MacLean–Mueller Prize
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Follow-up of patients after resection for colorectal cancer: a position paper of the Canadian Society of Surgical Oncology and the Canadian Society of Colon and Rectal Surgeons

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Objective: To provide recommendations for postoperative follow-up of patients with colorectal carcinoma.

Options: Postoperative follow-up surveillance versus no surveillance.

Evidence: A MEDLINE search for articles published between 1966 and February 1996 with the terms "colorectal neoplasm" and "follow-up studies." Pertinent citations from references of reviewed articles were also retrieved.

Methodology: With the evidence-based methodology of the Canadian Task Force on the Periodic Health Examination, a thorough review of the value of postoperative follow-up for colorectal cancer patients was performed. Studies were categorized according to their study design and submitted to critical appraisal. Randomized trials, cohort studies and descriptive studies were assessed. A benefit of follow-up was defined as an overall increase in survival.

Recommendation: To date, there is insufficient evidence to make a recommendation on the benefit of postoperative surveillance in colorectal cancer patients. Further clinical trials are needed to clarify the role of postoperative follow-up for patients after resection for colorectal cancer.

Objectif : Fournir des recommandations sur le suivi postopératoire des patients atteints d'un cancer colorectal.

Options : Surveillance de suivi postopératoire ou aucune surveillance.

Preuves : Recherche dans MEDLINE d'articles publiés entre 1966 et février 1996 comportant les expressions «colorectal neoplasm» et «follow-up studies». On a aussi extrait des citations pertinentes de références contenues dans des articles critiqués.

Méthodologie : On a analysé en détail la valeur du suivi postopératoire des patients atteints d'un cancer colorectal en utilisant la méthode fondée sur les données probantes du Groupe d'étude canadien sur l'examen médical périodique. Les études ont été classées selon leur conception et soumises à une évaluation critique. On a évalué des études randomisées, des études par cohorte et des études descriptives. On a défini l'avantage du suivi comme une augmentation globale de la survie.

Recommandation : Jusqu'à maintenant, il n'y a pas suffisamment de données probantes pour formuler une recommandation sur l'avantage de la surveillance postopératoire de patients atteints d'un cancer colorectal. D'autres études cliniques s'imposent si l'on veut clarifier le rôle du suivi postopératoire des patients après une résection d'un cancer colorectal.

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**Winner of the 1996 MacLean–Muller Prize. Supported in part by a fellowship from the Crohn's & Colitis Foundation of Canada*

Accepted for publication Dec. 10, 1996

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The incidence of colorectal cancer in Canada is among the highest in the world. Colorectal cancer ranks third in cancer incidence and second in cancer mortality.[1] It was estimated that over 16 300 new cases of colorectal cancer would be diagnosed and more than 5000 patients would die from the disease in 1995.[1] Currently, 1 in 16 Canadians is expected to suffer from colorectal cancer and 1 in 35 will die of the disease.

Surgery is the primary treatment modality for most colorectal cancers. Adjuvant chemotherapy or radiotherapy, or both, is recommended for specific subgroups of patients.[2,3] However, although approximately two-thirds of patients with colorectal cancer are initially treated for cure,[3] 30% to 50% have a recurrence.[4–9] Most recurrences occur within 2 years of the initial surgery, and less than 5% after 5 years.[10–13] Recurrences can occur either within the area of the original cancer (locoregional recurrence) or distant from the site of the original cancer (metastatic disease). Locoregional recurrences are infrequent in colon cancer, whereas the reported local recurrence rates for rectal cancer range from 10% to 50%.[14] The most frequent sites for metastatic disease are the liver and the lungs. Approximately 35% of patients will have hepatic metastases.[15] Of these, the liver is the only site of recurrence in approximately 20%.[16,17] Between 10% and 22% will have pulmonary metastases, and approximately 10% of these patients will have disease isolated to the lungs.[13,18,19]

Various factors may affect the risk of recurrence. The most important prognostic variable is the stage of the disease, which takes into consideration both the nodal status and the depth of penetration of the tumour. Histologic characteristics, tumour location and the presence of obstruction or perforation at the time of presentation have been reported to be associated with higher recurrence rates.[13] In the future, molecular tumour markers will likely be important prognosticators.[20–22]

Given the high risk of recurrence and often dismal prognosis of patients with symptomatic recurrence, there has been widespread enthusiasm for surveillance programs to detect local or distant recurrences when they are amenable to surgical resection. In the early 1950s, Wangensteen, Lewis and Tongen[23] were among the first to advocate aggressive follow-up including second-look laparotomy for all patients. More recently, Martin, Minton and Carey[24] have been proponents of second-look laparotomy, based on elevated serum carcinoembryonic antigen (CEA) levels. Others have since aimed to prove or disprove the value of follow-up programs.[8–10,25–31] However, controversy exists in regard to the benefit of postoperative surveillance programs. A recent survey of more than 1000 colorectal surgeons across the United States revealed that there is little consensus as to what is optimal postoperative follow-up.[32] Although the majority of the surveyed surgeons do enrol patients into regular follow-up schedules for a mean of 5 years, there is much variation in the frequency of scheduled visits, performance of serum CEA determinations and endoscopies. There are also major differences in the use of invasive tests such as CT scanning. Based on this survey, the authors concluded that there is uncertainty about the type of follow-up to recommend, and further trials are required to evaluate the benefit of various follow-up strategies. In a cost analysis of follow-up after potential curative colorectal cancer treatment, Virgo and colleagues[33] compared 11 follow-up programs and reported that the charges per patient, for a follow-up of 5 years, varied from US$910 to US$26 717. They concluded that this wide variation in cost was not justified and stressed the need for clinical trials to assess the effectiveness of follow-up programs.

Whereas in the past, treatment guidelines were developed from expert opinion and consensus, there is now increasing agreement that guidelines and recommendations should be evidence based. Therefore, the objective of this paper is to review the evidence for follow-up strategies for patients with colorectal cancer who have undergone curative resection and to make recommendations regarding their value.

METHODS

The evidence-based methodology of the Canadian Task Force for the Periodic Health Examination was used to develop these recommendations.[34] The process included defining criteria for effectiveness, performing a systematic critical appraisal of the reports, and classifying the studies according to the rigour of the study design (Table I). The recommendations followed the grading used by the task force (Table II).

Articles were identified through a MEDLINE search including English and French articles published between 1966 and February 1996 that had the following MESH headings: colorectal neoplasm and follow-up studies. As well, references of the retrieved articles and articles from personal collections were reviewed, and pertinent citations were included.

Studies retained for critical appraisal were those in which survival analysis, in some form, was provided. Studies in which the only available outcome measures were detection rates of recurrence or reoperation rates without survival assessments were not included because they do not provide direct evidence of benefit.

Because only a very small number of published studies have compared a no-follow-up program to a follow-up program, studies that compared intensive surveillance programs to less-intensive surveillance programs were also included. If a significant difference in outcome was found when an intensive follow-up schedule was compared to a minimal follow-up schedule, it was assumed that the difference between the intensive follow-up schedule and a no follow-up program would be at least the same or potentially bigger. However, if there was no significant difference, no conclusion was drawn.

RESULTS

Tests for detection of recurrence

Because colorectal cancer recurrences occur locoregionally and distally, different tests need to be incorporated into surveillance programs. Moreover, because patients with prior colorectal cancer are at significant risk for the development of a second colorectal cancer,[35] follow-up strategies need to include tests to detect metachronous lesions.

History-taking and physical examination, liver function testing, CEA determination, colonoscopy or double-contrast barium enema examination, chest radiography, and abdominal ultrasonography or CT scanning are among the most frequently performed follow-up tests.[36] Generally, most authors have advocated intensive follow-up during the first 2 years, more moderate follow-up from 2 to 5 years and minimal follow-up after 5 years.[32,36]

Many studies have attempted to assess the value of serum CEA levels alone in detecting colorectal cancer recurrence.[10,25,26,37–41] The reported sensitivity of CEA ranges from 58% to 89% and the specificity from 75% to 98%. Most of the studies listed above have considerable diagnostic and investigation biases incorporated into their study design, and this probably explains the considerable variation in sensitivity and specificity between studies. The data were based on a mixed population of asymptomatic and symptomatic patients. Moreover, the level at which CEA values were considered abnormal varied greatly between studies. On the basis of methodologic requirements for assessment of a screening test, the studies by McCall and colleagues[41] and Tate[37] provide the highest quality data for assessment of the value of a test. On the basis of these latter studies, the sensitivity and specificity of CEA are, respectively, in the range of 55% and 92%.

The other most frequently prescribed tests included in follow-up programs have variable degrees of accuracy. The sensitivities of ultrasonography and CT scanning for detection of liver metastasis range from 50% to 70% and 60% to 90% respectively, with

Table I

Grade of Evidence Based on the Study Design

Grade	Type of study
I	Evidence obtained from at least one properly randomized controlled trial
II-1	Evidence obtained from well-designed trials without randomization*
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group
II-3	Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports or expert committees

*Included in grade II-1 are randomized trials that are not of high quality or that have negative results but lack adequate power to prove that there is no difference between treatments.

Table II

Levels of Recommendation Based on Those of the Canadian Task Force for the Periodic Health Examination

Level of recommendation	Description
A	There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
B	There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
C	There is poor evidence regarding the inclusion of the condition in a periodic health examination and recommendations may be made on other grounds.
D	There is fair evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.
E	There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

a specificity for both tests of over 90%.[42,43] The detection of recurrent disease by history-taking and physical examination is less accurate, although rates of 48% to 83% have been reported.[10,25,44,45] Chest radiography is fairly accurate in detecting pulmonary metastases, but because less than 10% of patients who have such metastases are amenable to curative resection,[18,19] its value can be questioned. Measurement of serum alkaline phosphatase levels has been reported to have a sensitivity of 77% for detection of liver metastases. However, it also has a high false-positive rate.[46,47] Moreover, as screening tests for the detection of treatable liver recurrence, serum liver function tests are probably of little benefit. Barkin and associates[48] attempted to evaluate the value of regular endoscopy for detecting intraluminal recurrence in colorectal cancer patients. Of 452 such patients who had regular-interval endoscopy after curative surgery for cancer, 49 were found to have a local recurrence, which was intraluminal in 15 of them. Six of these 15 intraluminal recurrences were initially diagnosed by endoscopy; 4 of the patients had a reresection for cure. Routine endoscopy detected a metachronous tumour in 4 additional patients. Nava and Pagana[49] reported an intraluminal detection rate of 7% (17 of 240 patients) in postoperative colorectal cancer patients who underwent to regular endoscopy, and Juhl and associates[50] reported a rate of 5% in 174 colorectal cancer patients who had annual colonoscopy. By the endoscopy follow-up, Juhl and associates also detected 4 metachronous tumours and 30 adenomatous polyps larger than 1 cm.

Most studies looking at the value of follow-up programs have not assessed the different tests independently from one another. Also, there is great study variability as to the type and frequency of tests selected for evaluation. It is therefore difficult to assess accurately the true value of individual tests aimed at detecting colorectal cancer recurrence. This lack of uniformity is a major obstacle for determining the effectiveness and benefit of the individual screening tests available.

Evidence from randomized controlled trials

To date, there are 3 randomized controlled trials[51-53] and one completed trial without official results (J.M. Northover, St. Mark's Hospital, London, UK: unpublished data, 1996) that have compared different postoperative surveillance programs for colorectal cancer-treated patients (Table III). Of these, only 1 compared an intensive surveillance program to a minimal follow-up program.[51]

Ohlsson and colleagues[51] randomized 107 patients with Dukes' class A, B or C cancers between 1983 and 1986. All patients were randomized within 3 months of their curative surgery. Before entry, patients had a full colonoscopy to exclude severe dysplasia, an early anastomotic recurrence or a synchronous cancer. The details of each strategy are listed in Table III.

Fifty-four patients were randomized to the follow-up group and 53 to the control group. Groups were comparable for age, sex, stage of disease and tumour location. Median follow-up time was 6.8 years (range from 5.5 to 8.8 years). In the control group, 18 patients (33%) had a recurrence. Fifteen had symptoms that prompted further investigation and led to the diagnosis of recurrence. The other 3 recurrences were detected, respectively, by physical examination, chest radiography and fecal occult blood testing. Thirteen patients in this group had positive fecal occult blood tests; of these, 4 were subsequently found to have a recurrence. Only 1 of the 4 patients was asymptomatic. In the follow-up group, 17 patients (32%) had a recurrence (8 were symptomatic and 9 were asymptomatic). Of the total number of patients in whom a recurrence was diagnosed, 3 in the control group and 5 in the follow-up group had an attempted curative reoperation. Only 2 patients were cured by reresection, both in the follow-up group. This represents a 3.7% curative reresection rate for the follow-up group and a 0% rate for the control group. The overall 5-year survival rates, assessed by the Kaplan–Meier technique, were 67% and 75% respectively for the control and follow-up groups ($p = 0.264$). The colorectal cancer-specific survival rates were 71% and 78% respectively ($p = 0.413$).

Although the title of this article suggests a comparison between intensive follow-up and no follow-up, in fact an intensive follow-up was compared to minimal follow-up with fecal occult blood testing. Although a difference in overall survival or death due to cancer was not found, the sample size was relatively small, and the study lacked adequate power to accept with reasonable confidence that a true difference was not missed.

A second randomized controlled trial was conducted in the United Kingdom to assess the value of CEA (J.M. Northover, St. Mark's Hospital, London, UK: unpublished data, 1996). Patients who were under the age of 76 years, had undergone a curative resection for adenocarcinoma of the colon or rectum and were fit and willing to follow a surveillance program were eligible for entry. This trial had a unique design in that all patients had "standard" follow-up, defined as 3-month visits for 2 years and 6-month visits for the following 3 years with CEA assays drawn monthly for

3 years and thereafter at 3-month intervals for 2 years. Treating physicians and patients were unaware of CEA results. If a CEA elevation was detected, patients were then randomized to 1 of 2 groups: a conventional follow-up group or an aggressive follow-up group. In the conventional arm, neither clinicians nor patients were informed of the CEA elevation, and follow-up schedules continued in the usual manner. If a patient in that arm had clinical evidence of recurrence, the physician investigated and treated the patient as considered appropriate. In the aggressive follow-up arm, patients and their physicians were immediately informed of the abnormal elevation. Patients were then submitted to a clinical work-up in search of recurrent disease and to exclude the possibility of a nonmalignant cause for the CEA elevation. A standardized second-look laparotomy was under-

Table III

Follow-Up Programs and Level of Evidence for Randomized Controlled Clinical Trials

Study/group and no. of patients	Follow-up		Survival	Grade of evidence
	Program	Time, yr		
Ohlsson et al, 1995[51] Control, 54 Follow-up, 54	Control: instructed to contact physician if any abnormal symptoms and recommended to leave fecal samples every 3 mo for 2 mo, then yearly. Follow-up: physical examination, rigid sigmoidoscopy, CEA determination, liver function testing every 3 mo for 2 yr, every 6 mo for 2 yr and at 5 yr. Fecal hemoglobin testing, chest radiography and endoscopy of anastomosis at 9, 21, 42 mo. Colonoscopy at 3, 15, 30, 60 mo. CT scan of pelvis (rectal cancer only) at 3, 6, 12, 18, 24 mo	Median: 6.8 yr, range 5.5-8.8 yr	5-yr: control 67%, follow-up75%*	II-1
Northover et al, 1996 (unpublished data) Control, 105 Follow-up, 108	Control: with an elevated CEA level, maintained regular follow-up visits without CEA results known. Follow-up: with an elevated CEA level, aggressive investigation, including second-look laparotomy	Not available	2-yr postrandomization. No difference	I
Makela, Laitinen and Kairaluoma, 1995[52] Control, 54 Follow-up, 52	Both groups: physical examination, medical history, complete blood count, CEA determination, chest radiography, fecal hemoglobin testing every 3 mo for 2 yr then every 6 mo for 3 yr. Control: rigid sigmoidoscopy every visit, barium enema examination every year. Follow-up: flexible sigmoidoscopy with video every visit, video colonoscopy 3 mo postop. then yearly, liver ultrasonography every 6 mo, CT scanning of liver and site of primary yearly.	All patients followed up for 5 yr or until death	Cumulative 5-yr: control 54%, follow-up 59%*	II-1
Kronborg et al, 1994[53] Control, 298 Follow-up, 282	Control: follow-up at 5, 10 and 15 yr. Follow-up: examinations at 6, 12, 18, 24 and 30 mo and 3, 4, 5, 10, 12.5 and 15 yr. At each follow-up: History-taking and clinical examination, hemoccult-II testing, colonoscopy, chest radiography, determination of hemoglobin level and sedimentation rate and liver function testing	15-yr follow-up planned	Interim analysis — crude survival (time not specified): control 71%, follow-up 72%*	To be determined

*$p > 0.05$, CEA = carcinoembryonic antigen

taken in all patients unless definite incurable disease was detected by the initial work-up.

Between 1983 and 1990, 1235 patients from 58 centres agreed to participate in the study. Of these, 216 patients (17.5%) were found to have elevated CEA levels. One hundred and eight of the 216 patients were randomized to an unblinded group for CEA elevation; 105 of them agreed to complete the tests. Thirteen of these 105 patients were already being investigated because recurrence was suspected clinically; 32 were unsuitable for a second operation because of inoperable disease. The other 108 patients were randomized to a group in which neither patients nor physicians were informed of the CEA elevation; in 89 of them, recurrent disease was confirmed. Preliminary unpublished results (J.M. Northover, Department of Surgery, St. Mark's Hospital, London, UK: Personal communication, 1996) 2 years after randomization suggests no significant difference in survival between the 2 groups.

In Northover's trial, because all patients received "standard follow-up" (which was not defined and probably was not standardized), a significant treatment effect may have been missed because of the intensity of follow-up that patients in both groups received. It does, however, suggest that after 2 years of follow-up, no additional benefit is gained by measurement of the CEA level, but the value of other tests used for surveillance remains unanswered. The results after 5 years of follow-up are pending.

Makela, Laitinen and Kairaluoma[52] from Finland published the results of a trial in which 106 patients who had undergone a curative colorectal cancer procedure (Dukes' class A, B or C) between 1988 and 1990 were randomized to usual follow-up (54 patients, control group) or a more aggressive follow-up program (52 patients, follow-up group). All patients were submitted to a relatively intensive follow-up schedule (Table III). The main difference between groups was that the follow-up patients had biannual abdominal ultrasonography, yearly CT scanning and flexible videotaped endoscopy, whereas control patients did not undergo liver imaging and rigid sigmoidoscopies were performed. The 2 groups were comparable for important prognostic factors. The primary outcome measure was the difference in the 5-year survival rates between groups.

Twenty-one patients in the control group compared with 22 patients in the follow-up group were found to have recurrent disease. Although there was a significant difference in the time to diagnosis of recurrence (15 ± 10 months for the control group v. 10 ± 5 months for the follow-up group, $p = 0.002$), there was not a significant difference in the 5-year survival rates (54% for the control group v. 59% for the follow-up group, $p = 0.5$).

This trial again failed to show an improvement in survival in patients receiving more intense follow-up. However, this study really assessed the benefit of adding sophisticated liver imagery to a follow-up program. Since patients in both groups received fairly intensive follow-up, one might predict a negative result, given the low frequency of isolated liver metastases and the small sample size. Only 1 patient in group I compared with 2 in group II had curative reresection. Therefore, a difference in treatment effect would not be expected with such a small sample size.

In 1986, Kronborg and associates[53] from Denmark started to enrol treated colorectal cancer patients in a randomized controlled trial to compare an intensive follow-up program to minimal follow-up. Pre-trial sample size was determined at 600 patients. Follow-up time was scheduled for 15 years. The difference between the two follow-up protocols was only in the frequency at which the tests or visits were scheduled (Table III). According to interim analysis of 580 patients, no significant difference in crude survival between groups was found, and it is unlikely that the final results will show a difference in survival between groups. The results of this trial do suggest that nonspecific tests, such as liver function tests and measurement of fecal hemoglobin and erythrocyte sedimentation rate, are of little benefit for the early detection of treatable recurrence.

In summary, complete data are now available from 3 randomized controlled trials. (J.M. Northover, St. Mark's Hospital, London, UK: unpublished data, 1996).[51,52] Although follow-up protocols varied between trials, in none of these studies was a survival benefit demonstrated in patients receiving more intense follow-up. However, all trials had small sample sizes (less than 110 patients per group). Given that treatable recurrences occur infrequently, many more patients would be required to be certain that a treatment effect was not missed. Further, since isolated hepatic and pulmonary metastases seem to be the most likely recurrence sites amenable to curative resection, more sophisticated tests with higher sensitivity to detect early lesions may be required to capture the benefit of follow-up. Finally, 3 of the 4 trials (J.M. Northover, St. Mark's Hospital, London, UK: unpublished data, 1996)[52,53] compared follow-up to more intense follow-up, and it is possible that the no-treatment effect was observed because follow-up protocols in both groups were relatively intense.

Evidence from cohort studies

There are 5 published cohort studies[27,29,54-56] in which follow-up has been compared to no follow-up. In 3 of these studies, follow-up was offered to all patients. The no-follow-up group consisted of patients who refused follow-up.[27,29,54] In the other 2 studies,[55,56] patients who received follow-up were compared with historic controls. Given the known biases of such studies, one must be cautious in the interpretation of their results.

Ovaska and colleagues[27] reported on 507 patients who had a curative colorectal cancer resection between 1976 and 1985. All patients were offered follow-up. However, 368 patients (follow-up group) adhered to the follow-up program and were followed prospectively and 139 patients (no-follow-up group) refused to comply with the follow-up program (102 patients had no follow-up at all and 37 were seen by other private surgeons). The 2 groups were comparable with respect to Dukes' stage, but no information was given of other prognostic factors, and patients in the follow-up group were significantly younger than patients in the other group. Eighty-five percent of patients were followed up for 5 years or until death, and the follow-up time ranged from 36 to 60 months. The mean (and SD) cancer-related 5-year survival rate was not statistically different between groups (Kaplan–Meier method, 72 [2]% v. 62 [5]%, $p = 0.13$).

In this study, in addition to the obvious potential bias due to lack of randomization (volunteer bias), 3 other important biases are noted, which render the results of this trial questionable. First, follow-up data were obtained differently for the 2 groups. Patients were followed up prospectively in group I whereas follow-up data were obtained through the Official Census Registry of Finland in the other group. This difference can account for less accurate data in the no-follow-up group. Because of the small number of patients in each group, the impact of this difference on results is a major concern. Second, there was potential contamination in the no-follow-up group (27% had some type of follow-up by a private physician). This may bias the results toward not finding a difference between groups. Third, because the groups differed significantly in mean age, one can question the overall comparability of the 2 groups.

Eckardt and associates[54] reported on the outcome of 212 patients who had curative surgery between 1978 and 1987. All patients were given written notices and instructed to attend an intensive surveillance program (Table IV). Eighty-eight patients (41.5%) were considered compliant to the follow-up. These patients reported for all endoscopic examinations, and no more than 6 months elapsed between a scheduled appointment and the performance of endoscopy. The remaining 124 patients were considered noncompliant (42.5% attended follow-up visits irregularly, and 16% did not attend any follow-up visits).

The 2 groups were similar for prognostic factors. Outcome data were obtained from 93% of the compliant and 77% of the noncompliant patients. The mean follow-up time was over 90 months in both groups. There was no significant difference in colorectal cancer death rate (30% v. 18%, $p > 0.05$). However, 80% of the compliant patients survived 5 years compared with 59% of the noncompliant patients ($p = 0.002$). The relative risk of a poor outcome (defined as death) in the noncompliant group compared with the compliant group was 2.5 (95% CI 1.5 to 4.2).

In this cohort study, a higher proportion of patients (23%) in the noncompliant group compared with the compliant group (7%) were unavailable for follow-up. Moreover, because compliance was variable in the noncompliant group, it is difficult to attribute the results to a specific type of follow-up. The accuracy of the cause of death is also questionable because it was obtained from hospital records or death certificate only. Finally, the discrepancy in the observed disease-specific and overall survival rates in such a small group may partially be explained by the obvious selection biases incorporated in this study.

Pugliese and colleagues[29] reported retrospectively on the outcome of 256 patients with Dukes' B or C lesions who had a curative resection between 1973 and 1979. Of these patients 115 (44.9%) adhered strictly to follow-up (Table IV) whereas 62 patients (24.2%) did not attend any follow-up visits. The 2 groups were comparable for sex, age, stage and location of disease.

There was no improvement in survival in those receiving follow-up (Dukes' B; 84% v. 79% $p > 0.6$, Dukes' C; 39% v. 21% $p = 0.1$). However, there were relatively few patients in each group. Moreover, patients in the 2 groups were not treated similarly: some patients in the follow-up group received adjuvant therapy, which potentially introduces a major bias.

Ekman, Gustavson and Henning[55] compared the outcome of 167 colorectal cancer patients who received intensive follow-up between 1968 and 1972 to that of a historic control group of 130 patients treated between 1964 and 1967 who did not receive follow-up. The crude 5-year survival rates were not significantly different (46% in the prospective group and 53% in the control group). The data from this study have limited validity since it is not clear that the 2 groups were comparable for important prognostic factors. Second, half of the pa-

tients in the prospective group received chemotherapy whereas none of the patients in the control group did. Finally, neither the cause of death nor the length of follow-up was provided.

Tornqvist, Ekelund and Leandoer[56] published the results of 363 patients who had been followed prospectively after curative resection for colorectal cancer. The outcome in these patients was compared to a historic control group of 639 colorectal cancer patients who had been followed at the same institution but with a much less intensive follow-up schedule (Table IV). The 2 groups were comparable for age, type of operation and Dukes' stage. Recurrent disease was diagnosed in 33% of patients in the follow-up group compared with 34% in the control group. Thirteen percent (15 patients) of follow-up patients and 14% (30 patients) of patients in the control group had a reoperation for cure, but only 8 and 7 patients, respectively, in each group were cured after reoperation.

Because of the difference in time frame between groups (potentially over 10 years), the comparability of the 2 groups in this study is questionable. There were probably differences in treatment, postoperative care and accuracy of data, between the early 1960s and 1970s. Most importantly, because of the major differences in technology and expertise, it could be difficult to generalize these data.

There is one published meta-analysis,[28] based on cumulative data of 7 cohort studies, assessing the benefit of intensive follow-up. Four of the 7 cohort studies were assessed in this review. The other 3 were not reviewed because 2 studies were published in foreign languages and 1 study did not assess survival. A 5-year survival difference of 12.4% (95% CI –5.4% to +30%) in favour of follow-up was reported, but this difference, as shown by the CI, was not statistically significant.

The value and accuracy of meta-analysis data are known to depend on the quality of the studies included. The results of this meta-analysis must be interpreted with caution because it only includes cohort studies, which

Table IV

Follow-Up Programs and Level of Evidence for Cohort Studies

Study	Follow-up		Survival/p value	Grade of evidence
	Program	Time, yr		
Ovaska et al, 1990[27]	Physical examination, blood chemistry, CEA determination, fecal occult blood testing, sigmoidoscopy at 3, 6, 12, 18, 24, 36, 48, 60 mo	85% followed up for 5 yr	5-yr survival: follow-up 72%, control 62%. $p = 0.13$	II-2
Eckardt et al, 1994[54]	History-taking, physical examination, CEA determination, ultrasonography at 3, 6, 9, 12, 18, 24, 36, 48, 60 mo. Chest radiography, colonoscopy yearly. Partial colonoscopy at 3, 6, 9, 18 mo	Mean follow-up 90 mo	Overall survival: follow-up 80%, control 59%. $p = 0.002$	II-2
Pugliese et al, 1984[29]	Physical examination, fecal occult blood testing, complete blood count, liver function testing, urinalysis, measurement of prothrombin time every 3 mo for 2 yr, then every 6 mo for 3 yr. Liver imaging, chest radiography, colon study every 6 mo for 2 yr then yearly	Median follow-up 33 mo	Overall survival: Dukes' class B: follow-up 84%, control 79%. Dukes' class C: follow-up 39%, control 21%. $p > 0.05$	II-2
Ekman, Gustavson, Henning, 1977[55]	Clinical examination, proctosigmoidoscopy, chest radiography, barium enema examination, routine blood analyses (not defined) every 3 mo for 1 yr then every 6 mo	Not specified	Crude 5-yr survival: follow-up 46%, control 53%. $p > 0.05$	II-3
Tornqvist, Ekelund, Leandoer, 1982[56]	Intensive follow-up: physical examination, proctoscopy, blood chemistry, chest radiography. Double-contrast enema every 3 mo for 2 yr, every 6 mo for 2 yr, then yearly. Minimal follow-up; same protocol but done only yearly for 5 yr	Not specified	Data of meta-analysis[24] 5-yr survival; follow-up 50%, control 54%	II-3

are subject to many biases as has been pointed out in this section. Moreover, as there was significant variability in the follow-up protocol between the included studies, the value of combining such data is even more questionable.

Evidence from descriptive studies

Eight case-series including more than 100 patients (range from 114 to 1217 patients) have been reported.[8,9,25,26,30,31,38,39] They assessed specific surveillance programs in which the type and frequency of tests varied between each study. Although these data can only be looked upon as hypothesis-generating because of the major limitations of purely descriptive data, including the lack of a control group, it is of interest that the percentage of patients in these studies who benefited from follow-up ranged from 0% to 6%. A benefit was defined as a reresection of recurrent disease for cure and a minimum documented disease-free survival of 1 year or more. Thus, from the combined data of these studies, 100 patients would have to be followed up postoperatively for 1 or 2 patients to be successfully treated for recurrent disease.

Recommendations and conclusion

From the findings of this review, there is inconclusive evidence either to support or to refute the value of follow-up surveillance programs to detect recurrence of colorectal cancer (Table V). Although the final results of 3 randomized controlled trials (J.M Northover, St. Mark's Hospital, London, UK: unpublished data, 1996)[51,52] and the preliminary results from a fourth[53] have not shown a significant survival benefit, all of these studies are relatively small in number. Given the infrequency of isolated recurrences amenable to surgical extirpation and based on the data from the trials reviewed, we would expect a survival benefit of not more than 10%, even if postoperative surveillance were effective. Thus, even by combining the data from the published trials, there is insufficient power to exclude with confidence that there is no benefit of follow-up programs. Furthermore, because the published trials include a variety of tests and follow-up programs, they preclude conclusions about the value of individual tests. Therefore, the recommendation for follow-up surveillance programs for detection of recurrence for colorectal cancer patients treated with an intention to cure is a C recommendation (Table II). Large randomized clinical trials evaluating the effectiveness of follow-up for colorectal cancer patients are therefore necessary before definite recommendations can be provided. Such trials would require large sample sizes and should compare very minimal or no follow-up to very intensive follow-up, including more sensitive imagery tests capable of detecting treatable recurrences such as local, hepatic and pulmonary metastases.

Table V

Summary of Manoeuvre, Effectiveness, Levels of Evidence and Recommendation on Follow-up Surveillance Program to Detect Recurrence in Patients Treated Surgically for Colorectal Cancer With Intent to Cure (Dukes' Classification A, B, C).

Manoeuvre	Effectiveness	Levels of evidence	Recommendation
Follow-up programs for detection of recurrence of colorectal cancer (includes physical examination and history-taking, CEA determination, endoscopy, liver imagery, chest radiography and endoscopy)	Evidence that follow-up programs increase overall or disease-specific survival in treated colorectal cancer is not conclusive.	Randomized controlled trial[51] (II-1). Cohort studies[27,29,54] (II-2). Historic cohort studies,[55,56] (II-3). Descriptive data[2,8,9,26,27,32,33] (III)	C (see Table II). Insufficient evidence of effectiveness to include or exclude follow-up programs to detect recurrence for colorectal cancer patients surgically treated with an intention to cure

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