lead to more radical surgery and improved survival. The preliminary results indicate that screening for CEA elevation alone is not a crucial test that would lead to improved survival. Furthermore, it was noted that more than 60% of patients with elevated CEA had symptoms suggestive of disease. How do we interpret these contradictory findings? First, there might be limitations in the findings of the trial by Northover et al. There was no control for other tests which may render the CEA screening ineffective. The criteria for CEA elevation required two values over 20 ng/ml or two values over 10 ng/ml but with a rise of greater than seven units. This conservative estimate of elevated CEA will decrease the diagnostic sensitivity of the test and may delay the diagnosis by two or three months, which may have an impact on patient survival. This trial required an “aggressive” pursuit of the diagnosis of recurrent disease that might include a second-look laparotomy. This “aggressive” approach may cause some harm, reducing the benefit of CEA monitoring. It is also of interest that this trial did not demonstrate an earlier diagnosis of recurrences with CEA, in contrast to several cohort studies (11-13,23,44) in which resectable recurrences were mostly discovered by CEA testing or other monitoring rather than by clinical assessment. A more likely explanation of the CEA effect is that it represents the effect of confounding factors. The earliest studies in the present series were from the early 1970s. Since that time, there have been gradual improvements in imaging and endoscopic testing as well as in surgical approaches and safety. These factors, rather than CEA testing, may have had an impact on survival results.

The question of patient compliance with programs of follow-up was investigated retrospectively in three cohort studies (40-42). The data suggest that compliance may have a significant effect on the efficacy of follow-up programs. It is known that compliant patients, on average, have a better prognosis than non-compliant patients for a variety of different interventions, and therefore, the difference may not be related to the interventions tested. Clearly, a subgroup analysis investigating the effect of compliance would have to be tested in randomized trials to confirm the potential effect.

In regard to the incidence of second bowel cancer, no definite comments can be made based on the evidence reviewed. Most studies had median observation periods around five years and some even less. Therefore, the expected number of metachronous cancers in these series is very small. In fact, only three randomized trials reported on the incidence of such tumors.

The improvement in survival for patients with resected colorectal cancer participating in programs of follow-up is achieved at the cost of frequent visits, more extensive testing, earlier knowledge of disease recurrence, and increased number of further testing and surgical interventions. This situation obviously raises questions about the harmful consequences of such extra testing and intervention. Harms have not been specifically measured in the randomized trials. Neither has there been a study of quality of life. A recent pilot study investigated the quality of life and the attitudes of patients with resected colorectal cancer towards follow-up (45). Results indicate that regular contact with a physician reassured patients and that visits and tests caused only slight anticipatory anxiety and other minor inconveniences. These preliminary findings are similar to those of one of the randomized trials in resected breast cancer where there was no impact of follow-up on the patients’ quality of life, even though they knew that the follow-up program had not improved their survival (16).

Research on screening procedures and interventions for recurrent disease and second colorectal
cancer should continue. These investigations will require support from sources other than those dedicated to patient care (14,17,46). Patients should be made aware of the importance of these research trials, and should be encouraged to participate in them. These clinical studies should be randomized to prevent biases and should be directed to homogeneous groups of patients stratified according to risks. Patients should be randomized to specific screening procedures (i.e., abdominal ultrasound or CT, immunoscintigraphy), and trials should measure quality of life and survival. Sufficiently long observation periods will be important to achieve reliable differential rates of risk, and sufficiently large sample sizes are necessary to obtain conclusive results. In planning such trials, a cost-benefit analysis must be performed to assess the economic costs of potential improvements in survival and quality of life (16). Results of these trials, and longer observation of patients in the studies reviewed, may change the present recommendation.

**Update**

Meta-analyses by Renihan et al (8u) and Jeffery et al (9u) have shown significant improvements in survival for patients on more intense follow-up. The results obtained in our pooled analysis of the six randomized trials comparing two intensities of follow-up also demonstrated that patients on more intensive programs of follow-up have improved survival compared with patients on minimal or no follow-up (RR 0.80; 95% CI, 0.70 to 0.91; p=0.0008).

The finding of improved survival with more intensive follow-up does not permit us to recommend a specific program of follow-up. In examining the role of CEA monitoring and use of liver imaging, our results demonstrate that only trials including CEA testing and/or liver imaging give significant improvements in survival (Figure 2 and 3). It must be stressed that all studies including liver imaging also used blood CEA monitoring.

In regard to liver imaging, three studies included in the original practice guideline (27,28,31) used computerized tomography (CT), while a study obtained during updating used ultrasonography (US) (11u). Computerized tomography was shown to be more sensitive than US in detecting liver metastases in both the original practice guideline (46) and this update (13u). In a cohort study of 100 patients with resected colorectal cancer (mostly Dukes' stage C) who had normal livers as determined by CT, US, and intra-operative palpation of the liver (14u), several imaging tests and CEA were performed after a median follow-up of 41 months (range 36 to 48). Sensitivity for the detection of liver metastases was: for CT 0.67 (95% CI, 0.43 to 0.91), for US 0.43 (95% CI, 0.17 to 0.69), and for CEA 0.33 (95% CI, 0.09 to 0.57). The addition of CEA to CT and US increased the sensitivity up to 0.73 and 0.53, respectively. This study did not address the question of whether the detection of resectable liver lesions was better by any of the screening methods.

Imaging of the chest by plain radiographs has been included in all intensive follow-up programs. Lung metastases occur in 25% of patients with resected colorectal cancer (Table 1); localized lesions are less common but resection led to 30% long-term survival (15u). In a large cohort study of 1247 patients with resected colon cancer (16u), recurrences occurred in 548 after a median follow-up of seven years. There were 22 patients with resectable lung metastases, all detected by plain chest radiographs, and six were long-term survivors. In the same study, only 49 patients had hepatic resections, and 32% survived more than five years. Thus, although plain radiographs detect very few patients with localized lung metastases, the situation is very similar to that of liver metastases. Computerized tomography of the chest has not been used as a screening test in colorectal cancer.

Patient compliance with follow-up plans was described in a randomized trial obtained during updating (11u). After considering all the trials obtained (26,28,11u), it appears that patients are quite willing to undergo frequent visits and tests.

A reference was obtained that noted the complication rate for polypectomy was similar to that of other colonoscopies (17u).

In summary, follow-up programs for patients with curatively resected colorectal cancer do improve survival, but which tests or frequency of visits are optimal is not clear. There is the suggestion that improved survival is due to the diagnosis of recurrence at an early and asymptomatic stage, which allows for more curative resection of the recurrence. There is almost no data on complications from testing and therapies. Patients’ quality of life does not appear to be affected.

**VI. ONGOING TRIALS**

In 1998, an Italian group began a randomized trial of intensive versus minimal follow-up in patients with resected high-risk colorectal cancer (47). Approximately 4000 patients will be enrolled from about 50 hospitals in Italy.
Outcomes include overall survival, quality of life, and an economic analysis.

**Update**
The information concerning the Italian GILDA trial was updated (18u). In 2002, this trial opened to centres in North America. The planned accrual has been decreased from 4000 to 1500 patients. This reduction in recruitment will still provide a sample adequately powered to detect a difference between the four treatment arms. By October 2002, 779 patients had been recruited from 40 centres. Results of this trial will be included in an update of this practice guideline when available.

**VII. DISEASE SITE GROUP CONSENSUS PROCESS**
Intense debate during several sessions centred on the interpretation of the presented evidence as well as the common practices and our role in clarifying for other physicians what is an acceptable follow-up program. The evidence presented clearly demonstrated a survival benefit for patients receiving programs of more intense follow-up. The evidence for the schedule of visits and screening tests to detect disease recurrence is soft or non-existent. The evidence for the use of colonoscopy to detect second colorectal cancer and its precursors derive from investigations by the Polyp Surveillance Study in the United States (48). Further, there are other goals for follow-up than to increase survival, including psychosocial support, documentation of disease course, and close contact to test new therapies. The common practice has been to follow patients at high risk of recurrence (stages II and III) with clinical assessment and blood tests, including CEA every three to four months for the first two or three years and every six to 12 months to complete five years following resection. Blood CEA monitoring seems to uncover resectable liver metastases, is relatively inexpensive, and causes minimal inconvenience. Patients also have a colonoscopy in the perioperative period, and if adenomatous polyps are present, colonoscopy is repeated yearly or, if no polyps are detected, every three to five years. This practice was recommended in a document prepared by the Gastrointestinal Cancer DSG in January 1997 (see Appendix 2) and a group of ASCO experts recently supported similar views (25). These recommendations encompass the available evidence from clinical trials, and what is known about the clinical biology of colorectal cancer recurrences and second tumours, and should serve as a guide to other physicians. The Gastrointestinal Cancer DSG is fully aware that further trials are needed to determine which tests lead to the detection of resectable recurrent disease and whether patients’ quality of life is also improved.

**Update**
Since the original practice guideline was approved, the Polyp Surveillance Study performed in the United States has been updated (19u). This Polyp Surveillance Study guideline continues to provide evidence for the use of colonoscopy to detect second colorectal cancer and its precursors.

**VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT**

**Draft Recommendations**

Based on the evidence described above, the Gastrointestinal Cancer DSG drafted the following recommendations:

**Target Population**
These recommendations apply to adult patients with “curatively resected” colorectal cancer.

**Draft Recommendations**
- Patients with “curatively resected” colorectal cancer should be alerted to the future risk of disease recurrence, which is related to tumour stage, and to the development of a second colorectal cancer.
- Patients should also be advised about the survival benefit produced by programs of follow-up. This benefit is due to the early diagnosis and resection of limited recurrent disease in the liver, lungs or local sites. It is not known at this time whether this diagnosis of resectable recurrences is due to early assessment of symptoms or to the use of screening tests (blood carcinoembryonic antigen, chest-x-ray, liver ultrasound, or colonoscopy). There is insufficient evidence on which to base a recommendation for specific screening tests.
- In light of the uncertainty of the schedule of visits and screening tests to be recommended, and based on the rate of recurrent disease and second neoplasms, we advise patients who are at high risk for relapse (stages II and III disease) and are fit and willing to undergo investigations and potential surgery:
  1. to be assessed early for potential symptoms of disease relapse, and
2. to enroll in a follow-up program comprising:
   a. clinical assessment every four months for the first two years and every six to 12 months for three years; during those visits patients may have blood hemoglobin and CEA measured; and
   b. colonoscopy in the perioperative period and to be repeated yearly while adenomatous polyps are present, otherwise every three to five years (see Appendix 2).

**Future Research**

Patients should be encouraged to participate in clinical trials investigating the addition of screening tests to their clinical assessment. Future clinical trials of follow-up need to target resectable disease.

**Practitioner Feedback**

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

**Methods**

Practitioner feedback was obtained through a mailed survey of 153 practitioners in Ontario (29 medical oncologists, 20 radiation oncologists, and 104 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal Cancer DSG reviewed the results of the survey.

**Results**

Key results of the practitioner feedback survey are summarized in Table 5. Ninety-three surveys (62%) were returned. Eighty-two respondents (88%) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey.

**Table 5. Practitioner responses to eight items on the practitioner feedback survey.**

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the &quot;Choice of Topic&quot; section of the report, is clear.</td>
<td>76 (93%)</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>74 (90%)</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>66 (80%)</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>72 (88%)</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>70 (85%)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>62 (76%)</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>60 (73%)</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?</td>
<td>Very likely or likely</td>
</tr>
<tr>
<td></td>
<td>66 (80%)</td>
</tr>
</tbody>
</table>

*Total may not add up to 100% due to missing data.

**Summary of Written Comments**

Thirty-six respondents (44%) provided written comments. The main points contained in the written comments were:

1. Liver and lung imaging should be included in the recommendations. The only positive study included liver ultrasound.
2. The lack of specificity of CEA testing, its cost, and the poor results with resection of intraperitoneal recurrences argue against its routine use. Based on the studies that were reviewed, it is not clear how
CEA testing every four months was recommended. It was suggested to add the following recommendation: “If a patient would not be considered fit for resection of liver, lung, or intraperitoneal metastases, there is no value to CEA monitoring.”

3. Clinical exam every four months will not be fruitful. No resectable disease can be diagnosed on exam.
4. If several randomized controlled studies generally show survival benefits for yearly colonoscopy on the intensive follow-up program, why is colonoscopy recommended every three to five years? Routine yearly colonoscopy should be recommended, as suggested by the literature review.
5. The lack of evidence for the schedule of visits should be emphasized.
6. There should be recommendations for the steps to take when the screening tests are positive, such as the appropriateness of surgical and systemic interventions after recurrence is detected. In the articles reviewed, was post-recurrence intervention optimal?
7. In the recommendations, the statement “to be assessed early” is vague and could be left out. If it is left in, specify what “assessed” means and what “early” means.
8. Patients with stage I disease also need surveillance colonoscopy.
9. A statement regarding current standard practice in Canada might be helpful. Data are available from a survey conducted by Grunfeld et al.
10. The grade of tumour, high or low rectum, and age of patient are not individualized in the recommendations. Are there data on whether younger patients (e.g. 50 to 55 years) should be followed more closely as they are most likely to be aggressively treated for recurrent disease?

Modifications/Actions
Although 80% of the responses were favourable to the draft recommendations, a significant 20% of responders were not in full agreement and wrote specific comments. Major concerns were low sensitivity of clinical assessment and blood CEA, and the more specific value in detecting resectable solitary metastases by liver and chest imaging (see 1 to 5 in the preceding section). These concerns are reflected in a recent survey of Canadian oncologists regarding the frequency of visits and tests performed in the follow-up of curatively resected colorectal cancer: 35% of oncologists recommend liver ultrasound and 50% recommend chest x-rays (Grunfeld et al., unpublished results). In the randomized trials reviewed (26-31), the more intensive follow-up programs that showed a modest increase in survival did indeed use liver and chest imaging. Reconsideration of these facts is reflected in the more permissive recommendations. Similarly, modifications were made to address the importance of an optimal decision regarding the treatment of disease recurrence. In regard to colonoscopy, we continue to advise using the U.S. Polyp Study recommendations. Other comments were also considered, including colonoscopy for patients with stage I disease and more intense follow-up of patients who are fit and willing to undergo investigations and potential intervention for recurrence, regardless of age. In regard to other subgroups of patients to be considered for this intense follow-up, there is no definitive information. Some editing suggestions to clarify the practice guideline were also accepted, including providing information to be given to the patient at the start of the follow-up (Appendix 1).

Practice Guidelines Coordinating Committee Approval Process
The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All 11 members of the PGCC returned ballots. Five PGCC members approved the practice guideline as written, and six members approved the guideline conditional on the Gastrointestinal DSG addressing specific concerns. PGCC members requested that the following issues be addressed prior to the approval of the guideline report.

One member thought that there should be a more explicit definition of curative resection and more definitive recommendations made regarding stage I and IIa colorectal cancer. Another stated that there is a difference between recommending follow-up every three months as opposed to every six months, and that it was not apparent from the guideline why “three to six months” every year had been used. Recommending follow-up every three to six months was suggested, unless a patient-related issue necessitated sooner or earlier follow-up. Another member felt that the “Letter to patients” appeared to be written by physicians, but should be written by a lay person if it is to be given to patients. Another felt that the recommendation of colonoscopy every three to five years if polyps are not present is based on the development of carcinoid in a pre-existing adenomatous polyp and suggested stating this in the document. Another suggested that the
section on Single Cohort Studies of Compliance with Follow-up should inform the reader that compliant patients (on average) have better prognosis than noncompliant patients for a variety of different interventions and that any difference may not be related to the specific interventions tested. Another made note that the relative risk reported by Rosen was in the opposite direction compared with the methods for pooling described for the meta-analysis conducted by the DSG.

**Modifications/Actions**

- The section detailing curative resection and the different stages of colorectal cancer was rewritten in the section on Choice of Topic and Rationale to read, “Clinical assessment at least every six months for three years, and then annually for an additional three years”, qualified by the statement that patients seek “prompt assessment for symptoms of potential disease relapse”.
- The “Dear Patient” letter was rewritten as suggested.
- The fact that polyps can potentially develop into carcinoid tumours has been added into the text in the Recommendations where colonoscopy is discussed.
- The sub-group analysis was redone, and single-tailed p-values were included in the text as suggested.
- The issue of patient compliance was discussed in the Interpretive Summary.
- The results of the study reported by Rosen are elaborated on in the Interpretive Summary.

Other minor editing changes were also made.

**Peer Review Feedback**

The manuscript for this practice guideline was submitted to BioMed Central for consideration, and changes were made to the original document based on the peer-review feedback obtained. A summary of the major comments appears below.

One reviewer agreed with the thoroughness of the guideline and how the studies were stratified for analysis. His main concern was in the lack of data presented on the risk of second primary tumour development, and therefore, the frequency of post-operative colonoscopy. The references for two recently published papers that detailed this risk were provided.

The second reviewer agreed with our recommendation that intensive follow-up should be reserved for those patients who would be fit and willing to undergo salvage therapy if a recurrence occurred, but requested that the following issues be addressed.
- Since the Gastrointestinal Cancer DSGs last literature search, two meta-analyses and one RCT had been published. The search should be updated and these papers included.
- Recommending specific follow-up programs in the guideline is inferential as no specific programs of follow-up were compared against any others in an RCT. Based on the evidence available, the only recommendation that could be made is that “no follow-up” is not acceptable.
- The search strategy needs to be described in greater detail.
- A quality assessment of the randomized trials included needs to be performed and reported.
- A formal test for publication bias needs to performed and reported.
- The use of quotation marks around the term “curative resection” was questioned, because these might confuse the reader.
- The inclusion of cohort studies when RCTs were available was questioned.
- The lack of data on quality of life was questioned, and two references were provided.
- Recommending chest radiographs and liver ultrasound rather than thoracic computer tomography was questioned.
- Recommending yearly colonoscopy on every polyp, including those labelled as being low-risk after polypectomy, was questioned, and the reference for the recently published American Gastroenterological Association (AGA) guidelines on polyp surveillance was provided.
- A list of relevant papers was provided.

**Modifications/Actions**

In response to the comprehensive feedback obtained from the reviewers, the following changes were made.
- The literature search was updated to May 2003.
The recommendations were modified.
The search strategy was described in greater detail.
A quality assessment was performed on the included studies, using the Detsky instrument.
A test for publication bias was performed in Review Manager (Metaview© Update Software).
The quotation marks around the term “curative resection” were removed.
The cohort study data, and all data from non-randomized trials, was removed from the manuscript.
The information on quality of life that was in the recommended papers was included.
The authors noted that chest x-rays were part of the follow-up package of all included RCTs and are part of the present practice of Ontarian and Canadian physicians. Although the test sensitivity is low, patients with resected lung metastases have been identified by a chest x-ray. CT scans are possibly better, but no randomized study has compared the two. Likewise, liver ultrasound has been part of general practice and although an inferior test compared to a CT scan [lower sensitivity and specificity], the availability of CT scanning and the cost are significant problems.
The authors agreed that tubular adenomas <1 cm should be considered benign and not an indication for a yearly colonoscopy. The text was revised to follow the AGA guidelines.

Approved Practice Guideline Recommendations
These practice guideline recommendations reflect the integration of the draft recommendations and feedback obtained from the external review process. They have been approved by the Gastrointestinal Cancer DSG and the Practice Guidelines Coordinating Committee.

Recommendations
- Patients with curatively resected colorectal cancer should be alerted to the future risk of disease recurrence, which is related to tumor stage, and to the development of a second colorectal cancer.
- There is evidence from one randomized trial and a meta-analysis of six randomized trials of a small survival benefit with more intensive follow-up compared to less intensive follow-up. This benefit is due to the early diagnosis and resection of limited recurrent disease in the liver, lungs, or local sites. It is not known at this time whether this diagnosis of resectable recurrences is due to early assessment of symptoms or to the use of screening tests (blood CEA, chest x-ray, liver ultrasound, or colonoscopy). There is insufficient evidence on which to base a recommendation for specific screening tests.
- In light of the uncertainty of the schedule of visits and screening tests to be recommended, and based on the rate of recurrent disease and second neoplasms, and on current practices, we advise:
  1. In patients who are at high risk of relapse (stages IIb and III disease) and are fit and willing to undergo investigations and treatment:
     - Prompt assessment for symptoms of potential disease relapse (see Appendix 1);
     - Clinical assessment at least every six months for three years and then annually for an additional three years;
     - During those visits patients may have blood CEA, chest x-rays, and liver ultrasound;
     - When recurrences of disease are detected, patients should be assessed by a multi-disciplinary oncology team including surgical, radiation, and medical oncologists to determine the best treatment options.
  2. In patients at high risk of relapse but who have co-morbidities that may interfere with prescribed tests or potential treatment for recurrence, or who are unwilling to undergo prescribed tests or potential treatment for recurrence:
     - Clinical assessments yearly or for suggestive symptoms of relapse.
  3. In all patients with resected colorectal cancer (stages I, II, and III) and based on the U.S. Polyp Study:
     - Colonoscopy postoperatively if not yet done;
       - if polyps are present, excise as they are potential precursors of colorectal cancer; repeat colonoscopy yearly as long as polyps are found.
       - if there are no polyps, repeat colonoscopy in three to five years.
      (see Appendix 2).
Patients should be encouraged to participate in clinical trials investigating screening tests added on to their clinical assessment. These trials of follow-up need to target patients with resectable recurrent disease and that are fit for required surgery.

**Update**
The recommendations were modified slightly due to the peer-review process prior to publication. The change in recommendations was not circulated for external review because the Gastrointestinal Cancer DSG considered them minor changes that did not significantly deviate from the approved recommendations.

**Recommendations**
The updated recommendations include:

- For patients at high-risk of recurrence (stages IIb and III), clinical assessment is recommended when symptoms occur or at least every six months the first three years and yearly for at least five years, instead of for at least three years as recommended in the original guideline.
- For patients at lower risk of recurrence (stages I and Ia) or those with co-morbidities impairing future surgery, only visits yearly or when symptoms occur are recommended. All patients should have a colonoscopy before or within six months of initial surgery, repeated yearly if villous or tubular adenomas >1 cm are found; otherwise, repeat every three to five years.

**IX. PRACTICE GUIDELINE**
This practice guideline reflects the most current information reviewed by the Gastrointestinal Cancer DSG.

**Target Population**
These recommendations apply to adult patients with curatively resected colorectal cancer, defined as patients who have had all apparent disease removed by surgery.

**Recommendations**

- Patients with curatively resected colorectal cancer should be alerted to the future risk of disease recurrence, which is related to tumour stage, and to the development of a second colorectal cancer.
- There is evidence from one randomized trial and a meta-analysis of six randomized trials of a small survival benefit with more intensive follow-up compared to less intensive follow-up. This benefit is due to the early diagnosis and resection of limited recurrent disease in the liver, lungs, or local sites. It is not known at this time whether this diagnosis of resectable recurrences is due to the early assessment of symptoms or to the use of screening tests (blood carcinoembryonic antigen, chest-x-ray, liver ultrasound, or colonoscopy). There is insufficient evidence on which to base a recommendation for specific screening tests.
- In light of the uncertainty of the schedule of visits and screening tests to be recommended, and based on the rate of recurrent disease and second neoplasms, and on current practices, we advise:
  1. In patients who are at high risk of relapse (stages IIb and III disease) and who are fit and willing to undergo investigations and treatment:
     - Prompt assessment for symptoms of potential disease relapse (see Appendix 1);
   **Update:**
     - For patients at high-risk of recurrence (stages IIb and III), clinical assessment is recommended when symptoms occur or at least every six months the first three years and yearly for at least five years, instead of for at least three years as recommended in the original guideline.
     - During those visits patients may have blood carcinoembryonic antigen, chest x-rays, and liver ultrasound;
     - When recurrences of disease are detected, patients should be assessed by a multi-disciplinary oncology team including surgical, radiation, and medical oncologists to determine the best treatment options.
  2. In patients at high risk of relapse but who have co-morbidities that may interfere with prescribed tests or potential treatment for recurrence, or who are unwilling to undergo prescribed tests or potential treatment for recurrence:
- Clinical assessments yearly or for suggestive symptoms of relapse.

3. In all patients with resected colorectal cancer (stages I, II, and III) and based on the U.S. Polyp Study:
   - Colonoscopy postoperatively if not yet done;
     - if polyps are present, excise as they are potential precursors of colorectal cancer; repeat colonoscopy yearly as long as polyps are found.
     - if there are no polyps, repeat colonoscopy in three to five years.
   - Colonoscopy postoperatively if not yet done;
   - if polyps are present, excise as they are potential precursors of colorectal cancer; repeat colonoscopy yearly as long as polyps are found.
   - if there are no polyps, repeat colonoscopy in three to five years. (see Appendix 2).
   - Patients should be encouraged to participate in clinical trials investigating screening tests added on to their clinical assessment. These trials of follow-up need to target patients with resectable recurrent disease who are fit for required surgery.

Update
- For patients at lower risk of recurrence (stages I and Ia) or those with co-morbidities impairing future surgery, only visits yearly or when symptoms occur are recommended. All patients should have a colonoscopy before or within six months of initial surgery, repeated yearly if villous or tubular adenomas >1 cm are found; otherwise, repeat every three to five years.

X. JOURNAL REFERENCE

ACKNOWLEDGEMENTS
The Gastrointestinal Cancer Disease Site Group would like to thank Dr. A Figueredo, Mr. RB Rumble, Dr. J Maroun, Dr. CC Earle, Dr. B Cummings, Dr. R McLeod, Ms. L Zuraw, and Ms. C Zwaal for taking the lead in drafting, revising, and updating this practice guideline report.

The Gastrointestinal Cancer DSG would also like to thank the two peer-reviewers selected by BioMed Central Cancer, Dr. Andrew Renehan and Dr. Rick Nelson, for their input and suggestions.

For a complete list of the Gastrointestinal Cancer Disease Site Group members, please visit the CCO website at: http://www.cancercare.on.ca/.
REFERENCES


**Update**

This section includes all references obtained from the peer-review and updating activities.


References that were included in the approved practice guideline but were removed from the published version based on the peer-review.
Appendix 1. Follow-Up after curative treatment for colorectal cancer.

Dear Patient:

You have now completed all the treatment needed to offer you the best chance for a cure of your colon/rectal cancer. We know how difficult this period of time has been for you, and we also acknowledge your concerns for the future. We hope the following guidelines will help you to understand how we are going to deal with problems in the future.

We plan to see you in the clinic at least every six months for the first three years, and then annually for another three years. During these visits we will ask about any significant symptoms you may have had and will perform a physical examination, some blood tests, and x-rays.

We will also arrange for a colonoscopy to be done now if you did not have one before the operation. The reason for this test is to be sure the remaining bowel contains no polyps that might develop into another cancer. If no polyps are found, the next colonoscopy would be in 3 to 5 years, the time a polyp may take to develop. However, if there are polyps, they would be removed during the colonoscopy, and the test would be repeated in one year to check that no more polyps are present.

There are some symptoms that may indicate the need for assessment between visits. These symptoms include:
- persistent changes in your bowel habits, such as constipation or diarrhea;
- persistent changes in the form or shape of your stools;
- presence of blood in the stools;
- persistent abdominal or back pain;
- persistent weakness;
- lack of appetite, in particular if associated with weight loss;
- a lump in the neck, or elsewhere.

If any of these symptoms occur or you have other concerns, please contact your family physician or oncologist for advice.
Appendix 2. Experts’ consensus for an interim policy for follow-up and tests in patients with colorectal cancer.

JANUARY, 1997

Prepared by the Gastrointestinal Cancer Disease Site Group for the Task Force to Review Systemic Therapy of the Ontario Cancer Treatment and Research Foundation

INTRODUCTION

Ongoing care is an important component in the management of cancer patients. The frequency of tests and follow-up during active treatment is dependent on the modality of treatment administered and the need to monitor associated side effects and outcome. The frequency of tests and follow-up in patients who have completed treatment and have no evidence of disease is controversial in view of the lack of evidence-based data for guidelines development. Several research initiatives are underway to address this issue.

Until evidence-based guidelines are developed, this interim policy, based on experts’ consensus, is proposed in order to standardize care delivery to patients with colorectal cancer.

It is important to note that the schedule outlined below does not specify who should perform the follow-up evaluation. This could be done by an oncologist, a family physician, physician assistants or nurse practitioners.

In this respect, the following should be considered.

- Duplication, particularly with other oncologists, should be avoided.
- Patients with rectal cancer who have received adjuvant radiation therapy are preferably followed by radiation oncologists to evaluate pelvic disease and assess long-term radiation therapy effect.
- The role of the family physician, physician assistant, palliative care physicians and nursing should be evaluated and optimized in each regional cancer centre.

PURPOSE OF FOLLOW UP

- Documentation of local and/or distant recurrence that is resectable and curable.
- Monitoring for a new primary.
- Monitoring for long-term toxicity associated with systemic therapy and/or radiation therapy.
- Early identification of local and/or systemic non-curable recurrence and initiation of clinical trials with new drug combinations and/or appropriate symptomatic or palliative therapy.
- Management/counseling on new developments, genetic counseling and screening for other primaries.
- Psychosocial and symptomatic/palliative support.
- Long-term outcome evaluation.
Stage I.  T1, T2, N0M0
- Patients are usually not referred to the cancer centres for follow-up.
- Should there be a special need for follow-up this could be done on a yearly basis. The main objective of follow-up in this group would be the identification of a local recurrence or the appearance of a new primary.
- Tests include a colonoscopy in the first postoperative year. If polyps are identified and excised a repeat colonoscopy is performed 1 year later and if free of polyps colonoscopy will be repeated every 3 years.

Stage II.  T3, T4, N0M0
- High-risk patients could be considered for adjuvant chemotherapy. Follow-up of patients receiving adjuvant therapy will depend on the regimen used.
- At the completion of adjuvant therapy, or in patients who receive no therapy, patients could be followed 4 monthly for the first 2 years then 6 monthly for the subsequent 3 years and yearly for another 2 years.

Tests During Follow-Up
At each visit, the patients should have a history and physical examination. The following tests could be ordered: hemoglobin and CEA. Colonoscopy will be performed on the first postoperative year. If polyps are identified and excised a repeat colonoscopy is performed 1 year later and if free of polyps colonoscopy will be repeated every 3 years. Chest X-ray could be performed on a yearly basis particularly in rectal cancer patients. Other imaging will be performed as indicated by clinical or laboratory findings.

Stage III.  Any T, N1, N2, M0
- Follow-up of patients receiving adjuvant therapy will depend on the regimen used.
- At the completion of adjuvant therapy, patients could be seen 4 monthly for the first 2 years, 6 monthly for the subsequent 3 years then yearly for the next 2 years.
- Tests during follow-up will be performed as described above.

Stage IV.  Any T, any N, M1
1) Patients receiving chemotherapy will be managed as follows:
   - Patients with evaluable/measurable disease could have imaging done every 3 cycles. This should be sufficient to assess the patient response to therapy. CEA tests should not be done. Other tests to assess toxicity will depend on the regimen used.
   - Patients who have no evaluable/measurable disease e.g., intra-abdominal disease not visible on imaging, could have CEA done every 2 cycles to document benefit from treatment. Other tests to assess toxicity will depend on the regimen used.

2) Patients on supportive/palliative care do not require routine blood tests and/or imaging unless dictated by clinical condition. Follow-up and symptomatic treatment should be based on clinical needs and should involve family physician and/or palliative care physician/team.