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ORIGINAL REPORT

The Value of Routine Serum Carcino-Embryonic Antigen Measurement and Computed Tomography in the Surveillance of Patients After Adjuvant Chemotherapy for Colorectal Cancer

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
This analysis aims to evaluate routine carcino-embryonic antigen (CEA) and computed tomography (CT) of thorax, abdomen, and pelvis as part of protocol-specified follow-up policy for colorectal cancer (CRC).

Patients and Methods
Patients with resected stage II and III CRC were randomly assigned to bolus fluorouracil/leucovorin or protracted venous infusion fluorouracil. Following completion of chemotherapy, patients were seen in clinic at regular intervals for 5 years. CEA was measured at each clinic visit, and CT of thorax, abdomen, and pelvis was performed at 12 and 24 months after commencement of chemotherapy.

Results
Between 1993 and 1999, 530 patients were recruited. The median follow-up was 5.6 years. Disease relapses were observed in 154 patients. Relapses were detected by symptoms (n = 65), CEA (n = 45), CT (n = 49), and others (n = 9). Fourteen patients, whose relapses were detected by CT, had a concomitant elevation of CEA and were included in both groups. The CT-detected group had a better survival compared with the symptomatic group from the time of relapse ($P = .0046$). Thirty-three patients (21%) proceeded to potentially curative surgery for relapse and enjoyed a better survival than those who did not ($P < .00001$). For patients who underwent hepatic or pulmonary metastatic resection, 13 (26.5%) were in the CT group, eight (17.8%) in the CEA group, and only two (3.1%) in the symptomatic group (CT *v* symptomatic, $P < .001$; CEA *v* symptomatic, $P = .015$).

Conclusion
Surveillance CT and CEA are valuable components of postoperative follow-up in stage II and III colorectal cancer.

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INTRODUCTION

Despite potentially curative surgery, nearly four of 10 patients with colorectal cancer (CRC) experience disease relapse.[1] The primary aims of follow-up for patients with resected stage II or III CRC are to detect either resectable metastases confined to organs such as liver or lung, resectable local recurrences, or metachronous (second primary colorectal) cancer. Aggressive surgical approaches to metastatic disease are increasingly practiced, with a proportion of patients enjoying long-term survival. With the advent of new drugs such as oxaliplatin, metastases confined to liver or lung can be downsized substantially to allow potentially curative surgery even if they are deemed unresectable before chemotherapy.[2] Even in patients with unresectable metastatic disease, early treatment is associated with an improved survival advantage,[3] and patients with access to fluoropyrimidines, irinotecan, and oxaliplatin can now achieve a median survival of 18 months or more.[4,5]

However, the value of follow-up after curative resection of CRC has been much debated. Two meta-analyses have been per-

formed pooling results from five randomized studies[6,7] and found a survival advantage in patients allocated to intensive follow-up. However, the definitions of intensive follow-up varied among studies and it is uncertain what frequency or modality of investigations would be most beneficial and cost-effective. Moreover, as the treatment paradigm in advanced CRC is shifting, the criteria for resectable metastases and local recurrences are constantly being redefined.

Between 1993 and 1999, we conducted a multi-center prospective randomized study comparing the efficacy of protracted venous infusion (PVI) fluorouracil (FU) with bolus FU/leucovorin (LV) as adjuvant therapy in patients with potentially curatively-resected colorectal cancer. The initial results of this study have been published previously.[8] In this secondary analysis, we evaluated the role of routine serum carcino-embryonic antigen (CEA) measurement and computed tomography (CT) as part of the trial protocol specified follow-up policy and their impact on survival in patients who experienced disease recurrence or developed metachronous primary colorectal cancer after adjuvant chemotherapy.

PATIENTS AND METHODS

Patients were entered onto the study within 12 weeks of curative resection of stage II and III adenocarcinoma of the colon or rectum. Before randomization, postoperative CT scan of thorax, abdomen, and pelvis, as well as CEA measurement, were performed to exclude previously unsuspected metastatic disease or development of metastatic disease postoperatively. Surgical specimens or representative slides were reviewed in the histopathology department to confirm tumor stage and resection margin status. Resection margins were required to be clear by at least 1 mm in all patients. Patients were required to have adequate hematologic, renal, and liver function and no concurrent severe or life-threatening illness. Preoperative radiotherapy was allowed in patients with rectal cancer. Participating patients gave written informed consent before they entered the study. The protocol was approved by the Scientific and Research Ethics Committee of the institutions taking part, as well as the North Thames Multicenter Research Ethics Committee.

Patients were randomly assigned to PVI FU given at a dose of 300 mg/m^2/d for 12 weeks or bolus FU (425 mg/m^2) and LV (20 mg/m^2) on days 1 to 5 every 4 weeks for six cycles. Patients, aged over 70 years and allocated to the bolus FU/LV arm, were treated with a reduced starting dose of 370 mg/m^2. Adjuvant radiotherapy was reserved for those patients at high risk of locoregional failure (T4 tumors), and was planned to start with the fourth cycle of bolus therapy or after completion of 12 weeks of PVI FU, which continued at a reduced dose of 200 mg/m^2 until completion of radiotherapy.

On completion of chemotherapy, the trial protocol-specified surveillance policy was followed. Patients were seen in the outpatient clinic every 3 months for the first year, every 6 months for the second year, and annually thereafter. Provided patients had remained disease-free, they could be discharged from further medical oncology follow-up after 5 years, although continued surgical surveillance was expected. Serum CEA was to be measured at baseline and at each clinic visit, and CT scans of thorax, abdomen, and pelvis were to be performed at baseline, 12 months, and 24 months following initial commencement of chemotherapy. Colonoscopy was recommended 12 months after the start of chemotherapy, although subsequent frequency of colonoscopy was left at the surgeons' discretion.

Seven hundred sixteen patients with colorectal cancer from seven oncology centers in the United Kingdom were randomly assigned to the study. Over three-quarters of the patients were recruited at our institution. For the purpose of this analysis, only those patients who were enrolled, and therefore underwent subsequent follow-up at our institution, were included. Although this analysis was planned before recruitment finished in 1999, it was a secondary analysis of this randomized study and was not protocol-predefined. In the initial analysis of the study, there were no differences in overall survival between the two treatment arms,[8] and therefore patients were not separated by treatment arms for the present analysis. Both disease recurrence and metachronous primary colorectal cancers were collectively classified as disease relapses. There were four principal ways in which relapse was detected: 1) symptomatic relapse (ie, relapse detected following the investigation of symptoms reported by the patients); 2) CEA-detected relapse (ie, relapse detected in asymptomatic patients following a rise in serum CEA level); 3) CT-detected relapse (ie, relapse detected in asymptomatic patients on 12-month or 24-month protocol specified routine CT scans). CT scans were undertaken usually within 2 weeks before the 12-month and 24-month routine clinic visit; 4) others (ie, other detection methods, such as colonoscopy).

Baseline characteristics among the four principal detection method (PDM) groups were compared using the χ^2 test for categoric variables (sex, site of primary tumor, tumor differentiation, tumor stage, and performance status). The only baseline continuous variable analyzed was age, which was tested for normality using the Kolmogorov-Smirnov test. This was found to be not normally distributed ($P = .03$), and therefore the Kruskal-Wallis test was used for comparing age among the four PDM groups.

Overall survival (OS) from randomization was calculated from the date of randomization onto the study to the date of death from any cause. OS from relapse was calculated from the date of either cancer recurrence or development of metachronous primary CRC to the date of death from any cause. Relapse-free survival (RFS) was calculated from the date of randomization onto the study to the date of either cancer recurrence or development of metachronous primary CRC. Both OS and RFS were estimated using the Kaplan and Meier method[9] and were compared among different PDM groups using the log-rank test.[10]

Univariate analysis was performed using the log-rank test to identify characteristics predictive for survival. The prognostic factors analyzed for effect were: performance status, age, sex, site of primary tumor, tumor differentiation, serum alkaline phosphatase, albumin, principal detection method, and potentially curative treatment for relapse (yes or no). Potentially curative treatment for relapse included hepatic or pulmonary resection for liver or lung metastases respectively, chemoradiotherapy with radical resection for local recurrences, and radical resection for metachronous cancers. Multivariate survival analysis was performed using Cox's proportional hazards model[11] and corrected for all the significant prognostic factors. Multivariate adjusted hazard ratios were estimated with the hazard ratio for symptomatic relapses set to 1. The proportions of patients undergoing hepatic or pulmo-

Table 1. Baseline Characteristics at Randomization

Characteristics	Principal Detection Methods: Symptomatic (n = 65) No. of Patients	%	CEA (n = 45) No. of Patients	%	CT (n = 49) No. of Patients	%	Others (n = 9) No. of Patients	%	Whole Cohort (N = 530)		P
Age, years											.333
Median	62		63		64		56		63		
Range	38–76		33–77		46–80		44–71		27–83		
Sex											.669
Male	36	55.4	22	48.9	26	53.1	3	33.3	267	50.4	
Female	29	44.6	23	51.1	23	46.9	6	66.7	263	49.6	
Site of primary tumor											.565
Colon	44	67.7	26	57.8	35	71.4	7	77.8	390	73.6	
Rectum	21	32.3	19	42.2	14	28.6	2	22.2	140	26.4	
Tumor differentiation											.461
Well	1	1.5	0	0	1	2.0	0	0	11	2.1	
Moderately	53	81.5	42	93.3	44	89.8	8	88.9	465	87.9	
Poorly	10	15.4	2	4.4	2	4.1	0	0	40	7.6	
Unknown	1	1.5	1	2.2	2	4.1	1	11.1	14	2.5	
Tumor stage											.692
Stage II	22	33.9	14	31	20	40.8	4	44.4	266	50.2	
Stage III	43	66.2	30	67	28	57.1	5	55.6	263	49.6	
Unknown	0	0	1	0.2	1	2	0	0	1	0.2	
Performance status											.674
0	27	41.5	19	42.2	20	40.8	3	33.3	243	45.9	
1	34	52.3	20	44.4	22	44.9	6	66.7	245	46.2	
2	3	4.6	4	8.9	6	12.2	0	0	38	7.2	
Unknown	1	1.5	2	4.4	1	2	0	0	4	0.8	

NOTE. *P* values refer to comparisons among principal detection method groups.
Abbreviations: CEA, carcino-embryonic antigen; CT, computed tomography.

nary resection for metastases in each PDM group were compared using Fisher's exact test.

All analyses were performed on an intention-to-treat basis. All end points were updated in February, 2003. Analyses were performed using the SPSS package (version 11.5, SPSS Inc, Chicago, IL).

RESULTS

Between August, 1993 and June, 1999, 530 patients were entered onto the trial at our institution. The median follow-up was 5.6 years. Disease relapses were detected in 155 patients (29%). Follow-up data were incomplete for one patient who was excluded from all analyses. Table 1 shows the baseline characteristics at randomization for the whole cohort and for different PDM groups. There were no significant differences among different PDM groups.

Figure 1 shows the number of patients detected by each PDM. Of the 49 patients whose recurrences were detected by CT, 14 patients had a concomitant elevated CEA at the clinic visit and were included in both the CEA and CT-detected groups. Thus, 35 (71%) asymptomatic patients in the CT-detected group had normal CEA and their relapses could not have been detected apart from surveillance CT. Of the 31 patients whose relapses were detected by CEA, sites of relapses were confirmed on CT in 24 patients. Relapse in the remaining patients was confirmed by positron emission tomography, apart from one patient who was found to have CEA of 1,282 μg/L, but refused to have radiologic confirmation by CT because of claustrophobia. Nine patients were detected by other methods; three were detected by routine colonoscopy (two local recurrences, one new primary), two were noted to have recurrent disease during surgery for stoma reversal or for unrelated intra-abdominal pathology, two were investigated for renal dysfunction, and two underwent CT scans at times other than those specified by the protocol.

Figure 2 shows the RFS for patients with relapses. There were significant differences among the PDM groups (log-rank, $P = .0027$). The median time to recurrence was: symptomatic, 20.6 months; CEA, 14.5 months; CT, 13.8 months; and others, 33 months. For the whole cohort of 530 patients, the 5-year RFS was 72.2% (95% CI, 67.1% to 75%). Thirty-four (22%) relapses occurred beyond 2 years (stage II, n = 13; stage III, n = 21). Table 2 shows the number of patients detected with each PDM by each completed year of follow-up.

Figure 3 shows the OS from randomization for patients with relapses. One hundred fifteen deaths have occurred. There were no significant differences among the PDM groups (log-rank, $P = .313$). Pairwise comparisons between

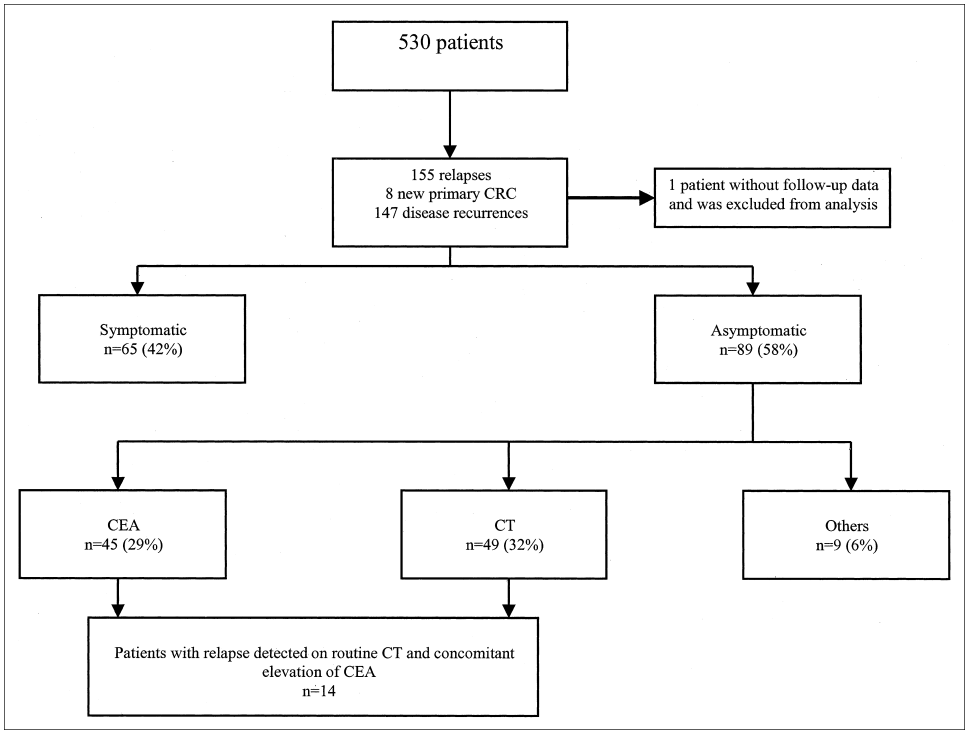

Fig 1. The number of patients detected by each principal detection method. Fourteen patients, with disease relapses detected on surveillance computed tomography (CT) and also had a concomitant elevation of carcino-embryonic antigen (CEA), were included in both CT and CEA-detected groups. CRC, colorectal cancer.

each PDM group showed: CT versus symptomatic log-rank, $P = .227$; CEA versus symptomatic log-rank, $P = .842$. Median OS from randomization was: symptomatic, 37.5 months; CEA, 37.3 months; and CT, 50.7 months. Five-year survival rates were: symptomatic, 30.6% (95% CI, 19.9% to 42.0%); CEA, 22.9% (95% CI, 11.7% to 36.3%); and CT, 30.8% (95% CI, 17.9% to 44.7%). For the whole cohort of 530 patients, the 5-year survival rate was 74.5% (95% CI, 70.3% to 78.1%).

Figure 4 shows the OS from the time of relapse of patients with relapses. There were significant differences among PDM groups (log-rank, $P = .021$). Pair-wise comparison between each PDM group showed: CT versus symptomatic log-rank, $P = .0046$; CEA versus symptomatic log-rank, $P = .098$. Median OS from the time of relapse was: symptomatic, 12.6 months; CEA, 19.2 months; and CT, 26.4 months. Five-year survival rates from the time of relapse were: symptomatic—no patients have reached 5 years yet; CEA, 18.6% (95% CI, 8.7% to 31.4%), and CT, 25.9% (95%CI, 12.8% to 41.2%).

Thirty-nine (26%) of 154 patients with relapses were referred for radical resection. Six of these patients were found to have unresectable disease at the time of surgery, so 33 patients actually proceeded to potentially curative treatment. Figure 5 shows the details of these patients. Patients who proceeded to potentially curative treatment had a highly significant survival advantage compared with those who did not (log-rank, $P < .00001$; Fig 6). Among those

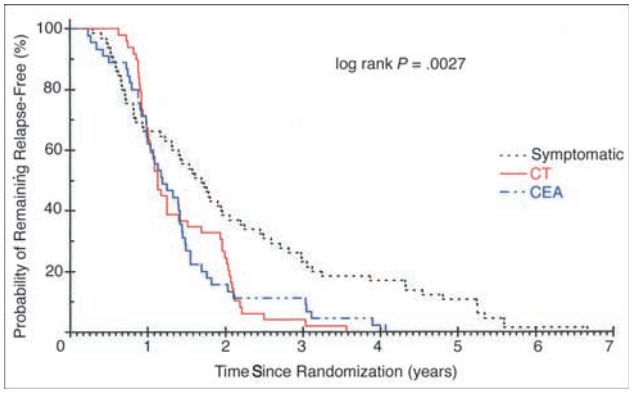

Fig 2. Relapse-free survival for all patients with relapses. CT, computed tomography; CEA, carcino-embryonic antigen.

Table 2. Number of Patients Detected With Each Principal Detection Method by Completed Year of Follow-Up

Completed Year of Follow-Up	Symptomatic (n = 65)	CEA (n = 45)	CT (n = 49)	Others (n = 9)
Year 1	22	18	23	4
Year 2	18	21	26	0
Year 3	10	1	0	1
Year 4	4	4	0	2
Year 5	4	1	0	1
Beyond 5 years	7	0	0	1

Abbreviations: CEA, carcino-embryonic antigen; CT, computed tomography.

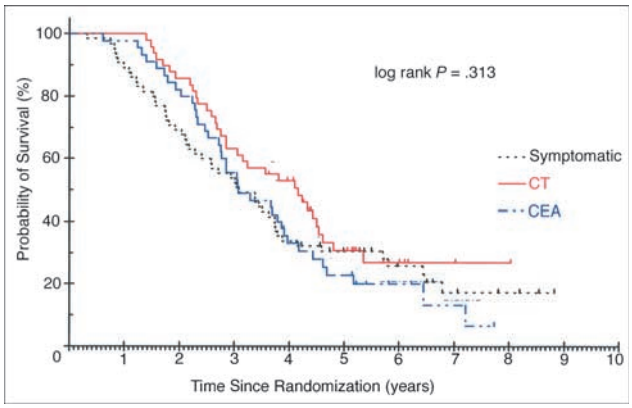

Fig 3. Overall survival from randomization. CT, computed tomography; CEA, carcino-embryonic antigen.

patients who underwent radical resection and whose relapses were detected on CT (n = 15), only two patients had a concomitant elevated CEA. Both patients underwent solitary liver metastasis resection. All CT-detected patients who proceeded to lung metastases resection had normal CEA and therefore could not have been detected otherwise. Twelve-month routine CT detected relapse in eight patients, whereas 24-month routine CT detected relapse in seven patients. The number of stage II and stage III CT-detected patients was approximately the same at 12 and 24 months.

However, in the CT-detected group, six patients underwent liver resection and seven underwent pulmonary metastatic resection, whereas only one patient underwent liver resection and one patient underwent pulmonary metastatic resection in the symptomatic group (13 [26.5%] of 49 patients in CT-detected group versus two [3.1%] of 65 patients in the symptomatic group; $P < .001$). Similarly, in the CEA-detected group, seven patients underwent liver resection and one patient underwent pulmonary metastatic resection, which was significantly more than in the symptomatic group (eight [17.8%] of 45 patients in the CEA-detected group versus two [3.1%] of 65 patients in the symptomatic group; $P = .015$). There was no difference between the CEA-detected and the CT-detected groups in the proportions of patients undergoing liver or pulmonary metastatic resection ($P = .309$).

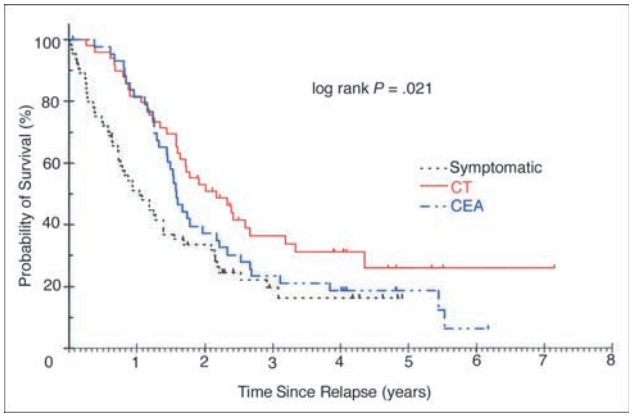

Fig 4. Overall survival from the time of relapse. CT, computed tomography; CEA, carcino-embryonic antigen.

Table 3 shows the relapses detected by each anatomic area of CT. Of the 49 asymptomatic patients whose relapses were detected by CT, 39 had solitary sites of relapse. Whereas CT abdomen detected the most number of patients with solitary site of relapse, CT thorax detected the greatest relative proportion of patients who could proceed to curative resection for solitary relapse. Two patients with colon cancer had solitary pelvic recurrences, both of whom could not undergo curative resection.

Table 4 shows the multivariate survival analysis. For multivariate survival analysis from randomization, factors associated with poor survival were: not proceeding to curative resection for disease relapse, elevated alkaline phosphatase, and high total protein. For multivariate survival analysis from time of relapse, factors associated with poor survival were: not proceeding to curative resection for disease relapse and elevated alkaline phosphatase. The CT-detected group was associated with a trend towards improved survival compared with the symptomatic group ($P = .072$). Time to disease relapse did not predict for survival after relapse ($P = .374$).

DISCUSSION

In this analysis, we evaluated the role of routine serum CEA measurement and CT scanning of thorax, abdomen, and pelvis at 12 and 24 months in the surveillance of patients after adjuvant chemotherapy for CRC. The follow-up policy was protocol-specified, thus uniform approach was applied to all patients. In addition, all 530 patients had received FU-based chemotherapy in this trial. The last patient was randomized 44 months before this analysis, thus the data for disease relapses were relatively mature.

Twenty-nine percent of our patients had disease recurrences or metachronous primary CRC. Of the 154 patients with follow-up data, symptomatic recurrences occurred in 42% of patients. Routine CEA and CT detected 90% of asymptomatic recurrences, with routine CT identifying the greatest number of patients who were able to have potentially curative surgery for their relapse. Although the OS from randomization for patients detected by different PDM did not show any significant differences, once the patients have been diagnosed with disease relapse, the CT-detected group had significantly prolonged survival compared with the symptomatic group (log-rank, $P = .0046$). This survival advantage could partly be as a result of lead time bias from earlier diagnoses because the CT group had a median time to recurrence that was 6.8 months less than the symptom-

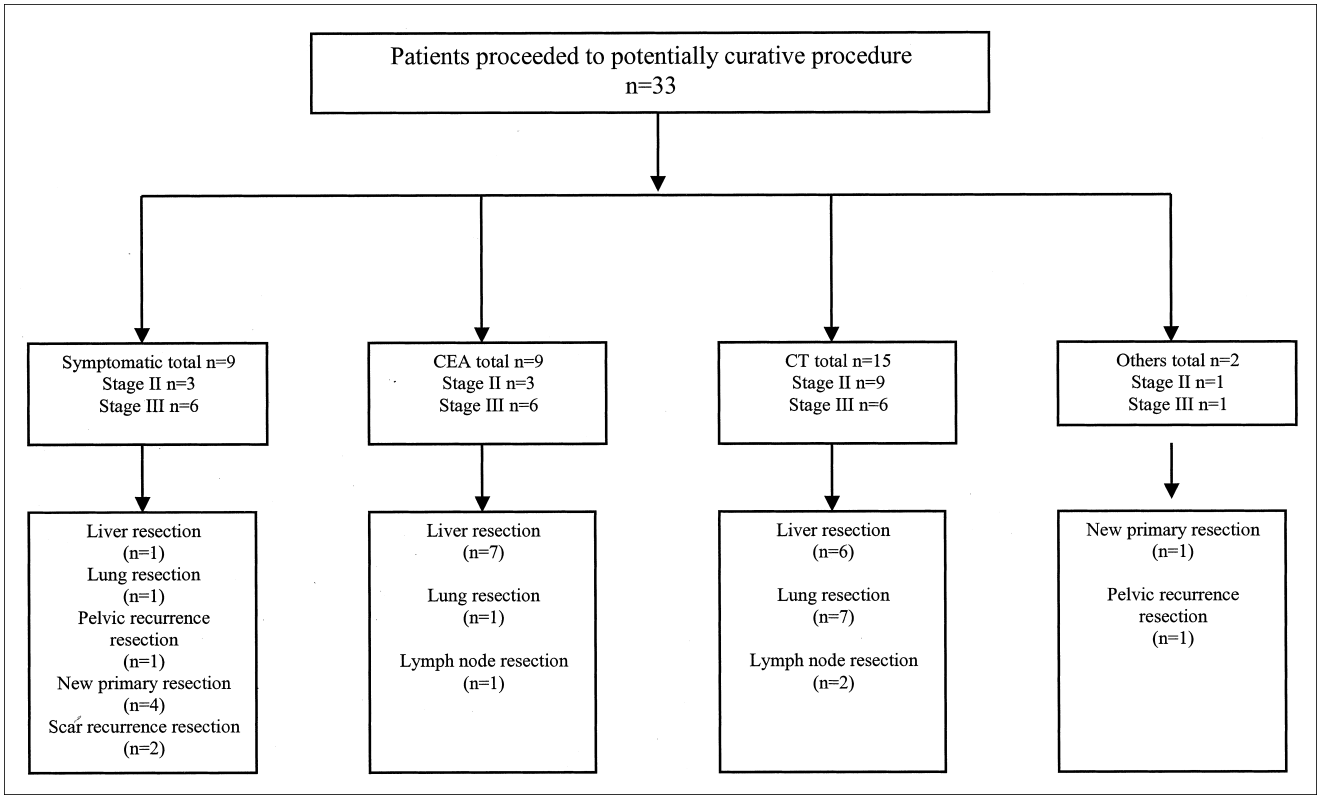

Fig 5. Patients who proceeded to potentially curative treatment. CT, computed tomography; CEA, carcino-embryonic antigen.

atic group. However, after relapse, the CT group had a 13.8-month median survival advantage compared to the symptomatic group—twice the potential lead time. This difference in survival could not be explained by the fact that the symptomatic group had biologically more aggressive disease as their relapses occurred significantly later compared with the CT group. In addition, time to disease relapse did not predict for survival after relapse in our cohort of patients in the univariate analysis. This survival advantage was more probably related to the fact that CT scanning was able to identify patients with small volume metastases amenable to radical resection. By the time patients became symptomatic from their recurrent disease, only a small proportion of patients (3.1%) could undergo curative resection for liver or lung metastases, whereas in asymptomatic patients in whom recurrence was detected by surveillance CEA and/or CT, 23.8% underwent liver or lung resection. The proportion of patients undergoing liver and pulmonary metastatic resection was significantly higher in the CT-detected group ($P < .001$) and the CEA group ($P = .015$) compared with the symptomatic group. In particular, CT scanning allowed more patients to undergo pulmonary resection—all of whom were asymptomatic and did not have concomitant elevated CEA, therefore would not have been identified otherwise.

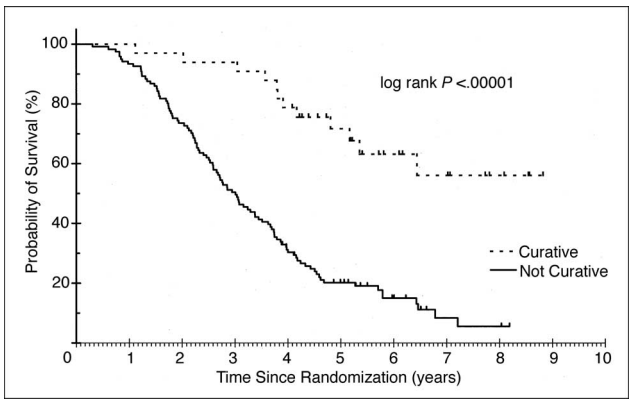

Fig 6. Overall survival from randomization for patients who proceeded to potentially curative treatment and those who did not.

Two recent systematic reviews and meta-analyses of follow-up strategies for 1,342 patients treated for localized CRC have found an OS advantage for patients undergoing more intensive follow-up (odds ratio [OR], 0.67; 95% CI, 0.53 to 0.84;[6] risk ratio [RR], 0.81; 95% CI, 0.70 to 0.94,[7] respectively). The effect was most pronounced in trials that used CT and frequent measurement of CEA (RR, 0.73; 95% CI, 0.60 to 0.89; $P = .002$).[7] Intensive follow-up was associated with significantly earlier detection of all recurrences

Table 3. Relapses Detected by Each Anatomical Area of CT

	Any Number of Sites of Relapse		Solitary Site of Relapse		Curative Resection for Solitary Relapse	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
CT thorax	17/49	35	11/39	28	8/11	72.7
CT abdomen	31/49	63	22/39	56	8/22	36.3
CT pelvis	12/49	24	6/39*	15	1/6	16.6

Abbreviation: CT, computed tomography.
*Two patients with colon cancer had solitary pelvic recurrence, both of whom could not undergo curative resection.

with a difference in means of 8.5 months ($P < .001$).[7] Our results were consistent with the conclusions from the meta-analysis, as both CT and CEA groups had significantly shorter time to tumor recurrence, and CT scanning was associated with a significantly better survival from the time of relapse compared to those who developed symptomatic relapse. However, the five randomized controlled trials included in these meta-analyses[12-16] recruited patients with resected CRC of all stages, and not all patients received adjuvant chemotherapy. Moreover, these studies were conducted between the 1980s and early 1990s, at a time when CT scanning was less widely available. Two of the studies advocated CT of the liver only[14,16] and one study performed CT of the pelvis.[13] Chest radiography was used in all studies to detect pulmonary recurrences. However, one must bear in mind that our surveillance program is not a randomized comparison, and therefore results are not directly comparable to those included in the meta-analyses.

In our study, CEA was the first method of detection in one fifth of the relapsed patients. One could argue that the relapses detected by CT that had a concomitant elevation of CEA would have been detected by CEA anyway. However, CT scans were still required to identify sites of recurrence. Nevertheless, excluding these patients, routine CT would still have detected more patients suitable for potentially curative surgery than routine CEA measurement. The value of postoperative CEA monitoring has been evaluated in a number of nonrandomized studies.[17-19] These studies illustrated the usefulness of CEA monitoring in detecting asymptomatic liver metastases which were amenable to resection. Survival in these studies, however, was not independently improved by CEA monitoring alone, consistent with the results of our study. Final results from the only randomized study evaluating the role of CEA in almost 1,500 patients are still pending.[20] In this study, patients with CEA rise were randomly assigned to the aggressive arm, leading to work-up towards second look surgery or the conventional arm, in which their clinicians remained unaware of the CEA rise or the randomization, and they could advise on further surgery when the recurrence became clinically evident. The initial results suggested that although the recurrence was detected earlier in the aggressive arm, no OS difference is discernable between the two arms.

Table 4. Multivariate Survival Analysis

Predictive Factors	*P*	Hazard Ratio	95% CI
Overall survival from randomization			
Proceeding to potentially curative surgery for disease relapse			
No	< .0001	4.421	2.405 to 8.124
Yes		1	
Alkaline phosphatase	.036	1.009	1.001 to 1.018
Total protein	.019	1.053	1.008 to 1.099
Overall survival from relapse			
Proceeding to potentially curative surgery for disease relapse			
No	< .0001	4.469	2.431 to 8.219
Yes		1	
Alkaline phosphatase	.007	1.011	1.003 to 1.019

Several studies evaluated surveillance policies in patients participating in adjuvant chemotherapy trials. Table 5 shows a selection of these studies.[21-24] In both US Intergroup studies for colon cancer, CT scanning was not mandated in the follow-up policy,[22,23] whereas the Dutch study included liver ultrasound or CT at every follow-up visit.[21] It is perhaps not surprising, therefore, that the proportion of relapses detected by imaging was considerably higher in both the Dutch study as well as our own. Consequently, the number of patients detected by imaging who could proceed to curative resection for their metastases or second primaries was also higher. The higher number of patients detected by symptoms in our study may be related to the inclusion of rectal cancer patients, which is consistent with the Intergroup 0114 study.[24]

After potentially curative surgery for their primary tumors, approximately one of every five patients will develop liver metastases, and approximately one out of every 12 patients will develop pulmonary metastases.[1] Despite the lack of randomized data, it is now an accepted practice for patients with potentially resectable disease to be offered surgery. Resection of liver metastases from colorectal carcinoma is associated with 5-year survival rates of approxi-

Table 5. Selected Studies Who Have Evaluated Surveillance Policies in Patients Participating in Adjuvant Chemotherapy Trials

	Intergroup 0035[22]		Intergroup 0089 ECOG Patients[23]		IKN Colon Trial Group[21]		Intergroup 0114[24]		Our Study	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total No. of patients	1,247		1,356		500		1,695		530	
Primary tumor	Colon		Colon		Colon		Rectum		Colon and rectum	
Patients with relapses	548	44	421	31	213	42.6	715	42	154	29
Median follow-up, months	84		43.6		43		106.8		68	
Tumor staging included	Stage II & III		Stage II & III		Stage III		Stage II & III		Stage II & III	
Patients detected by each relapse detection method										
Symptoms	NR		130	30.9	49	23	65†		65	42
CEA	NR		161	38.2	40	18.8	17†		31	20
Colonoscopy	NR		29	6.9	13	6.1	4†		3	1.9
Imaging	NR		28	6.7	94	44.1	NR†		49	32
Others/combination	NR		73	17.4	17	8.0	NR†		6	3.9
No. of patients proceeding to curative resection	109	19.9	96	22.8	42	19.7	171	23.9‡	33	21.4
Patients detected by each diagnostic category and proceeding to curative resection										
Symptoms	27	24.8	24	25	12	28.6	NR§		9	27.3
CEA	41	37.6	30	31.2	3	7.1	NR§		7	21.2
Colonoscopy	12	11	14	14.6	8	19	NR§		1	3
Imaging*	24	22	12	12.5	16	38.1	NR§		15	45.5
Others/combination	5	4.6	16	16.7	3	7.1	NR§		1	3

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IKN, Integraal Kankercentrum Noord Nederland; CEA, carcino-embryonic antigen; NR, not reported.

*Imaging included ultrasound, computed tomography and chest radiography.

†Precise manner in which recurrent disease was detected was not determined.

‡Only patients with solitary site of relapse were analyzed.

§Exact values not reported, but no difference among the relapse detection methods for patients who proceeded to curative resection.

mately 25%.[25] However, more recently, introduction of new drugs such as oxaliplatin has allowed sufficient down-sizing of unresectable liver metastases to render them resectable following chemotherapy. In one study, half of the patients with previously unresectable metastases were down-sized to enable potentially curative hepatic resection.[26] Although lung metastases are less common than liver metastases, similar long-term survival has been observed after complete resection with 5-year survival ranging from 30% to 60%.[24,27-32] Moreover, pulmonary resection can be performed safely after previous resection of hepatic metastases with long-term survivors.[28] The need to detect small volume metastases amenable to metastatic resection has become increasingly important in the surveillance of resected colorectal cancer.

However, two areas of our surveillance policy require refinement. First of all, more than one fifth of our relapses occurred beyond 2 years and secondly, 40 symptomatic relapses occurred in the first 2 years despite annual CT scanning and more frequent CEA monitoring. Additional CT scanning of thorax, abdomen, and pelvis at 36 months and ultrasound imaging of liver at 6, 18, and 30 months may allow more asymptomatic patients with small tumor burden to be detected, thus potentially allowing more curative surgery to be performed for disease relapse. However, although a meta-analysis did not find any difference in the accuracy of detecting liver metastases between ultrasound and CT imaging, two-thirds of CT studies included in the meta-analysis were using nonhelical CT.[33] With the advent of spiral and multidetector CT scanners with improved spatial resolution and multiplanar capability, the accuracy of detecting liver metastases has improved considerably and imaging of entire liver can take as little time as 10 seconds.[34] CT scanning should now be considered to be the surveillance imaging of choice after curative resection of colorectal cancer. In patients with colon cancer, routine pelvic CT did not lead to detection of recurrent disease amenable to curative resection in our cohort, thus its value may be limited to the surveillance of rectal cancer patients.

Our analysis has several limitations. The comparisons among different principal detection methods were not randomized, although the baseline characteristics for these patients did not differ significantly. In addition, this analysis was based on patients treated at our institution only, but there are no biologic reasons why their relapse patterns should be different from those treated outside our institu-

tion since this includes over three quarters of patients in the study. Our observations are therefore hypothesis-generating and might arguably require confirmation in future randomized studies. Two large randomized studies are being conducted or planned in Italy and the United Kingdom evaluating "intervention" versus "minimalist" follow-up with CEA monitoring and CT/ultrasound scanning, recruiting 7,810 patients in total. Survival, quality of life, and economic implications will all be addressed in these studies.[6]

Although several studies have estimated the cost of follow-up per diagnosed resectable recurrence, they typically report cost-effectiveness ratios that are not incremental.[35] If one follow-up strategy detected fewer recurrences with lower cost, a more expensive strategy that detected more recurrences may still be worth the extra cost. Although we have not attempted to perform cost-effectiveness analysis in our cohort of patients, three studies have estimated the effect of follow-up on (quality adjusted) life expectancy.[36-38] A high degree of modeling was used in all these studies to aggregate estimates from different data sources.[35] Modeling is especially important because of long time horizon, large number of feasible follow-up strategies, possibly small differences in survival between the strategies, and it also allows prompt corrections of the estimate if recurrence rates decrease because of improved adjuvant treatment.[35] However, the assumptions used in these models will require close scrutiny when their results are used for policy making.

In conclusion, only 3.1% of patients with symptomatic, recurrent colorectal cancer underwent a curative resection for liver or lung metastases. In asymptomatic patients in whom recurrence was detected by surveillance CEA and/or CT, 23.8% underwent liver or lung resections. CT surveillance detected the majority of patients who were suitable for pulmonary metastasectomy, and who otherwise had a normal CEA. In patients with colon cancer, surveillance pelvic CT did not lead to detection of recurrent disease suitable for curative resection. Surveillance CT and CEA are valuable components of postoperative follow-up in stage II and III colorectal cancer.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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