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Carcinoembryonic Antigen (CEA) and Alkaline Phosphatase in Progressive Colorectal Cancer with Special Reference to Patient Survival

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Abstract—*The prognostic value of serial CEA tests was evaluated in* 175 *consecutive patients with progressive colorectal cancer who subsequently died of their disease. The upper normal plasma CEA limit was determined to be* 8 ng/ml *from serial CEA determinations in* 31 *patients radically operated on for colorectal cancer and observed in median* 40 months *without evidence of recurrence. A CEA value of* >8 ng/ml *was highly suggestive of residual disease or recurrence, even when no clinical evidence was present. Approximately* 90% *of the patients dying from colorectal cancer showed an increase in CEA to* >8 ng/ml *during the course of the disease. In* 63% *of the patients CEA increase preceded clinical progression or relapse, with a median time period of* 4 months. *Sixty-eight per cent of the patients had rising CEA values over an extended time period of many* months, 14% *had a preterminal increase,* 13% *had constantly normal and* 5% *constantly elevated CEA. As* 6/9 *patients developed a drop in CEA in relation to initiation of chemotherapy without clinical response, it is concluded that CEA is not a reliable indicator of clinical response to chemotherapy. Patients with liver metastases had higher CEA and alkaline phosphatase levels than patients with only localized disease. However, no good statistical correlation between CEA and serum alkaline phosphatase was found in patients with liver metastases (coefficient of correlation* r = 0.35). *An increase in CEA from normal to above* 8 ng/ml *predicted a decrease in survival time of median* 60% *counted from the time of diagnosis. The numerical CEA value was predictive of shortening of survival only when greater than* 3000 ng/ml. *Such high values were observed only in a minority of the patients* (12%). *Greater than* 1000 U/l (27% *of the patients) alkaline phosphatase predicted an extremely poor prognosis, with a median survival of* 1 month (*range* 0.5–4 months). *It is concluded that a rise in CEA to* >8 ng/ml *indicates with high degree of certainty relapse or disease progression in colorectal cancer patients. CEA is not a reliable indicator of clinical response to chemotherapy, and an increase in the CEA level is of little prognostic value concerning survival. Alkaline phosphatase seems to be a more valuable predictor of a worsening of prognosis.*

INTRODUCTION

CARCINOEMBRYONIC antigen (CEA) is an acid glycoprotein first described in colonic cancer tissue by Gold and Freedman in 1965 [1]. Subsequently, in 1969 Thompson *et al.* showed that CEA could be measured in serum using a radioimmunoassay [2]. Since then plasma CEA has been the subject of numerous studies especially focusing on the prognostic value of the preoperative level and the value of postoperative follow-up in relation to recurrence [3].

However, so far no studies have tried to evaluate the prognostic significance of a CEA increase during the course of the progressive disease with regard to survival. To elucidate the relationship between the level of plasma CEA and survival of the patients, as well as the relation to alkaline phosphatase as an expression of liver metastases, we examined 206 consecutive patients with colorectal carcinoma referred for either adjuvant or palliative chemotherapy and followed with serial CEA determinations.

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MATERIALS AND METHODS

A total of 206 consecutive patients with histologically proven colorectal cancer and no history of other malignant disease, who were referred for adjuvant or palliative chemotherapy, were subjected to this analysis. The patients were treated according to the following master chemotherapy protocols: (1) adjuvant treatment with methylcyclohexylchlorethylnitrosourea and 5-fluorouracil vs no treatment, or (2) palliative treatment of progressive disease with 5-fluorouracil v furanidyl-5-fluorouracil (Ftorafur).

Physical examination including rectal and pelvic examinations, if applicable, were performed in relation to initiation of each treatment series. Plasma CEA, alkaline phosphatase, bilirubin, aminoaspartate transferase, creatinine and complete blood count were performed at approximately every other month. Chest X-ray, liver scintigrams and/or abdominal ultrasound examination were performed every 2–3 months. Proctoscopy and barium enema were done when indicated. Plasma CEA was measured by the Abbott CEA-RIA assay [4].

Retrospectively the records were examined for age, sex, primary tumor location, extent of disease at the time of referral, metastases, all pair values of CEA and alkaline phosphatase and their relation to the time of death and response to therapy according to the WHO criteria. In 58 patients with normal postoperative CEA values the reduction in survival from the time of CEA increase to abnormal values (>8 ng/ml) was assessed. If progression or relapse was detected, this was registered as well as autopsy results. Thirty-one patients still alive without evidence of disease and observed for a considerable period of time were analyzed to define an upper normal CEA limit in a colorectal cancer patient population. As 19% of these patients had one or more values between 5 and 8 ng/ml, even though multiple analyses showed a bimondal distribution of CEA values with an upper 95% confidence limit (Fig. 1) of the normally used 5 ng/ml (defined from blood tests often from younger, healthy persons), we defined the upper normal value as 8 ng/ml in order to achieve a higher specificity, on account of a lower sensitivity using a more relevant reference population. The remaining 175 patients who died from colorectal cancer were subjected to analysis of the prognostic significance with regard to survival of increase in CEA during the progressive disease.

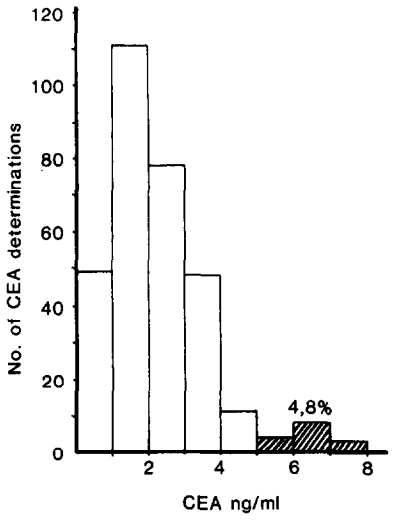

Fig. 1. Distribution of 312 CEA values measured in 31 patients radically operated on for colorectal cancer and observed for median 40 months (20–72 months) without evidence of recurrence. Most (95.2%) of the values were <5 ng/ml. The highest value was 7.8 ng/ml. Of the patients 6/31 (19%) had at least one value between 5 and 8 ng/ml.

RESULTS

Definition of upper normal CEA limit in a population of colorectal cancer patients

Thirty-one radically operated patients alive and observed for a considerable period of time (median 40 months, range: 20–72 months) without evidence of recurrence served to define the upper normal limit of CEA. The highest observed value among 312 observations was 7.8 ng/ml. Thus the upper normal limit was defined as 8 ng/ml. The distribution of the 312 CEA values is shown in Fig. 1. Most (95.2%) of the values were <5 ng/ml. Twelve patients (39%) had maximum values below 2.5 ng/ml, 13 patients (42%) from 2.5 to 4.9 ng/ml and six patients (19%) from 5 to 7.8 ng/ml. Of six patients living more than 5 yr without disease, two had CEA values between 5 and 8 ng/ml.

Preterminal CEA and alkaline phosphatase levels

Of the 175 patients who died from colorectal cancer, 115 had a CEA test taken within 2 months of death. Among these, 100 patients (87%) had values > 8 ng/ml and 15 patients (13%) had values below 8 ng/ml, among which eight patients (7%) had values < 5 ng/ml (Table 1). Fourteen patients (12%) had a CEA value > 3000 ng/ml. Parallel to this, 81 patients (70%) had an alkaline phosphatase value > 275 U/l (upper normal limit) and 34 patients (30%) normal values prior to death (Table 1). Thus CEA was more frequently abnormal during progressive colorectal cancer than alkaline phosphatase.

CEA increase related to relapse or disease progression

Of 75 patients with or developing recurrent evaluable disease, an increase in CEA from a stable level preceded clinical progression or relapse in 47 (63%), with a median of 4 months (range 1–23 months). In only one case did the clinical progression precede increase in CEA. In the remaining 27 patients clinical progression was concomitant with increase in CEA.

CEA patterns of variation

Of the 115 patients with the last CEA value measured within 2 months of death, 97 had serial CEA determinations. Twelve of these (13%) had constantly normal CEA values during the course of the disease (Fig. 2). Five of the patients (5%) had a

Table 1. *The distribution of plasma CEA and serum alkaline phosphatase values measured within* 2 months *of death in* 115 *patients who died from colorectal cancer*

CEA (ng/ml)	No. of patients	(%)	Akaline phosphatase (U/l)	No. of patients	(%)
<5	8	(7)			
5–8	7	(6)	<275	34	(30)
8–19	11	(9.5)	275–499	22	(19)
20–99	25	(22)	500–999	28	(24)
100–999	38	(33)	≥1000	31	(27)
≥1000	26	(22.5)			

Highest CEA: 145,445 ng/ml; highest alkaline phosphatase: 5070 U/l.

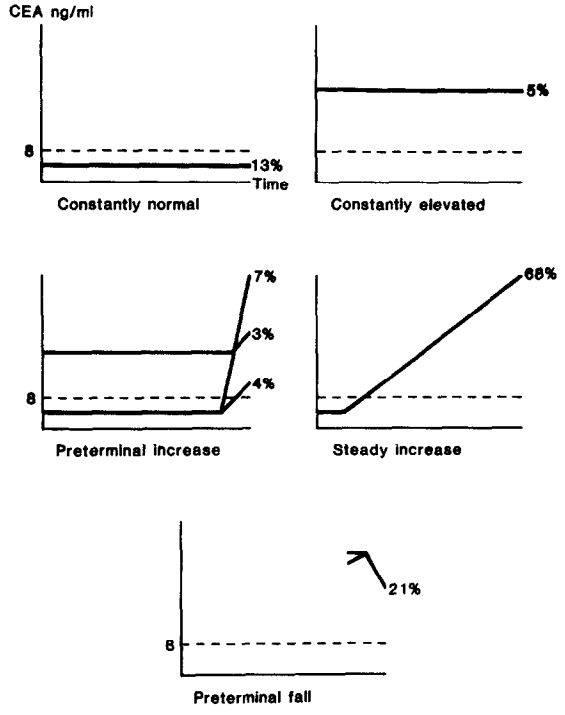

Fig. 2. Schematic representation of CEA patterns of variation during the progressive course of colorectal cancer.

constantly elevated value and 80 patients (82%) showed an increase, including 14 patients (14%) with a preterminal increase and 66 patients (68%) with a steady, more or less pronounced increase over many months. Minor fluctuations were frequently observed. Of the 85 patients with elevated CEA, 18 (21%) showed a preterminal drop, which in four patients might be related to initiation of chemotherapy, even though no objective response was detected. In the remaining 14 patients no explanation of this CEA decrease was obvious.

CEA and response to treatment

In 13 patients CEA decreased after starting treatment, including a normalization of CEA in three complete responders (two chemotherapy and one hemihepatectomy), a decrease in four partial responders (two surgery, one irradiation and one chemotherapy) and a decrease in six patients with no clinical demonstrable objective response to chemotherapy.

CEA and alkaline phosphatase in relation to liver metastases

Patients with surgically verified liver metastases had at the time of referral to chemotherapy significantly higher CEA values ($\chi^2 = 19.38$, $P < 0.001$) than patients without liver metastases (Table 2). Of the 68 patients who presented with liver metastases, 12 (18%) had a normal alkaline phosphatase value (<275 U/l) and 31 (45%) a value ≥ 500 U/l. In patients who died with liver metastases the fraction of patients with very high CEA values was even more pronounced (Table 3).

Among the 91 patients presenting with or known to develop liver metastases during the course of the disease no good correlation between CEA and alkaline phosphatase (coefficient of correlation: $r = 0.35$) was demonstrated by regression analysis of 448 CEA–alkaline phosphatase pair values.

Increase in CEA and alkaline phosphatase as prognostic factors of survival

In 58 patients who postoperatively had a normal CEA value and subsequently developed increase in CEA to >8 ng/ml, survival was significantly reduced by a median of 60% at the time of CEA increase (from median 23 months to median 9 months; log rank analysis: $\chi^2 = 33.59$, $P < 0.001$).

The numerical value of CEA, however, was a poor prognostic indicator. Seventy-nine patients who showed an increase from one of the following CEA categories: <8, 8–19, 20–49, 50–99, 100–299, 300–499, 500–999, 1000–2999, ≥3000, were analyzed for survival from the time of increase in CEA from one category to another. As no statistically significant difference was found between the categories 20–2999 a repeat analysis was performed with the following categories: 8–19, 20–2999 and ≥3000. There was no statistically significant differ-

Table 2. CEA values in relation to the presence of liver metastases at the time of referral to chemotherapy in 156 patients with colorectal cancer who subsequently died from the disease

CEA (ng/ml)	Liver metastases No. of patients	(%)	Other metastatic disease No. of patients	(%)	Local disease only* No. of patients	(%)
<8	8	(12)	17	(42.5)	22	(46)
8–19	10	(15)	8	(20)	10	(21)
20–99	13	(19)	8	(20)	9	(19)
100–999	23	(34)	6	(15)	7	(14)
≥1000	14	(20)	1	(2.5)		

*Normal liver at surgery or normal liver scan and/or ultrasound of the liver together with a normal serum alkaline phosphatase.

Table 3. The distribution of CEA and alkaline phosphatase values measured within 2 months of death in 70 patients with liver metastases who died from colorectal cancer

CEA (ng/ml)	No. of patients	(%)	Alkaline phosphatase (U/l)	No. of patients	(%)
<8	4	(6)	<275	5	(7)
8–19	6	(9)	275–499	8	(11)
20–99	14	(20)	500–999	25	(36)
100–999	24	(34)	≥1000	32	(46)
≥1000	22	(31)			

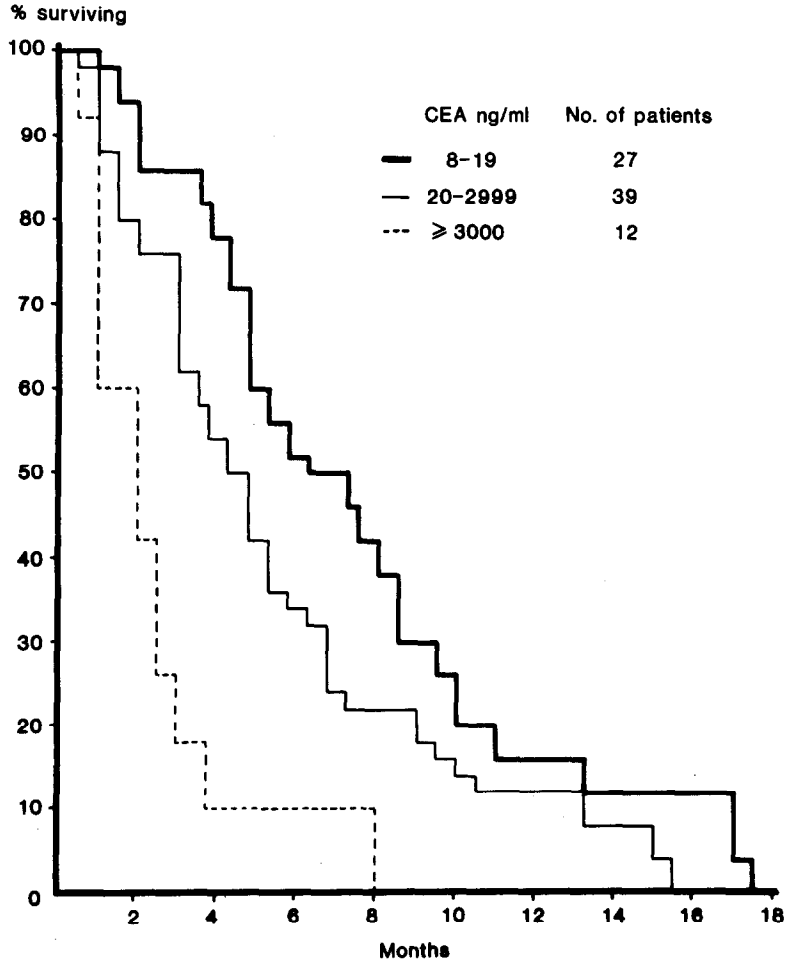

Fig. 3. *Survival analysis concerning the prognostic significance of the numerical CEA value. The survival measured from the time of increase in CEA was significantly reduced when CEA increased from a value below to a value* ⩾ 3000 ng/ml (*log rank analysis:* $\chi^2 = 8.10$, $P < 0.005$).

ence between category 8–19 and category 20–2999, but category ≥3000 had a significantly reduced survival (50% reduction of median survival) compared to the two other categories (log rank analysis of category 20–2999 against category ≥3000: χ^2 = 8.10, P <0.005; Fig. 3).

Parallel to this, alkaline phosphatase was tested as a prognostic indicator. No significant difference was found between category 275–499 and category 500–999. However, the median survival was reduced by 60% when the alkaline phosphatase value increased to ≥1000 U/l (log rank analysis of category 500–999 against category ≥1000: χ^2 = 13.13, P <0.001; Fig. 4).

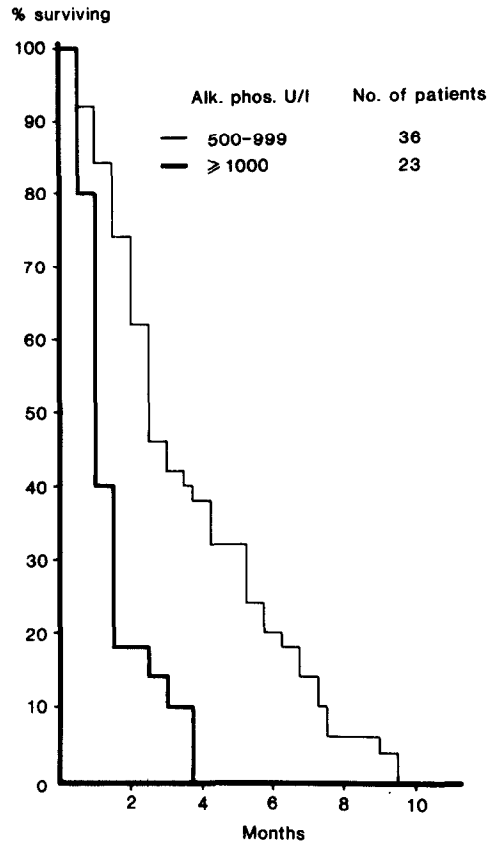

Fig. 4. Survival analysis concerning the prognostic significance of the numerical alkaline phosphatase value. The survival measured from the time of increase in alkaline phosphatase was significantly reduced when alkaline phosphatase increased from a value below to a value ≥1000 U/l *(log rank analysis:* χ^2 = 13.13, P <0.001).

DISCUSSION

The most commonly used upper normal plasma CEA level has been 2.5 or 5 ng/ml, determined from examination of normal control subjects [3]. On the other hand, in a population of colorectal cancer patients who have been radically treated, we found that an upper level of 8 ng/ml will secure a false-positive rate close to 0. Therefore a value >8 ng/ml is highly suggestive of residual or recurrent disease.

As the majority of the patients had a rise in CEA preceding detectable clinical progression or recurrence by several months, we find that an increase in CEA is a reliable predictor of progression or recurrence, especially when part of a steadily rising trend, as pointed out by Steele *et al.* [5]. This conclusion is in accordance with most other reports [6–19]; however, Moertel *et al.* did not agree with this [20].

Two patterns of CEA changes have been described in patients with progressive colorectal cancer: a fast and a slow rise [12, 21]. We observed a more varied pattern (Fig. 2). Two-thirds of the patients had a progressive rise over months whereas 7% had a pronounced terminal increase. The slope of the CEA-time curve was not predictive of survival. A rather large proportion of the patients (21%) had an unexplained preterminal drop in CEA, a phenomenon also observed by Ravry *et al.* [22].

In several studies response to treatment has been followed by a decrease in CEA. This is most commonly reported in patients undergoing tumor resection. A drop in CEA concomitant with tumor regression induced by chemotherapy [22–26] and by irradiation [27] has also been reported. In our study all three patients responding to chemotherapy had a decrease in CEA; however, an additional six patients developed a decrease in CEA without an objective tumor response. The same was observed by Shani *et al.* [28]. It is concluded that a drop in CEA as a response to initiation of chemotherapy is not a reliable indicator of a clinical response.

The appearance of liver metastases in colorectal cancer is a frequent complication tantamount to an incurable condition. A significant elevation in serum alkaline phosphatase is almost invariably associated with liver metastatic disease in colorectal cancer provided that bone metastases and extrahepatic bile stasis are excluded.

Patients with liver metastases had significantly higher CEA values than patients with localized disease only or metastatic disease elsewhere. This has also been shown in other studies [6, 23, 29–31]. Despite this, we found no simple linear correlation between CEA and alkaline phosphatase levels, a fact also described by others [6, 32]. The rate of normal values for patients dying with liver metastases was the same for CEA and alkaline phosphatase (6 and 7% respectively).

Because of a great variation in individual CEA production and in change in production in relation to tumor growth, we found that not until CEA increased to >3000 ng/ml did it predict a significant reduction in survival. When serum alkaline phosphatase increased to >1000 U/l it was a more reliable and valuable predictor of a worsening of

prognosis than CEA as the range in survival was more narrow and as more patients developed this high value.

However, an increase in serum alkaline phosphatase to >1000 U/l tends to happen later in the course of the disease than an increase in CEA to >3000 ng/ml.

In summary, it is concluded that a rise in CEA to >8 ng/ml does warn of relapse or disease progression in colorectal cancer patients. However, in the individual patient the given numerical CEA value and the change in the CEA level during the clinical course of the disease is so variable that it is not a reliable indicator of response to chemotherapy and is of little prognostic value with regard to survival.

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REFERENCES

1. Gold P, Freedmann SO. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. *J Exp Med* 1965, **121**, 439–462.
2. Thompson DMP, Krupey J, Freedman SO, Gold P. The radioimmunoassay of circulating carcinoembryonic antigen of the human digestive system. *Proc Nat Acad Sci USA* 1969, **64**, 161–170.
3. NIH consensus Development Conference Statement. Carcinoembryonic antigen: its role as a marker in the management of cancer. *Cancer Res* 1981, **41**, 2017–2018.
4. Abbott Diagnostics Division. Anti-carcinoembryonic antigen ^{125}I (Goat) Abbott CEA-RIA: radioimmunoassay for the detection of carcinoembryonic antigen. 1982.
5. Steele G, Ellenberg S, Ramming K *et al.* CEA monitoring among patients in multi-institutional adjuvant G.I. therapy protocols. *Ann Surg* 1982, **196**, 162–169.
6. Booth SN, Jamieson GC, King JPG, Leonard J, Oates GD, Dykes PW. Carcinoembryonic antigen in management of colorectal carcinoma. *Br Med J* 1974, **4**, 183–187.
7. Sorokin JJ, Sugarbaker PH, Zamcheck N, Pisick M, Kupchik HZ, Moore FD. Serial carcinoembryonic antigen assays. Use in detection of cancer recurrence. *JAMA* 1974, **228**, 49–53.
8. Mackay AM, Patel S, Carter S *et al.* Role of serial plasma CEA assays in detection of recurrent and metastatic colorectal carcinomas. *Br Med J* 1974, **4**, 382–385.
9. Evans JT, Mittelman A, Chu M, Holyoke ED. Pre- and postoperative uses of CEA. *Cancer* 1978, **42**, 1419–1421.
10. Mach J-P, Vienny H, Jaeger P, Haldermann B, Egely R, Pettavel J. Long term follow-up of colorectal carcinoma patients by repeated CEA radioimmunoassay. *Cancer* 1978, **42**, 1439–1447.
11. Staab HJ, Anderer FA, Stumpf E, Fischer R. Carcinoembryonic antigen follow-up and selection of patients for second-look operation in management of gastrointestinal carcinoma. *J Surg Oncol* 1978, **10**, 273–282.
12. Wood CB, Ratcliffe JG, Burt RW, Malcolm AJH, Blumgart LH. The clinical signficance of the pattern of elevated serum carcinoembryonic antigen (CEA) levels in recurrent colorectal cancer. *Br J Surg* 1980, **67**, 46–48.
13. Arnaud JP, Koehl C, Adloff M. Carcinoembryonic antigen (CEA) in diagnosis and prognosis of colorectal carcinoma. *Dis Col Rect* 1980, **23**, 141–144.
14. Persinj JP, Hart AAM. Prognostic significance of CEA in colorectal cancer: a statistical study. *J Clin Chem Clin Biochem* 1981, **19**, 1117–1123.
15. Lavin PT, Day J, Holyoke ED, Mittelman A, Chu TM. A statistical evaluation of baseline and follow-up carcinoembryonic antigen in patients with resectable colorectal carcinoma. *Cancer* 1981, **47**, 823–826.
16. Tate H. Plasma CEA in the post-surgical monitoring of colorectal carcinoma. *Br J Cancer* 1982, **46**, 323–330.
17. Lunde OCH, Havig Ø. Clinical significance of carcinoembryonic antigen (CEA) in patients with adenocarcinoma in colon and rectum. *Acta Chir Scand* 1982, **148**, 189–193.
18. Attiyeh FF, Stearns MW. Second-look laparotomy based on CEA elevations in colorectal cancer. *Cancer* 1981, **47**, 2119–2125.
19. Martin EW, Cooperman M, Carey LC, Minton JP. Sixty second-look procedures indicated primarily by rise in serial carcinoembryonic antigen. *J Surg Res* 1980, **28**, 389–394.
20. Moertel CG, Schutt AJ, Go VLW. Carcinoembryonic antigen test for recurrent colorectal carcinoma. *JAMA* 1978, **239**, 1065–1066.
21. Staab HJ, Anderer FA, Stumpf E, Fisher R. Slope analysis of the postoperative CEA time course and its possible application as an aid in diagnosis of disease progression in gastrointestinal cancer. *Am J Surg* 1978, **136**, 322–327.

22. Ravry M, Moertel CG, Schutt AJ, Go VLW. Usefulness of serial serum carcinoembryonic antigen (CEA) determinations during anticancer therapy or long-term follow up of gastrointestinal carcinoma. *Cancer* 1974, **34**, 1230–1234.
23. Mayer RJ, Garnick MB, Steele GD, Zamcheck N. Carcinoembryonic antigen (CEA) as a monitor of chemotherapy in disseminated colorectal cancer. *Cancer* 1978, **42**, 1428–1433.
24. Holyoke ED, Chu TM, Murphy GP. CEA as a monitor of gastrointestinal malignancy. *Cancer* 1975, **35**, 830–836.
25. Herrera MA, Chu TM, Holyoke ED, Mittelman A. CEA monitoring of palliative treatment for colorectal carcinoma. *Ann Surg* 1977, **185**, 23–30.
26. Al-Sarraf M, Baker L, Talley RW, Kithier K, Vaitkevicius VK. The value of serial carcinomebyronic antigen (CEA) in predicting response rate and survival of patients with gastrointestinal cancer treated with chemotherapy. *Cancer* 1979, **44**, 1222–1225.
27. Lokich J, Kinsella T, Perri J, Malcolm A, Clouse M. Concomitant hepatic radiation and intraarterial fluorinated pyrimidine therapy: correlation of liver scan, liver function tests and plasma CEA with tumor response. *Cancer* 1981, **48**, 2569–2574.
28. Shani A, O'Connell MJ, Moertel CG, Schutt AJ, Silvers A, Go VLW. Serial plasma carcinoembryonic antigen measurements in the management of metastatic colorectal carcinoma. *Ann Intern Med* 1978, **88**, 627–630.
29. Livingstone AS, Hampson LG, Shuster J, Gould P, Hinchey EJ. Carcinoembryonic antigen in the diagnosis and management of colorectal carcinoma. *Arch Surg* 1974, **109**, 259–263.
30. Rieger A, Wahren B. CEA levels at recurrence and metastases; importance for detecting secondary disease. *Scand J Gastroent* 1975, **10**, 869–874.
31. Wanebo HJ, Stearns M, Schwartz MK. Use of CEA as an indicator of early recurrence and as a guide to a selected second-look procedure in patients with colorectal cancer. *Ann Surg* 1978, **188**, 481–492.
32. Tartter PI, Slater G, Gelernt I, Aufses AH. Screening for liver metastases from colorectal cancer with carcinoembryonic antigen and alkaline phosphatase. *Ann Surg* 1981, **193**, 357–360.