Tumor Markers in Patients with Relapse of Colorectal Carcinoma

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Abstract. *Aim: To evaluate CEA and CA19-9 in a long-term follow-up after radical surgery for colorectal cancer. Patients and Methods: A total of 1,090 patients were operated on for colorectal cancer, 716 patients underwent R0 resection, 631 patients were under further surveillance, relapse was diagnosed in 122 patients (20%), 74 patients were indicated for reoperation The resectability of the relapse was 35%. An AxSYM instrument (Abbott) was used for analysis. Results: At the time of relapse both markers were normal in 31% of the patients. When relapse was diagnosed, in patients with normal preoperative levels, CEA and CA19-9 were below cut-off in 48% and 79%, respectively, and in those with primary elevation, they were again elevated in 78% and 64%, respectively. Conclusion: The surveillance based only on CEA and/or CA19-9 was cost-effective, but failed to disclose 1/3 of patients suffering from relapse; these markers must be combined with liver and chest imaging methods and colonoscopy.*

Carcinoembryonic antigen (CEA) is an important tumor marker in the management of colorectal cancer. An increased level of CEA in the follow-up suggests a relapse of the disease. A preoperative high CEA value suggests advanced disease either locally or distant metastases (1, 2). After curative resection, the preoperative serum CEA level can be a useful predicting factor with regard to the outcome of the surgical operation (3). A combined assay of CEA and CA 19-9 showed significantly higher sensitivity and specificity than in either CA 19-9 or CEA alone and was more useful in finding postoperative recurrences or metastases (4, 5).

The aim of the study was to evaluate the contribution of monitoring CEA and CA19-9 in a long-term surveillance of patients after radical surgery for colorectal cancer in a retrospective study at a single Surgical Department, where the patients are routinely followed up according to a standard protocol.

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Patients and Methods

A total of 1090 patients were operated on for colorectal cancer in the years 1992-2004 at the Surgical Department of the Thomayer Teaching Hospital and the 1st Faculty of Medicine, Charles University, Prague, Czech Republic.

The tumor site was classified according to the International Classification of Diseases (6): Colon cancer with diagnosis C180-C189, and C 19 for rectosigmoid and C20 for rectal cancer. For classification of the stage of the tumor, the TNM Classification of Malignant Tumours was used with pTNM description (7). The radicality of the surgical procedure was expressed using the R classification. Operative mortality was defined as death within 30 days of the operation during the years 1992-1999. Since 2000, this has been extended to the whole postoperative hospital stay. Statistical analysis was performed using CRAN 2.4.0 for Windows.

Each patient with colorectal carcinoma was counselled by a clinical oncologist. Clinical status of the patients during follow-up was classified according to WHO criteria and EGTM recommendations (8). Preoperative radiotherapy for rectal tumors T3 and T4 without diagnosed extrapelvic dissemination is indicated. Chemoradiotherapy prior to the operation is only performed on selected patients in good general condition. In patients with synchronous liver metastases, a primary operation – simultaneous resection of the colon or rectum and liver – is indicated. Postoperative chemotherapy is indicated in patients in stage pTNM III and pTNM IV. In stage pTNM II, adjuvant chemotherapy is used if the tumor is T3 or T4 , as well as any TNM with N X.

From the total number of 1,090 patients operated on for colorectal cancer, 716 patients underwent radical surgery (R0 resection), 631 patients were in further follow-up according to our standards (Table I) and 85 patients were lost to follow-up.

Both CEA and CA19-9 were investigated preoperatively in 584 patients and compared with the pTNM stage.

A relapse of the disease was diagnosed in 122 patients – or 20% of cases (Table II), 74 patients were indicated for reoperation, and a second R0 resection was performed in 43 (35%) patients. The median follow-up after reresection was 14.5 months.

Table I. *System of follow-up.*

	Months after operation														
	3	6	12	18	24	30	36	42	48	54	60	72	84	96, 120	108, 144, 166
Anamnesis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical investigation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CEA, CA19-9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ultrasonography	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT			X		X		X		X		X	X	X	X	X
Coloscopy			X		X		X		X		X	X	X	X	X
Chest X ray					X				X			X		X	
PET, PET/CT	If the markers are elevated and other results are negative and/or before indication for reoperation														

Both CEA and CA 19-9 were examined in 75 patients before the primary operation and at the time of relapse, in 47 patients the results of both markers were not complete. CEA and CA19-9 were assessed using the AxSYM instrument (Abbott). The cut-off level for CEA was 3.2 μg/l and for CA 19-9 it was 24 kU/l.

Results

Preoperative CEA and CA19-9 were investigated in 584 patients and compared with the pTNM stage (Figures 1, 2).

Relapse of the colorectal carcinoma was diagnosed in 122 patients. Both CEA and CA 19-9 were examined before the primary operation and at the time of the relapse in 75 patients (Figure 3). When comparing preoperative tumor markers and those associated with relapse, in the subgroup of the patients with normal preoperative levels of CEA and CA 19-9, the markers were normal at the time of relapse in 48% and 77%, respectively. In the subgroup of the patients with elevated markers before primary surgery, CEA was above the normal range in 78% of patients with relapse and CA19-9 in 64% of these patients (Figures 4-5, Table IV).

There was a statistical significant difference (Chi-square test) in CEA ($p=0.0283$) and CA 19-9 ($p=0.0014$) comparing preoperative levels with levels in relapse. Estimates of the relative risk (odds ratio) were 3.22 in CEA and 6.64 in CA 19-9. Spearman's correlation coefficients were 0.25326 in CEA and 0.36778 in CA 19-9. This means that patients with elevated preoperative CEA or CA 19-9 had a tendency for elevation of examined markers in relapse. Correlation of CEA and CA19-9 levels before operation with pTNM stage were statistically significant (Chi-square test in CEA $p<0.0001$ and in CA 19-9 $p<0.0001$. Combination of CEA and CA 19-9 gave $p<0.0001$).

Discussion

The principal aim of follow-up programmes after curative resection of colorectal cancer is to improve survival. To achieve this goal, patients are screened for early recurrent disease and a second colorectal cancer with the intent of a second curative surgery. There is evidence that an overall survival benefit at 5 years exists for patients undergoing more intensive follow-up (9).

Meta-analyses of randomised controlled studies show that intensive follow-up programmes after radical surgery for colorectal cancer have a more positive effect on total survival than do less intensive programmes, but the ideal programme has not yet been found (10). The degree of resectability of a relapse of colorectal cancer is shown in Table III.

Table II. *Diagnosed relapse.*

Site of relapse	Number of patients			%
	Diagnosed	Operated	R0 resected	
Liver metachronous	44	32	21	47.7%
Multiple dissemination	25	7	0	0%
Local recurrence	18	12	9	50%
Lung metachronous	16	12	10	62.5%
Lymph nodes	10	5	1	10%
Peritoneum	5	4	1	20%
Bone metastases	2	1	0	0%
Liver and lung	1	1	1	0%
Brain	1	0	0	0%
Total	122	74	43	35.2%

Table III. *Resectability of relapse in intensive follow-up.*

Author	Resecability of relapse in intensive follow-up
Makela (13)	23%
Ohlson (14)	29%
Pietra (15)	65%
Secco (16)	31%
Our results	35%

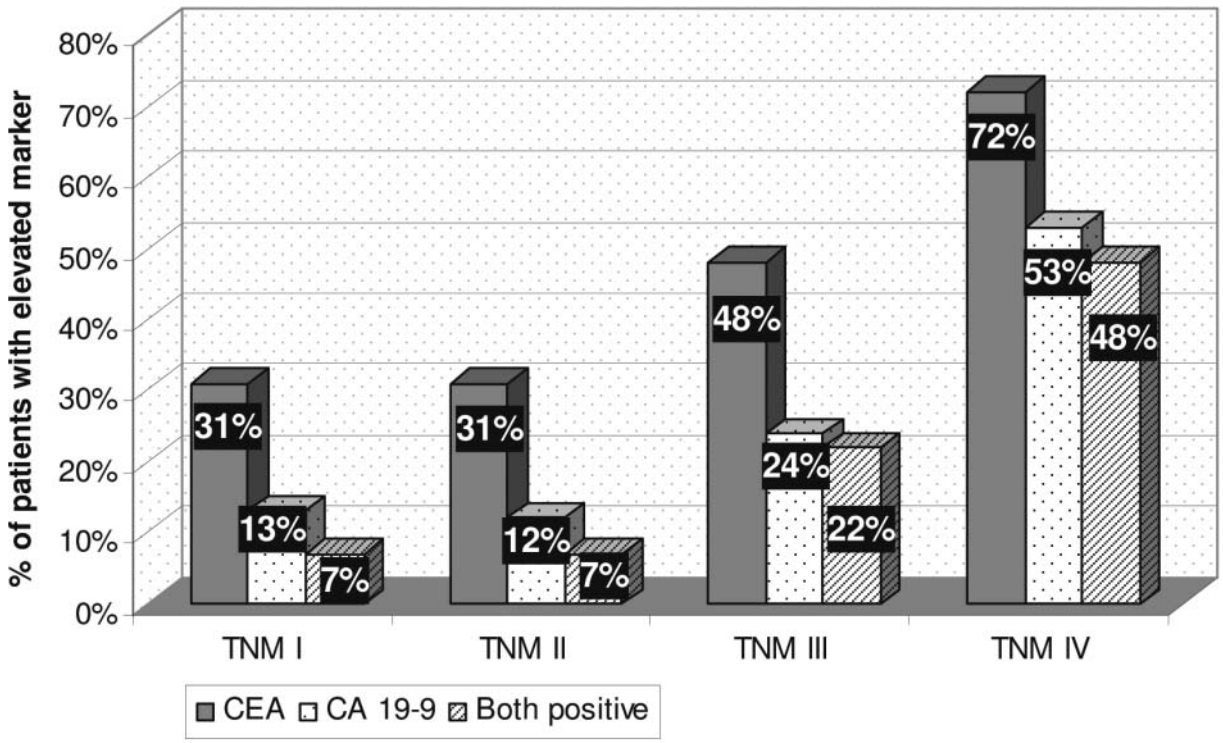

Figure 1. *Elevation of preoperative levels of CEA and CA 19-9 according to TNM stage (n=584; 1992-2004).*

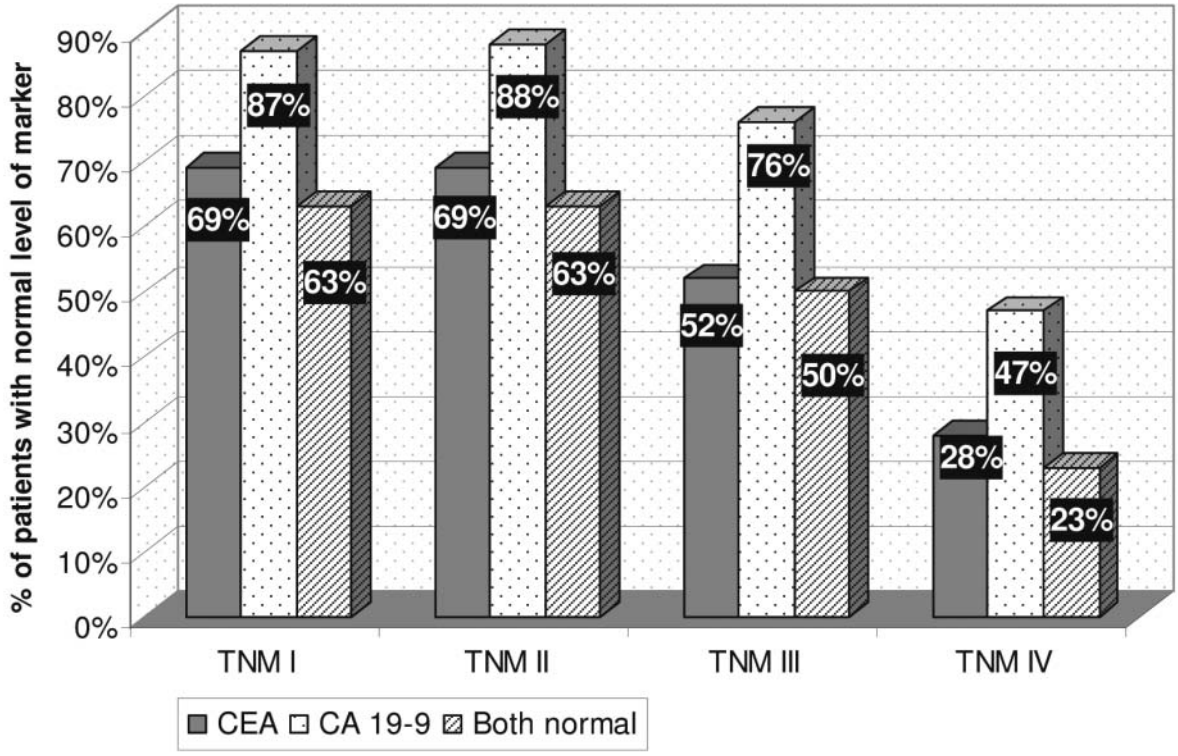

Figure 2. *Normal preoperative levels of CEA and CA 19-9 according to TNM stage (n=584; 1992-2004).*

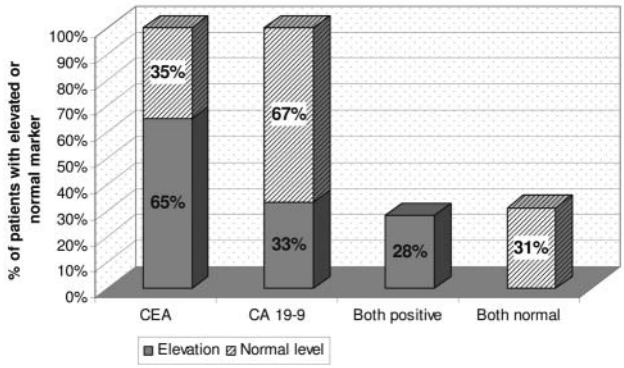

Figure 3. *Postoperative follow-up: levels of markers at the time of relapse (n=75; 1992-2004).*

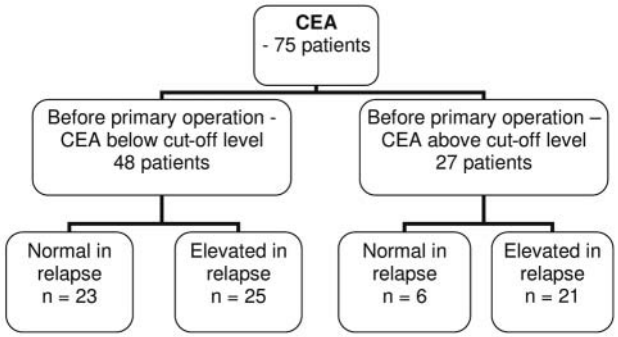

Figure 4. *CEA in relapse.*

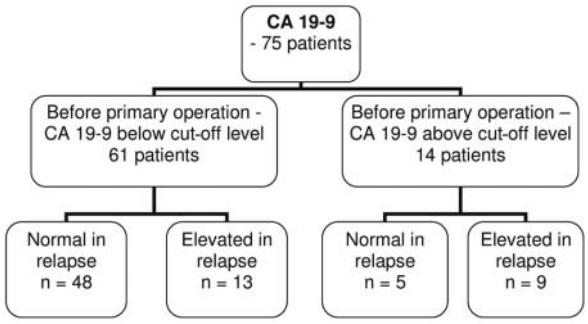

Figure 5. *CA 19-9 in relapse.*

There is evidence from six randomized trials and two meta-analyses of a small but significant survival benefit with more intensive follow-up compared to less intensive follow-up. This benefit is due to the early diagnosis and resection of limited recurrent disease in the liver, lungs, or local sites (11).

Based on our results, it can be concluded that monitoring of the tumor markers is valuable, mainly in those cases where preoperative CEA and/or CA19-9 were elevated. The level of CEA and CA19-9 increases according to the pTNM stage of the disease. CEA or CA19-9 below the cut-off level does not exclude even a very advanced colorectal cancer (5). To evaluate the stage of the disease, treatment strategy and prognosis, a combination of investigations is necessary (12). Surveillance based only on CEA and/or CA19-9 is cost-effective, but does not disclose more than 1/3 of patients with relapse. The more effective the treatment of patients with colorectal cancer, the less cost-effective is the follow-up with regard to diagnosis of a relapse. In general practice, CEA is often used as the only parameter in the follow-up regimen. Based on this system, CEA seems highly effective, but when other investigations are included, 1/3 of relapsed patients are diagnosed by a method other than CEA. At our Surgical Department the complex follow-up described above is used as a standard. This seems to be one of the reasons for the 35% resectability of relapse.

Table IV. *Results – markers in relapse.*

	Primary operation	Relapse
CEA	Normal	48% Normal
	Elevated	77% Elevated
CA 19-9	Normal	78% Normal
	Elevated	64% Elevated

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