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Prognostic Significance of CEA in Breast Cancer: a Statistical Study*

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Abstract—*A statistical evaluation was carried out of serial CEA plasma levels in breast cancer patients. The study included 206 patients with operable primary tumor, 108 patients who were inoperable, 55 patients with advanced disease treated by oophorectomy and 77 post-menopausal patients treated with various endocrine regimens. The pre-treatment CEA level was found to have no relation to prognosis. A rise in CEA during the follow-up period was usually associated with progressive disease. In 35% of the cases a rise in CEA preceded clinical signs of recurrence and metastases by an average of 200 days. The practical value of CEA in the management of breast cancer is limited because many tumors do not produce CEA. In CEA-producing tumors it provides a useful aid in clinical evaluation. The need for a strict statistical evaluation of CEA data in the follow-up of breast cancer patients is stressed.*

INTRODUCTION

THE TEST for carcinoembryonic antigen (CEA) is probably not sensitive and specific enough to be used in the diagnosis of breast cancer. Several investigators have reported on the value of serial assays [1–10] in determining the prognosis and in the monitoring of treatment of advanced disease. In this paper the results of a longitudinal study of serial CEA plasma levels in several groups of patients are reported. These include patients who had treatment for a primary tumor, patients irradiated for inoperable disease and patients with metastatic tumor treated with oophorectomy or hormones. The results are expressed in actuarial plots as percentages tumor-free, survival and no progression.

MATERIALS AND METHODS

Patients

From November 1974 until March 1979 serial CEA plasma levels were measured in five groups of breast cancer patients.

The first group consisted of 206 consecutive patients with operable primary breast cancer. The age of the patients ranged from 18 to 84 years, with a median of 57 years. The patients were staged according to UICC criteria [11]. The pre-operative investigations included a complete physical examination, haematological and biochemical blood tests, X-ray of the chest and, in patients with symptoms or pathological laboratory tests, an isotope scan of the skeleton. The surgical treatment was a classical Halsted procedure. Plasma samples for CEA measurement were taken before surgery and at regular intervals of 2–3 months thereafter. At the time of blood sampling the patients were checked for local recurrence and metastatic disease.

The second group of patients consisted of 52 patients with inoperable breast cancer. The criteria of inoperability were those of Haagensen [12] and a tumor-positive subclavicular lymph node biopsy. Routine work-up was similar to that in the first group of patients. The age of the patients ranged from 40 years to 87 years, with a median of 66 years. The schedule of blood sampling for CEA measurement was the same as in the first group. Only in 43 patients could a pre-treatment CEA value be obtained. Treatment consisted of local megavoltage radiotherapy.

The third group of patients consisted of 56 patients with inoperable breast cancer, accord-

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ing to the same criteria as the second group and with the same routine work-up. The age of the patients ranged from 19 years to 67 years, with a median of 51 years. These patients were involved in a pilot study for adjuvant chemotherapy after local irradiation. Adjuvant chemotherapy consisted of twelve monthly courses of the CMF regimen. A pre-treatment CEA level was only available for 25 out of 56 patients. Blood was sampled for CEA measurement at monthly intervals.

The fourth group of patients consisted of 55 pre-menopausal patients with progressive disseminated disease, in whom oophorectomy was the first treatment of choice. Their ages ranged from 26 to 55 years, with a median of 45 years. The clinical evaluation prior to oophorectomy included haematological and biochemical blood tests, an X-ray of the chest, isotope scan of the skeleton and, if possible, an E2-receptor assay of a tumor biopsy. Blood for CEA treatment was obtained before, and at regular 2–3 monthly intervals after, oophorectomy.

The fifth group of patients consisted of 77 post-menopausal patients with progressive dissiminated disease, in whom the treatment consisted of ethinyl oestradiol in 58, Calusteron® in 2 and Tamoxifen® in 17. Their ages ranged for 37 years to 81 years, with a median of 64 years. The schedule for routine work-up and for blood sampling was the same as in the previous group. Routine examination in the patients treated for dissiminated disease included X-ray of the chest, isotope scan of the skeleton and blood tests. Response to treatment was defined according to the EORTC criteria [13].

The CEA assay

For the determination of CEA in serum a direct double-antibody radioimmunoassay was employed, as described earlier [14]. The lower limit of detection with this method is 3 ng/ml. To ensure the reproducibility of the test in a prolonged longitudinal study, normal sera checked against a standard serum pool were used for the standard inhibition curve. In this assay special care is taken to maintain a reliable and constant cut-off level in follow-up studies. In addition, within every run, 4–6 different serum pools were incorporated at various positions scattered throughout the whole series. The range of each pool has been determined by calculation of the mean value and the 95% confidence limits obtained from results within at least 30 runs. New serum pools were only incorporated as controls after their range was established. A sufficient reproducibility for a long period, which is a pre-requisite for long term follow-up studies, was thus obtained. Results of assays were not accepted if more than one of the serum pools showed values outside the established ranges.

Statistical analysis

The relationship between CEA pre-treatment values and prognosis (relapse, survival) was analysed using the method of Kaplan and Meier [15] to produce the graphs (Fig. 1–5) and the log-rank test [16] to calculate the *P*-values. For the CEA pre-treatment value (CEA,PV), the last CEA value before treatment was chosen, but only if this measurement was performed within thirty days before treatment. To analyse the relationship between serial CEA values after treatment and prognosis, the following definitions have been used.

CEA values (ng/ml). Normal (N): 5; Lightly Increased (LI): 5–9.9; Moderately Increased (MI): 10–19.9; Highly Increased (HI): 20.

CEA decrease following treatment. A CEA decrease was defined by the occurrence of at least two subsequent CEA values satisfying the following criterion: N if the CEA PV was LI; at least 5 lower than the CEA PV if this was MI; or at least 10 lower than the CEA PV if this was HI. Of course, if CEA PV was N, no CEA decrease could be observed.

CEA Lower Point (LP) and Lowest Value (LV). If a CEA decrease occurred, the CEA LP was defined by the time at which during this decrease the highest of any two subsequent CEA measurements reached a minimum. This minimum was termed the CEA LV. If no CEA decrease occurred, the CEA LV was equated to the CEA PV.

CEA increase. A CEA increase was defined by the occurrence of at least two subsequent CEA measurements satisfying the following crierion: LI, MI or HI, if the CEA was N; at least 5 higher than the CEA LV if this was LI or MI; or at least 10 higher than the CEA LV if this was HI.

CEA stable. If neither a CEA decrease nor a CEA increase was observed, the CEA values were termed stable. These definitions were used so as to minimize, on the one hand, the influence of occasionally occurring outliers, retaining, on the other hand, as much resolution as possible. The statistical significance of the relationship between CEA increase and prognosis was analysed using a method given by Clayton [17] in a different context. This method can be seen to be a generalization of the log-rank test: for each time point at which CEA increase occurred, the prognosis of the

patient whose CEA increase did occur on that time was compared using the log-rank test, to the prognosis of patients who, up to that time, did not(yet) have a CEA increase; these separate comparisons were then combined, using the Mantel–Haenszel procedure [18]. In the case of relapse as prognostic parameter, a CEA increase occurring after the relapse was discounted in this procedure. To obtain a graphed impression of the relationship between CEA increase and prognosis, for those patients who at some time during their follow-up showed a CEA increase, the intervals between CEA and relapse/death has been displayed graphically in the same way that survival time, etc., generally are. In the same graph comparable curves are given for patients who, within specified intervals from treatment, did not show a CEA increase, measuring relapse time or survival time from the end of the specified interval.

RESULTS

Pre-treatment CEA levels in all groups of patients

The plasma CEA levels before treatment are shown in Table 1. The distribution of the 206 operable patients according to the stage was: 63 in stage I, 106 in stage II and 34 in stage III. All inoperable patients had stage III tumor. In the adjuvant chemotherapy group of patients, 38 were stage III and 18 were stage II with a positive apex biopsy. The highest percentage of CEA positive patients were in the advanced disease and in the inoperable groups.

Association of elevated CEA pre-treatment levels with recurrence in patients with primary disease

In Fig. 1, actuarial plots of tumor-free period for different levels of CEA in each of the three groups of patients are given. There was no significant difference between positive and negative patients, even when patients with the highest pre-treatment levels (CEA > 10 ng/ml) were compared to those with normal levels.

Association of elevated CEA pre-treatment levels with survival in patients with advanced disease

In Fig. 2 actuarial plots of survival for different levels of CEA in patients with oophorectomy and other forms of endocrine treatment are given. In the oophorectomy group (a), a significant difference was found between patients with moderately increased and those with highly increased CEA levels. The patients with a normal pre-treatment CEA level had a relatively poor survival. The

Table 1. CEA levels before treatment

Patients	Primary disease			Advanced disease	
	Operable	Inoperable	Adjuvant	Oophorectomy	Endocrine therapy
Total number	206	52	56	55	77
Number with pre-treatment assay	206	43	25	55	77
Number with elevated CEA	34	18	5	36	50
Per cent elevated CEA	18%	42%	20%	65%	65%

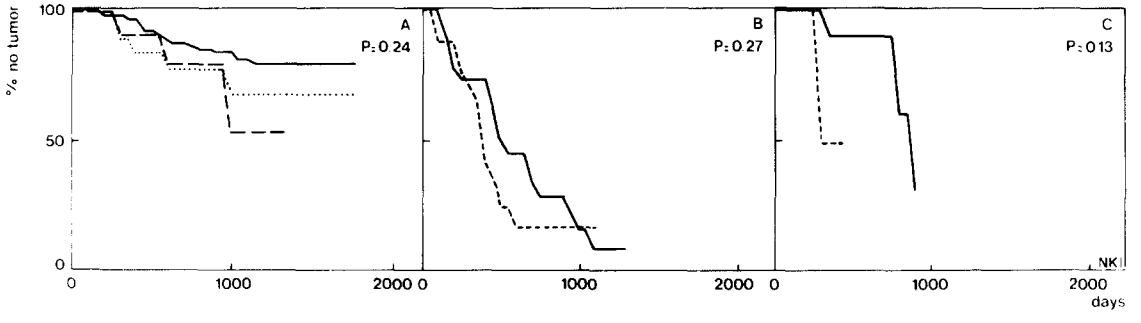

Fig. 1. (A) The association of pre-treatment CEA level with recurrence in operable (A), inoperable (B) and adjuvant (C) patients. The numbers of patients at risk are given in the bottom of the figure. (A) ———, CEA < 5 (172); · · · · ·, CEA 5–10 (23); – – – –, CEA > 10 (11). (—152—131—98—79—62—42—21—7—1—; · · · 20 · · · 14 · · · 12 · · · 10 · · · 7 · · · 4 · · · 3 · · · 1 · · · 1 · · ·; – – – 11 – – – 9 – – – 7 – – – 3 – – – 2 – – – 1 – – –). (B) ——, CEA < 5 (25); – – – –, CEA > 5 (18). (—17—15—9—5—2—1; – – – 16 – – – 7 – – – 2 – – – 2 – – – 1 – – –). (C) ———, CEA < 5 (19); – – –, CES > 5 (6). (—16—8—3—2—; – – – 4 – – – 2 – – –).

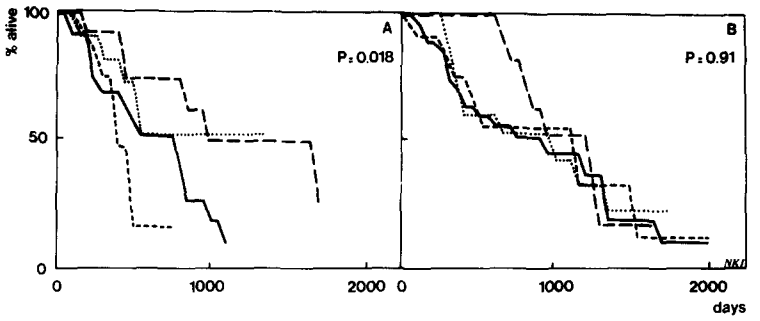

Fig. 2. The association of pre-treatment CEA level with survival in patients with advanced disease. Oophorectomy (A), hormone therapy (B). (A)———, CEA < 5(19); · · ·, CEA 5–10(11); ---, CEA 10–20(13);-----, CEA > 20 (12). (—17—12—9—5—2—; · · · 10 · · · 9 · · · 4 · · · 3 · · · 2 · · · 1 · · ·; ---12---10---7---6---4---3---2---2---; ---10---5---1---). (B) ———, CEA < 5 (27); · · · · ·, CEA 5–10 (15); -----, CEA 10–20 (12); -----, CEA > 20 (24). (—24—17—13—9—6—4—2—2—1—1—; · · · 15 · · · 9 · · · 8 · · · 7 · · · 4 · · · 3 · · · 2 · · · 2 · · ; ---12---11---11---7---5---5---3---1---; ---22---18---13---10---8---2---1---1---).

patients with other forms of endocrine treatment were all post-menopausal. There were no significant differences in survival with relation to the CEA levels.

Association of a rise in CEA levels and tumor recurrence

In Fig. 3 actuarial plots of tumor-free periods following a rise in plasma CEA level, indicating the probability of developing a recurrence, are given. For comparison, curves are shown of patients who, within specified intervals after treatment, did not show an increase of CEA levels. The relapse times were measured from the end of these intervals. Significant differences in recurrence rate between patients with or without a rise in CEA level were found in the operable and inoperable groups. No such difference could be demonstrated in the adjuvant chemotherapy group. The recurrence rate was highest in the inoperable group. In Fig. 3a it can be seen that 68% of the patients in the operable group with a CEA rise preceding the recurrence were free of tumor at 200 days after the CEA rise.

By contrast, 95% of the patients who did not show a CEA rise within a certain period after treatment were free of tumor 200 days later. A similar difference can be seen in Figs 3b and 3c for the inoperable and adjuvant chemotherapy groups.

About 50% of the patients with a CEA rise in the operable group (Fig. 3a) remained free of tumor. This contradictory finding can be explained in most patients by transient rises in CEA caused by conditions other than breast cancer, such as smoking, heart failure and cholecystitis. In Table 2 the number of patients with normal and increased levels of CEA at the time of recurrence are given. The pattern of metastases is shown in Table 3. The difference in time of a CEA rise relative to the moment of

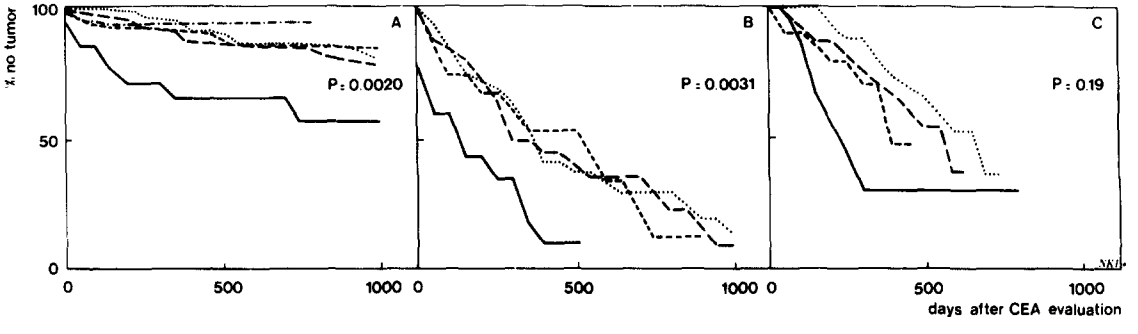

Fig. 3. The association of a rise in CEA level and subsequent tumor recurrence. CEA rise indicates an increase in CEA level prior to tumor recurrence. For further explanation see Materials and Methods. (A) Operable, (B) inoperable, (C) adjuvant. (A) ———, CEA rise (26); · · · ·, no rise 50d (186); -----, no rise 200d (169); -----, no rise 500d (119); -·-·-, no rise 1000d (63). (· · · 168 · · · 138 · · · 105 · · · 84 · · · 64 · · ·; ---143---109---87---68---45---; ---93---77---60---36---11---; -·-·-43-·-·-23-·-·-8-·-·-2-·-·-0-·-·-; —14—11—8—3—2—). (B) ———, CEA rise (14); · · · · ·, no rise 100d (36); -----, no rise 200d (27); -----, no rise 400d (17). (—5—1—; · · ·23 · · · 12 · · · 9 · · · 6 · · · 2 · · ·; ---19---10---8---3---1---; ---10---7---7---1). (C) ———, CEA rise (11); · · · · ·, no rise 100d (53); -----, no rise 200d (47); -----, no rise 400d (29). (—5—1—1—1—; · · · 45 · · · 19 · · · 7 · · ·; ---33---11---3---; ---10---3---).

Table 2. CEA plasma level at recurrence

Patients	Total no recurrences	Increased CEA(%)	Normal CEA (%)
Operable	29	11 (38)	18 (62)
Inoperable	42	26 (62)	16 (38)
Adjuvant chemotherapy	16	8 (50)	8 (50)

Table 3. Patterns of metastases according to CEA level

Metastases	Increased CEA	Normal CEA
Liver	15 (45)	2 (42)
Skeleton	18 (45)	20 (42)
Soft tissue	7 (45)	17 (42)
Lung	10 (45)	8 (42)

( ) Total number of patients.

diagnosis of recurrence (To) is shown in Fig. 4. In the operable group (Fig. 4a) 30% of the patients have a CEA rise before the detection of recurrence with an average lead time of 200 days.

In the inoperable group of patients 45% had a CEA rise prior to the diagnosis of recurrence. This percentage was 30 for the adjuvant chemotherapy group. Both had the same lead time.

Association of CEA rise and subsequent tumor progression and survival in patients with advanced disease

In Fig. 5 actuarial plots showing the association of a CEA rise and subsequent progression in patients with advanced disease are given. Although in both graphs the curves of the patients with a CEA rise run below the other curves, this difference was only significant ($P = 0.047$) in the group of patients treated with hormones. In Fig. 6 the difference in survival between patients with a rise in CEA levels compared to patients without a rise is shown. The difference is highly significant for

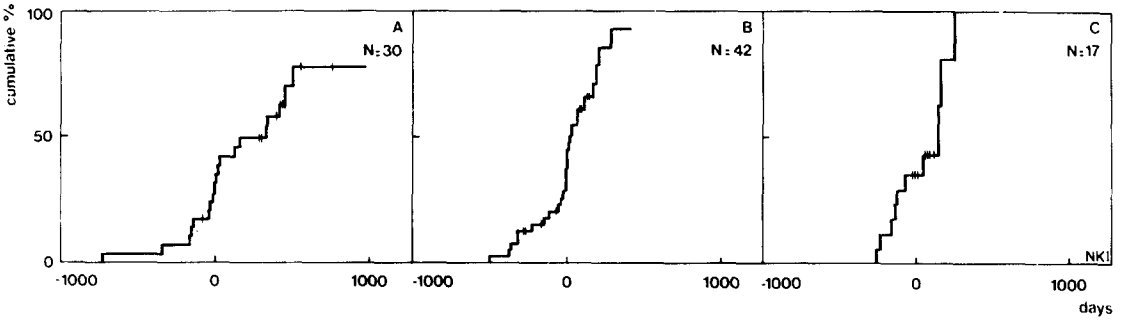

Fig. 4. Cumulative frequency of negative lead time of CEA rise relative to tumor recurrence in the operable (A), inoperable (B) and adjuvant (C) groups.

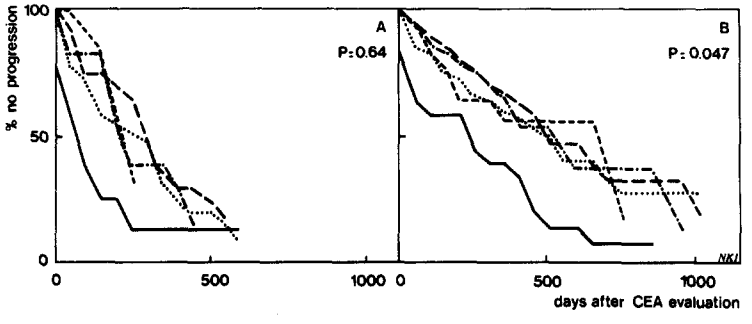

Fig. 5. The association of a rise in CEA level and subsequent tumor progression in the oophorectomy (A) and hormone therapy (B) groups. Two types of curves are given, one for CEA rise prior to tumor recurrence and four for patients who showed no rise in CEA at various intervals after the start of treatment. (*A*) ———, *CEA rise* (10); · · · · ·, *no rise* 50*d* (33); – – – – –, *no rise* 100*d* (25); – · – ·, *no rise* 200*d* (14); – – – –, *no rise* 400*d* (6). (· · · 15 · · · 5 · · · 1 · · ·; — — 14 — — 5 — — 1 — —; – · – · 7 – · – · 3 – · – · 0 – · – ·; — 3 — 0 — —; — 2 — 1 — 1 —). (*B*) ———, *CEA rise* (46); · · · · ·, *no rise* 50*d* (68); – – – – –, *no rise* 100*d* (65); – · · –, *no rise* 200*d* (52); – – – – – –, *no rise* 400*d* (36). (· · · 34 · · 24 · · · 10 · · · 5 · · · 3 · · ·; — — 30 — — 21 — — 10 — — 5 — — 2 — —; – · – 26 – · – 21 – · – 10 – · – 5 – · – 5 – · – 0 – · – ·; — — 5 — — 0 — —; — 12 — 5 — 2 — 1 —).

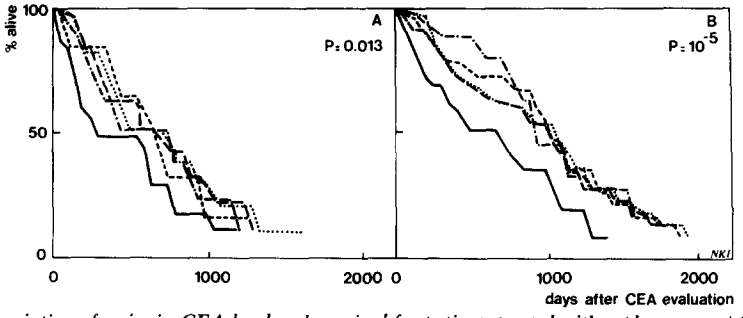

Fig. 6. The association of a rise in CEA level and survival for patients treated with oophorectomy (A) and hormones (B). (A) ———, CEA rise (33); · · · · ·, no rise 50d (50); – – – –, no rise 100d (46); – – – –, no rise 200d (33); – · – ·, no rise 400d (28). (· · · 44 · · · 17 · · · 9 · · · 7 · · · 2 · · · 1 · · · 1; – – – 39 – – – 22 – – – 15 – – – 9 – – – 5 – – – 2 – – – 1 – – –; – – – 27 – – – 16 – – – 10 – – – 6 – – – 3 – – – 1; – · – · – 15 – · – · – 8 – · – · – 5 – · – · – 3 – · – · – 1 – · – · – 1 – · – · –; — 16 — 10 — 9 — 3 — 3 — 1 — 1 — 1 —). (B) ———, CEA rise (46); · · · · ·, no rise 50d (68); – – – –, no rise 100d (65); – – – –, no rise 200d (52); – · – ·, no rise 400d (36). (· · · 65 · · · 49 · · · 39 · · · 27 · · · 20 · · · 11 · · · 8 · · · 6 · · · 2; – – – 57 – – – 46 – – – 38 – – – 27 – – – 10 – – – 10 – – – 11 – – – 8 – – – 4 – – – 2 – – –; – – – 45 – – – 38 – – – 28 – – – 21 – – – 18 – – – 6 – – – 2 – – – 1 – – –; – · – · – 31 – · – · – 23 – · – · – 18 – · – · – 11 – · – · – 7 – · – · – 5 – · – · – 2 – · – · – 1 – · – · –; — 32 — 22 — 18 — 11 — 8 — 3 — 1 —).

Table 4. Change in CEA in relation to the effect of treatment with elevated pretreatment CEA levels

		CEA decrease	CEA stable	CEA increase
Total number	86			
Remission	33	31	2	
No change	22	12	7	3
Progression	31	3	8	20

the patients on hormonal therapy. In patients with elevated CEA levels the change in CEA is clearly related to the effect of treatment (Table 4).

DISCUSSION

The CEA levels observed in patients in different stages of breast cancer are in general agreement with those reported by Tormey [2] and Mijers [4]. The pre-treatment level of CEA had no relation with prognosis in all groups of patients, except for those treated by oophorectomy (Fig. 2a). In these patients a significant difference was found only between groups with moderately (10–20 ng) and highly (> 20 ng) increased levels. These findings are contradictory to those of Wang [1] and Mijers [4].

We were primarily interested in the relation between CEA levels and the course of the disease. It was necessary to define strict criteria for an increase or a decrease of CEA levels. A significant change in CEA level was defined as a change in at least two subsequent measurements. The interval between the two measurements was not standardized, but was largely determined by the follow-up schedule, which varied for the different groups of patients. A long interval between the measurements could therefore decrease the sensitivity of the method. This interval was highest for the post-operative patients, on average, three months; only about a quarter of them had a rise in CEA that preceded tumor recurrence. The relation between a rise in CEA and recurrence was further weakened by transient rises in CEA which were not due to tumor growth. The patients on adjuvant chemotherapy were sampled every month. This may explain why tumor recurrence was more often preceded by a rise in CEA.

In most patients a rise in CEA predicted recurrence or progression of tumor growth. This was not significant for the patients treated by oophorectomy and on adjuvant chemotherapy, but the trend was in the same direction (Figs. 3,5). In patients treated for advanced disease a rise in CEA was associated with a shorter survival. The practical value of serial CEA measurements during the follow-up of patients with breast cancer is limited. For instance, only half of the patients with primary breast cancer had an elevated CEA level at the time of recurrence. Twenty-six out of 42 patients with a normal CEA level remained negative despite progression of disease, and 17 of these remained negative until death (Fig. 4a). It is obvious that some tumors never give a rise in CEA plasma level and that it is dangerous to relate CEA levels to tumor burden. Several investigators [2, 6] reported a relation-

ship between CEA and the pattern of metastatic spread. This may reflect a certain biologic behaviour of the tumor.

In patients with metastatic disease and elevated plasma CEA levels, the method provides a useful aid in the evaluation of treatment (Table 4).

REFERENCES

1. WANG DY, BULBROOK RD, HAYWARD JL, HENDRICK JC, FRANCHIMONT P. Relationship between plasma carcinoembyronic antigen and prognosis in women with breast cancer. *Eur J Cancer* 1975; **11**: 615–618.
2. TORMEY DC, WAALKES TP, SNYDER JJ, SIMON RM. Biological markers in breast carcinoma. *Cancer* 1977; **39**: 2397–2404.
3. COWEN DM, SEARLE F, WARD AM *et al.* Multivariate biochemical indicators of breast cancer: An evaluation of their potential in routine practice. *Eur J Cancer* 1978; **14**: 885–893.
4. MIJERS RE, SUTHERLAND DJ, MEAKIN JW, KELLEN JA, MALKIN DG, MALKIN A. Carcinoembryonic antigen in breast cancer. *Cancer* (*Suppl*) 1978; **42**: 1520–1526.
5. LOKICH JJ, ZAMCHECK N, LOWENSTEIN M. Sequential carcinoembryonic antigen levels in the therapy of metastatic breast cancer. *Ann Intern Med* 1978, **89**: 902–905.
6. TASHIMA CK, FRITSCHE HA, JR. Blood carcinoembryonic antigen (CEA) in breast **13**: 89–94.
7. COOMBES RC, GAZET JC, FORD HT *et al.* Assessment of biochemical tests to screen for metastases in patients with breast cancer. *Lancet* 1980; 296–298.
8. HAAGENSEN DE, BARRY WF, JR, MCCOOK TA, GIANNOLA J, AMMIRATA S, WELLS SA, JR. The value of serial plasma levels of carcinoembryonic antigen and gross cyst disease fluid protein in patients with breast carcinoma and osseous metastases. *Ann Surg* 1980; **191**: 599–603.
9. DISTEFANO A, HORTOBAGYI GN, TASHIMA CK, YAP HY, BUZDAR AU, BLUMENSCHEIN GR. The rate of carcinoembryonic antigen (CEA) production may be a prognostic factor for breast cancer patients treated with chemotherapy. *Proc Am Assoc Cancer Res* 1980; **21**: 156.
10. FALKSON HC, VAN DER WATT JJ, PORTUGAL MA, SCHOEMAN HS, FALKSON G. Role of plasma carcinoembryonic antigen in evaluating patients with breast cancer treated with adjuvant chemotherapy. *Cancer Treat Rep* 1979; **63**: 1303–1309.
11. International Union Against Cancer. *T.N.M. Classification of Malignant Tumors.* Geneva (1978).
12. HAAGENSEN CD. *Diseases of the Breast.* Philadelphia, W. B. Saunders, 1971.
13. HAYWARD JL, CARBONE PP, HEUSON JC, KUMAOKA S, SEGALOFF A, RUBENS RD. Assessment of response to therapy in advanced breast cancer. *Eur J Cancer* 1977; **13**: 89–94.
14. PERSIJN JP, KORSTEN CB. The development of a radioimmunoassay for carcinoembryonic antigen with some applications. *J Clin Chem Clin Biochem* 1976; **14**: 377–387.
15. KAPLAN EL, MEIER P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958; **53**: 457–481.
16. MANTEL N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemoth Rep* 1966; **50**: 163–170.
17. CLAYTON DG. A model for association in bivariate life tables and its application in epidemiological studies of family tendency in chronic disease incidence. *Biometrika* 1978; 141–152.
18. MANTEL N, HAENSZEL W. Statistical aspects of the analysis of data from retrospective studies. *J Natl Cancer Inst* 1959; **22**: 718–748.