CHAPTER - V

CEA, TPA AND CA 15-3 AS TUMOR MARKERS IN BREAST CARCINOMA PATIENTS

INTRODUCTION

Tumor markers are used to help in the diagnosis and monitoring of disease course. No marker with definite specificity and sensitivity for early detection of recurrent disease at a subclinical stage has yet been identified. CEA has been found useful in a very small percentage of breast cancer patients (Staab et al, 1985). We have shown that the predictive value of CEA in general is weak and therefore, the use of sequential CEA estimation in these patients is of limited value (Bhatavdekar et al, 1987). Another tumor associated antigen is, tissue polypeptide antigen (TPA), first indentified by Bjorklund and Bjorklund (1957). The utility of TPA has not yet been clearly defined in staging and post-therapeutic surveillance as most of the reports were based on single determinations. Moreover, the value of TPA has been questioned due to the insensitivity and non-specificity in monitoring breast carcinoma patients.

A new tumor marker introduced recently is CA 15-3, a carcinoma-associated antigenic determinant indentified by two monoclonal antibodies (115D8 and DF3) expressed on the

membrane or in the cytoplsm of human breast cancer cells (Hilkens et al, 1984; Pons-Anicet et al, 1987).

This sequential evaluation compares the merits of CEA, TPA and CA 15-3 in breast cancer patients considering stage, nodal status, histologic grade and disease progression/remission.

STUDY DESIGN

The normal circulating levels of plasma CEA and serum tissue polypeptide antigen (TPA) and CA 15-3 were measured in pre-menopausal controls (N=3Ø). The clinical data collection, pathologic staging and assessment of disease activity was investigated for CEA in 1Ø1 patients, TPA in 29 patients and CA 15-3 in 47 patients attending The Gujarat Cancer and Research Institute, Ahmedabad, India as described in previous Chapters. The surgical procedures were performed by Surgical Oncology units and adjuvant therapy was instituted by Medical Oncology units of the Institute. The treatment schedules were described in Chapter II. Serial samples were obtained from pre-menopausal breast cancer patients pretherapeutically and at intervals of 3-6 months for stage II and at monthly/bimonthly intervals for stages III and IV. Blood samples were collected in plain vials for TPA and CA

15-3 and in ethylenediaminetetraacetic acid (EDTA), disodium salt (1-2 mg/ml) coated vials for CEA in patients and controls in the morning between 9-11 AM pretherapeutically, to obtain baseline levels of individual patient. The serum and plasma were separated within 1-2 hours, aliquoted and stored at -7Ø °C until assayed. The assays were performed within 1 month. The studies were performed retrospectively using frozen samples.

TUMOR MARKER ASSAYS:

CEA, TPA and CA 15-3 were assayed using RIA/IRMA kits supplied by Diagnostic Products Corporation, Los Angeles, U.S.A., Prolifigen Sangtec Medical, Sweden and CIS, France respectively using manufacturers' protocol. The reference samples of the kit were considered for internal quality control purpose and an intraassay and interassay coefficient of variation (CV) was 3%-5% and 5%-8% respectively of CEA, TPA and CA 15-3 respectively. The sensitivity of CEA assay was Ø.9 ng/ml,while that of TPA was 4 U/L. The cut-off values for CEA, TPA and CA 15-3 respectively were 3 ng/ml, 85 U/L and 26 U/ml in accordance with Pons-Anicet et al (1987) and Schmidt-Rhode et al (1987).

TUMOR MARKERS IN BREAST CARCINOMA MONITORING:

The sensitivity, specificity and predictive values of individual markers and their combination were calculated according to Tondini et al (1988) and Caponigro et al (199Ø) (Chapter III).

STATISTICS:

Signficance was calculated using (i) X^2 - analysis and (ii) an exact contingency table for order data and Fisher' two exact test (Mehta and Patel, 1983). P values less than Ø.Ø5 were considered significant.

RESULTS

All the three tumor markers exhibited a statistically significant elevation as compared to controls (Table - 1). CEA, TPA and CA 15-3 were above normal limit in 51/1Ø1 (5Ø.4%), 12/29 (41.3%) and 17/47 (36.1%) patients respectively. At diagnosis, 2Ø/52 (38.4%) patients showed normal marker levels while any one marker or more were elevated in 32/52 (61.5%) follow-up patients.

TUMOR MARKERS IN RELATION TO STAGE:

The mean values of all the markers demonstrated an increase as stage advanced. The differences, however, were statistically significant only for CA 15-3. (Table - 2).

12/27 (44.4%), 2Ø/52 (38.4%), 9/11 (81.8%) and 1Ø/11 (9Ø.9%) patients evidenced CEA levels above normal amongst stages II, III, IV and patients entered at relapse respectively. These differences were statistically significant (X^2 = 14.915, $P < Ø.ØØ5$). Thus abmormal incidence of CEA showed a statistically significant increase as stage advanced. On the

other hand, the abnormal incidence of TPA was statistically non-significant. 1/7 (14.2%), 6/14 (42.8%), 1/2 (5Ø.Ø%), 4/6 (66.6%) patients exhibited a higher TPA in stage II, III, IV and recurrent patients respectively (X^2 = 3.77, P - non-significant). Conversely, the abnormal incidence of CA 15-3 was significantly increased with advaning stages. 3/12 (25.Ø%), 7/25 (28.Ø%), 5/5 (1ØØ.Ø%), 2/5 (4Ø.Ø%) patients demonstrated an elevated CA 15-3 incidence amidst stages II, III, IV and recurrent patients respectively (X^2 = 1Ø.198; P < Ø.Ø25).

A comparison of stage II vs advanced tumors produced non-significant differences for CEA and TPA while difference was statistically significant for CA 15-3.

TUMOR MARKERS IN RELATION TO NODAL STATUS:

The node positive patients expressed higher CEA, TPA and CA 15-3 levels in comparison to node negative patients (Table - 3).

TUMOR MARKERS AND HISTOLOGIC GRADE:

The mean circulating levels of TPA and CA 15-3 except CEA were higher in patients with histologic grade III as compared to patients with grade I tumors (Table - 4). The differences however, were statistically non-significant.

PRETHERAPEUTIC TUMOR MARKER LEVELS IN RELATION TO DISEASE OUTCOME:

At diagnosis, a lower expression of TPA and CA 15-3 amongst responders was noted in comparison to patients who developed recurrence. Such a trend was not observed for CEA. (Table - 5). The differences were statistically significant only for CA 15-3.

16/31 (51.6%) non-responders and 1Ø/21 (47.6%) responders showed pretherapeutic CEA levels above normal using 3 ng/ml as cut-off point. When a cut-off point of 5 ng/ml was used 13/31 (41.9%) non-responders and 6/21 (28.5%) responders demonstrated pretherapeutic levels above normal. None of the above differences were statistically significant. Similarly, 6/14 (42.8%) non-responders had TPA levels above normal in comparison to 2/1Ø (2Ø.Ø%) responders who evidenced pretherapeutic levels above normal. These differences were also statistically non-significant. On the other hand, 12/25 (48.Ø%) non-responders exhibited pretherapeutic CA 15-3 levels above normal in sharp contrast to only 1/12 (8.3%) responder who showed pretherapeutic CA 15-3 above normal. The differences were statistically significant (X^2 = 5.216; P <Ø..Ø25). In additon to the abvoe, it was also marked that in 5/25 (2Ø.Ø%) non-responders and in 1Ø/12 (83.3%)

responders, CA 15-3 levels did not exceed the normal limits (26 U/ml) during the follow-up period of 2 years. Moreover, amongst the responders with normal CA 15-3 levels during the disease course, 5/1Ø (5Ø.Ø%) had stage II disease.

MARKERS IN RELATION TO DISEASE STATUS:

Pretherapeutic CEA, TPA and CA 15-3 levels demonstated an increase at progression. The elevation of TPA and CA 15-3 but not CEA was statistically significant (Table - 6; Figs. 1-4). The tumor marker levels before progression also showed a statistically non-significant elevation when compared to pretherapeutic levels. Moreover, the levels of tumor markers also exhibited a statistically non-significant increase at progression as compared to the levels of preceding samples. On the other hand, no differences in the pretherapeutic CEA, CA 15-3 and TPA levels were noted amongst the responders at the end of 2 years (Table - 6; Figs. 5-6).

TUMOR MARKERS IN RELATION TO SITE AT RELAPSE:

Pretherapeutic marker levels were compared with levels at progression in relation to site at relapse (Table - 7). It was observed that the magnitude of rise in CEA with progression was highest with bone metastasis. The magnitude of rise in TPA and CA 15-3 was high with both visceral and bony metastasis in comparison to soft tissue metastasis. None of the above differences however, were statistically significant owing to small number.

PRETHERAPEUTIC MARKERS IN RELATION TO RELAPSE FREE SURVIVAL IN PATIENTS WHO DEVELOPED RECURRENCE:

The patients with normal pretherapeutic markers had a longer relapse free survival in comparison to the patients with elevated tumor markers (Table - 8). The differences in relapse free survival between these groups for any of the markers were statistically non-significant.

16/31 (15.6%), 6/14 (42.8%) and 12/26 (46.1%) patients presented elevated CEA, TPA and CA 15-3 levels respectively as compared to 15/31 (48.3%), 8/14 (57.1%) and 14/26 (53.8%) patients with normal CEA, TPA and CA 15-3 levels respectively.

EFFECT OF TREATMENT ON MARKER LEVELS:

A statistically non-significant increase in the levels of CEA, TPA and CA 15-3 was observed after all therapeutic modalities (Chemotherapy, endocrine therapy and chemoendocrine therapy; Table - 9). Similar non-significant increase in CEA was demonstated amongst responders treated with chemotherapy while the levels of TPA exhibited a decline and CA 15-3 levels were unchanged after chemotherapy in these patients (Table - 10). Amongst the patients who were treated either with endocrine therapy alone or with chemoendocrine therapy, CEA levels were unchanged. The magnitude of increase in CEA, TPA and CA 15-3 after various

treatment modalities was higher in non-responders as compared to responders.

TUMOR MARKERS IN PRE-MENOPAUSAL BREAST CARCINOMA MONITORING:

Sensitivity, spacificity and predective values were calculated only for CEA and CA 15-3. TPA was not considered because it was analysed only in 24 patients.

The sensitivity of CA 15-3 was 92.Ø% and that of CEA was 67.74%. The combination of CEA + CA 15-3 exhibited a sensitivity of 96.Ø%. The specificity was highest for CEA (55.Ø%) followed by CA 15-3 (18.18%). A combination of markers consequenced into small increments of specificity. A specificity of 36.36% for CEA + CA 15-3 was observed. The predictive value of CA 15-3 was highest (71.87%) followed by CEA (7Ø.Ø%). A combination of tumor markers culminated into minor increases in predictive values. The predictive value for CEA + CA 15-3 was 77.41% (Table - 11).

DISCUSSION

The present findings indicate that determinations of CEA, TPA and CA 15-3 were not useful for stage II breast carcinoma patients when compared with controls. This might be due to the low sensitivity on one hand and the absence of organ or tumor specificity on the other. Several invetigators also reported similar results (Wang et al, 1984; Kausitz et al,

1986; Schmidt-Rhode et al, 1987). De Jong Bakker et al (1981) have also pointed out that all tumors do not produce tumor markers. On the contrary, in advanced stages these markers were significantly elevated. Moreover, the higher expression of tumor markers with advancing stages observed in the present study was significant only for CA 15-3 and not for CEA and TPA. We report a prevalance of elevated CEA as 44.4%, 38.4% and 81.8% for stages II, III and IV respectively. Our results corroborate those of Beard and Haskell (1986) which were as follows : stage I - Ø - 15%, stage II - Ø - 43%, stage III - 3 - 64% and stage IV - 29 - 1ØØ%.

The distribution of these markers in node negative patients was similar to that found in normal women. Similarly, an increased prevalance of CEA, TPA and CA 15-3 noted amongst node positive patients of the present study was comparable to Meyers et al (1978).

Poorly differentiated tumors express relative autonomy reflecting the higher antigen production as observed in the present study in pre-menopausal patients. Such tumors behave aggressively and have been associated with poor prognosis (Bhatavdekar et al, 1989). Similar conclusions were drawn by Wang et al (1984) for CEA.

The patients were grouped according to disease progression/ remission. However, we did not find any significant differences in pretherapeutic CEA levels in patients who developed recurrence and in responders. Occasionally discordant effects were observed such as decreasing CEA levels in progressive disease. This may be related to dedifferentiation of the tumor or a change in the physiologic disposition of the CEA (Bhatavdekar et al, 1987). These observations were in agreement of Mughal et al (1983). Contrary to the above, Lang et al (1984) found a significant higher prevalence of elevated CEA amongst non-responders. The pretherapeutic CA 15-3 levels were significantly higher amongst patients who developed recurrence in comparison to responders. Similarly, Kalliomiemi et al (1988) also have observed high preoperative levels in non-responders.

The above finding was further supported by the fact that non-responders with elevated tumor markers exhibited a shorter relapse free survival in comparison to non-responders having tumor marker levels within normal limits.

Since a high proportion of patients with bone and liver metastases have elevated CEA levels, sequential CEA monitoring can provide important information about disease

status and response to treatment. Moreover, Mross and Bandlow (1986) and Paulick et al (1987) observed lesser expression of CEA and TPA amongst locoregional relapses and regarded CEA as the most sensitive in bone metastasis. CEA determination appears especially valuable in monitoring patients with metastatic disease in bone, a condition often difficult to follow by other means (Bhatavdekar et al, 1987). Furthermore, lower expression of CEA with soft tissue metastasis was explained by the fact that the soft tissue metastasis were diagnosed more readily due to their localization (Paulick and Caffier, 1988). This also extends to TPA and CA 15-3 expressions with soft tissue relapses.

When monitoring breast cancer patients by these markers, the observation of each patients' individual antigen plasma profile is the most important criterion in surveillance. The retrospective serial marker measurements made during the follow-up of breast cancer patients who relapsed, indicated that CA 15-3 determination could announce the onset of dissemination before it was detectable by the usual clinical criteria. The levels of CEA, CA 15-3 and TPA in the present study demonstrated a rise with disease progression. Moreover, the marker levels of preceding sample were also elevated reflecting into a lead time of 2-5 months before the progression was validated by other established criteria.

The elevations of CEA were statistically non-significant limiting its application only to small group of patients. Neville et al (1978) reported that 44% patients evidenced no change in CEA with the development of relapse. FalKson et al (1982) observed no increase in CEA in 36% of patients throughout their disease course. In addition to the above, Haagensen et al (1978) and De Jong Bakker et al (1981) concluded that CEA lacks sufficient sensitivity and variations in serum CEA levels appear to correlate poorly with the disease course. All these data alongwith that obtained in the present study point towards a limited scope for CEA estimations in monitoring pre-menopausal breast carcinoma.

TPA levels exhibited a statistically non-significant rise amongst responders. Moreover, 6/1Ø (6Ø.Ø%) responders had elevated TPA levels. Various literary evidences support such false positive occurence of TPA (Kausitz et al, 1986; Mross and Bandlow, 1986; Bhatavdekar et al, 1989). All these evidences with the high false positivity rate, seriously limits the use of TPA in pre-menopausal breast carcinoma monitoring.

The CA 15-3 levels in our study were correlated better with disease progression than CEA and TPA (Tondini et al,1988;

Caponigro et al, 1990). They have observed that some patients had progressive disease inspite of persistently low serum CA 15-3 levels. In our study it was recorded that 20% of non-responders showed normal CA 15-3 levels during the entire disease course. Amongst responders, we observed 83.3% patients with normal CA 15-3 levels throughout the disease course. Moreover , 50% of such responders had stage II disease.

CEA and CA 15-3 appears valuable in the surveillance of breast cancer patients, for early recognition of recurrent disease and for keeping check on various treatment modalities. The sensitivity, specificity and predictive values for combined use of these markers was 96.0%, 36.36% and 77.41% respectively. The high false positive/ nevative rate of TPA and low sensitivity, specificity and predictive value of CEA and CA 15-3 prevents its use as an indicator of disease status.

The effectiveness of cytotoxic treatment was not accurately indicated by TPA and CA 15-3 (Fig. 2-3). This might be due to the involvement of more than one site at the time of recurrence or increased production of the antigen or decreased clearence through kidney due to high molecular weight of antigens (Colomer et al , 1989). On the other

hand, Schmidt-Rhode et al (1987) showed that CA 15-3 accurately predicted the response to treatment. In our study 1Ø/37 patients with advanced breast cancer had CA 15-3 concentrations not different from those of controls. Therefore, these patients can not be monitored by CA 15-3 determinations. Hayes et al (1986) and Tondini et al (1988) have mentioned that a small fraction of breast cancer patients did not have elevated CA 15-3 levels at any time during the clinical course.

ABSTRACT

Estimation of tumour markers during the course of breast cancer is crucial for the therapeutic monitoring. With the introduction of Carcinoembryonic antigen (CEA) by Gold and Freedman (1965), its estimation gained a routine practice in breast cancer monitoring. Eventually it was recognised that only a small percentage of patients availed the fruits of CEA estimations. Tissue polypeptide antigen (TPA) was another potential marker whose utility has not yet been clearly defined in staging and post-therapeutic surveillance. Very recently, a new specific marker introduced is CA 15-3, a carcinoma associated antigenic determinant identified by two different monoclonal antibodies ([1] DF-3 raised against a membrance enriched

extract of human breast carcinoma metastatic to liver [2] 115 D 8- raised against antigen of human milk fat globule). This chapter is concerned with the estimation of CEA, CA 15-3 and TPA in breast carcinoma. The appearance of markers at first clinical presentation is subgrouped taking stage, nodal status, degree of tumor differentiation and later developed disease status into consideration. All the three markers were significantly elevated as compared to controls. Yet, the precentages of patients in whom the levels were above upper limit of normal were only 35.Ø% for CEA, 36.1% for CA 15-3 and 41.3% for TPA. Thus none of them was of a distinct specificity and utility in monitoring the disease. There were significant differences in CA 15-3 and TPA but not in CEA between node positive and node nagative patients. Similarly, there were significant differences in CA 15-3 and TPA levels amongst the responders and nonresponders.

The changes of markers in responders and nonresponders is compared in section B of the chapter taking the Mean ± standard error values and percentage change in antigen levels into consideration. All the three markers seem to have a usefulness only amongst non-responders and not in responders, limiting their application. Their sensitivity, specificity and predictive value in breast cancer monitoring is discussed. The section also contains graphic

representations of tumor marker levels during the course of disease.

REFERENCES:

Beard DB, Haskell CM.
Carcinoembryonic antigen in breast cancer. Clinical review.
Am J Med 1986; 8Ø : 241-245.

Bhatavdekar JM, Balar DB, Shah NG, Trivedi SN, Bhaduri A, Patel DD, Karelia NH, Shukla MK, Ghosh N.
Prognosis in breast carcinoma utilizing plasma carcinoembryonic antigen and histologic characteristics of the primary tumor.
Tumor Biol 1987 ; 8 : 233-24Ø.

Bhatavdekar JM, Trivedi SN, Shah NG, Patel DD, Karelia NH, Shukla MK, Ghosh N, Vora HH.
Comparison of prolactin, CA 15-3 and TPA in breast carcinomas.
Int J Biol Markers 1989 ; 4 : 15Ø-156.

Bjõrklund B, Bjõrklund V.
Antigenicity of pooled human malignant and normal tissues by cytoimmunological technique : Presence of an insoluble heat - labile tumour antigen.
Int Arch Allergy 1957 ; 1Ø : 153-184.

Caponigro F, Iaffaioli RV, Pagliarulo C, De Placido S, Frasci G, Ungaro B, Matano E, Bianco AR.
CA 15-3 in human breast cancer. Comparison with tissue polypeptide antigen (TPA) and carcinoembryonic antigen (CEA).
Int J Biol Markers 1990 ; 5 : 73-76.

Colomer R, Ruibal A, Genolla J, Rubio D, Del Campo JM, Bodi R, Salvador L.
Circulating CA 15-3 levels in the postsurgical follow-up of breast cancer patients and in non malignant diseases.
Breast Cancer Res Treat 1989 ; 13 : 123-133.

De JongBakker M, Hart AAM, Persijn JP, Cleton FJ.
Prognostic significance of CEA in breast cancer : A statistical study.
Eur J Cancer Clin Oncol 1981 ; 17 : 1307-1313.

Falkson HC, Falkson G, Portugal MA, Watt van der JJ, Schoeman HS.
Carcinoembryonic antigen as a marker in patients with breast cancer receiving post surgical adjuvant chemotherapy.
Cancer 1982 ; 49 : 1859-1865.

Haagensen DE, Kister SJ, Vandevoorde JP, Gates JE, Smart EK, Hansen JH, Wells SA.
Evaluation of carcinoembryonic antigen as a plasma monitor for human breast carcinoma.
Cancer 1978 ; 42 : 1512-1519.

Hayes DF, Zurawski VR, Kufe DW
Comparison of circulating CA 15-3 and carcinoembryonic antigen levels in patients with breast cancer.
J Clin Oncol 1986 ; 4 : 1542-155Ø.

Hilkens J, Buijs F, Hilgers J, Hageman PH, Calfat J, Sonnenberg A, Van der Valk M.
Monoclonal antibodies against human milk fat globule membranes detecting differentiation antigens of the mammary gland and its tumors.
Int J Cancer 1984 ; 34 : 197-2Ø6.

Kalliomiemi O-P, Oksa H, Aaran R-K, Hietanen T, Lehtinen M, Koivula T.
Serum CA 15-3 assay in the diagnosis and follow-up of breast cancer.
Brit J Cancer 1988 ; 58 : 213-215.

Kausitz J, Hupka S, Makaiova I, Michalikova B, Urbanova M Bohunicky D, Belovicova C.
Significance of carcinoembryonic and tissue polypeptide antigen determination in the diagnosis of metastases in breast cancer.
Neoplasma 1986 ; 33 : 471-476.

Lang BA, Kocent A, Nekulova M, Hlavkova J.
Three year follow-up of carcinoembryonic antigen levels in the serum of patients with breast cancer.
Neoplasma 1984 ; 31 : 79-87.

Mehta CR, Patel NR.
A network algorithm for fisher's exact test in RxC contingency tables,
J Am Stat Assoc 1983 ; 78 : 427-434.

Mross K, Bandlow G.
The clinical significance of tissue polypeptide antigen in breast cancer patients.
Anticancer Res 1986 ; 6 : 223-226.

Mughal AW, Hortobagyi GN, Fritsche HA, Beuzdar AU, Yap H-Y, Blumenscheim GR.
Serial plasma carcinoembryonic antigen measurements during treatment of metastatic breast cancer.
JAMA 1983 ; 249 : 1881-1886.

Meyers RE, Sutherland DJ, Meakin JW, Kellen JA, Malkin DG, Malkin A.
Carcinoembryonic antigen in breast cancer.
Cancer 1978 ; 42 : 152Ø-1526.

Neville AM, Patel S, Capp M, Laurence DJ, Cooper EH, Turberville C, Coombes RC.
The monitoring role of plasma CEA alone and in association with other tumor markers in colorectal and mammary carcinoma.
Cancer 1978 ; 42 : 1448-1451.

Paulick R, Caffier H, Paulick M.
Comparison of serum CEA, PHI, and TPA as tumor markers in breast cancer patients.
Cance detect preven 1987 ; 1Ø : 197-2Ø3.

Paulick R, Caffier H.
Elevated serum carcinoembryonic antigen and prognosis of breast cancer patients postmastectomy.
Cancer detec preven 1988 ; 11 : 311-317.

Pons-Anicet DMF, Krebs BP, Mira R, Namer M.
Value of CA 15:3 in the follow-up of breast cancer patients.
Brit J Cancer 1987 ; 55 : 567-569.

Schmidt-Rhode P, Schulz K-D, Sturm G, Raab-Frick A, Prinzh CA.
Ca 15.3 as a tumor markar in breast cancer.
Int J Biol Markers 1987 ; 2 : 135-142.

Staab HJ, Ahlemann LM, Anderer FA, Zwirner M, Schindler AE.
Optimizing tumor markers in breast cancer : Monitoring, prognosis and therapy control.
Cancer detect preven 1985 ; 8 : 35-45.

Tondini C, Hayes Df, Gelman R, Henderson IC, Kufe DW.
Comparison of CA 15-3 and carcinoembryonic antigen in monitoring the clinical course of patients with metastatic breast cancer.
Cancer Res 1988 ; 48 : 41Ø7-4112.

Wang DY, Knyba RE, Bulbrook RD, Millis RR, Hayward JL.
Serum carcinoembryonic antigen in the diagnosis and prognosis of women with breast cancer.
Eur J Cancer Clin Oncol 1984 ; 2Ø : 25-31.

TABLES

TABLE I : Markers in pre-menopausal breast carcinoma (M ± SE)

	CEA ng/ml	TPA U/L	CA 15-3 U/ml
Breast Cancer Patients	7.32 ± 1.34 (101) *	96.90 ± 16.14 (29) *	59.94 ± 17.17 (47) @
Controls	1.44 ± 0.24 (030) *	33.72 ± 02.38 (30) *	09.76 ± 02.94 (30) @
Above normal limit	51/101 (50.4%)	12/29 (41.3%)	17/47 (36.1%)

* - P < 0.001 @ - P < 0.01

Figures in parenthesis show number of patients

TABLE 2 : Markers in relation to stage (M ± SE)

Stage	CEA ng/ml	TPA U/L	CA 15-3 U/ml
II	04.70 ± 1.17 (27)	056.88 ± 21.59 (07)	014.62 ± 03.77 (12) ‡,@
III	06.65 ± 1.50 (52)	090.36 ± 21.16 (14)	040.20 ± 15.53 (25)
IV	19.23 ± 9.20 (11)	160.12 ± 79.87 (02)	288.41 ± 90.01 (05) @
Entered at relapse	04.98 ± 0.75 (11)	124.66 ± 46.57 (06)	029.25 ± 13.80 (05)
III + IV + Rec.	08.27 ± 1.77 (74)	106.06 ± 19.22 (22)	074.10 ± 22.05 (35) ‡

@ - P < 0.01 ‡ - P < 0.02 .

Figures in parenthesis show number of patients

TABLE 3 : Markers in relation to nodal status (M ± SE)

Nodal status	CEA ng/ml	TPA U/L	CA 15-3 U/ml
Node negative patients	2.45 ± 0.96 (11) ‡	27.72 ± 19.36 (03) @	10.38 ± 01.42 (03) ‡
Node positive patients	8.29 ± 1.69 (79) ‡	90.49 ± 17.29 (21) @	66.44 ± 20.03 (39) ‡

@ - P < 0.05 ‡ - P < 0.01

Figures in parenthesis show number of patients

TABLE 4 : Markers in relation to histologic grade * (M ± SE)

Histologic grade	CEA ng/ml	TPA U/L	CA 15-3 U/ml
I	13.45 ± 6.53 (05)	065.00 (01)	27.21 (01)
II	07.76 ± 3.18 (33)	050.55 ± 15.49 (08)	57.32 ± 26.72 (16)
III	05.31 ± 1.88 (22)	120.45 ± 50.39 (05)	68.27 ± 45.66 (11)
II + III	06.78 ± 2.04 (55)	077.43 ± 22.54 (13)	61.78 ± 23.91 (27)

* Data statistically not significant

Figures in parenthesis show number of patients

TABLE 5 : Pretherapeutic marker levels and disease outcome (M ± SE)

	CEA ng/ml	TPA U/L	CA 15-3 U/ml
Patients who developed recurrence	6.28 ± 1.53 (31)	107.15 ± 23.48 (14)	79.27 ± 26.32 (25) *
Responders	5.18 ± 1.89 (21)	046.31 ± 18.01 (10)	10.14 ± 03.09 (12) *

* - P < 0.02

Figures in parenthesis show number of patients

TABLE 6 : Markers in relation to site at relapse (M ± SE)

		CEA ng/ml	TPA U/L	CA 15-3 U/ml
Soft tissue	pretherapeutic	004.72 ± 01.89 (11)	032.90 ± 015.32 (3)	012.96 ± 006.60 (7)
	At progression	006.85 ± 03.77 (11)	282.96 ± 238.62 (3)	042.84 ± 016.38 (7)
Viscera	Pretherapeutic	011.98 ± 09.01 (04)	225.66 ± 048.73 (3)	150.78 ± 120.95 (4)
	At progression	020.78 ± 10.74 (04)	710.00 ± 399.96 (3)	241.20 ± 121.62 (4)
Bone	Pretherapeutic	005.35 ± 00.94 (09)	099.00 ± 034.77 (4)	068.68 ± 011.04 (7)
	At progression	031.41 ± 15.64 (09)	442.53 ± 118.09 (4)	133.28 ± 044.90 (7)
> 1 site	Pretherapeutic	006.68 ± 03.71 (07)	082.10 ± 026.99 (4)	116.81 ± 060.96 (7)
	At progression	106.40 ± 58.04 (07)	746.58 ± 391.70 (4)	373.99 ± 110.38 (7)

Figures in parenthesis show number of patients

TABLE 7 : Pretherapeutic levels of markers in relation to relapse free survival (RFS) in patients who developed recurrence (N ± SE)

	CEA	TPA	CA 15-3
Markers within normal limit	15/31 (48.3%)	8/14 (57.1%)	14/26 (53.8%)
RFS in months	13.50 ± 1.80	13.00 ± 3.05	11.75 ± 2.01
Markers above normal limit	16/31 (15.6%)	6/14 (42.8%)	12/26 (46.1%)
RFS in months	09.40 ± 1.49	06.75 ± 1.05	10.29 ± 1.91

TABLE 8 : Markers according to disease status (M ± SE)

	CEA ng/ml	TPA U/L	CA 15-3 U/ml
I. Patients who developed recurrence			
pretherapeutic	06.28 ± 01.53 (31)	107.15 ± 023.48 (14) ¥	079.27 ± 26.32 (25) @
before progression	23.29 ± 15.96 (31)	124.87 ± 027.29 (14)	119.53 ± 41.74 (25)
At progression	34.48 ± 14.90 (31)	552.52 ± 144.52 (14) ¥	195.95 ± 44.37 (25) @
II. Responders			
Pretherapeutic	05.18 ± 01.89 (21)	046.31 ± 017.10 (10)	010.14 ± 03.09 (12)
At last F / U	04.16 ± 00.78 (21)	052.25 ± 016.22 (10)	011.81 ± 02.17 (12)

@ - P < 0.05 ¥ - P < 0.01

Figures in parenthesis show number of patients

TABLE 9 : Effect of treatment on tumor marker levels in non-responders (M ± SE)

		CEA ng/ml	TPA U/L	CA 15-3 U/ml
Chemotherapy N = 17	pretherapeutic	04.09 ± 00.76 (17)	127.44 ± 039.48 (7)	044.55 ± 020.08 (15)
	After therapy	19.29 ± 08.34 (17)	604.28 ± 281.09 (7)	104.30 ± 028.34 (15)
Endocrine therapy N = 3	Pretherapeutic	02.33 ± 01.85 (03)	053.48 ± 026.76 (2)	193.44 ± 188.57 (02)
	After therapy	04.03 ± 02.63 (03)	247.92 ± 191.03 (2)	219.14 ± 211.83 (02)
Chemoendocrine therapy N = 9	Pretherapeutic	18.49 ± 08.23 (09)	563.28 ± 218.09 (5)	201.76 ± 098.18 (08)
	After therapy	57.70 ± 20.94 (09)	712.95 ± 315.89 (5)	213.89 ± 063.29 (09)

Figures in parenthesis show number of patients

TABLE 10 : Effect of treatment on tumor marker levels in responders (M ± SE)

		CEA ng/ml	TPA U/L	CA 15-3 U/ml
Chemotherapy N = 5	pretherapeutic	04.01 ± 01.84 (5)	50.20 ± 29.92 (3)	13.15 ± 3.37 (4)
	After therapy	21.10 ± 13.82 (5)	25.76 ± 12.90 (3)	16.39 ± 4.70 (4)
Endocrine therapy N = 5	Pretherapeutic	03.02 ± 01.11 (5)	65.00 ± 00.00 (2)	03.90 ± 1.85 (2)
	After therapy	04.30 ± 01.23 (5)	67.50 ± 00.50 (2)	05.17 ± 0.50 (2)
Chemoendocrine therapy N = 2	Pretherapeutic	03.50 ± 03.49 (2)	20.00 ± 20.00 (2)	11.88 (1)
	After therapy	05.35 ± 00.95 (2)	15.10 ± 01.00 (2)	10.00 (1)

Figures in parenthesis show number of patients

Table 11 : Sensitivity, specificity and predictive value of tumor markers in pre-menopausal breast carcinoma monitoring

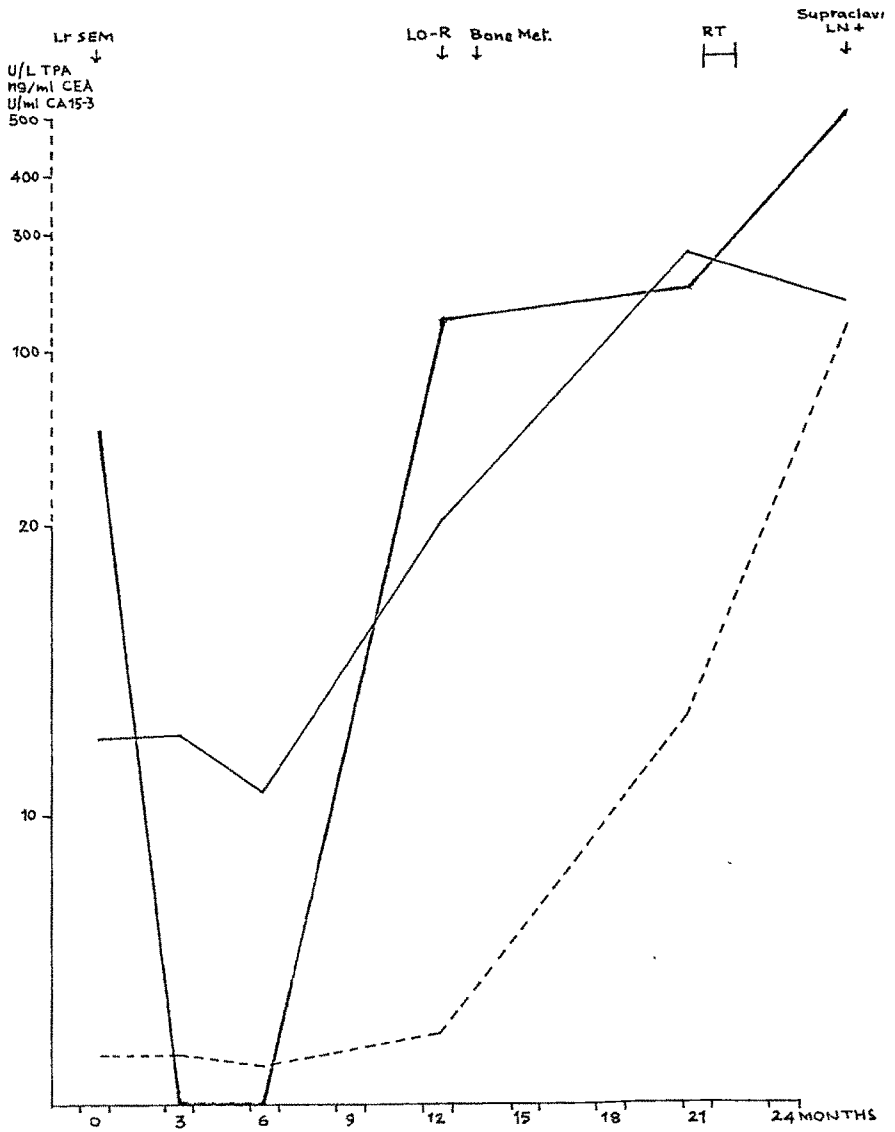
	CEA N = 52	CA 15-3 N = 36	CEA + CA 15-3 N = 36
Sensitivity	67.74 %	92.ØØ %	96.ØØ %
Specificity	55.ØØ %	18.18 %	36.36 %
Predictive value	7Ø.ØØ %	71.87 %	77.41 %

FIGURES

PATIENTS WHO DEVELOPED RECURRENCE (FIGS. 1-4):

Fig. 1

Stage II patient treated with SEM. Patient developed local recurrence followed by bone metastasis. Patient was lost to follow-up for 3-5 months. Then she was given RT. Inspite of RT, she developed metastasis in supraclavicular lymph nodes. TPA and CA 15-3 showed correlation with disease status. Initially for 1Ø months CEA levels were < 3.Ø ng/ml which increased significantly with the development of metastasis in supraclavicular lymph node.



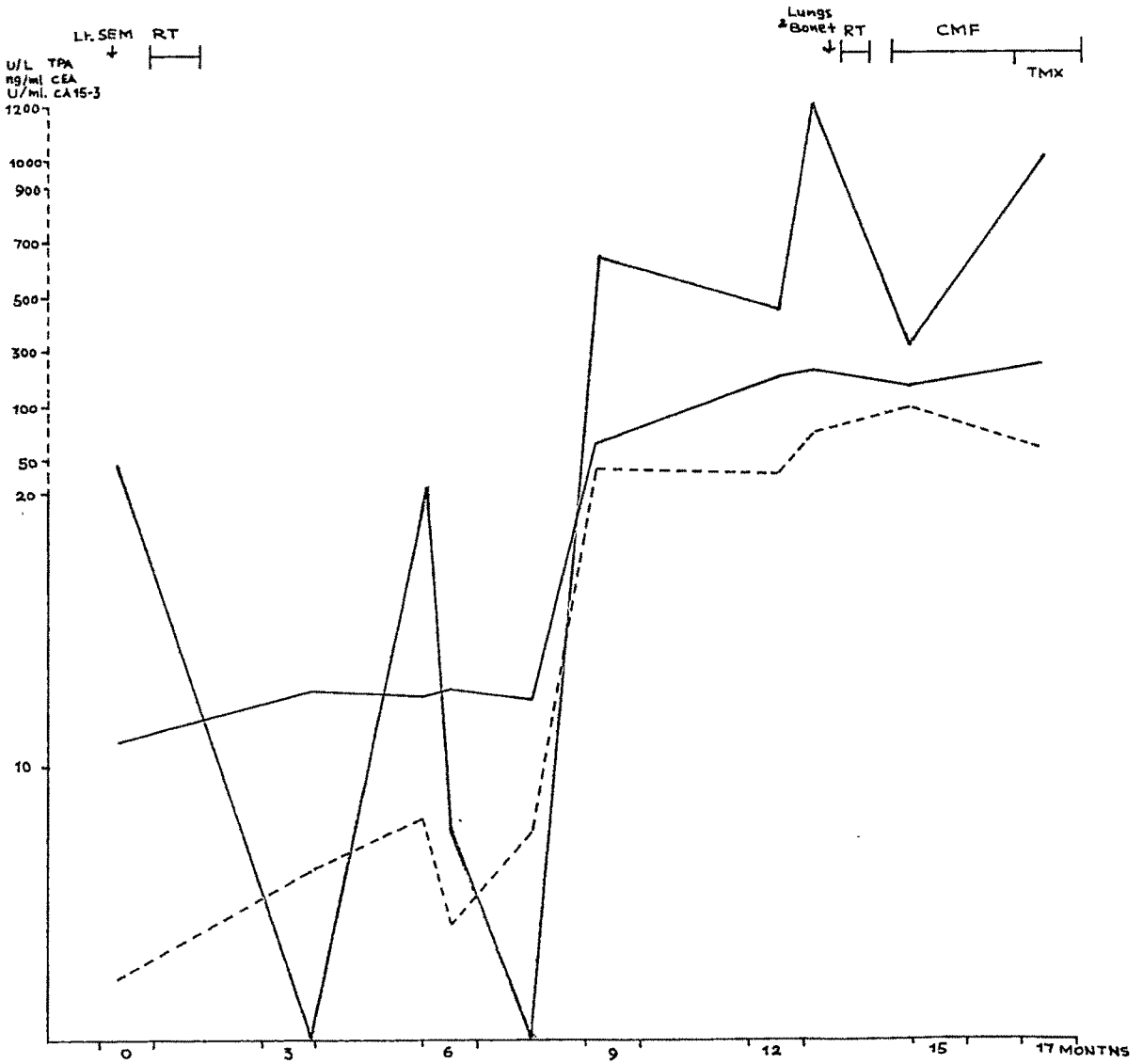
Stage II
HG II

CA 15-3
CEA
TPA

Fig.1

Fig. 2

Stage III patient treated with SEM followed by RT. Patient refused for CMF but she responded to it and was relapse free for 40 months. Then she developed metastasis in lungs and bone, was treated with RT followed by CMF and TMX. She did not respond to it and had increased bone metastasis. CEA, CA 15-3 and TPA correlated well with disease and even showed a lead time of 4-5 months. Moreover, TPA post-operatively and post-RT showed increased concentrations thereby showing non-specificity of the marker.



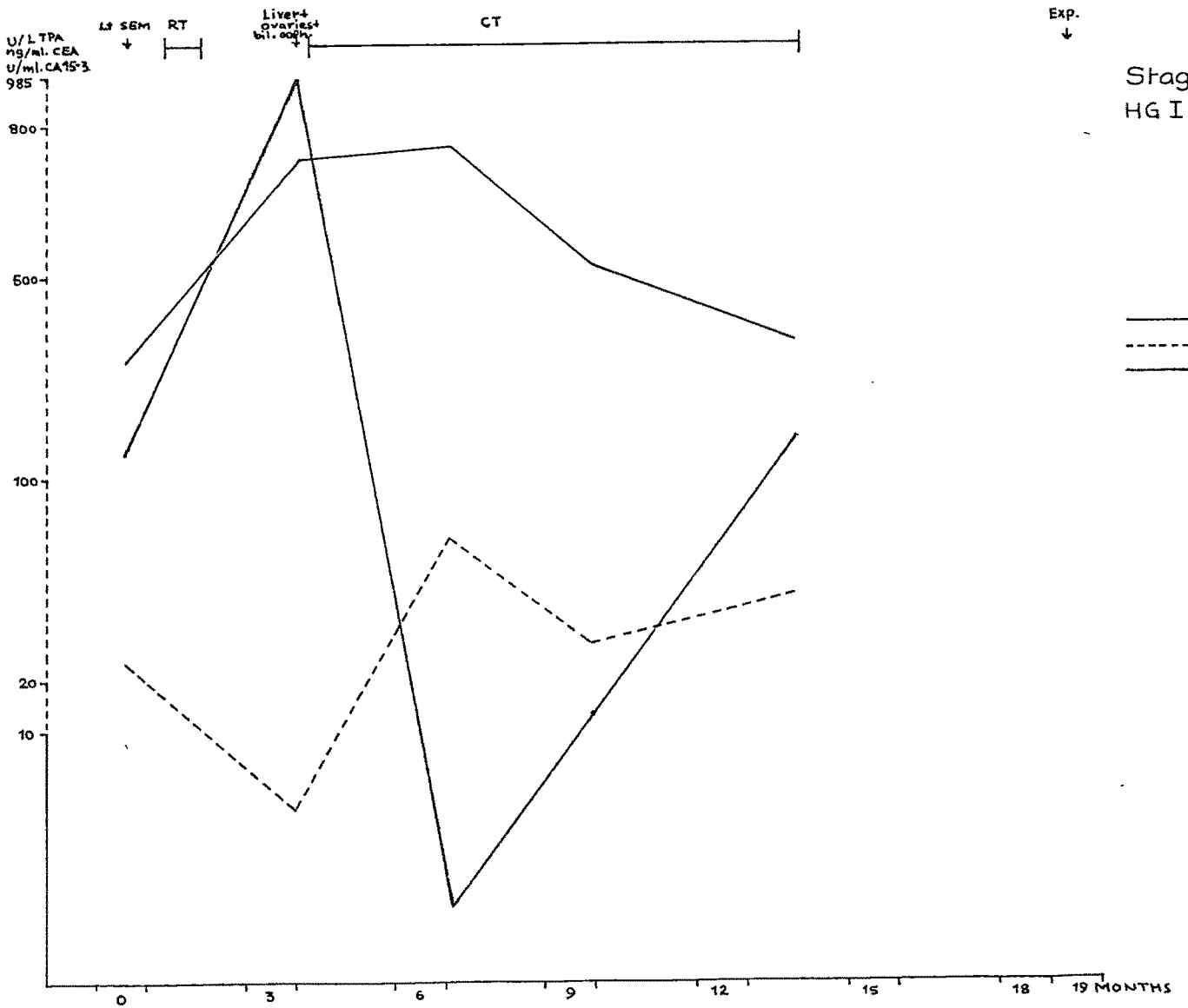
Stage III
HG II

Fig.2

Fig. 3

Stage III patient treated with SEM followed by RT. At the time of bilateral oophorectomy she had liver and ovarian metastases. She was given adjuvant chemotherapy.

CEA and CA 15-3 showed parallel levels with disease course as compared with TPA. False -ve levels were recorded for TPA.



Stage III
HG I

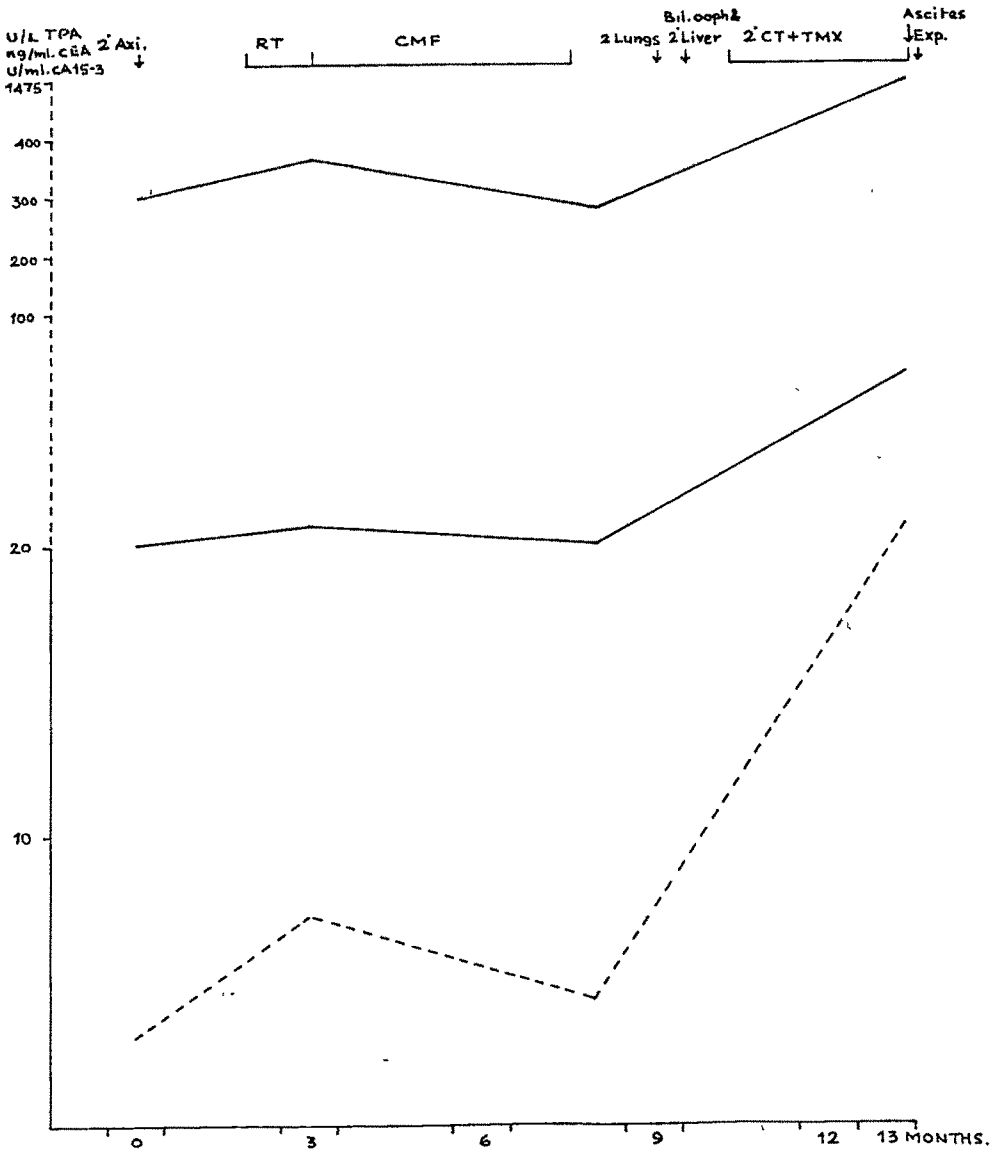
CA 15-3
CEA
TPA

Fig. 3

Fig. 4

Patient came with recurrent disease in axilla, was treated with surgery followed by RT and CMF. After completion of CMF within 1.5 months she developed secondaries in lungs and liver, and was treated with second line chemotherapy and TMX. She did not respond to it and developed ascitis and died immediately.

CEA and TPA levels correlated well with the disease course whereas CA 15-3 levels were below 20 U/ml initially but last sample had significantly increased levels.



Rec. Ca.
HG II

CA 15-3
CEA
TPA

Fig. 4

RESPONDERS (FIGS. 5-6):

Fig. 5

Patient had stage II disease. Patient was treated with SEM followed by CMF. Patient responded to it and was relapse free at the end of two years.

CMF resulted into increase in CEA levels . TPA and CA 15-3 levels were within normal limits throughout the disease course.

Stage II
HG II

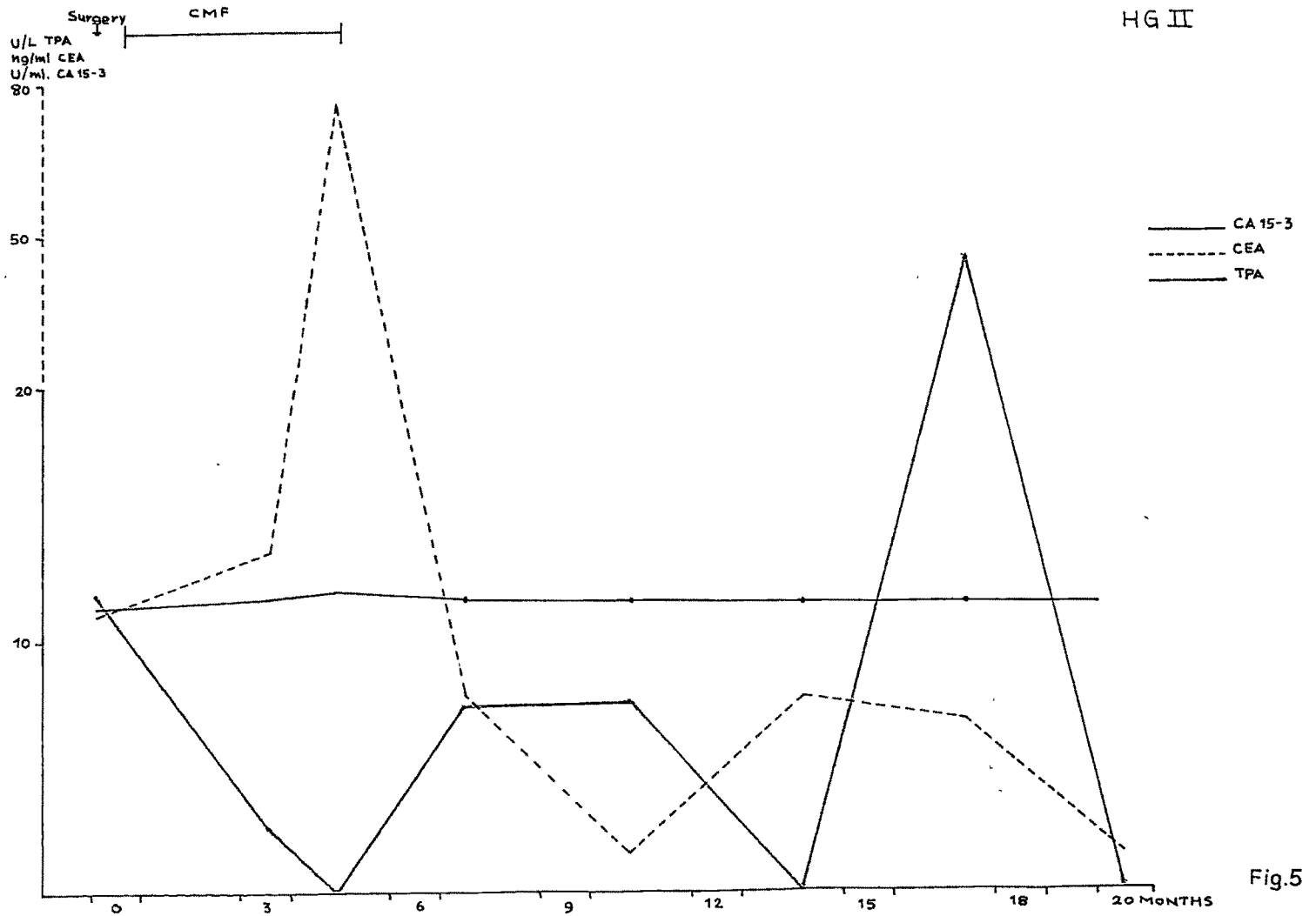
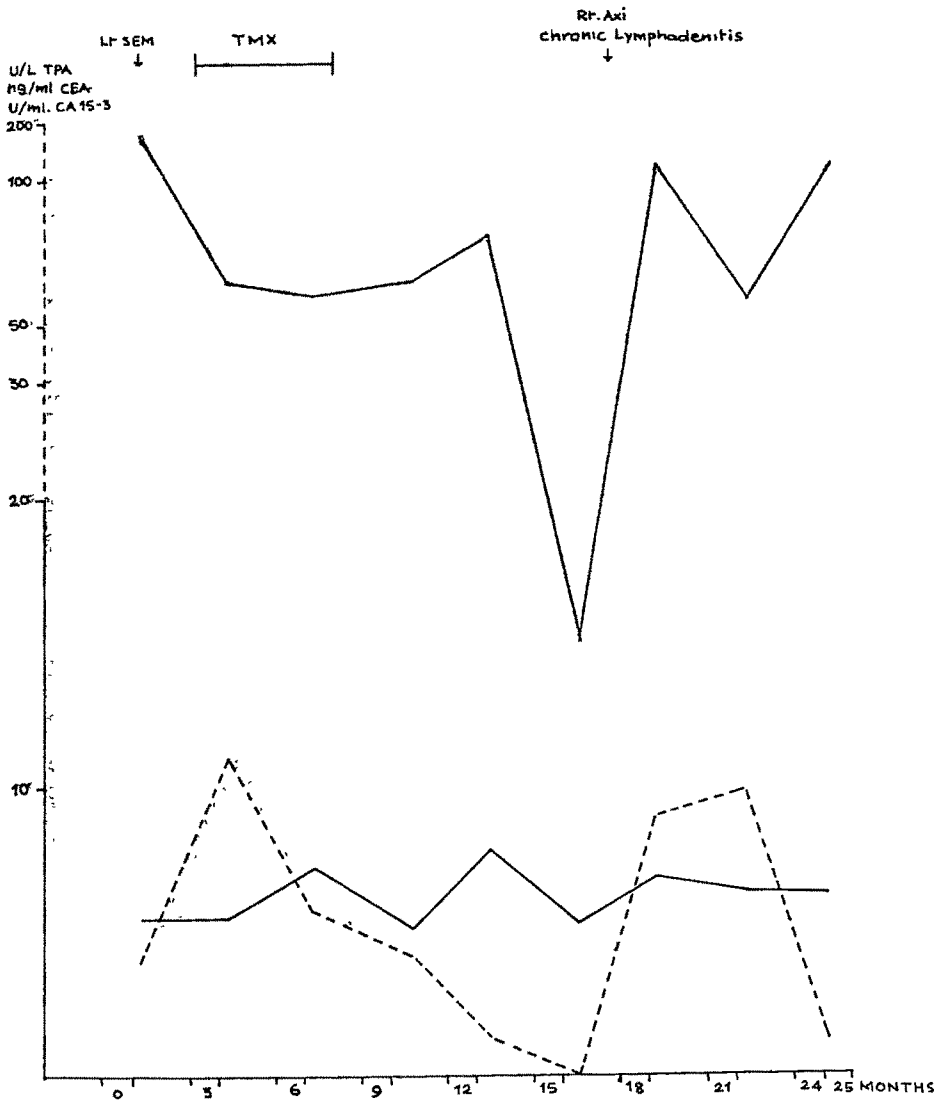


Fig.5

Fig. 6

Stage II patient treated with SEM followed by TMX.

CEA and TPA showed no specific increased titres while CA 15-3 was less than 8 U/ml throughout disease course.



Stage II
HG II

CA 15-3
CEA
TPA

Fig. 6