Does Methodic Long-Term Follow-Up Affect Survival After Curative Resection of Colorectal Carcinoma?

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Records of 487 patients in long-term follow-up after R_0 resection of colorectal carcinomas between January 1, 1980 and December 31, 1989 were analyzed. Every patient underwent regular examinations according to a defined schedule after curative resection of colorectal carcinoma. The date of evaluation was June 31, 1991. During a median observation time of 48 months (range, 15–132 months), tumor recurrence was observed in 149 patients (30.6 percent), with 56.4 percent of these suffering from tumor-associated symptoms. As the primary manifestation of tumor recurrence, only distant metastases (DM) were found in 76 patients (51 percent), only local recurrence (LR) in 46 patients (30.9 percent), and both DM and LR in 27 patients (18.1 percent). Patients with rectal carcinoma developed LR more frequently ($P < 0.05$) (19.5 percent) than patients with colon carcinoma (11.8 percent). The probability of developing distant metastases was not different ($P < 0.05$) for colon or rectal carcinoma but depended on primary tumor stage ($P < 0.05$). Only 36 patients (24.2 percent) with recurrence could undergo further curative resection. Fifty patients (33.5 percent) were given palliative therapy, and 63 patients (42.3 percent) were given no oncologic treatment. Only 9 of the 36 patients (6 percent of all recurrence patients) undergoing R_0 resection were free of tumor for more than two years. In no case was a third R_0 resection possible. The survival time of these patients was increased significantly after R_0 resection of tumor recurrence ($P = 0.03$). Our study suggests that only a very few patients may live longer as a result of regular follow-up programs after curative resection for colorectal carcinoma. [Key words: Colorectal carcinoma; Follow-up; Recurrences]

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For many years a regular follow-up regimen has been the standard of care in oncologic treatment after curative resection of colorectal carcinoma.[1–4] Follow-up naturally includes psychologic care following large intestine resection, but the most important purpose of follow-up is early detection of recurrent and metachronous carcinoma.[5–8]

Because asymptomatic early recurrences and carcinomas can be operated on with curative intention more often than can symptomatic ones,[9, 10] follow-up programs with regular examinations were introduced to detect recurrence in the asymptomatic stage. In our department, follow-up after curative resection of colorectal carcinoma has been carried out since 1980 according to a defined schedule for all patients with colorectal carcinoma[4, 11] (Table 1). The aim of this study is to evaluate whether patients undergoing this regular long-term follow-up regimen derive any benefit in survival from the program.

METHODS

The endpoints of our study were the proportion of further curative resections and the prolongation of survival time following oncologic treatment of recurrences.

Between January 1, 1980 and December 31, 1989, 539 patients undergoing R_0 resection of colorectal carcinoma were entered into a regular follow-up program (Table 1). Only 487 patients underwent regular checkups. The dropout rate was 12.4 percent.

These 487 patients form the basis of this study. They underwent only primary surgical treatment with no added adjuvant chemotherapy or radiotherapy. Follow-up examinations were carried out following a defined schedule (Table 1).

The following clinical data of the 487 patients were analyzed: sex, age, primary tumor stage, primary tumor localization, preoperative and postoperative carcinoembryonic antigen (CEA) levels, localization of recurrence, recurrence-free interval, and survival time. The date of evaluation was June 30, 1991.

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Table 1.
Follow-Up Program for all Patients After R_0 Resection of Colorectal Carcinomas

Months After Primary Resection	3	6	9	12	18	24	36	48	60
History, physical examination	x	x	x	x	x	x	x	x	x
CEA* level, blood tests	x	x	x	x	x	x	x	x	x
Abdominal sonography	x	x	x	x	x	x	x	x	x
Rectoscopy	x		x						
Colonoscopy or barium enema		x		x	x	x	x	x	x
Chest x-ray		x		x		x	x	x	x

* CEA = carcinoembryonic antigen.

At the time of primary resection, all tumors were classified according to the four stages of the TNM system of the UICC[12] and according to anatomic tumor location.[13]

If patients had tumor-associated symptoms at the time of the diagnosis of recurrence, recurrence was classified as symptomatic.

For our study, recurrences were subdivided into two groups: local recurrences and distant metastases.

During the 10-year period, any oncologic treatment carried out (further curative, palliative, or no oncologic treatment) was recorded for all patients with recurrence. R_0 resection has been defined as curative oncologic treatment, and radiotherapy, chemotherapy, or R_2 resection of recurrences has been defined as palliative oncologic treatment. For all patients who underwent further curative treatment, it was recorded whether they had developed a second recurrence and how long their recurrence-free interval had been.

The five-year mean survival time of patients was estimated for each primary tumor stage. The one-year mean survival time of patients with recurrence of carcinoma was estimated for each oncologic treatment (none, palliative, or curative).

Survival curves were estimated according to Kaplan-Meier, and differences were tested using the log-rank test.[14] Associations between qualitative parameters were analyzed with Fisher's exact test for contingency tables. Comparisons with reference to continuous parameters were carried out using the *t*-test. The probability of Type I error was set to $\alpha = 0.05$.

RESULTS

Following R_0 resection of colorectal carcinoma, 487 patients underwent long-term follow-up between January 1, 1980 and December 31, 1989. The mean time of follow-up was 48 months (range, 15–132 months).

The proportion of women was 56.8 percent (Fig. 1). The mean age of the patients was 67.6 years at the time of primary resection and was on average 2.3 years higher ($P < 0.01$) for women than for men. Most primary tumors (43.2 percent) were resected in Stage 2. Stages 1 and 3 were found in 25.9 percent, and Stage 4 was found in 5 percent.

Recurrences were detected in 149 patients (30.6 percent). As the primary manifestation of tumor recurrence, only local recurrence was found in 46 patients (30.9 percent), only distant metastases were found in 76 patients (51 percent), and both local recurrence and distant metastases were found in 27 patients (18.1 percent).

Local Recurrence

Local recurrence as the first manifestation of tumor recurrence was found in 73 patients. Local recurrence occurred more often ($P < 0.05$) after resection of rectal carcinoma than after resection of colon carcinoma. The cumulative percentage after five years was 19.5 percent for rectal carcinoma and 11.8 percent for colon carcinoma (Fig. 2).

There was an association between frequency of local recurrence and tumor stage for both colon and rectal carcinomas ($P < 0.05$). After five years, local recurrences were detected in 9.9 percent of the patients for Stage 1, in 13.6 percent of Stage 2, in 21.5 percent for Stage 3, and in 20 percent for Stage 4 (Fig. 3).

Metastases

During follow-up, 103 patients (21.1 percent) developed distant metastases as the primary manifestation of recurrence. Metastases were found in the liver in 80 percent and in the lung in 20 percent.

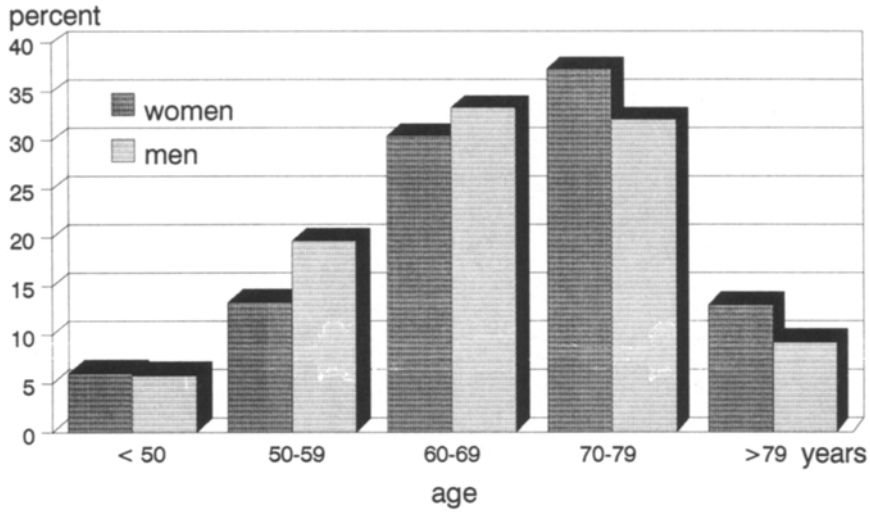

Figure 1. Sex and age of patients after R_0 resection of colorectal carcinomas (N = 487).

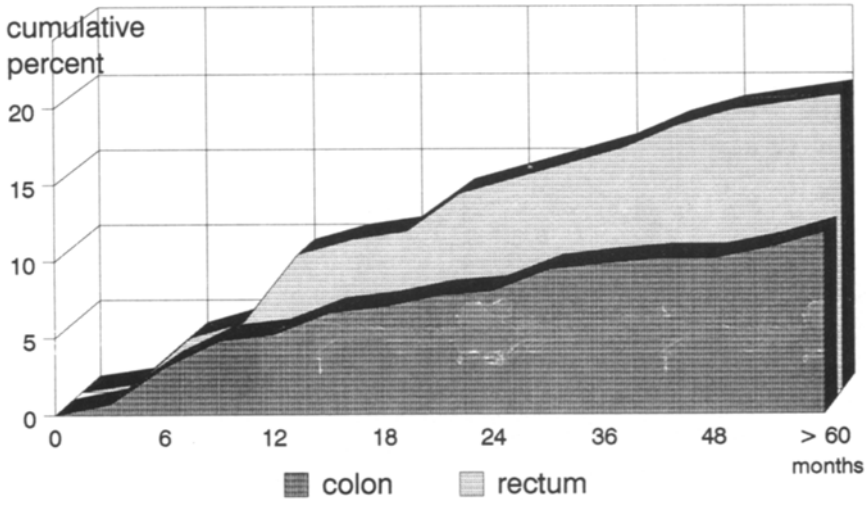

Figure 2. Cumulative percentage of local recurrence (N = 73) after R_0 resection of carcinomas of the rectum and colon.

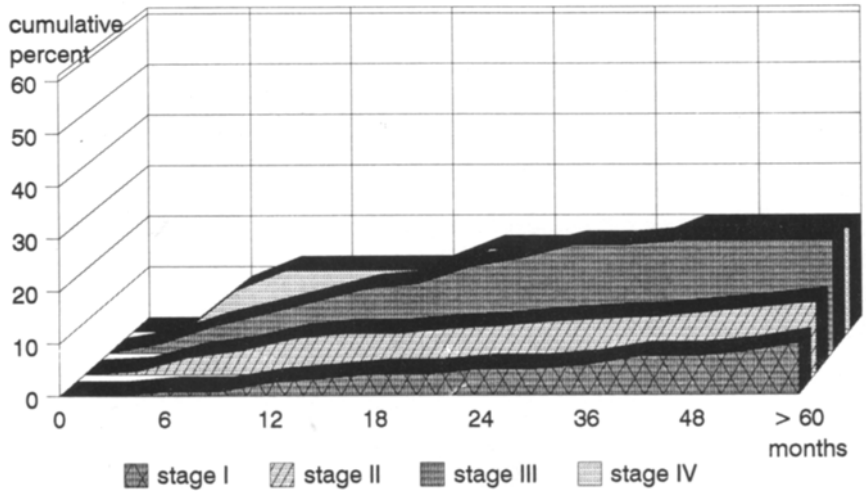

Figure 3. Cumulative percentage of local recurrence (N = 73) after R_0 resection of colorectal carcinoma for each tumor stage.

Nine patients presented with both. The frequency of metastases increased with the primary tumor stage ($P < 0.05$) (Fig. 4), but there was no association with the location of the primary tumor (colon *vs.* rectum) ($P > 0.05$).

CEA Levels

Preoperative CEA level was in the normal range (0.5–5.0) in 86 percent. Elevation of preoperative CEA level correlated with tumor stage ($P < 0.05$).

Only 10.4 percent of patients with preoperative normal CEA levels developed tumor recurrence, whereas recurrence was found in 56.9 percent of patients with preoperative increased CEA level (>5 ng/ml) ($P < 0.01$). The correlation between a preoperative elevated CEA level (>5 ng/ml) and the probability of recurrence did not depend only on advanced tumor stage. Regression analysis revealed that increased preoperative CEA level was an independent risk factor for tumor recurrences in Stages 2 and 3 ($P < 0.05$).

Only 75 patients (50.3 percent) had an increased CEA level at the time tumor recurrence was diagnosed. Increased CEA level was found in 31 patients three months before tumor recurrence could be localized by physical examination, chest x-ray, pelvic or liver CT scan, endoscopy, or endoluminal sonography.

Some 53.9 percent of patients with metastases and 74.1 percent of patients with both metastases and local recurrence showed an increased CEA level at the time recurrence was diagnosed. However, only 23.3 percent of the patients with local recurrence had an increased CEA level.

Only one case was a false-positive increased CEA level found in follow-up. This patient had a primary preoperative CEA level of 400 ng/ml and also had a postoperative CEA level of 400 ng/ml. He has been free of tumor recurrence for six years.

Oncologic Treatment of Recurrent Disease

During the period of the study, malignancy recurred in 149 cases (30.6 percent). At the time of diagnosis of recurrence, only 43.6 percent of these patients had no tumor-associated symptoms (Table 2).

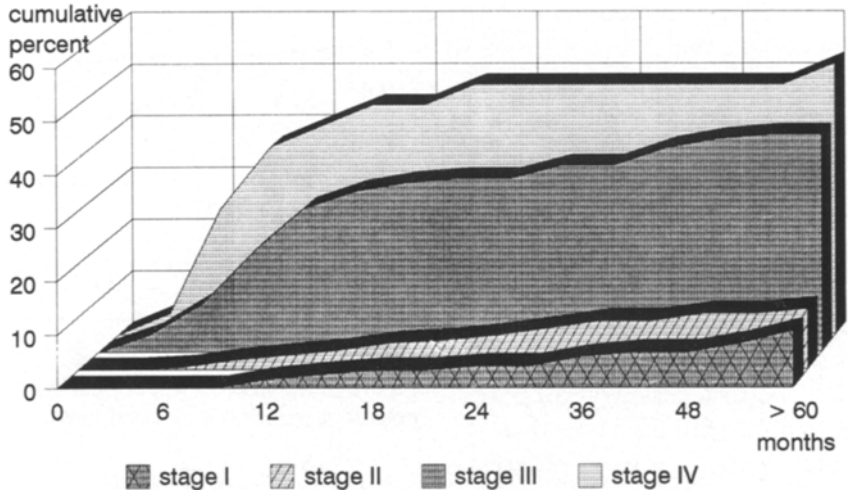

Figure 4. Cumulative percentage of metastases (N = 103) after R_0 resection of colorectal carcinoma for each tumor stage.

Table 2.
Asymptomatic and Symptomatic Tumor Recurrences of Colorectal Carcinomas (n = 149) in Relation to Oncologic Treatment Carried Out

	Asymptomatic		Symptomatic		All	
	n	%	n	%	n	%
No oncologic therapy	26	17.4	37	24.8	63	42.3
Palliative therapy	17	11.4	33	22.1	50	33.5
Curative resection	22	14.8	14	9.4	36	24.4
All	65	43.6	84	56.4	149	100.0

Thirty-six of these patients (24.2 percent) had isolated recurrent disease and underwent further curative resection (Table 3). Fifty patients (33.5 percent) were given only palliative therapy (chemotherapy, radiation, or R_2 resection). Sixty-three patients (42.3 percent) could not undergo any oncologic treatment because of advanced age, poor general condition, or advanced recurrence.

For patients with distant recurrence, the average recurrence-free interval was significantly less ($P < 0.05$) between those able to undergo curative resection (31 months) and candidates for only palliative treatment (18 months). The longer the recurrence-free interval, the greater the probability to curatively resect the recurrence. This seemed valid for local recurrence although there was only a slight difference ($P = 0.2$) between the average recurrence-free intervals for curative resection (26 months) and for noncurative treatment (18 months).

Thirty-six (24.2 percent) of the 149 patients who developed recurrence could undergo further R_0 resection (Table 2). This is only 7.4 percent of the 487 patients who were regularly followed. Asymptomatic recurrences could be treated curatively more often than symptomatic ones.

After curative resection of recurrence, only 9 of the 36 were free from tumor for more than two years. Twenty-seven of the 36 died within two years after surgery or developed a second recurrence and could only be given palliative treatment (radiotherapy or chemotherapy). In no case was a third R_0 resection possible.

If the success of the follow-up program was defined as the proportion of asymptomatic curative re-resection (n = 22), then success would be 4.5 percent. In fact, only nine patients (less than 2 percent of all patients) in the follow-up program were free from tumor for more than two years after curative re-resection.

Table 3.
R_0 Resections of Tumor Recurrences (n = 36)

Pneumonectomy	1
Atypical lung resection	4
Major hepatic resection	5
Hepatic wedge resection	13
Colon re-resection	4
Abdominoperineal excision	7
Sacral excision	2

Survival

The five-year-survival probability after primary R_0 resection was 0.81 in Stage 1, 0.74 in Stage 2, 0.43 in Stage 3, and 0.16 in Stage 4 (Fig. 5).

The survival curve of patients with recurrence showed that patients able to undergo R_0 resection of recurrence survived longer at nine months of follow-up than did patients who did not undergo curative resection ($P = 0.03$) (Fig. 6). There was no difference in median survival time between palliative and no oncologic treatment. Subdivision of these groups into symptomatic and asymptomatic recurrences did not change the survival curves significantly ($P = 0.8$).

DISCUSSION

Standardized long-term follow-up programs for colorectal carcinomas have been established in many institutions. Outpatient follow-up is important for treatment of postoperative complications or to palliate incurable recurrences, but the purported primary aim of outpatient follow-up programs after curative resection is to discover recur-

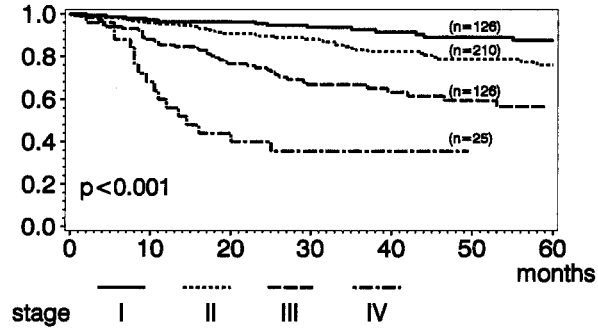

Figure 5. Survival curves of patients after R_0 resection of colorectal carcinoma for each tumor stage (N = 487).

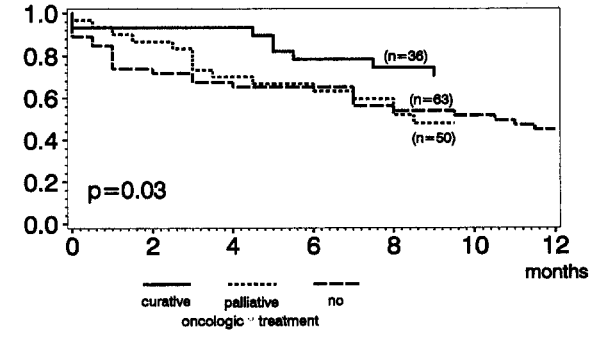

Figure 6. Survival curves of patients with tumor recurrence (N = 149) in relation to oncologic treatment (none, palliative, and curative).

rent or metachronous carcinoma at an early asymptomatic stage so that further potentially curative treatment can be carried out.

To detect or treat symptomatic recurrences or metachronous carcinoma, it is not necessary to establish follow-up programs. There would be no need to bother patients after curative resections, and one would wait until patients with recurrences became symptomatic. In this case, one would introduce further examinations. Therefore, to evaluate the success of a long-term follow-up program after primary R_0 resection, one must determine the proportion of all asymptomatic patients who underwent further curative resection. Only this proportion should count as a clear measure of success of long-term systematic follow-up.

Some authors[2, 5, 7, 8, 15–18] describe their long-term follow-up as successful, while others[6, 19–24] are more critical. It has not been proven that long-term follow-up prolongs survival time after curative resection of colorectal carcinoma.

Most studies to date, however, have not considered the difference between asymptomatic and symptomatic recurrences. It is true that early, asymptomatic recurrences can be cured more often than can symptomatic recurrences.[9] It is only the detection of early recurrences, which are potentially curable, that justifies regular follow-up. Symptomatic recurrences can be detected without follow-up schedules.

Although similar follow-up programs were used, Fritsch *et al.*[2] and Schiessel *et al.*[8, 18] reported about 50 percent asymptomatic recurrence, Cochrane *et al.*[25] found only about 42 percent, and Schildberg,[26] evaluating local recurrences only, found only 21 percent recurrences in the asymptomatic stage. It is not possible to compare these results, however, because each study defines the terms asymptomatic and symptomatic differently. In our study, tumor recurrence was considered symptomatic if, at the time of diagnosis, the patient suffered from any tumor-associated complaint such as loss of weight, abdominal or pelvic pain, rectal or vaginal bleeding, or change in bowel habit. Even without a follow-up schedule, such tumor-associated complaints would cause the doctor to carry out further examination to exclude the possibility of recurrence.

Patients only benefit from follow-up programs if tumor recurrence is detected in the early stage and resection with curative intent can be done. In general, the proportion of curative resection for all cases of recurrence is 15 to 30 percent, and the proportion of curative resection for all patients in follow-up is only 3 to 7 percent.[5, 7, 8, 16–18, 23, 26, 27] These figures are for both asymptomatic and symptomatic recurrences. Our results also suggest that only a few patients actually benefit from follow-up.

Local recurrence can seldom be resected curatively.[26, 28] The proportion of further curative resections, that is, the success of follow-up, depends on the primary operation. The more radical this is, the less possible further curative resection becomes. It is more often possible to resect distant metastases in the liver and lung than local recurrences. In our study, local recurrences of colon carcinoma could be curatively reoperated on as frequently as local recurrences of rectal carcinoma (Table 2).

Curative resection of tumor recurrence does not equate with cure. Mentges and Brueckner[3] report a 44.1 percent recurrence rate (N = 193) following primary resection of 438 rectal carcinomas. Only 80 of these (18.2 percent) could undergo a further operation, 31 of the 80 with curative intention. In long-term follow-up, only 7 of the 31 (1.6 percent overall) were free of tumor longer than five years. In our study, only 9 of 487 patients (1.8 percent) were free of tumor more than two years after a second "curative" resection.

New operative procedures for surgery of metastases have been shown to prolong survival time, but few patients are actually cured.[29–31] At the present time, the number of patients cured is still small, but it may increase as new methods (CT portography and CEA immunoscintigraphy) can detect more recurrences in the asymptomatic stage.

Because further curative resection does prolong survival time, long-term follow-up can be recommended for the future but not for all patients.

It is evident that not many patients with recurrence benefit from the follow-up program utilized in this study. Based on these data, we have now introduced an individual, risk-adapted, follow-up program in our department.[32] Patients more prone to recurrence (all Dukes C and D carcinomas, Stage T_3 for rectal carcinoma, and preoperative elevated CEA level [>5 ng/ml]) are examined more often and according to their individual risk factors so that more asymptomatic recurrences can be found and operated on with curative intention.

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