CHAPTER - I

STEROID RECEPTORS IN PRE-MENOPAUSAL BREAST CANCER PATIENTS: CORRELATIONS WITH CLINICALLY IMPORTANT PROGNOSTICATORS AND SURVIVAL

INTRODUCTION :

Since 1896, when Beatson first reported that oophorectomy can effect striking remission of advanced breast cancer in pre-menopausal women, it has been recognized that some human breast cancers depend on sex steroid hormones for their continued proliferation. However, for several decades thereafter, the precise role of hormones in this cancer was not elucidated. In the sixties and thereafter, mediation of these hormonal effects became understood (Glascock and Hoekstra, 1959; Jensen and Jacobson, 196Ø; Folca et al, 1961) when their receptor protein was isolated and in due course characterized. This brought a new dimension to breast cancer studies and clinical decisions on additive (Cole et al, 1971; Ward, 1973) or ablative endocrine therapy were based on results of assays of these receptor proteins. Since then, the use of these assays have increased enormously as have their potential applications. Initially the information obtained was used to identify those patients with advanced disease who were most likely to benefit from endocrine

therapy. This was important, because in the early 198Ø's when steroid receptor measurment became possible, palliative treatment of advanced breast cancer usually involved oophorectomy (Beatson, 1896), estrogens, androgens (Nathanson, 1952) or major ablative surgery such as adrenalectomy (Huggins and Bergenstal, 1952) and hypophysectomy (Luft and Olivercrona, 1953; Pearson et al, 1956). The two later procedures were associated with significant morbidity and mortality.

In 1975, McGuire noted that patients with ER in their tumors had a better prognosis than patients whose tumors were devoid of such receptors. In 1975, Horwitz and her colleagues drew attention to the potential value of a second steroid receptor, the progesterone receptor and subsequent studies Jenson (198Ø) and McGuire (198Ø) had suggested that the progesterone receptors may be a better prognostic indicator than the estrogen receptor.

Although, not the number one female cancer cause in India, breast cancer ranks second. Breast cancer contributes significantly towards female cancer related morbidity and mortality in this region. At the Gujarat Cancer and Research Institute, we have been studying the role of steroid and peptide hormones as well as steroid receptors in breast cancer patients for the last seven years.

The estrogen and progesterone receptors are now well recognized as important determinants of breast cancer biology. The other important variables in the assessment of tumor aggressiveness are stage at diagnosis, lymph node status, histologic variables viz : histologic grade, presence/absence of necrosis and lymphocytic infiltration and survival. An attempt therfore, was made here to correlate the estrogen- and progesterone-receptors with above mentioned important variables so as to further validate their role. Several studies indicated that the biology of breast cancer differed depending on the menopausal status of the patient. This study addresses itself to only **PRE-MENOPAUSAL** patients.

STUDY DESIGN

CLINICAL DATA :

A total 111 pre-menopausal patients randomly selected for the study were attending the Gujarat Cancer and Research Institute, Ahmedabad, India for the diagnosis and treatment of their disease during August 1983 to July 1988.

The clinical diagnosis was confirmed with the assistance of mammography, chest radiographs, scintiscanning, ultrasonography, CT scanning, hemogram, liver function

tests, renal function tests and histopathological reporting as, when and where indicated during the course of the disease. The disease progress charts maintained at the institute were consulted from time to time. The surgical procedures were performed by the Surgical Oncology units and adjuvant therapy was instituted by the Medical Oncology units of the Institute. Assessment of disease activity was carried out according to recommendations of Hayward et al (1977).

TREATMENT SCHEDULE :

The treatment schedules were implemented by Medical Oncology units of the Institute. The CMF regimen was cyclophosphamide, 100 mg/sqm orally, days 1 to 14; methotrexate, 40 mg/sqm and 5-fluorouracil, 600 mgm/sqm intravenously, days 1 and 8. After a two week rest period an identical cycle of chemotherapy was repeated. Drug doses were modified according to toxic side effects. The dose of Tamoxifen was 10 mg twice daily orally. The second line treatment given was with MMC, 10 mg/sqm, VLB 10 mg/sqm every 15 days and Adriamycin 40 mg/sqm either singly or in combination with Tamoxifen.

COLLECTION OF MATERIAL :

The tissues from primary tumors and malignant lymph-nodes wherever possible were collected on ice at mastectomy (SEM,

RM) or in icecold buffer (TEND-1ØG) at 4 C at the time of biopsy. The tissues were rushed to Endocrinology Division within 5 min. of excision. The malignant tissues were divided into two parts. One part submitted for histopathologic examination was fixed in formalin and the counterpart devoid of fat, blood and necrotic material, selected by the pathologist was used for steroid receptor estimation. The tissues were rinsed with icecold buffer (TEND-1ØG) and were snap frozen in liquid nitrogen and subsequently preserved at - 7Ø C in a Revco freezer till analysis. The total time between excision of specimen and snap freezing never exceeded 1Ø min. The tissues were analyzed within a fortnight.

STEROID RECEPTOR ESTIMATION :

(i) PREPARATION OF CYTOSOLS :

The tissues to be analyzed were thawed in coldroom at 4 C. They were then minced and added with 5 - 7 ml TEND - 1ØG buffer (Tris-HCl 1Ø mmol ; EDTA 1.5 mmol ; NaN3 mmol; DTT 2 mmol ; Glycerol 1Ø% v/v ; pH 7.5) (Vihko et al, 198Ø; Bhatavdekar et al, 1988). The chemicals were procured from Sigma Chemicals, USA.

Homogenization was carried out with 3 cycles each of 15 sec. bursts with 45 sec. cooling interval in crushed ice in coldroom.

The homogenate was centrifuged at 105,000 xg at 2 C for 1 hr. in TGA-75 ultracentrifuge. The supernatant was collected by shifting aside the fat layer from the top. An aliquot from this cytosol was submitted for total protein estimation and rest of the cytosol was left in the coldroom in ice till assay (usually 1 hr.).

(ii) PROTEIN ESTIMATION :

Protein estimation was carried out using folin phenol reagent according to Lowry et al (1951). A regression equation for protein estimation was calibrated using Bovine Serum Albumin Cohn fraction - V (Sigma) on Beckman DU 8B spectrophotometer. The procedure of NEN (New England Nuclear, USA) ER protocol was followed.

For receptor assays, the protein concentration of cytosols were adjusted to 2-4 mg/ml. Diluted cytosols were assayed again to find out exact protein concentration.

(iii) RECEPTOR ASSAYS :

Standardization of estrogen- and progesterone-receptor assay was done using NEN-ER assay kit using kit positive and negative controls. Standardization was performed using immature rat uteri as follows : 23 days old Swiss albino rats were injected i.p. 5 ug 17-β Estradiol (Steraloids) in 0.5 ml. normal saline with 1% ethanol. Rats were sacrificed

after 24 hrs., uteri were collected and cytosols were prepared as described above. For 6 point titration curves performed in the study, the requirements were :

(A) Estrogen receptor (ER) : (2,4,6,7- ^{3}H) Oestradiol. (Specific activity 3.848 TBq/mmol; Amersham International plc,UK) 6 different concentrations prepared diluting the stock with TEND-1ØG. The concentrations were Ø.13, Ø.26, Ø.63, 1.29, 2.26, 4.97 nm per litre.

Progesterone receptor (PR) : ^{3}H-ORG 2Ø58. (Specific activity 1.665 TBq/mmol; Amersham International plc, UK) 6 different concentrations prepared diluting the stock with TEND-1ØG. The concentrations were Ø.21, Ø.42, Ø.93, 1.68, 3.69, 13.56 nm per litre.

(B) 1ØØ fold molar excess of Diethylstilbesterol (DES) for ER and cold ORG 2Ø58 for PR was used to assess nonspecific binding.

(C) DCC: Ø.Ø5% Dextran (D 4626-Sigma) and Ø.5% Norit-A in 1 lit. Tris-HCl pH 7.5 was prepared. The charcoal was washed once in Tris-HCl pH 7.5 to obtain an efficiency of > 99%. The charcoal should not retain > 1% of ^{3}H-E2 level I to be considered satisfactory in the receptor assays.

(D) Scintillation fluor : 16.5 gms PPO was dissolved in 2 litres toluene followed by Ø.5 gms POPOP. After complete dissolution, 1 lit. triton-X-1ØØ was added to the scintillation fluor.

(iv) Scatchard plot :

All calculations were performed using the NEN-ER, protocol and the Scatchard plot was constructed (Scatchard, 1949). The Kd values for ER $1-9 \times 10^{-10}$ to $1-9 \times 10^{-11}$ molar and for PR $1-9 \times 10^{-9}$ to $1-9 \times 10^{-10}$ molar were considered for high affinity receptors. The cut off value both for ER and PR was 10 fmol/mg cytosol protein as per EORTC recommendation (1980).

PATHOLOGIC STAGING :

UICC TNM Pathologic staging (1980) was followed. The histologic examination was performed by a single pathologist unaware of the receptor status to avoid individual bias. Histologic typing of hematoxylin-eosin stained paraffin sections was done according to WHO classification (1981). The histologic grading was done as described by Bloom and Richardson (1957) and was expressed on a scale of I-well differentiated, II-moderately differentiated and III-poorly differentiated. The necrosis was noted either as absent or present and graded into +(low), ++ (moderate) and +++ (marked). The lymphocytic infiltration was recorded either as absent or present and categorized as mild, moderate and dense.

STEROID RECEPTOR ESTIMATIONS IN SYNCHRONOUS TISSUES :

The tissues of primary tumors and malignant lymph nodes collected simultaneously from mastectomy specimens and

assayed in the same batch for steroid receptor estimation, were termed as **synchronous**. The synchronous tissues were termed to be in accordance if similar steroid receptor status were obtained for the primary tumor and malignant lymph node (LN) :

(i) Primary tumor ER^{+}/PR^{+} and malignant LN ER^{+}/PR^{+}

(ii) Primary tumor ER^{-}/PR^{-} and malignant LN ER^{-}/PR^{-}

The synchronous tissues were termed to be discordant if dissimilar steroid receptor status were obtained for the primary tumour and malignant lymph node (Type I discordance - primary tumor ER^{+}/PR^{+} and lymph node ER^{-}/PR^{-} ; Type II discordance - primary tumor ER^{-}/PR^{-} and lymph node ER^{+}/PR^{+}).

STATISTICAL ANALYSIS :

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

RESULTS

The pre-menopausal patients included in the study were in the age range of 23-48 years with a median age of 35.5 years. 58/111 (52.2%) patients had the disease of the left breast and 52/111 (46.8%) patients were suffering from the disease of the right breast. Only 1/111 (Ø.9%) patient was recorded with bilateral disease at the time of diagnosis.

INCIDENCE OF STEROID RECEPTORS :

From a cohort of 111 pre-menopausal breast carcinoma patients, 48/111 (43.2%) exhibited ER^+ PR^+ tumors. Either ER or PR was positive in 44/111 (39.6%) patients while both the receptors were negative in 19/111 (17.1%) patients. Thus 68/111 (61.2%) patients presented ER^+ and 72/111 (64.8%) patients demonstrated PR^+ tumors (Table - 1 ; Fig.1). A statistically non-significant higher PR expression was noted that ER expression amongst these patients.

STEROID RECEPTORS - CORRELATION WITH STAGE :

At diagnosis, 27/111 (24.3%) patients demonstrated stage II disease. Stage III and IV disease was documented in 57/111 (51.3%) and 16/111 (14.4%) patients respectively. In 11/111 (9.9%) patients, the disease stage was unknown since the primary surgical treatment was given elsewhere and these patients presented to us with relapse. The distribution of PR but not ER was unequivocal amongst all stages ($P < Ø.Ø5$; Table-2). 63/1ØØ (63.Ø%) pretherapeutic patients presented ER^+ tumors in comparison to 5/11 (45.4%) patients at relapse presented ER^+ tumors. Similarly 66/1ØØ (66.Ø%) pretherapeutic patients exhibited PR^+ tumors in comparison to 6/11 (54.5%) patients at relapse presented PR^+ tumors. These differences however, were statistically non-significant.

DISTRIBUTION OF STEROID RECEPTORS IN STAGE IV PATIENTS :

3/16 (18.7%) patients each were documented with lung and bone metastasis.5/16(31.2%) patients had liver metastasis and 5/16(31.2%) patients exhibited involvement of > 1 site (Table - 3). No significant difference in steroid receptor distribution was observed when considering involvement of different metastatic site (Table - 3).

STEROID RECEPTORS AND NODAL STATUS :

Nodal involvement was observed in 89/100 (89.0%) patients while the remaining patients showed no nodal involvement. Though, steroid receptor negativity was higher amongst node positive patients [ER^- PR^-, 14/89 (15.7%)] than node negative patients [ER^- PR^-, 1/11 (9.0%)] no significant differences in steroid receptor distribution were observed in these groups (Table - 4).

Moreover, when number of lymph nodes amongst N, tumors were taken into account , no significant differences were observed in the distribution of steroid receptors.

STEROID RECEPTORS AND DISEASE OUTCOME :

12/31 (38.7%) patients with progressive disease exhibited ER^+ PR^+ tumors in contrast to 11/21 (52.3%) patients who demonstrated ER^+ PR^+ tumors in responsive disease. Contrary to the above, 6/31 (19.3%) patients with ER^- PR^- tumors

progressed as opposed to 3/21 (14.2%) patients with ER^- PR^- tumors, who had responsive disease.

Further, amidst the patients showing progressive disease, 21/31 (67.7%) were ER^+ PR^+ and 16/31 (51.6%) were PR^+ which was lesser than the patients experiencing responsive disease in whom, 15/21 (71.4%) were ER^+ and 14/21 (66.6%) were PR^+ (Table - 5). These differences however, were statistically non-significant.

STEROID RECEPTORS IN RELATION TO SITE AT RELAPSE :

No statistically significant relationship between steroid receptor expression and the relapse site was observed (Table - 6). However, the expression of both ER and PR was lower in patients who developed bone metastasis than in patients with metastasis at other sites.

STEROID RECEPTORS AND HISTOLOGIC TYPES :

Majority of tumors, 42/7Ø (6Ø.Ø%) were classified as invasive duct carcinoma, 1Ø/7Ø (14.2%) had invasive lobular carcinoma and 4/7Ø (5.7%) had medullary carcinoma. Moreover, 14/7Ø (2Ø.Ø%) tumors were mixtures of > 1 histologic types (Table - 7). All 1Ø lobular carcinomas exhibited presence of PR. No statistically significant relationship was observed between steroid receptor concentration and other histologic types.

The PR expression of invasive lobular carcinomas was significantly higher as compared to ER expression ($P < .Ø5$). Such a discrepancy was not seen with other histologic types.

STEROID RECEPTORS VERSUS HISTOLOGIC GRADE :

8/68 (11.7%) tumors were graded as I is contrast to 23/68 (33.8%) tumors graded as III. The steroid receptors were not uniformly distributed amongst all histologic grades ($P < Ø.Ø5$). The well differentiated tumors 8/8 (1ØØ%) were PR^+ in contrast to 13/23 (56.5%) poorly differentiated PR^+ tumors while 3/8 (37.5%) well differentiated tumors were ER^+ tumors in comparison to 16/23 (69.5%) poorly differentiated ER^+ tumor (Table - 8). These differences however, were statistically non-significant.

STEROID RECEPTORS IN RELATION TO TUMOR NECROSIS :

Amongst the non-necrotic tumors, $ER^+ PR^+$ tumors were noted in 2Ø/44 (45.4%), either ER^+ or PR^+ tumors were noted in 19/44 (43.1%) and $ER^- PR^-$ tumors were noted in 5/44 (11.3%) of patients. This was in contrast to tumors with necrosis which showed $ER^+ PR^+$ in 1Ø/23 (43.4%) , either ER^+ or PR^+ tumors in 7/23 (3Ø.4%) and $ER^- PR^-$ tumors were noted in 6/23 (26.Ø%) of patients (Table - 9). The differences, however did not reach statistical significance.

Moreover, a statistically non-significant trend of decline in receptors was observed as the extent of necrosis increased from + to +++.

STEROID RECEPTORS IN RELATION TO LYMPHOCYTIC INFILTRATION :

Lymphocytic infiltration was present in 48/68 (70.5%) tumors and absent in 20/68 (29.4%) tumors. No significant differences were seen with regard to presence or absence of lymphocytic infiltration and steroid receptor concentration. A nonuniform distribution of steroid receptors was observed amongst tumors with various degrees of lymphocytic infiltration (P = 0.01 ; Table - 10). A statistically non-significant trend of higher PR content was noted with mild as compared to dense lymphocytic infiltration.Such a trend was not seen for ER.

STEROID RECEPTORS IN SYNCHRONOUS TISSUES :

The results obtained on steroid receptor estimations from synchronous tissues were presented in Table - 11 A. 22/33 (66.6%) tissues showed accordance for both ER and PR while 11/33 (33.3%) tissues were discordant.

STEROID RECEPTORS IN ACCORDANCE :

A statistically non-significant increase in the expression of both ER and PR was observed in malignant lymph nodes as compared to primary tumors. 5/22 (22.7%) tissues in accordance showed a decrease in ER and 9/22 (40.9%) tissues demonstrated a decrease in PR with disease extension to lymph nodes (Table - 11 B).

3/4 (75.0%) and 4/6 (66.6%) patients with low levels of ER

and PR respectively developed progressive disease. Conversely, 6/9 (66.6%) and 2/5 (40.0%) patients with high content of ER and PR responded to the treatment.

STEROID RECEPTORS IN DISCORDANCE :

Type II discordance (gain of receptors with disease extension) of PR was more prevalent than ER in tissues with discordant steroid receptors ($P < 0.05$; Table - 11 C). Type I discordance (loss of receptors with diesease extension) was demonstrated in 7/11 (63.6%) and 2/11 (18.1%) tissues for ER and PR respectively in contrast to Type II discordance (gain of receptors with disease extension) was noted in 4/11 (36.3%) and 9/11 (81.8%) tissues for ER and PR respectively.

The details regarding relapse free survival (RFS) were available in 76/111 (68.4%) patients. 43/76 (56.5%) patients relapsed and 33/76 (43.4%) patients remained relapse free at the end of 2 years (Fig.2).

From the cohort of 111 pre-menopausal patients, overall survival (OS) details were available in 61/111 (54.9%) patients. 15/61 (24.5%) patients died and 46/61 (75.4%) patients were alive at the end of 2 years (Fig.3).

STAGE AND SURVIVAL :

Significantly more patients died as stage advanced (X^2 =

8.731 ; P < Ø.Ø5 ; Fig. 4 ; Table - 12) during the follow-up period of two years.

Significantly more patients relapsed as stage advanced (X^2 = 11.475 ; P < Ø.Ø25 ; Fig.5 ; Table-12) during the span of two years.

STEROID RECEPTORS AND SURVIVAL :

Only 3/28 (1Ø.7%) $ER^+ PR^+$ patients died as opposed to 4/1Ø (4Ø.Ø%) $ER^- PR^-$ patients during 2 years (Table - 13; Fig.6). The differences were statistically non-significant.

7/15 (46.6%) ER^+ patients died in comparison to 8/15 (53.2%) ER^- patients at the end of 2 years (Fig.7). The extent of ER (Fig.8) also resulted into non-significant differences. Similarly, 7/15 (46.6%) PR= and 8/15 (53.3%) PR^- patients died in 2 years (Fig.9). The extent of PR in these groups (Fig.1Ø) resulted into non-significant differences.

The impact of steroid receptors on relapse free survival was shown in Table - 13. 16/35 (45.7%) $ER^+ PR^+$ patients relapsed as opposed to 7/12 (58.3%) $ER^- PR^-$ patients in 2 years (Fig.11). 28/43 (65.1%) ER^+ patients relapsed in comparison to 24/33 (72.7%) ER^+ patient did not relapse in 2 years. Opposite to the above, 15/43 (34.8%) ER^- patients relapsed as compared to 9/33 (27.2%) ER^- patients did not relapse in 2 years (Fig.12). The differences, however were

statistically non-significant. Similarly, 24/43 (55.8%) PR^+ patients relapsed as opposed to 23/33 (69.6%) PR^+ patients who did not relapse in 2 years (Fig.13). Moreover, a higher PR expression was noted amongst the patients who remained relapse free at 2 years. All the above differences were statistically non-significant as majority of the patients were grieved of advanced tumors.

STEROID RECEPTORS + STAGE IN SURVIVAL :

When steroid receptors and stage in combination were considered for survival, the following results were obtained (Table - 14 A) :

1/3 (7.6%), 4/21 (19.Ø%), 1/2 (5Ø.Ø%) and 1/4 (25.Ø%) ER^+ patients with stages II, III, IV and patients entered at relapse respectively died as opposed to 1/9 (11.1%), 4/6 (66.6%), 2/2 (1ØØ.Ø%) and 1/4 (25.Ø%) ER^- patients with stages II, III, IV and patients entered at relapse respectively died in 2 years. These differences were statistically non-significant.

On the other hand, a similar comparison of PR^+ and PR^- patients resulted into significant differences (Table -14A ; $P < Ø.ØØ5$). 2/13 (15.3%), 2/17 (11.7%), 3/4 (75.Ø%) and Ø/4 (Ø%) PR^+ patients, with stages II,III,IV and patients entered at relapse respectively died as compared to Ø/9

(Ø%), 6/1Ø (6Ø.Ø%) and 2/4 (5Ø.Ø%) PR^- patients with stages II,III and patients at relapse respectively died in 2 years.

A combination of steroid receptors and stage in relapse free survival was noted with the following results (Table - 14 B): Significantly more ER^- patients with advancing stages relapsed in comparison to ER^+ patients with advancing stages. 4/14 (28.5%) , 18/29 (62.Ø%), 4/5 (8Ø.Ø%) and 3/5 (6Ø.Ø%) ER^+ patients with stages II,III,IV and patients entered at relapse respectively as opposed to 2/8 (25.Ø%), 7/8 (87.5%), 1/1 (1ØØ%) and 4/6 (66.6%) ER^- patients with stages II,III,IV and recurrent patients respectively relapsed in 2 years. ($X2 = 19.Ø39$; $P < Ø.Ø25$).

3/13 (23.Ø%), 13/23 (56.5%) , 4/5 (8Ø.Ø%) and 4/6 (66.6%) PR^+ patients with stages II,III,IV and recurrent patients respectively relapsed as opposed to 3/9 (33.3%) 12/14 (85.7%), 1/1 (1ØØ%) and 3/5 (6Ø.Ø%) PR^- patients with stages II,III,IV and recurrent patients respectively relapsed in 2 years. These differences however, were statistically non-significant.

HISTOLOGIC GRADE IN SURVIVAL :

2/7 (28.5%) patients with Grade-I tumors died as compared to 4/13 (3Ø.7%) patients with poorly differentiated tumors died in 2 years (Table -15, Fig.14). The differences

however, were not statistically significant probably because of small number of patients.

Similarly 3/7 (42.8%) patients with Grade-I tumors relapsed as compared to 1Ø/16 (62.5%) patients with poorly differentiated tumors relapsed in 2 years (Table - 15 ; Fig. 15). There was a trend towards higher relapse rate with advancing stages. However, the differences were statistically non-significant.

STEROID RECEPTORS + HISTOLOGIC GRADE AND SURVIVAL :

When steroid receptors and histologic grade were combined together to find out its influence on survival, the results obtained were as follows (Table - 16 A): 1/8 (12.5%) patient with ER^+ moderately differentiated tumor died and 3/9 (33.3%) patients with ER^+ poorly differentiated tumors died as compared to 2/4 (5Ø.Ø%) patients with ER^- well differetiated tumors and 1/4(25.Ø%) patient with ER^- poorly differentiated tumor died in 2 years. The differences were statistically non-significant.

Similarly, 2/7 (28.5%) patients with PR^+ grade I tumors and 3/8 (37.5%) patients with PR^+ grade III tumors died as compared to 3/8 (37.5%) patients with PR^- grade II tumors and 1/5 (2Ø.Ø%) patient with PR^- grade III tumors died in 2 years. The differences however, were statistically non-significant.

The impact of receptors and histologic grade in combination on relapse free survival was seen with the following results (Table - 16 B) : None of the patients with ER^{+} well differentiated tumors as compared to 3/4 (75.Ø%) patients with ER^{-} well differentiated tumors relapsed in 2 years. In contrast, 8/12 (66.6%) patients with ER^{+} poorly differentiated tumors relapsed in 2 years in comparision to 2/4 (5Ø.Ø%) patients with ER^{-} poorly differentiated tumors.

Similarly, 3/7 (42.8%) patients with ER^{+} well differentiated tumors relapsed in comparison to 5/7 (71.4%) patients with PR^{-} poorly differentiated tumors relapsed in 2 years.

The data obtained on impact of receptors + histologic grade on relapse free survival was statistically non-significant.

NECROSIS IN RELATION TO SURVIVAL :

Significantly more patients with necrotic tumors died as compared to the patients with non-necrotic tumors in 2 years (Table - 17; Fig. 16; $P < Ø.Ø5$.).

Similarly, 11/13 (84.6%) patients with necrotic tumors relapsed as compared to 16/3Ø (53.3%) patients with non-necrotic tumors. The differences however, were statistically non-significant (Table - 17; Fig. 17).

RECEPTORS + NECROSIS IN SURVIVAL:

Amalgamation of receptors and necrosis yielded the following impact on survival (Table - 18) : 2/15 (13.3%) patients with ER^+ non-necrotic tumors died in comparison to 3/4 (75.Ø%) patients with ER^- necrotic tumors died in 2 years. Similarly, 4/18 (22.2%) patients with PR^+ non-necrotic tumors died as compared to 3/5 (6Ø.Ø%) patients with PR^- necrotic tumors.

On the other hand, 1Ø/2Ø (5Ø.Ø%) patients with ER^+ non-necrotic tumors relapsed in comparison to 3/4 (75.Ø%) patients with ER^- necrotic tumors relapsed in 2 years. Similarly 11/21 (52.3%) patients with PR^+ non-necrotic tumors relapsed as compared to 6/7 (85.7%) patients with PR^- necrotic tumors relapsed in 2 years. None of the above differences were statistically significant because of small number of patients. Thus, a non-significant trend of shorter overall and relapse free survival was observed with receptor negative necrotic tumors.

LYMPHOCYTIC INFILTRATION IN SURVIVAL :

None of the patients with lymphocytic infiltration of their tumors died in contrast to 1Ø/25 (4Ø.Ø%) patients with lymphocytic infiltration of their tumors died during the span of 2 years (Table - 19 A; $P < Ø.Ø25$.)

2/7 (28.5%) patients with mild lymphocytic infiltration of the tumor died in 2 years in comparison to 4/6 (66.6%) patients with dense lymphocytic infiltration of the tumors. The differences were statistically non-significant due to small number of patients.

5/12 (41.6%) patients with no lymphocytic infiltration of their tumors relapsed in comparison to 23/32 (71.8%) patients with lymphocytic infiltration of the tumors relapsed in 2 years (Table - 19 B; X^2 = 3.44; nonsignificant; Fig. 18). 8/11 (72.7%) patients with mild lymphocytic infiltration of the tumors relapsed as compared to 6/7 (85.7%) patients with dense lymphocytic infiltration of their tumors. The data however, was statistically non-significant due to small number (Fig. 19).

(2Ø) RECEPTORS + LYMPHOCYTIC INFILTRATION AND SURVIVAL :

The alliance of receptors and lymphocytic infiltration yielded the following impact on survival :

None of the patients with ER^+ tumors without lymphocytic infiltration died and none of the patients with ER^- tumors without lymphocytic infiltration of the tumors died in 2 years. This was in sharp contrast to 4/16(25.Ø%) patients who had ER^+ tumors with lymphocytic infiltration died and 6/9 (66.6%) patients with ER^- tumors with lymphocytic

infiltration died in 2 years. The data was statistically significant (X^2 = 8.54; P < Ø.Ø5 ; Table - 2Ø A).

Similarly, none of the patients with either PR^+ or PR^- tumors without lymphocytic infiltration died in contrast to 6/17 (35.2%) patients with PR^+ and 4/8 (5Ø.Ø%) patients with PR^- tumors with lymphocytic infiltration died in 2 years. These differences were statistically non-significant.

On the other hand, few patients 2/6 (33.3%) with ER^+ tumors without lymphocytic infiltration relapsed in comparison to 7/9 (77.7%) patients with ER^- tumors with lymphocytic infiltration relapsed in 2 years. The differences, however, were statistically non-significant (Table - 2Ø B). Significantly more, 11/12 (91.6%), patients harbouring PR^- tumors with lymphoid infiltrate relapsed as opposed to only 4/7 (57.1%) patients with PR^+ and no lymphoid infiltrate relapsed in 2 years (Table - 2Ø B; X^2 = 9.235; P < Ø.Ø5).

DISCUSSION

India is a vast subcontinent with an estimated current population of over 83Ø million people. As is the case with other less developed nations, communicable diseases and health problems related to pregnancy, childbirth and infancy and the challenge of exploding population remain the most

urgent national health priorities. However, there is an increasing awareness, that in spite of rising longevity, changes in life style and progressive control of the major communicable diseases, the morbidity and mortality due to cancer (including the breast cancer) is increasing steadily. It is estimated that every two out of three breast cancers diagnosed in the country is advanced breast cancer (Mittra, 1988). It is apparent that a large proportion of breast cancer have the disease at diagnosis which is beyond the scope of curative therapy. Factors influencing delay in seeking treatment include low socioeconomic status, ignorance and fear, poor facilities for transport and communication, lack of easily accessible facilities and poor follow-up.

Since Fellenberg (194Ø), a small but consistent predominance of left sided breast cancer is known. A left/right ratio of 1.26 has been shown (Senie et al, 198Ø). This asymmetry of breast carcinoma, attributed to differences in breast size reflects the unequal volumes of breast tissue at risk to develop carcinoma due to hormonal stimulation. The present study revealed a left/right ratio of 1.11.

The steroid hormone receptors of foremost interest in breast cancer are the estrogen- (ER) and progesterone-receptors

(PR). ER is found in normal, oestrogen responsive tissues provided oestrogen is present. PR is synthesized in tissues with normally functioning ER. While ER and PR are assumed to be involved in the development and function of the normal breast, little data can be found in this regard. In contrast, a multitude of studies of malignant biopsies of the breast have been conducted and ER and PR are detected in the majority of these tumors.

The present study, reports a frequency of 43.2% ER^{+} PR^{+}, 18% ER^{+} PR^{-}, 21.6% ER^{-} PR^{+} and 17.1% ER^{-} PR^{-} comparable to Brdar (1988). Circulating estradiol is known to stimulate the formation of progesterone receptors (Horwitz and McGuire, 1975), and therefore,it was obvious to encounter a relative increase of only PR^{+} tumors in the present study on pre-menopausal breast cancer patients. The frequency of steroid receptors reported from Western investigators (Thorpe & Rose, 1978; Osborne et al, 1980; Wittliff, 1984; Hahnel, 1985; Alexieva-Figusch et al, 1988) ranged from 30.7% to 61.0% ER^{+} PR^{+}, 7% to 12% ER^{+} PR^{-}, 9% to 22.8% ER^{-} PR^{+}, 21% to 38.6% ER^{-} PR^{-}. Some of the studies were unselected for menopausal status. In addition to the above, a large ethnic variation in breast cancer has been ascribed to some combination of genetic and environmental factors, although the exact nature of these variables is not clear. However,

the frequency of ER^+ tumors in the pre-menopausal Japanese and western patients were similar (Matsumoto et al,1986) and the frequency of PR^+ was slightly lesser (36% using a cut off point 5 fmol/mg cytosol protein in comparison to western patients 40-60% McGuire, 1980). The present study reports ER^+ of 61.2% and PR^+ of 64.8% not different from the western investigators.

Human breast cancers are composed of steroid receptor positive (hormone sensitive) and steroid receptor negative (hormone insensitive) cells (Osborne,1985). Potential shifts in the majority cell populations are likely either due to natural selection processes (i.e. differences in population kinetics between clones) or due to the selection pressure of therapy. Thus it was observed that receptor status could deviate over time. There could be qualitative and/or quantitative differences in receptor status. The available reports are reviewed by Osborne (1985) and Hahnel et al (1985). In the absence of intervening therapy, the discordance rate for ER was 15% to 20% between sequential biopsy. The ER discordance of 29% in asynchronous tissues was subgrouped into (i) major discordance - 21% (one specimen ER^+ and other ER^-) and (ii) minor discordance - 8% (one specimen ER^+ or ER^- and the other borderline ER^+) (Osborne, 1985). He further pointed, that the changes in PR

content may be clinically more important as it appears to be a better marker of hormone-dependence. Gross et al (1984) observed PR discordance of 9% in initially PR^- cases and the discordance was 44% if the first biopsy was PR^+.

The present study revealed an ER discordance rate of 17.5% and PR discordance rate of 11.5% between the samples of previously untreated patients and in patients who came with recurrent disease. The ER and PR expression in previously untreated patients was non signigicantly higher than the patients with recurrent disease. Thus reduction in steroid receptor levels with the time or intervening therapy indicated increased biological aggressiveness of tumors.

Over the years from 1951 - 1989, the stage at diagnosis in the western world (Saez et al, 1983 ; Leivonen, 1986 ; Vollenweider et al, 1986 ; Godolphin et al, 1981 ;Kamby et al, 1987 ; Ciatto et al, 1988 ; Shek & Godolphin ,1989) has been the following : 25% stage I, 54% stage II, 16% stage III, 5% stage IV and intermidiates. The present study revealed no stage I, 24.3% stage II, 51.3% stage III, 14.4% stage IV and 9.9% recurrent patients. Thus 75.6% of patients were presented with advanced breast tumors. An expected Indian incidence of breast cancers based on a survey, Mittra (1988), presented the following figures :

5% stage I, 14% stage II, 36% stage III, 24% stage IV and 21% unknown stages. The cost of mammographic screening is beyond the reach for the subcontinent. Much of the population of Gujarat lives in rural areas. The population is served by Primary Health Centres and Community Health Centres to deliver basic medical care. The facilities for cancer treatment are available only at one or two specialized centres in the state. There are 5 medical colleges in the state and in spite of numerous district hospitals, private hospitals and nursing homes, the patients had to travel long distances which made it difficult for them due to financial constrains. Moreover, surgical expertise in the treatment also varies. It is not uncommon to see patients referred at The Gujarat Cancer and Research Institute with complications of imperfect surgery or gross local recurrences due to surgery without proper assessment of the stage of the disease. This is the reason why such a large proportion of patients are recorded with recurrent (unknown stage) disease.

The present study has brought in a frequency of ER^+ of 62.9% stage II, 64.9% stage III, 56.2% stage IV and a frequency of PR^+ of 62.9% stage II, 63.1% stage III, 81.2% stage IV patients.

Godolphin (1981) observed ER^+ (using 1Ø fmol/mg cytosol protein as cut off point) of 72.1% stage I, 69.1% stage II, 7Ø.8% stage III, 79.Ø% stage IV tumors without correcting for menopausal status. Saez (1983) observed a frequency of ER^+ (using 3 fmol/mg cytosol protein as cut off point) of 63% stage I, 68% stage II, 64% stage III, 7Ø% stage IV and a PR^+ (using 1Ø fmol/mg cytosol protein as cut off point) of 39% each for stage I and II, 4Ø% stage III, 48% stage IV. A small but consistent increase in PR^+ frequency was obtained as stage advances. Moreover, it is known that PR positivity is more often with pre-menopausal as compared to post-menopausal breast cancer patients.

The present study covered only 16 pre-menopausal stage IV patients with the following distant metastatic sites involved : lung + pleura - 18%, bone - 18%, liver - 31%. Various studies (Cutler et al, 1969; Lee, 1984, 1985) from 194Ø-1982, demonstrated the following frequency of distant metastatic sites in stage IV breast cancers : soft tissues - 15% to 52%, lung + pleura - 11% to 33%, bone - 16% to 34%, liver - 2% to 8%. None of the studies had shown the frequency considering only pre-menopausal patients. There are no report available which demonstrates significant differences in the steriod receptor frequency within these distant metastatic sites as of present study. However, all

stage IV patients of the present study expressed PR at a higher level than ER for unknown reasons.

Assessment of nodal status plays a pivotal role in the TNM staging of breast cancer. As mentioned earlier, most of the patients of the present study had advanced tumors as opposed to early tumors found in western countries. The present study with pre-menopausal advanced tumors reports 23% $N_Ø$ and 77% node +ve tumors. Amongst the N_1 tumors, 41.1% 1-3 LN +ve, 32.3% 4-1Ø LN +ve, 26.4% > 1Ø LN +ve were observed. The frequency of nodal involvement from the western studies (Alexieva-Figusch et al, 1988; Ciatto et al, 1988; Shek and Godolphin, 1989) ranged from 38.9% $N_Ø$, 24% to 35.3% 1-3 LN +ve, 2Ø%-25.6% > 4 LN +ve.

The present study revealed a ER^+ frequency of 6Ø.8% $-N_Ø$, 63.6% - node +ve, 57.1% 1-3 LN +ve, 7Ø% > 4 LN +ve and PR^+ frequency of 73.9% $N_Ø$, 63.6% node +ve, 42.8% 1-3 LN +ve, 5Ø% > 4 LN +ve. Thus there were no significant differences in the distribution of steroid receptors in the groups of different nodal involvements similar to Brdar (1988), where: ER^+ - 48% to 71% and PR^+ - 38% to 59% in $N_Ø$ patients, ER^+ 5Ø% to 67% and PR^+ - 46% to 61% in node +ve patients, ER^+ - 67%, 71% & PR^+ 4Ø% in 1-3 LN +ve patients, ER^+ - 62%, 67.3% and PR^+ 36% in > 4 LN +ve patients. None of the authors had

corrected the said frequencies only for pre-menopausal patients.

The prognostic significance of steroid receptors is still debatable (Hilf et al, 1980; Alanko et al, 1985; Butler et al, 1985). ER seems to be the foremost prognostic factor in node negative patients while only PR positivity appears to be significant in node positive patients (McGuire, 1987). This is with regard to the 'early breast tumors' of western countries.

As regards the rapidly metastasizing 'advanced breast tumors' similar to that in the present study, most clinicians would recommend cytotoxic chemotherapy and the role of receptors in the selection of adjuvant therapy is controversial (Barnes et al, 1989). 83.8% patients of the present study presented with advanced tumors amongst non-responders. They were treated with (i) only chemotherapy - 54.8% (ii) only hormonal manipulation - 9.6% (iii) chemohormonal therapy 29%. These patients ultimately turned out with progressive disease. In contrast, only 52.3%, patients amongst responders had advanced tumors. They were treated with (i) only chemotherapy (CMF) - 23.8% (ii) only hormonal manipulation (Bil. oophorectomy and/or TMX) - 23.8% (iii) chemohormonal therapy (CMF + TMX or CMF followed by Bil. oophorectomy) - 9.5%.

In the present study, an increased ER and PR positivity (though statistically non-significant) amongst responders was observed in comparison to non-responders (ER^+ - 71.4%, PR^+ - 66.8% amongst responders vs ER^+ - 67.7%, PR^+ - 51.6% amongst non-responder. ($ER\ X^{-2}$ = Ø.797, P < Ø.9 : $PR\ X^{-2}$ = 1.161, P < Ø.5)

Various reports in the literature (Fisher et al, 197Ø; Lee, 1985; Kamby et al, 1987), showed local recurrences in the range of 6% to 22%, only regional involvement in 1% to 28%, distant relapses in 69% to 81%, bone involvement in 26% to 44% and lung + pleural involvement in 17% to 29% of patients. The above frequencies are uncorrected for the menopausal status. The present study has brought in the frequency as 35.4% locoregional relapses and 64.5% distant metastasis, 29% bone involvement and 9.6% liver involvements.

It emerged from several studies (Alexieva-Figusch et al, 1988 and Clark et al, 1987) that ER^- patients had significantly more recurrences of viscera and soft tissues and ER^+ patients were more likely to recur for bony sites. All these studies included the patients from all menopausal status. Contrary to the above, Kamby (1986) could not find significant association between the distribution of patients

with bony, visceral metastasis and receptors and his findings are similar to the present study. They accounted this difference to (i) the methods of detecting the relapse and (ii) growth rate of tumors.

Majority of breast tumors reported in the literature were infiltrating duct carcinomas (Lesser et al, 1981; Blanco et al, 1984; Gallanger, 1984) as in the present study. Moreover, 20% of tumors in the present study were mixtures of more than one histologic types.

The frequency of ER^{+} amongst different histologic types of tumors in the present study was similar to that reported by other investigators (Howat et al, 1983; Gallanger, 1984). Additionally, the distribution of ER and PR was not uniform in infiltrating duct carcinomas, medullary carcinomas and lobular carcinomas. All the lobular carcinomas were PR^{+}. The lobular carcinomas (Muresan, 1986) are known to contain high cytosolic PR.

11.7% well, 33.8% each moderate and poorly differentiated tumors were observed in the pre-menopausal advanced cancers of the present study. Studies from western countries (Thoresen, 1982 ; Kamby et al, 1987 ; Rank et al, 1987) revealed 26% to 36% well differentiated, 44% to 51% moderately differentiated, 13% to 28% poorly differentiated

tumors. Additionally, a small but consistent rise in poorly differentiated tumors was shown as stage advanced (Shek and Godolphin, 1989). Moreover, Mohla et al (1982) demonstrated higher proportion of poorly differentiated tumors in black patients which remained unexplained.

The present study, exhibited ER^+ in 37.5 %, 62.1% and 69.5% well, moderate and poorly differentiated tumors respectively. The rise in ER^+ with the advancing histologic grade though statistically non-significant remained unexplained for these advanced pre-menopausal tumors. On the other hand, various investigators (Blanco et al, 1984 ; Chua et al, 1985 ; Williams et al, 1987) demonstrated ER^+ in 73% to 83% well differentiated, 64.6% to 83.4% moderately differentiated and 40% to 67.7% in poorly differentiated tumors.

The present study, also revealed a non-significant decrease in PR^+ from well to poor differentiation which was in agreement to Blanco et al (1984). The present study however, concluded that the steroid receptor frequency was dissimilar amongst all histologic grades but could not assign as to which histologic grade the prevalence of either ER or PR was augmented. The factors which might play a role in such a divergence are (i) advanced stage at presentation (ii) pre-

menopausal status and (iii) small number of study population.

Majority of studies have shown a decrease in ER^+ and PR^+ with the advancement of histologic grade. All these studies however, were not included with simultaneous corrections of menopausal status and stage at presentation.

The content of steroid receptors in breast tumors depends partly upon size of tumors. The growing cells are usually at the periphery. The necrosed cells are pushed towards the centre of the tumor. The present study concluded a non-significant association of steroid receptors and necrosis similar to Roberts and Hahnel (1981). There are reports in the literature showing lower ER contents from the central portions of large tumors. The reason for the above, is that it contains smaller number of viable cells and it would be logical to relate necrosis with decreased receptors.

Lymphocytic infiltration of the tumor is a cell mediated immune response to the developing tumor in the human body. Rosen et al (1975) suggested that the intensity of lymphoid response in a given tumor could interfere with the measurement of ER . Howat et at (1983) found an inverse relation of ER and lymphoid infiltrate of the tumor. The similar relations were noted for PR also. The present study

observed an unequal distribution of steriod receptors amongst the tumors of varying degree of lymphoid infiltrate and an inverse relation of PR and not ER with the extent of lymphoid infiltrate. Moreover, Howat et al (1983) thought it unlikely that lymphocytes per se were responsible for the absence of receptors. He attributed such inverse relation in conjuction with degree of malignancy (i.e. degree of differentiation). On the other hand, Leclercq et al (1975) observed close association between the two factors was reported (Taylor et al 1982).

Leclercq et al (1975) found a significant correlation between receptor concentration of primary tumor and lymph nodal metastatic lesions and concluded that 'the receptor content of a primary tumor and metastasis could be regarded as one'. Brennan (1979) opposed his views by showing ER^{+} accordance only in 19/29 (65.5%) cases. Subsequently various reports (Webster et al, 1978; Hoehn et al, 1979 ; Mass & Jonat, 1983 ; Hahnel et al, 1985) appeared in the literature showing discordance rates from 18% to 32% for ER as well as PR. Leonard (1979) explained basic differences between primary tumors and metastasis and regarded them as 'separate disease entity'. Hawkins et al (1981) demostrated higher malignant epithelial cell count in invaded lymph nodes than in primary tumors from the same patient. Additionally, Mass

and Jonat (1983) concluded that 'there is a change in the receptor status within the process of metastasizing (mainly from positive to negative). Possibly this takes place mainly at the first step ; primary to regional lymph nodes'. In the present study, the discordance of 33% was found both for ER and PR in synchronous tissues and the gain of PR was more prevelant than ER. Similarly, when primary tumors and malignant lymph nodes were in accordance, 6/9 (66.6%)patients experiencing incereased ER concentration with diesease extension and 2/5 (4Ø.Ø%) patients experiencing increased PR concentration, evidenced response. This was in contrast to 1/4 (25.Ø%) patients experiencing decreased ER concentration and 2/6 (33.3%) patients experiencing decreased PR concentration who evidenced response. Thus, it was concluded that discordance was related more to disease outcome (progression/remission) than accordance.

The malignant tumors of breast continues to strike women with undiminished force and still baffles science. They have a potential to spread. It is belived that metastasis is not an orderly predictable process. To bring out meaningful forecast of the chances of metastasis, the clinical and laboratory experiences are put together to generate data and the experiences of one set of patients is extended onto

another set of patients for their management. Numerous factors - termed as prognosticators - are known to date which influence prediction of death or reappearance of disease. Some of them are discussed here.

It is abundantly clear that a large proportion of breast cancers occuring in our study were advanced tumors and are beyond the scope of 'curative therapy'. Some of the reasons are discussed earlier. Moreover, there are no systematic studies or clinical experience which suggests that a marked difference in the biological behaviour of breast cancer exists between India and the western countries which might account for such an advanced presentation of the disease in the country.

75.6% patients in the present study were advanced breast cancers. 13.1% and 11.4% patients died during the first and second year respectively. Similarly, 39.4% and 17.1% patients relapsed during the first and second year respectively.

The prognostic importance of steroid receptor status is still debatable (Hilf et al, 1980; Alanko et al, 1985 ; Butler et al, 1985). The presence of both ER and PR predicts a favourable prognosis. Only ER is the most important prognosticator in node negative patients. On the other hand,

the degree of prognostication offered by PR alone is higher in node positive patients than in node negative patients (McGuire, 1987).

The role of steroid receptors in advanced pre-menopausal breast cancers has limited therapeutic considerations, mainly in the assessment of cases for oophorectomy. King et al (1982) found a significant relationship between the response rate and presence of steroid receptors in 'early' but not 'advanced' breast cancer. Several reports are available in the literature where no significant differences in overall survival or relapse free survival were observed using steroid receptors (Raemaekers et al, 1985; Williams et al, 1986; Hawkins et al, 1987; Gelbfish et al, 1988) similar to the present study. All these studies point towards relative non-utility of steroid receptors in the management of 'advanced' cases and in pre-menopausal patients.

In fact at some centres, combination of chemotherapy with hormone therapy is administered for control of breast cancer (Osborne, 1981), particularly in pre-menopausal patients. Results over the next five years will help to confirm or reject the hypothesis. In the present study, steroid receptors alone can not be used as prognosticators in advanced pre-menopausal breast carcinomas but when they

were combined with stage can be used as prognosticator. It was found that PR but not ER was significant in prognostication of overall survival within given stages. Conversely, ER but not PR was a significant prognosticator of relapse free survival.

Histologic grade has been reported by a number of investigators (William et al, 1986; Contesso et al, 1987,1989; Russo et al, 1987) as an independent prognosticator almost as important as the degree of lymph node involvement. The present study showed a non-significant prognosticator of histologic grade for 2 years overall and relapse free survival possibly because of (i) less number of patients and (ii) only 2 years follow-up period. Moreover, statistically non-significant correlations were obtained when a combination of histologic grade and receptors was applied in prognostication of advanced pre-menopausal carcinomas. However, 91.5% patients had grade II + III tumors. In contrast to the above it has been proclaimed (Davis et al, 1986) that most of the predictive power of histologic grade could be obtained from only two of the three important determinants of histologic grade namely, tubule formation and mitosis. Histologic grade was shown to be an effective predictor of mortality within 5 years.

It would be logical to regard larger tumors as admixtures of live and dead cells and such mixtures could result into deviated biologic behaviour. The extent of necrosis thereby, may participate in biological aggressiveness, imparting some prognostic power. The data of the present study, showed that presence of significant necrosis in breast cancers is an independent prognosticator. A significant difference in the 2 years overall survival but not relapse free survival was observed between the presence and absence of necrosis in advanced pre-menopausal breast cancers. Amalgamation of receptors and necrosis did not show any significance in prognostication as the relation of necrosis to receptors was non-significant.

Reports in the literature (Rosen et al, 1975; Howat et al, 1983) regarding inverse association of lymphoid infiltrate of the tumor and steroid receptors offered some hope of its role in prognostication of breast carcinomas. In the present study, a significant difference in 2 years overall survival and not in the relapse free survival was observed between the presence and absence of lymphocytic infiltration. Yet the consideration of extent of lymphoid infiltrate yielded non-significant finding and therefore lymphocytic infiltration independently could not be implied in prognostication of advanced pre-menopausal breast carcinoma.

However, a combination of ER to lymphocytic infiltration offered a significant finding in 2 years survival and not in relapse free survival, while a combination of PR to lymphocytic infiltration resulted into a significant finding in 2 years relapse free survival and not in the overall survival.

ABSTRACT

The first chapter includes the data on receptor estimations from a cohort of 111 pre-menopausal breast cancer patients. Part A details the incidence of steroid receptors and its relation to other important variables such as stage of the disease, lymph node status, histologic type and histologic variables. The histologic variables discussed here are histologic grade, necrosis and lymphocytic infiltration of the tumor. In addition, steroid receptors were estimated simultaneously on malignant breast primaries and lymph node specimens in 33 breast cancer patients.

68/111 (61.2%) tumors were ER^+ and 72/111 (64.8%) tumors were PR^+. ER^+ tumors were present in 17/27 (62.9%),37/57 (64.9%) and 9/16 (56.2%) patients of stages II,III and IV respectively. However, the extent of progesterone receptor expression at first relapse was significantly reduced ($P < Ø.Ø2$). The distribution of ER and PR amongst N_1, N_2 and N_3 tumors were not significantly diffrent.

ER and PR of primary tumor and lymph nodes were in accordance in 22/33 (66.6%) patients while 11/33 (33.3%) patients showed discordance. In 7/11 (63.6%) ER discordant cases, there was a shift from ER^+ primary to ER^- lymph nodes which was in contrast to 9/11 (81.8%) PR discordant cases in whom there was a shift from PR^- primary to PR^+ lymph nodes.

Part B discusses the data obtained on the patients who were completely followed for a minimum period of 2 years. For the computation of overall survival and relapse free survival, only 2 year period was taken into consideration. 15/61 (24.5%) patients died and 44/76 (57.8%) patients relapsed during the span of 2 years.

The impact of receptors, stage, lymph node status, histologic variables on overall and relapse free survival alone and in combination will be presented and discussed. Only 2/22 (9.0%) of stage II patients have died in contrast to 3/4 (75.0%) stage IV patients. Amongst stage III patients, only 4/21 (19.0%) ER^+ patients have died which was in sharp contrast to 4/6 (66.6%) ER^- patients who have died.

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TABLES

Table 1 : Incidence of steroid receptors

	+ ER fmol/mg cytosol protein	- ER	+ PR fmol/mg cytosol protein	- PR
Breast Cancer Patients(111)	45.01 ± 5.68 (68)	(43)	91.37 ± 18.87 (72)	(39)

Figures in parenthesis show number of patients

Table 2 : Steroid receptors - Correlation with stage

stage		+ ER fmol/mg cytosol protein	- ER	+ PR * fmol/mg cytosol protein	- PR *
II	(027)	40.07±06.27 (17)	(10)	76.28±27.68 (17)	(10)
III	(057)	48.32±09.22 (37)	(20)	93.81±35.01 (36)	(21)
IV	(016)	30.27±05.16 (09)	(07)	76.13±17.27 (13)	(03)
Pretherapeutic	(100)	43.51±05.73 (63)	(37)	85.81±20.51 (66)	(34)
Entered at first relapse	(011)	63.95±28.77 (05)	(06)	32.46±06.74 (06)	(05)

Figures in parenthesis show number of patients * - $P < 0.05$

Table 3 : Steroid receptors in stage IV patients according to distant metastatic site

Distant metastatic site		+ ER fmol/mg cytosol protein		- ER	+ PR fmol/mg cytosol protein		- PR
Lungs	(03)	12.0	(1)	(2)	049.56±25.69	(02)	(1)
Bone	(03)	28.20±20.00	(2)	(1)	100.89±54.56	(03)	(-)
Liver	(05)	40.0 ±02.00	(2)	(3)	065.50±32.17	(04)	(1)
> 1 Site	(05)	26.60±06.09	(4)	(1)	075.47±28.68	(04)	(1)
Total	(16)	30.27±05.16	(9)	(7)	076.13±17.27	(13)	(3)

Figures in parenthesis show number of patients

Table 4 : Steroid receptors and nodal status

		+ ER + PR		+ ER		+ PR		+ ER - PR		- ER + PR		- ER - PR	
Node negative	(11)	36.00±07.57	(03)	045.00±15.53	(03)			28.33±07.79	(03)	53.11±13.67	(04)		(01)
Node positive	(89)	40.17±06.06	(41)	110.88±32.54	(41)			56.33±16.28	(16)	42.78±07.39	(18)		(14)
N1 tumors													
1-3 LN + ve	(14)	28.22±07.19	(05)	127.75±95.47	(05)			42.33±14.76	(03)	40.41	(01)		(05)
4-10 LN + ve	(11)	60.68±35.99	(05)	066.73±32.63	(05)			64.75±24.72	(03)	87.0	(01)		(02)
> 10 LN + ve	(09)	43.00	(01)	052.00	(01)			38.80±10.49	(05)	62.89±22.92	(03)		(00)

Values expressed as fmol/mg cytosol protein.

Figures in parenthesis show number of patients

Table 5 : Steroid receptors and disease outcome

	+ ER fmol/mg cytosol protein		- ER	+ PR fmol/mg cytosol protein		- PR
Progressive disease	(31) 70.14±15.52	(21)	(10)	49.40±8.90	(16)	(15)
Responsive disease	(21) 37.27±07.59	(15)	(06)	42.05±9.91	(14)	(07)

Figures in parenthesis show number of patients

Table 6 : Steroid receptors in relation to site at relapse

	+ ER fmol/mg cytosol protein		- ER	+ PR fmol/mg cytosol protein		- PR
Soft tissue only	(11)	046.41±11.33	(08)	(3)	39.80±09.29	(05)	(06)
Viscera only	(04)	074.33±48.82	(03)	(1)	13.00	(01)	(03)
Bone only	(09)	036.80±10.21	(05)	(4)	41.05±06.34	(05)	(04)
Only 1 site	(24)	048.64±10.46	(16)	(6)	41.93±07.35	(11)	(13)
> 1 site	(07)	138.95±46.80	(05)	(2)	74.64±23.63	(05)	(02)

Figures in parenthesis show number of patients

Table 7 : Steroid receptors in relation to histologic types

		+ ER fmol/mg cytosol protein		- ER		+ PR fmol/mg cytosol protein		- PR
Invasive duct Ca.	(42)	36.25±05.05	(29)	(13)		112.14±49.42	(25)	(17)
Invasive lobular Ca.	(10)	30.20±08.30	(05)+	(05)		053.99±21.17	(10)+	(00)
Medullary Ca.	(04)	42.50±12.50	(02)	(02)		021.50±07.50	(02)	(02)
Invasive duct Ca. + Intraduct Ca.	(08)	62.50±23.82	(04)	(04)		048.08±11.89	(05)	(03)
Invasive lobular Ca. + Intraduct Ca.	(01)	-	(00)	(01)		107.69	(01)	(00)
Invasive lobular Ca. + Mucinous Ca.	(01)	19.00	(01)	(00)		194.00	(01)	(00)
Invasive duct Ca. + Invasive lobular Ca.	(04)	56.66±33.51	(03)	(01)		102.0±64.00	(02)	(02)

+ - $P < 0.05$ Figures in parenthesis show number of patients

Table 8 : Steroid receptors and histologic grade *

Histologic grade		+ ER		+ PR		+ ER + PR		+ ER - PR		- ER + PR		- ER	
I	(08)	20.00±02.08	(03)	082.0 ±56.35	(03)	-	(00)	43.00±16.79	(05)	(00)			
II	(37)	38.18±10.02	(15)	138.52±74.56	(15)	32.91±04.88	(08)	41.90±05.37	(09)	(05)			
III	(23)	36.55±04.87	(12)	087.11±48.11	(12)	50.50±22.03	(04)	75.25	(01)	(06)			
II+III	(60)	37.46±05.87	(27)	115.67±46.08	(27)	41.27±08.14	(12)	45.23±09.11	(10)	(11)			

* P < 0.05

Values expressed as fmol/mg cytosol protein.

Figures in parenthesis show number of patients

Table 9 : Steroid receptors in relation to tumor necrosis

		+ + ER PR	Either ER OR PR +ve	- - ER PR
No necrosis	(44)	20 (45.4%)	19 (43.1%)	5 (11.3%)
Necrosis present	(23)	10 (43.4%)	07 (30.4%)	6 (26.0%)
+ (Low)	(09)	05 (55.5%)	03 (33.3%)	1 (11.1%)
++ (Moderate)	(09)	03 (33.3%)	03 (33.3%)	3 (33.3%)
+++ (Marked)	(05)	02 (40.0%)	01 (20.0%)	2 (40.0%)

Figures in parenthesis show number of patients

Table 10 : Steroid receptors in relation to lymphocytic infillration

		+ ER fmol/mg cytosol protein		- ER	+ PR fmol/mg cytosol protein		- PR
Lympho. infil. Absent	(20)	32.19±09.62	(10)	(10)	039.78±10.43	(13)	(07)
Lympho. infil. Present	(48)	30.90±05.06	(32)	(16)	109.98±39.00	(32)	(16)
Mild	(19)$	26.66±03.35	(15)	(04)	099.37±39.67	(15)	(04)
Moderate	(17)$	54.56±10.30	(13)	(04)	149.90±92.62	(12)	(05)
Dense	(12)$	33.90±08.95	(04)	(08)	045.98±16.00	(05)	(07)

$ - P = 0.01

Figures in parenthesis show number of patients

TABLE II A : Steroid receptors in synchronous tissues

	ER	PR
Total patients	33	33
Accordance	22 (66,6%)	22 (66,6%)
Discordance	11 (33,3%)	11 (33,3%)

TABLE II B : Steroid receptors in accordance.

	ER		PR	
	fmol/mg cytosol protein		fmol/mg cytosol protein	
Primary	39.90±13.22	(22)*	47.11±11.97	(22)*
Lymph node	45.55±08.37	(22)*	51.59±13.08	(22)*
Decreased expression with disease extension	5/22	(22.7%)	9/22	(40.9%)
Increased expression with disease extension	11/22	(50.0%)	8/22	(36.3%)
Decreased expression with disease extension				
Progression	3/4	(75.0%)	4/6	(66.6%)
Response	1/4	(25.0%)	2/6	(33.3%)
Increased expression with disease extension				
progression	3/9	(33.3%)	3/5	(60.0%)
Response	6/9	(66.6%)	2/5	(40.0%)

* - Number of patients ; expressed as Mean ± SE

TABLE II C : Steroid receptors in discordance.

	ER	PR
Total discordant cases*	11	11
Type I (Primary ER+ /PR+ ; LN ER- /PR-)	7/11 (63.6%)	2/11 (18.1%)
Type II (Primary ER- /PR- ; LN ER+ /PR+)	4/11 (36.3%)	9/11 (81.8%)

* - P < 0.05

Table 12 : Stage at diagnosis in relation to survival.

STAGE	N	Died in 2 years +	Alive after 2 years +
II	22	2/22 (09.0%)	20/22 (90.9%)
III	27	8/27 (29.6%)	19/27 (70.3%)
IV	04	3/4 (75.0%)	1/4 (25.0%)
Entered at rec.	08	2/8 (25.0%)	6/8 (75.0%)

STAGE	N	Relapsed in 2 years ‡	Not relapsed in 2 years ‡
II	22	6/22 (27.2%)	16/22 (72.7%)
III	37	25/37 (67.5%)	12/37 (32.4%)
IV	06	5/6 (83.3%)	1/6 (16.8%)
Entered at rec.	11	7/11 (63.6%)	4/11 (36.3%)

+ $P < 0.05$ ‡ $P < 0.025$

Table 13 : Receptors and survival

	N	+ + ER PR	+ - ER PR	- + ER PR	- - ER PR
Patients died in 2 years	15	03 (10.7%)	4 (30.7%)	4 (40.0%)	4 (40.0%)
Patients not died in 2 years	46	25 (89.2%)	9 (69.2%)	6 (60.0%)	6 (60.0%)
TOTAL	61	28	13	10	10
Patients relapsed in 2 years	43	16 (45.7%)	12 (70.5%)	8 (66.6%)	7 (58.3%)
Patients not relapsed in 2 years	33	19 (54.2%)	05 (29.4%)	4 (33.3%)	5 (41.6%)
TOTAL	76	35	17	12	12

Table 14 A : Stage + Receptors in survival

STAGE	N	+ ER	Died	‡	- ER	Died	‡
II	22	1/13	(07.6%)		1/9	(011.1%)	
III	27	4/21	(19.0%)		4/6	(066.6%)	
IV	04	1/2	(50.0%)		2/2	(100.0%)	
Entered at rec.	08	1/4	(25.0%)		1/4	(025.0%)	

STAGE	N	+ PR	Died	@	- PR	Died	@
II	22	2/13	(15.3%)		0/9	(00.0%)	
III	27	2/17	(11.7%)		6/10	(60.0%)	
IV	04	3/4	(75.0%)		-		
Entered at rec.	08	0/4	(00.0%)		2/4	(50.0%)	

‡ P ⁄ 0.1 - Not significant
@ P < 0.005

Table 14 B : Stage + Receptors in relapse free survival

STAGE	N	+ ER Relapsed	*	- ER Relpased	*
II	22	4/14	(28.5%)	2/8	(025.0%)
III	37	18/29	(62.0%)	7/8	(087.5%)
IV	06	4/5	(80.0%)	1/1	(100.0%)
Entered at rec.	09	3/5	(60.0%)	4/6	(066.6%)

STAGE	N	+ PR Relapsed	*	- PR Relpased	*
II	22	3/13	(23.0%)	3/9	(033.3%)
III	37	13/23	(56.5%)	12/14	(085.7%)
IV	06	4/5	(80.0%)	1/1	(100.0%)
Entered at rec.	09	4/6	(66.6%)	3/5	(060.0%)

* - P < .025

Table 15 : Histologic grade and survival.

Histologic Grade	N	Died in 2 years	Not died in 2 years
I	07	02 (28.5%)	05 (71.4%)
II	15	04 (26.6%)	11 (73.3%)
III	13	04 (30.7%)	09 (69.2%)

Histologic Grade	N	Relapsed in 2 years	Not Relapsed in 2 years
I	07	03 (42.8%)	04 (57.1%)
II	21	15 (71.4%)	06 (28.5%)
III	16	10 (62.5%)	06 (37.5%)

N Number of patients

Table 16 A : Histologic grade + Receptors and survival

Histologic Grade	N	Died in 2 years	Not died in 2 years	died in 2 years	Not died in 2 years
		+ ER		- ER	
I	7	0	3 (100.0%)	2 (50.0%)	2 (50.0%)
II	15	1 (12.5%)	7 (087.5%)	3 (42.8%)	4 (57.1%)
III	13	3 (33.3%)	6 (066.6%)	1 (25.0%)	3 (75.0%)
		+ PR		- PR	
I	7	2 (28.5%)	5 (71.4%)	0	0
II	15	1 (14.2%)	6 (85.7%)	3 (37.5%)	5 (62.5%)
III	13	3 (37.5%)	5 (62.5%)	1 (20.0%)	4 (80.0%)

N Number of patients

Table 16 B : Histologic grade+ Receptors and replapse free survival

Histologic Grade	N	Relapsed	Not relapsed	Relapsed	Not Replased
			+ ER		- ER
I	07	00	3 (100.0%)	3 (75.0%)	1 (25.0%)
II	21	11 (73.3%)	4 (026.6%)	4 (66.6%)	2 (33.3%)
III	16	08 (66.6%)	4 (033.3%)	2 (50.0%)	2 (50.0%)
			+ PR		- PR
I	07	3 (42.8%)	4 (57.1%)	0	0
II	21	8 (72.7%)	3 (27.2%)	7 (70.0%)	3 (30.0%)
III	16	5 (55.5%)	4 (44.4%)	5 (71.4%)	2 (28.5%)

N Number of patients

Table 17 : Necrosis and survival

	N	Died in 2 years	%	Not died in 2 years	%
No necrosis	25	5	(20.0%)	20	(80.0%)
Necrosis present	09	5	(55.5%)	04	(44.4%)

	N	Relapsed in 2 years	Not Relapsed in 2 years
No necrosis	30	16 (53.3%)	14 (46.8%)
Necrosis present	13	11 (84.6%)	02 (15.3%)

N Number of patients

P < 0.05

Table 18 : Necrosis + Receptors & survival

	N	+ ER		- ER	
		Died	Not died	Died	Not died
No Necrosis	25	2 (13.3%)	13 (86.6%)	3 (30.3%)	7 (70.0%)
Necrosis present	9	2 (40.0%)	3 (60.0%)	3 (75.0%)	1 (25.0%)
		+ PR		- PR	
No necrosis	25	4 (22.2%)	14 (77.7%)	1 (14.2%)	6 (85.7%)
Necrosis present	9	2 (50.0%)	2 (50.0%)	3 (60.0%)	2 (40.0%)
		+ ER		- ER	
		Relapsed	Not relapsed	Relapsed	Not relapsed
No necrosis	30	10 (50.0%)	10 (50.0%)	6 (60.0%)	4 (40.0%)
Necrosis present	13	8 (88.8%)	1 (11.1%)	3 (75.0%)	1 (25.0%)
		+ PR		- PR	
No necrosis	30	11 (52.3%)	10 (47.8%)	5 (55.5%)	4 (44.4%)
Necrosis present	13	5 (83.5%)	1 (16.6%)	6 (85.7%)	1 (14.2%)

N Number of patients

Table 19 : Lymphocutic infiltration and survival

	N	Died in 2 years	Not died in 2 years
No Lymphocytic infiltration	10	00	10 (100%)
Lymphocytic infiltration present	25	10 (40.0%)	15 (60.0%)
Mild	07	02 (28.5%)	05 (71.4%)
Moderate	12	04 (33.3%)	08 (66.6%)
Dense	06	04 (66.6%)	02 (33.3%)

		Relapsed	Not relapsed
No lymphocytic infiltration	12	05 (41.6%)	07 (58.3%)
Lymphocytic infiltration present	32	23 (71.8%)	09 (28.1%)
Mild	11	08 (72.7%)	03 (27.2%)
Moderate	14	09 (64.2%)	05 (35.7%)
Dense	07	06 (85.7%)	01 (14.2%)

Table 20 A : Lymphocytic infiltration + Receptors and survival

	N	Died in 2 yrs.	Not died in 2 yrs.	Died in 2 yrs.	Not died in 2 yrs.
		+ ER		- ER	
No lymphocytic infiltration	10*	0	05 (100.0%)	0	5 (100.0%)
Lymphocytic infiltration present	25*	4 (25.0%)	12 (075.0%)	6 (66.6%)	3 (033.3%)
		+ PR		- PR	
No lymphocytic infiltration	10	0	05 (100.0%)	0	5 (100.0%)
Lymphocytic infiltration present	25	6 (35.2%)	11 (064.7%)	4 (50.0%)	4 (050.0%)

* - P < 0.05

Table 20 B : Lymphocytic infiltration + Receptors and repapse free survival

	N	Relapsed in 2 yrs.	Not Relapsed in 2 yrs.	Relapsed in 2 yrs.	Not Relapsed in 2 yrs.
		+ ER		- ER	
No lymphocytic infiltration	12	02 (33.3%)	4 (66.6%)	3 (50.0%)	3 (50.0%)
Lymphocytic infiltration present	32	16 (69.5%)	7 (30.4%)	7 (77.7%)	2 (22.2%)
		+ PR		- PR	
No lymphocytic infiltration	12*	04 (57.1%)	3 (42.8%)	01 (20.0%)	4 (80.0%)
Lymphocytic infiltration present	32*	12 (60.0%)	8 (40.0%)	11 (91.6%)	1 (08.3%)

N Number of patients

* - P < 0.05

Fig. 1

Scatterogram showing distribution of ER and PR in pre-menopausal breast carcinoma patients.

FIGURES

STEROID RECEPTORS
IN PRE-MENOPAUSAL
BREAST
CARCINOMA

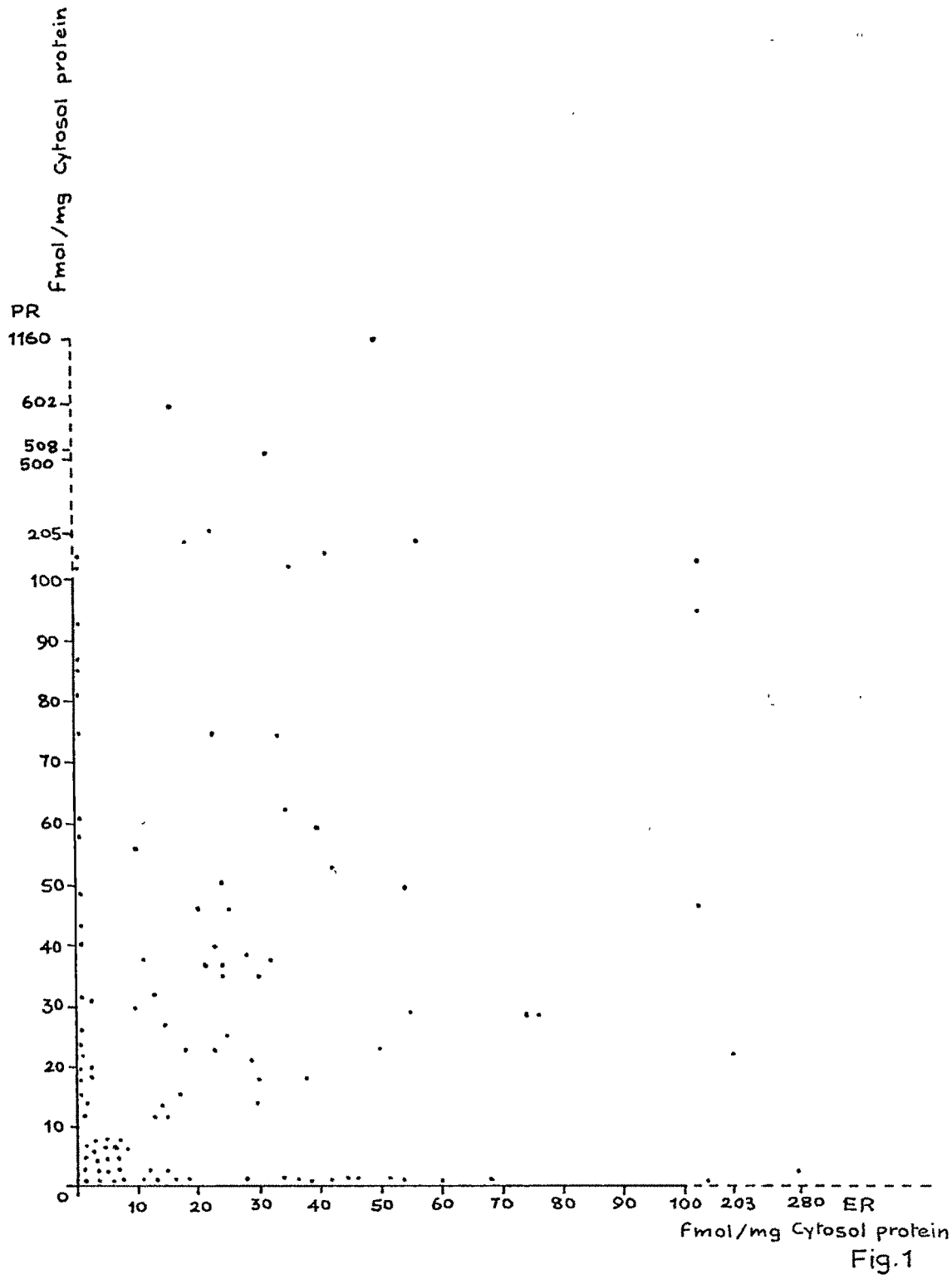

Fig.1

Fig. 2

Relapse free survival (2years) in pre-menopausal breast carcinoma patients.

Fig. 3

Two years overall survival in pre-menopausal breast carcinoma patients.

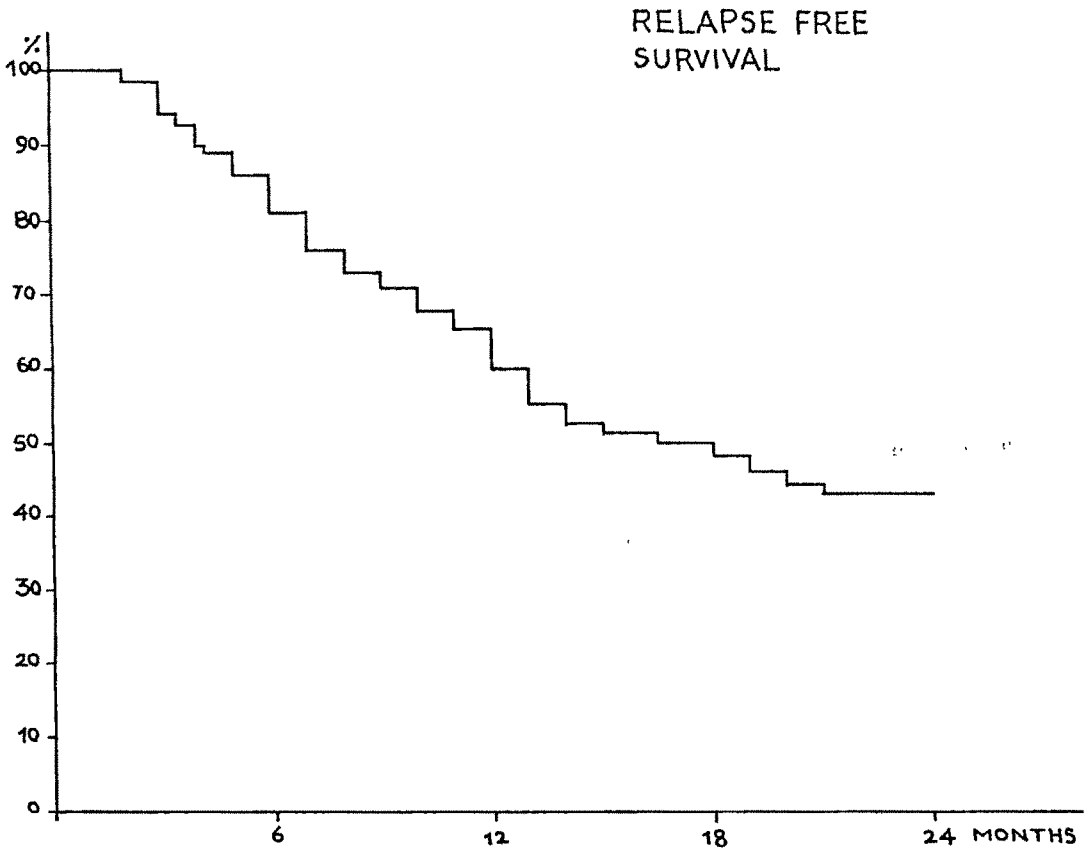
RELAPSE FREE
SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS

Fig.2

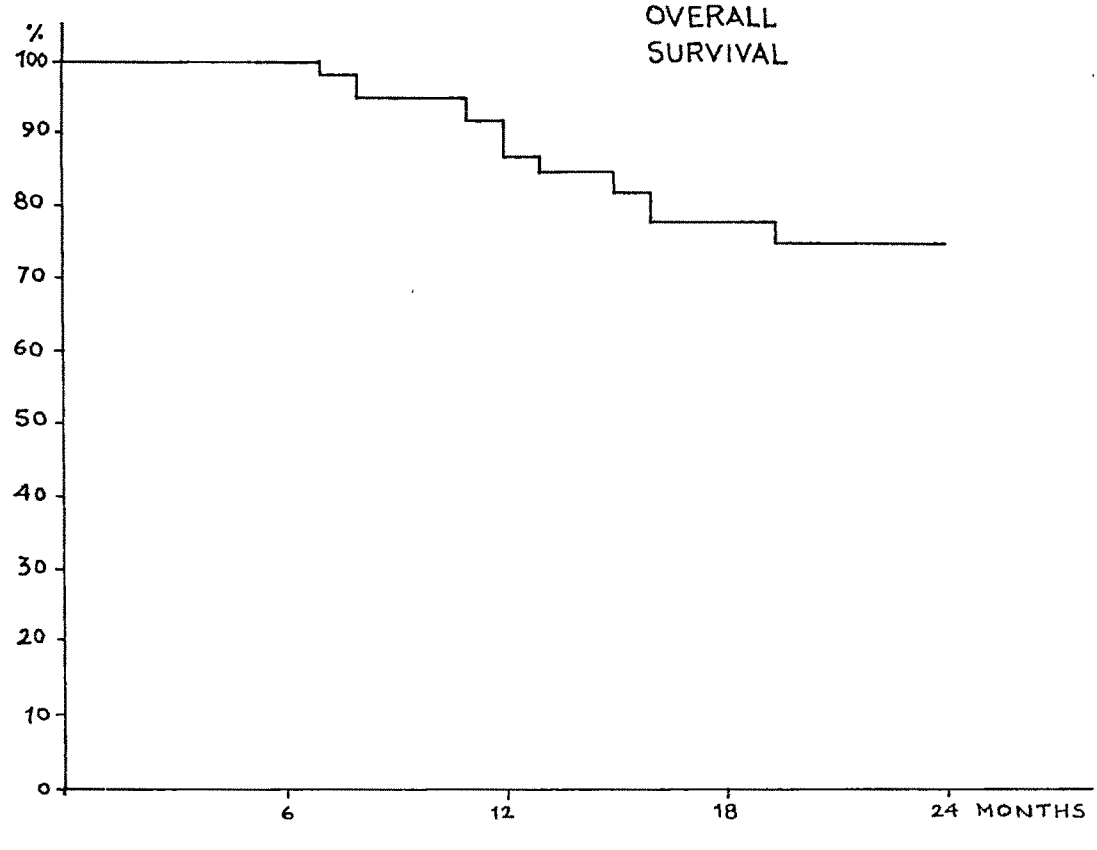
OVERALL
SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS

Fig.3

Fig. 4

Stage in relation to overall survival.

Fig. 5

Stage in relation to relapse free survival.

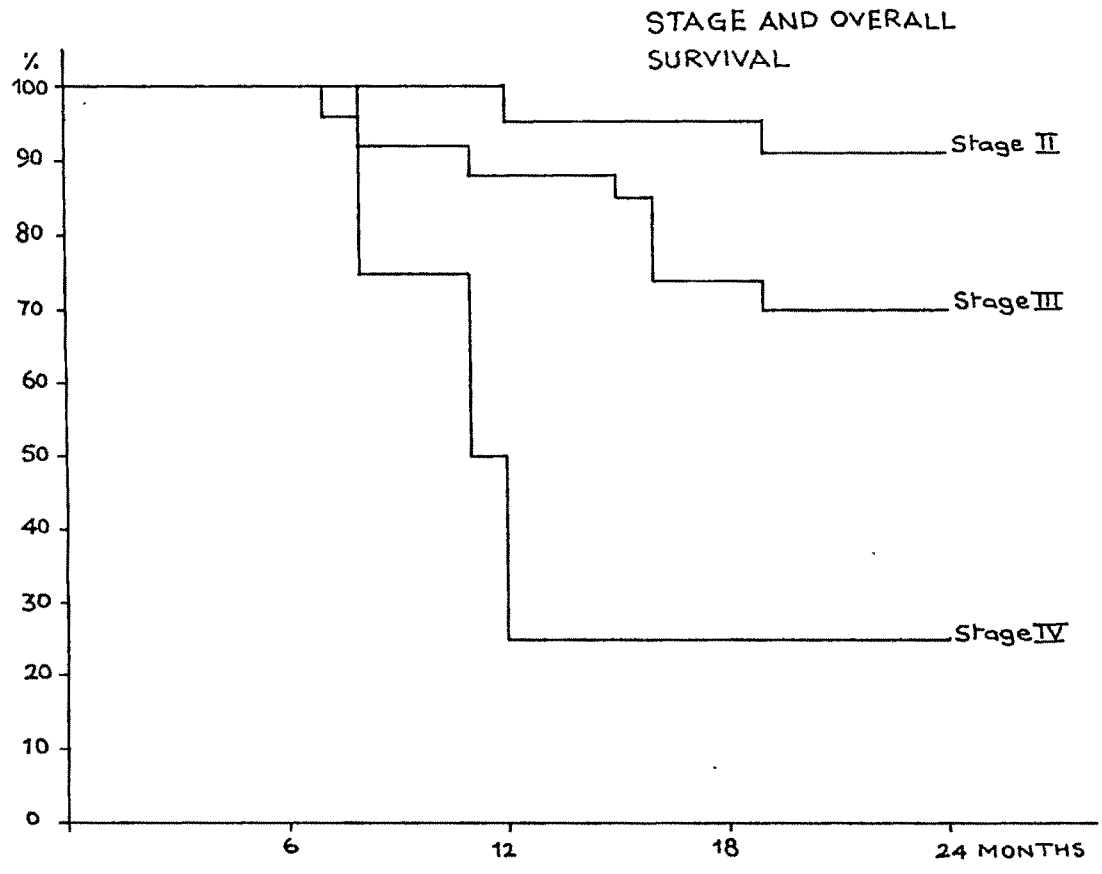
STAGE AND OVERALL SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
Stage II
Stage III
Stage IV
6
12
18
24 MONTHS

Fig.4

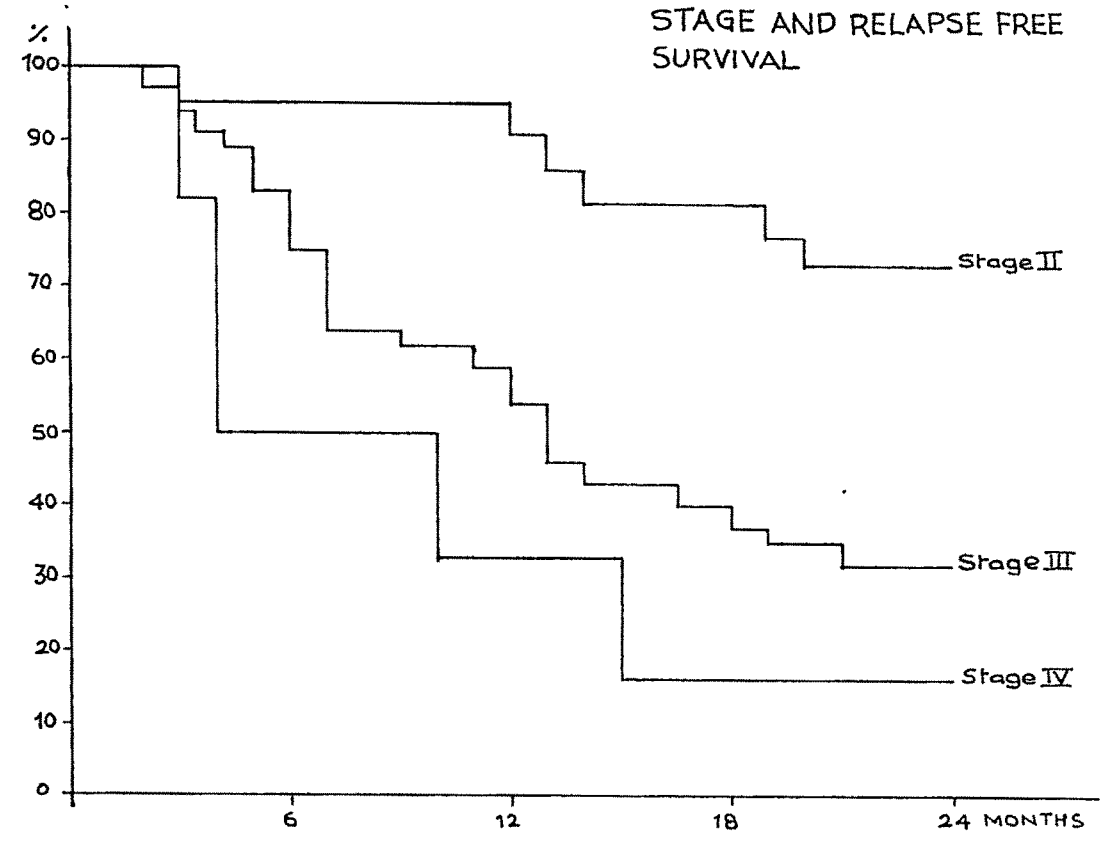
STAGE AND RELAPSE FREE SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
Stage II
Stage III
Stage IV
6
12
18
24 MONTHS

Fig.5

Fig. 6

Steriod receptors and overall survival (2years) in premenopausal breast carcinomas.

Fig. 7

ER and two years overall survival.

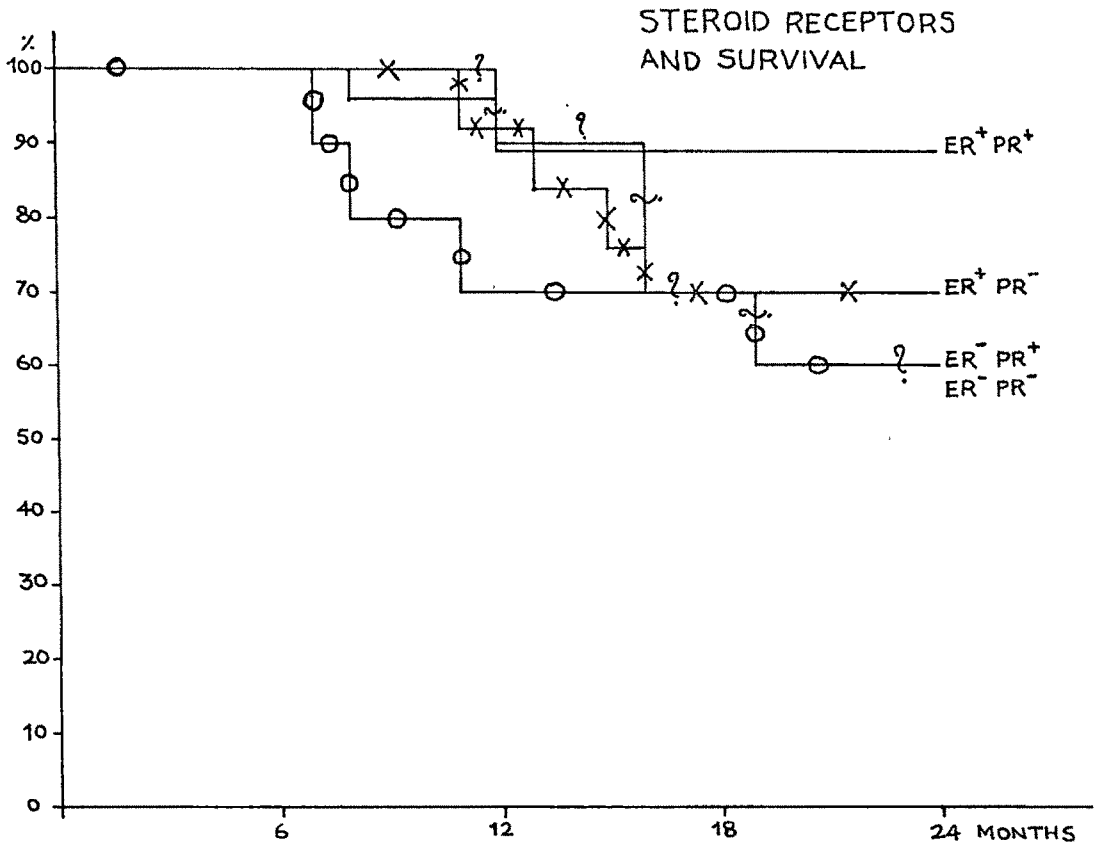
STEROID RECEPTORS
AND SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS
ER+ PR+
ER+ PR-
ER- PR+
ER- PR-

Fig. 6

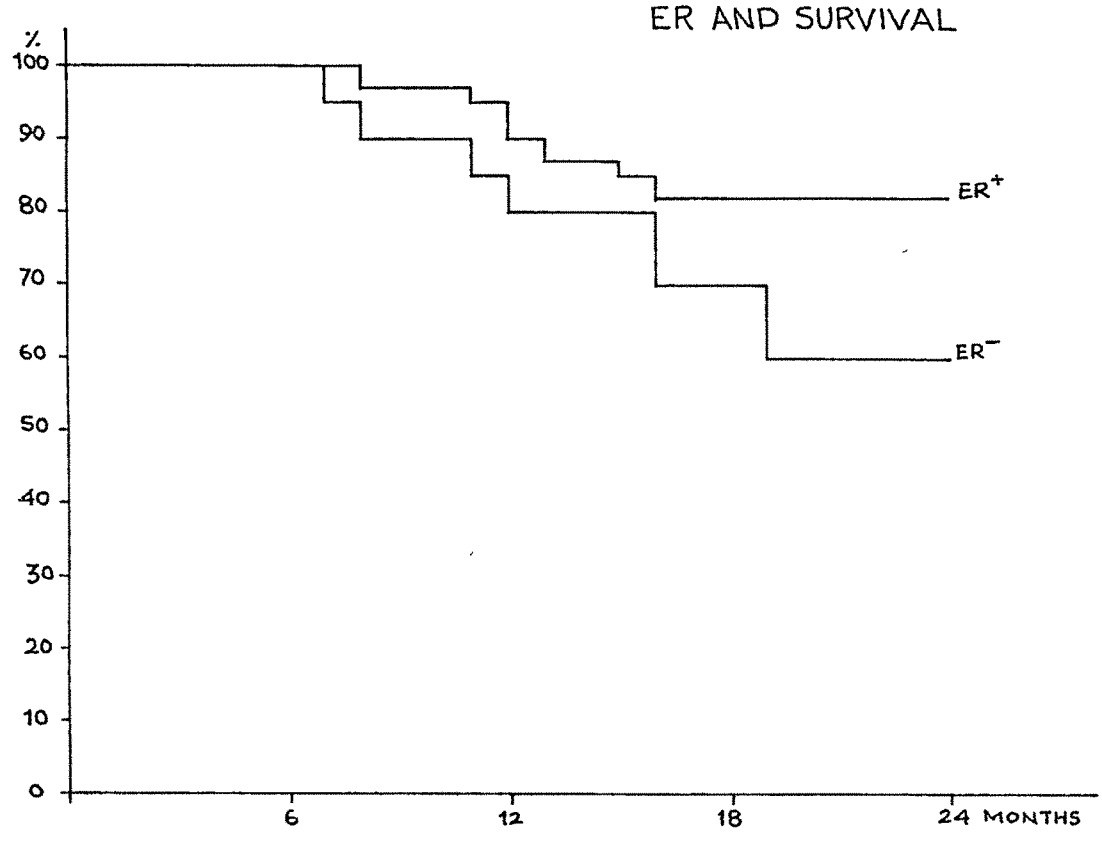
ER AND SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS
ER+
ER-

Fig. 7

Fig. 8

ER in relation to overall survival (2years).

Fig. 9

PR and two years overall survival.

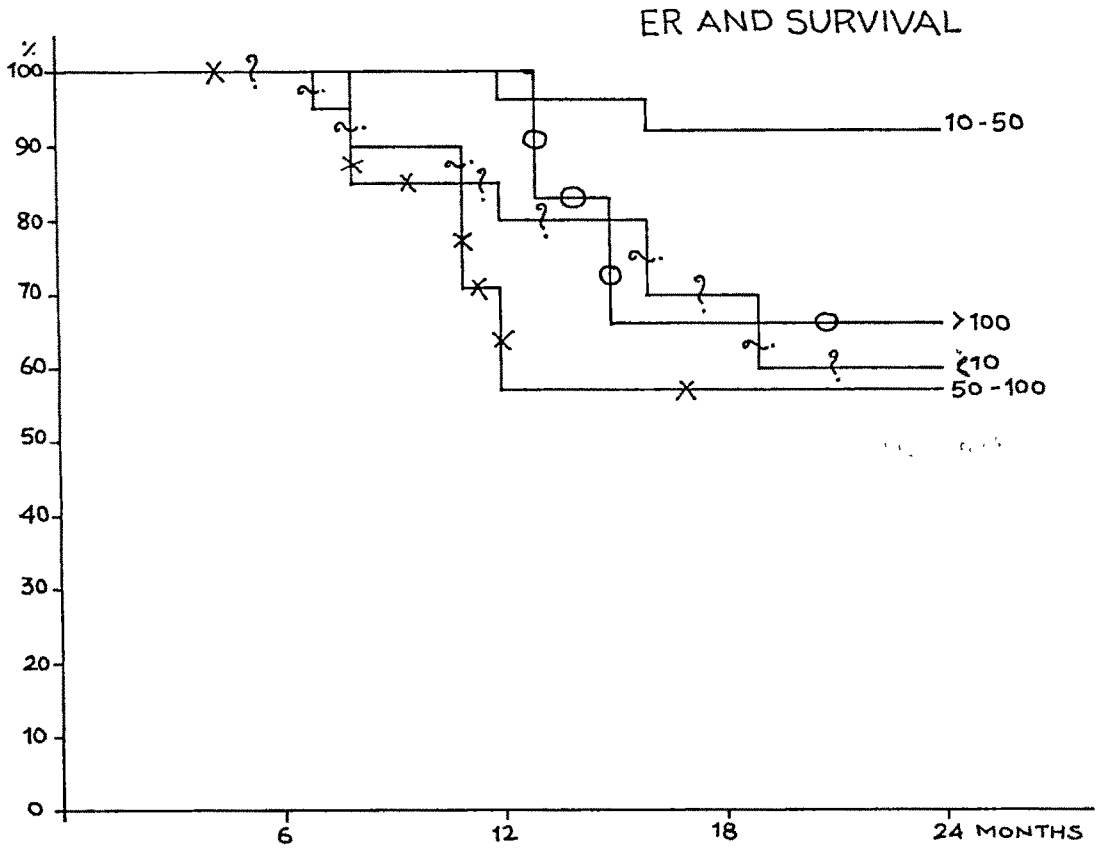
ER AND SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
10-50
>100
<10
50-100
6
12
18
24 MONTHS

Fig.8

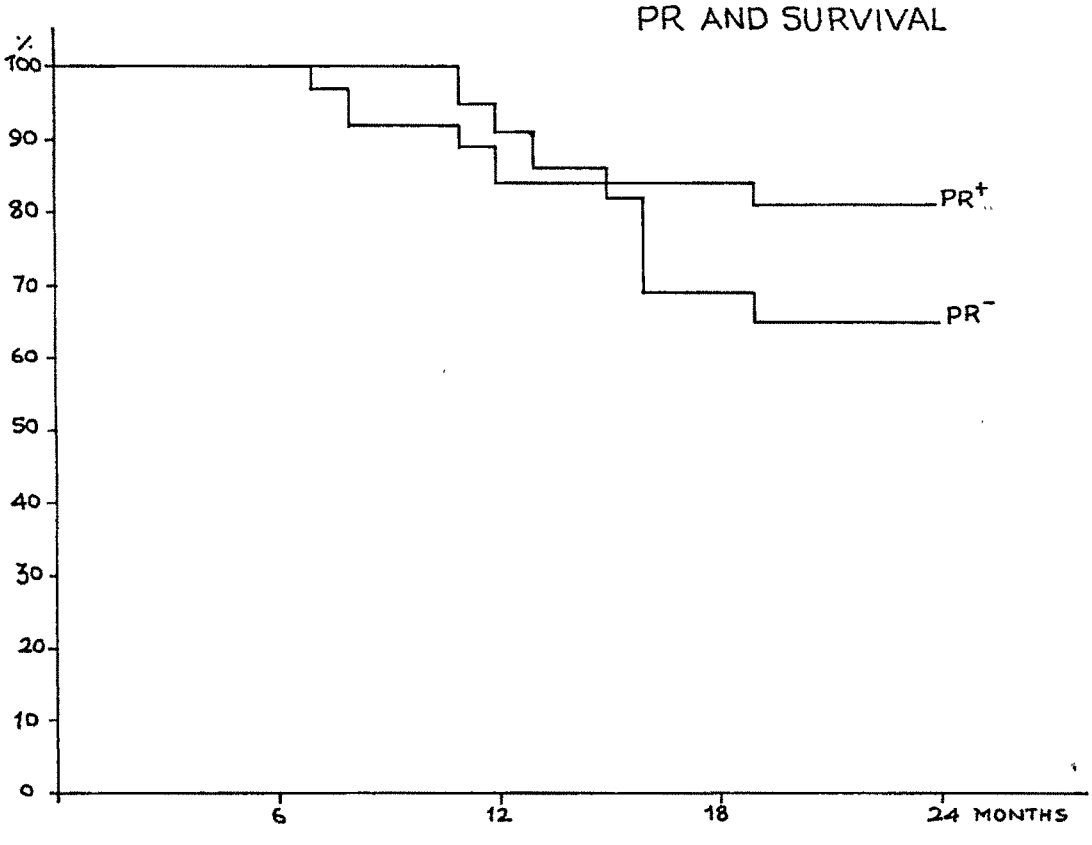
PR AND SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
PR+
PR−
6
12
18
24 MONTHS

Fig.9

Fig. 1Ø

PR in relation to overall survival (2years).

Fig. 11

Steroid receptors in relation to relapse free survival (2 years) in pre-menopausal breast carcinoma patients.

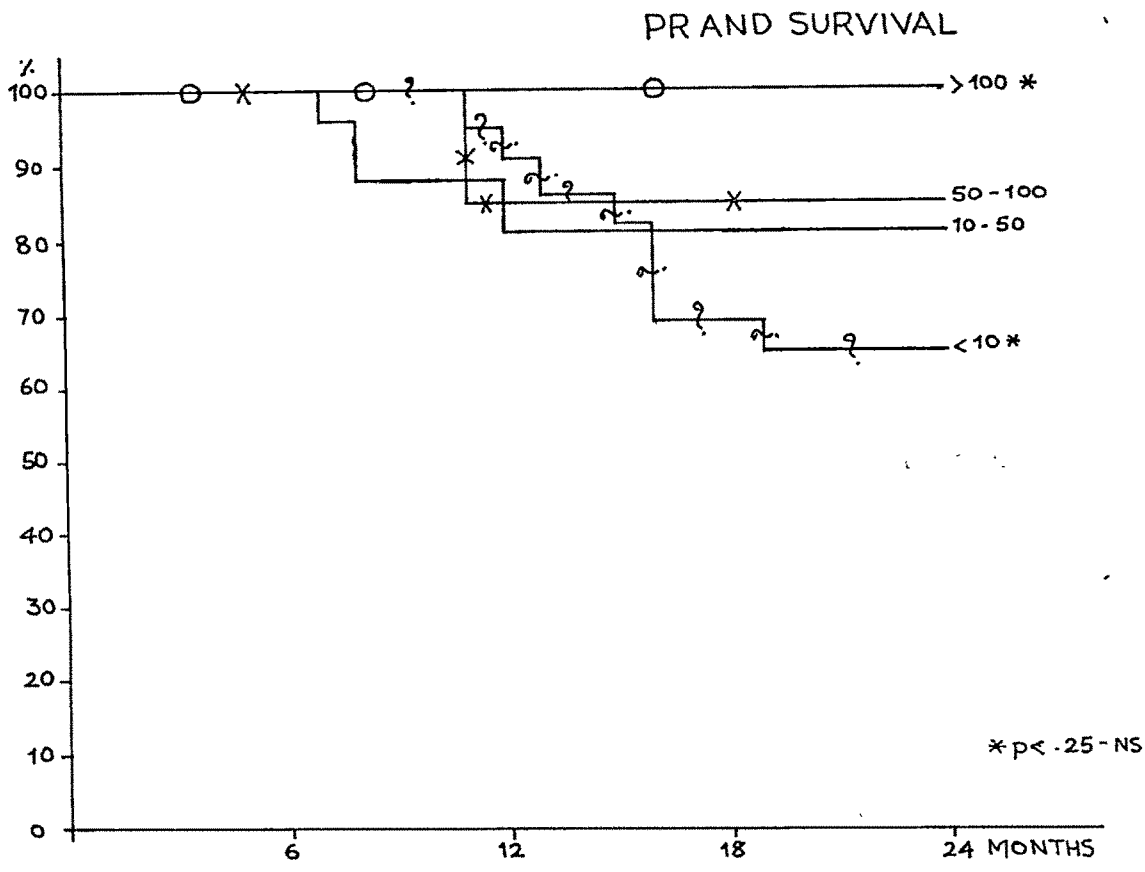
PR AND SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
>100 *
50-100
10-50
<10 *
* p< .25 - NS
6
12
18
24 MONTHS

Fig.10

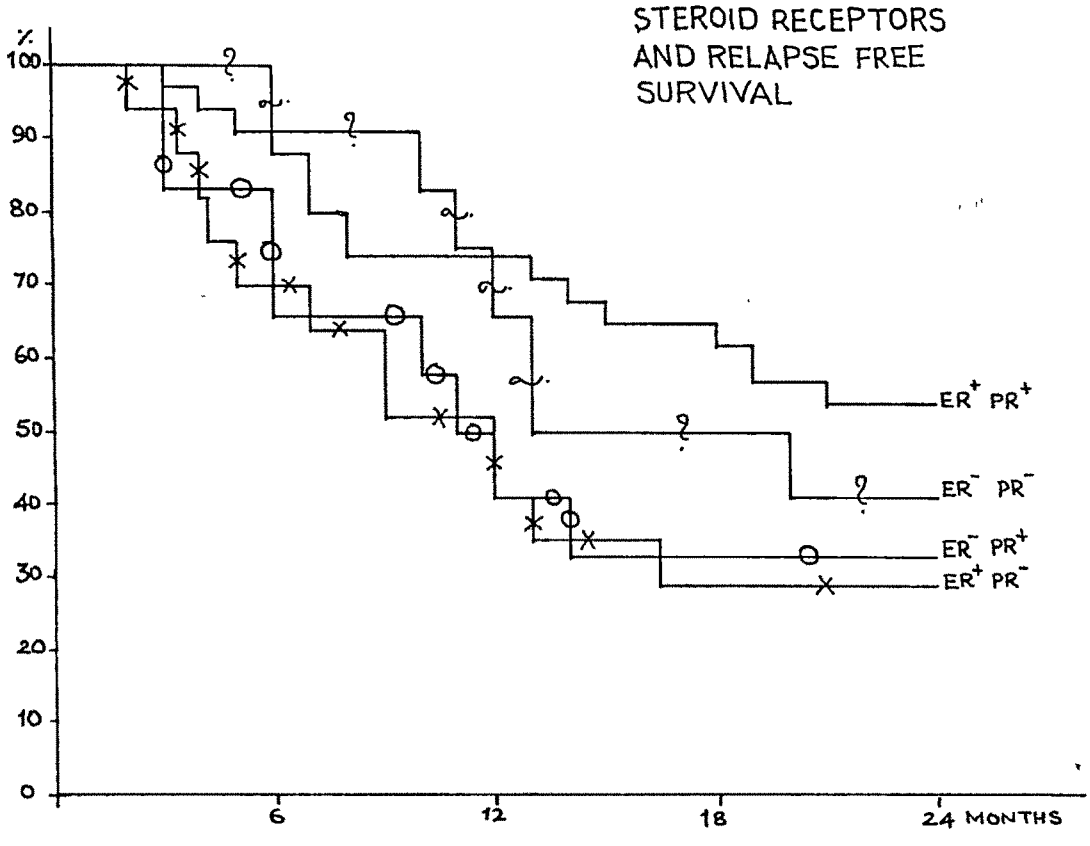
STEROID RECEPTORS
AND RELAPSE FREE
SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
ER+ PR+
ER- PR-
ER- PR+
ER+ PR-
6
12
18
24 MONTHS

Fig.11

Fig. 12

ER and relapse free survival.

Fig. 13

PR and relapse free survival.

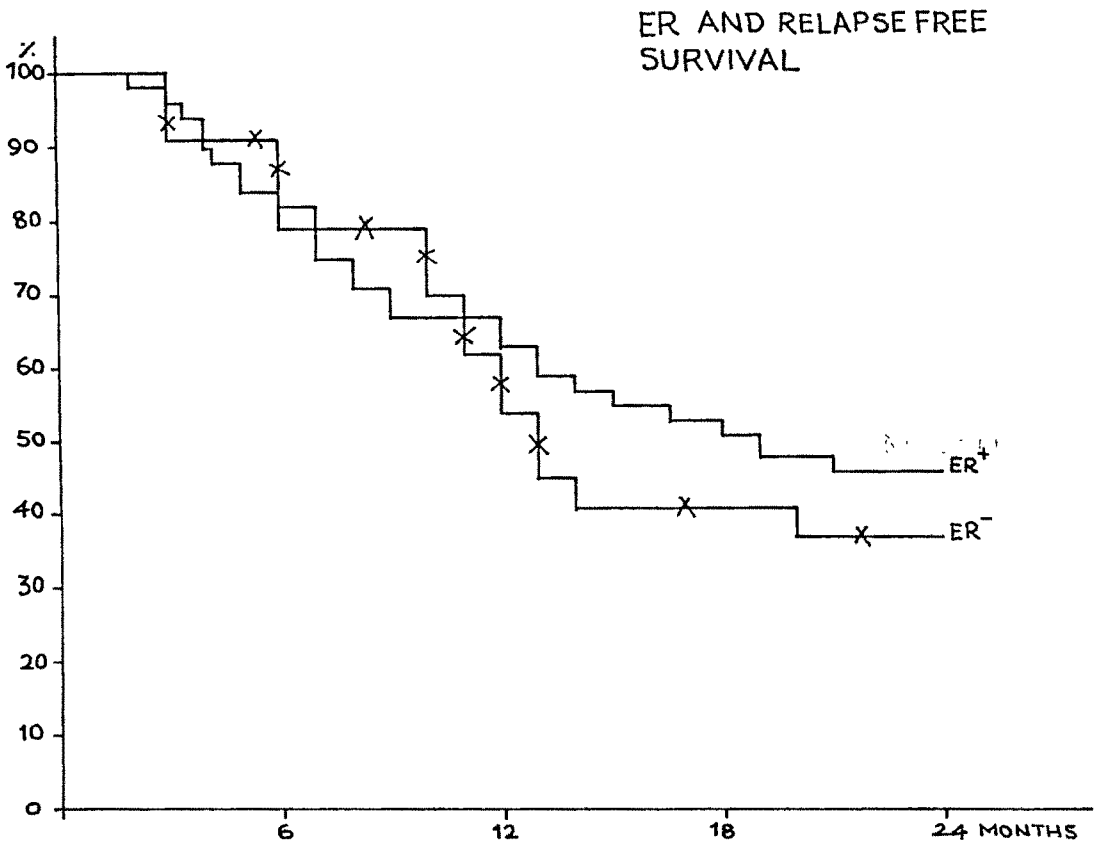
ER AND RELAPSE FREE SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS
ER+
ER-

Fig.12

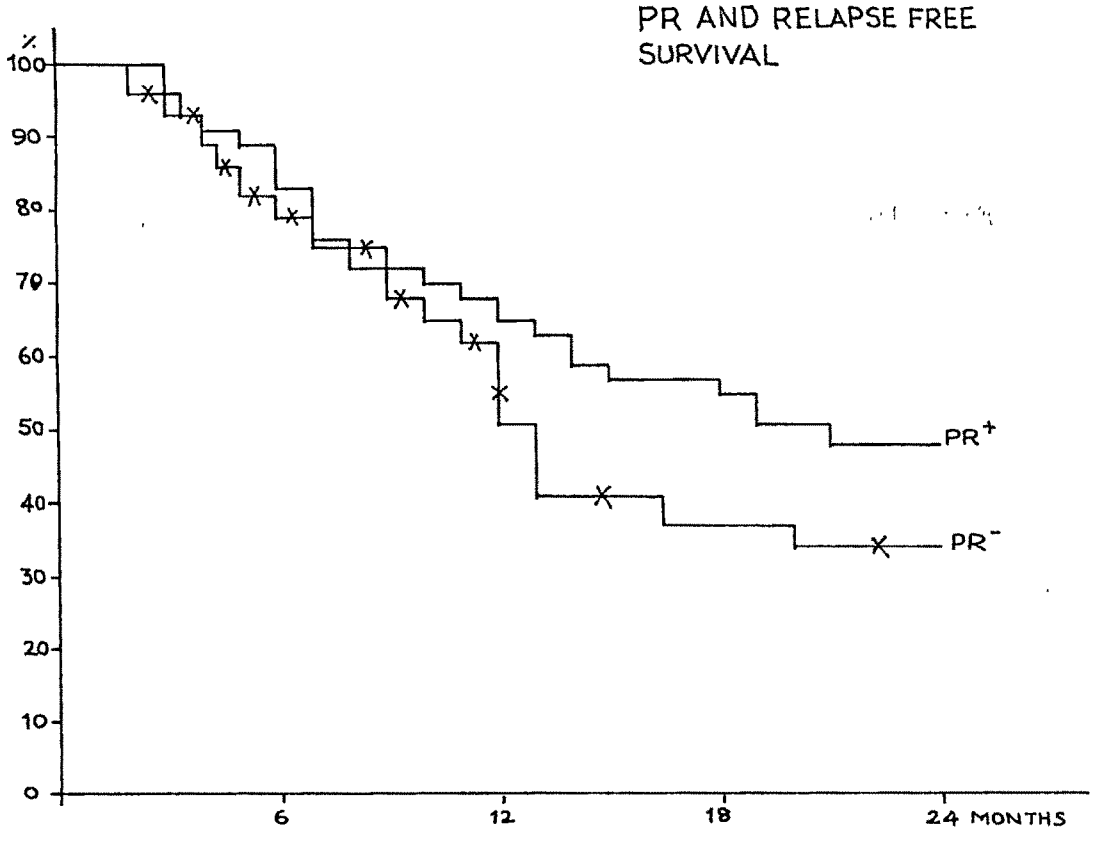
PR AND RELAPSE FREE SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS
PR+
PR-

Fig.13

Fig. 14

Histologic grade in relation to overall survival.

Fig. 15

Histologic grade in relation to relapse free survival

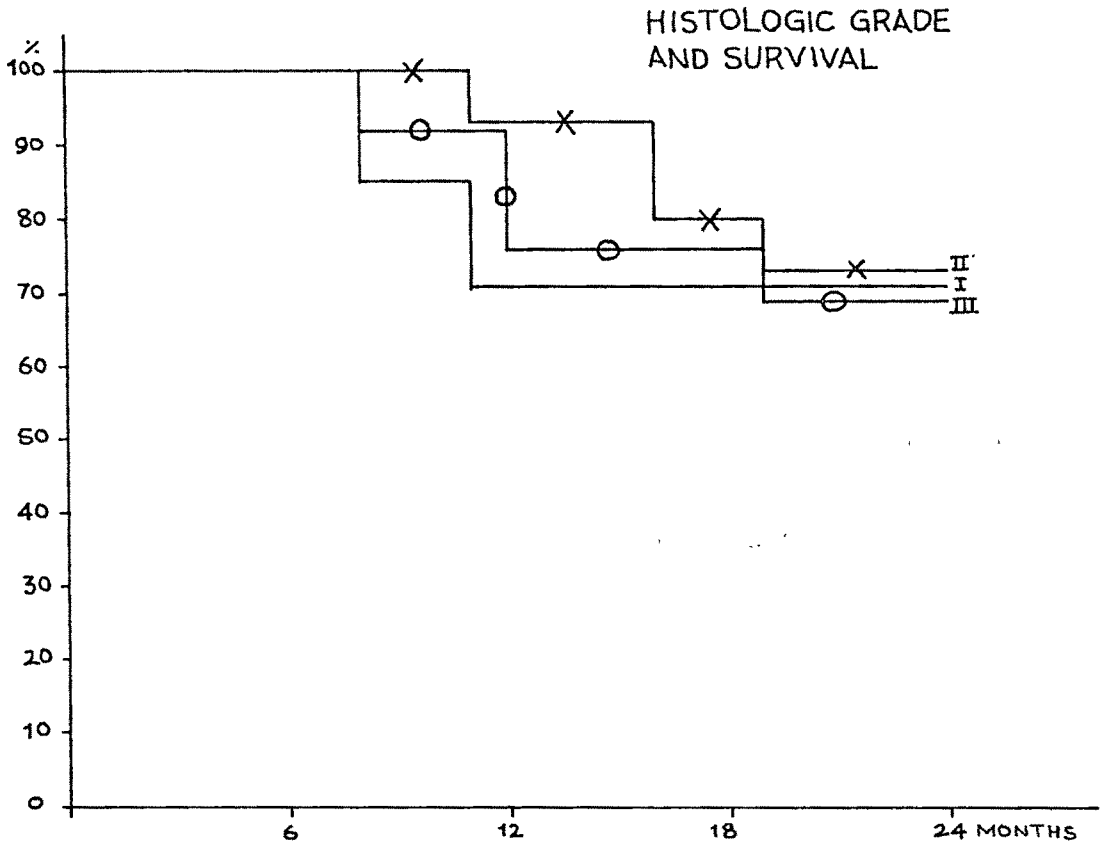
HISTOLOGIC GRADE
AND SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS
II
I
III

Fig. 14

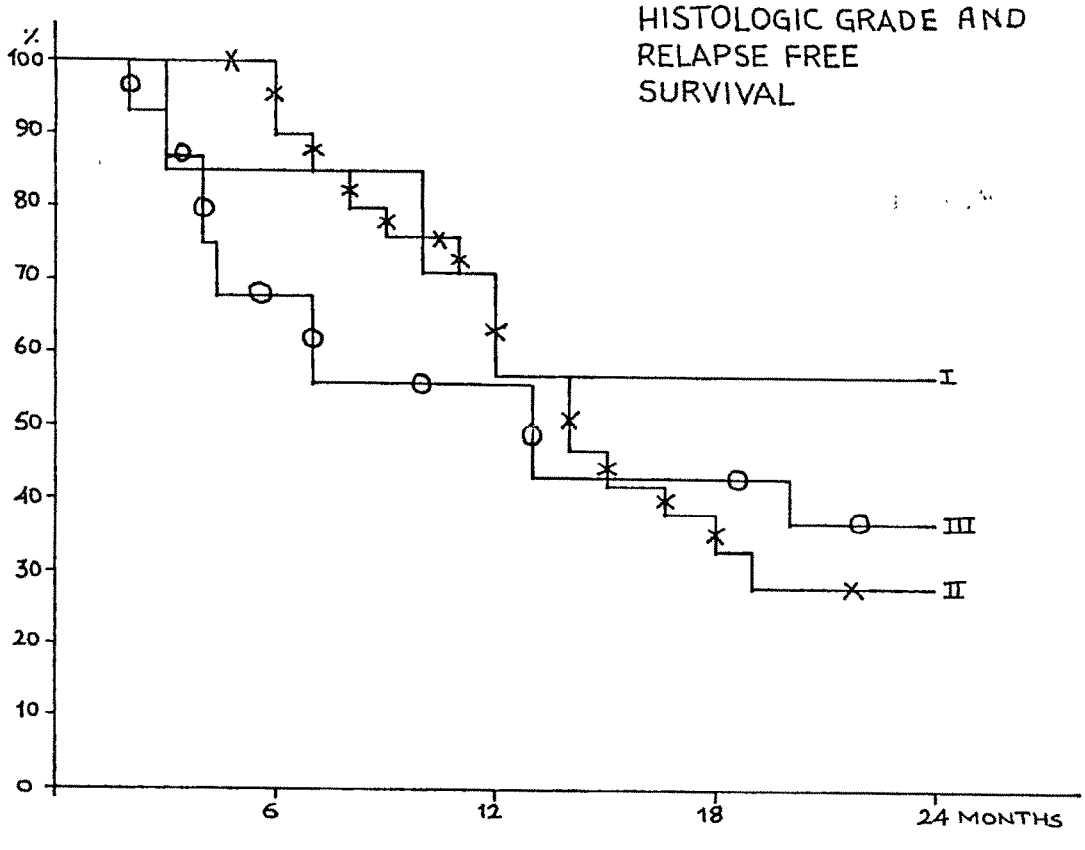
HISTOLOGIC GRADE AND
RELAPSE FREE
SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS
I
III
II

Fig. 15

Fig. 16

Necrosis in relation to overall survival.

Fig. 17

Necrosis in relation to relapse free survival.

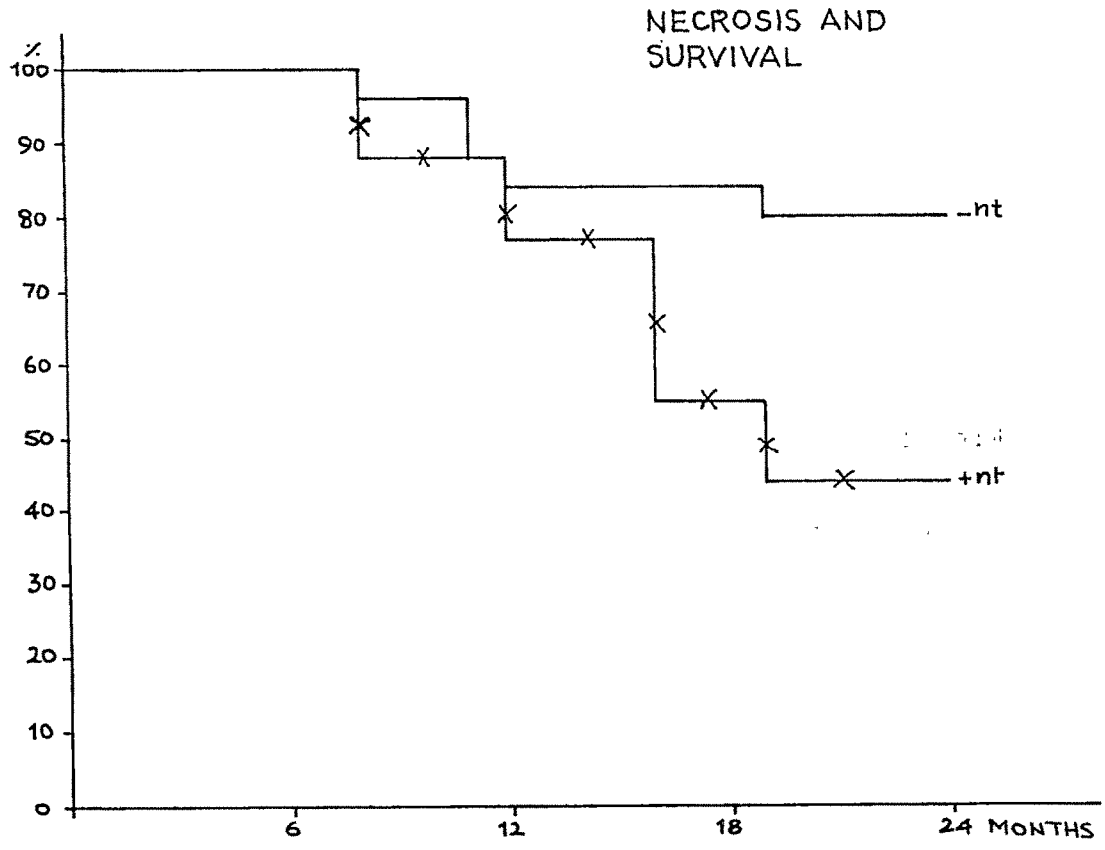
NECROSIS AND
SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS
-nt
+nt

Fig. 16

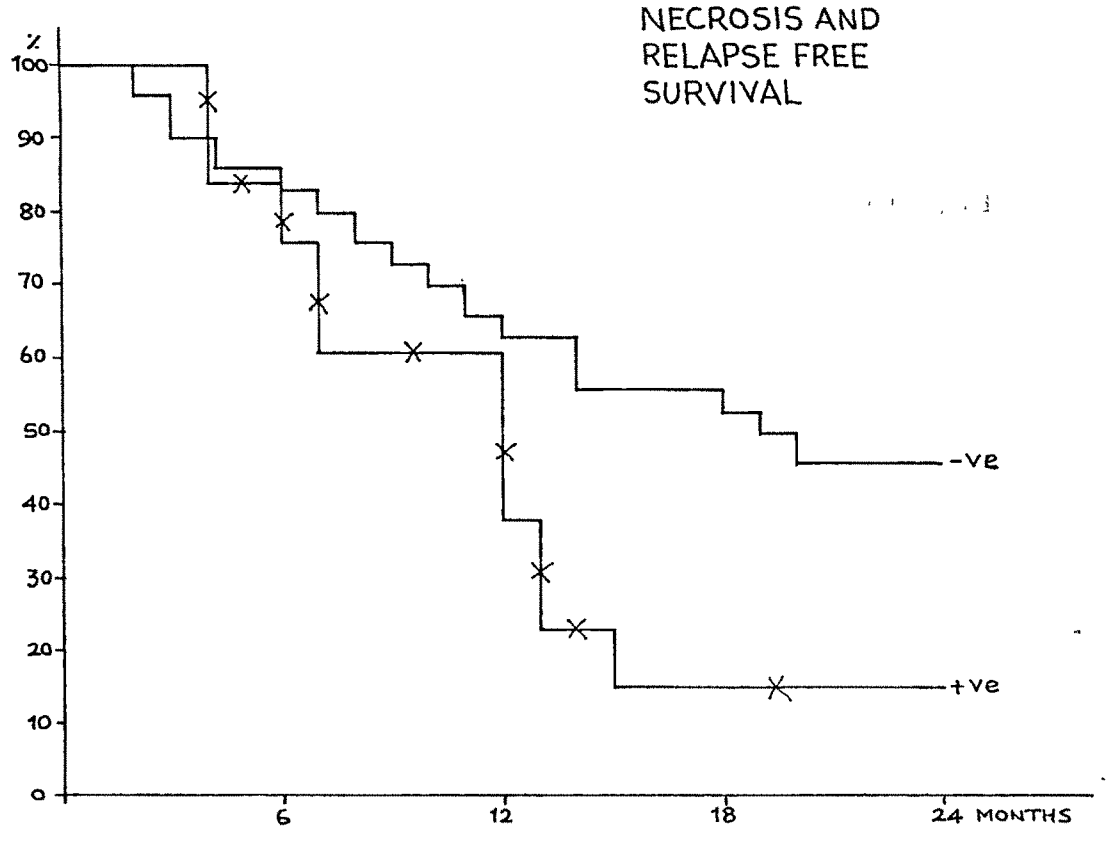
NECROSIS AND
RELAPSE FREE
SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS
-ve
+ve

Fig. 17

Fig. 18

Lymphocytic infiltration and relapse free survival

Fig. 19

Degree of lymphocytic infiltration and relapse free survival.

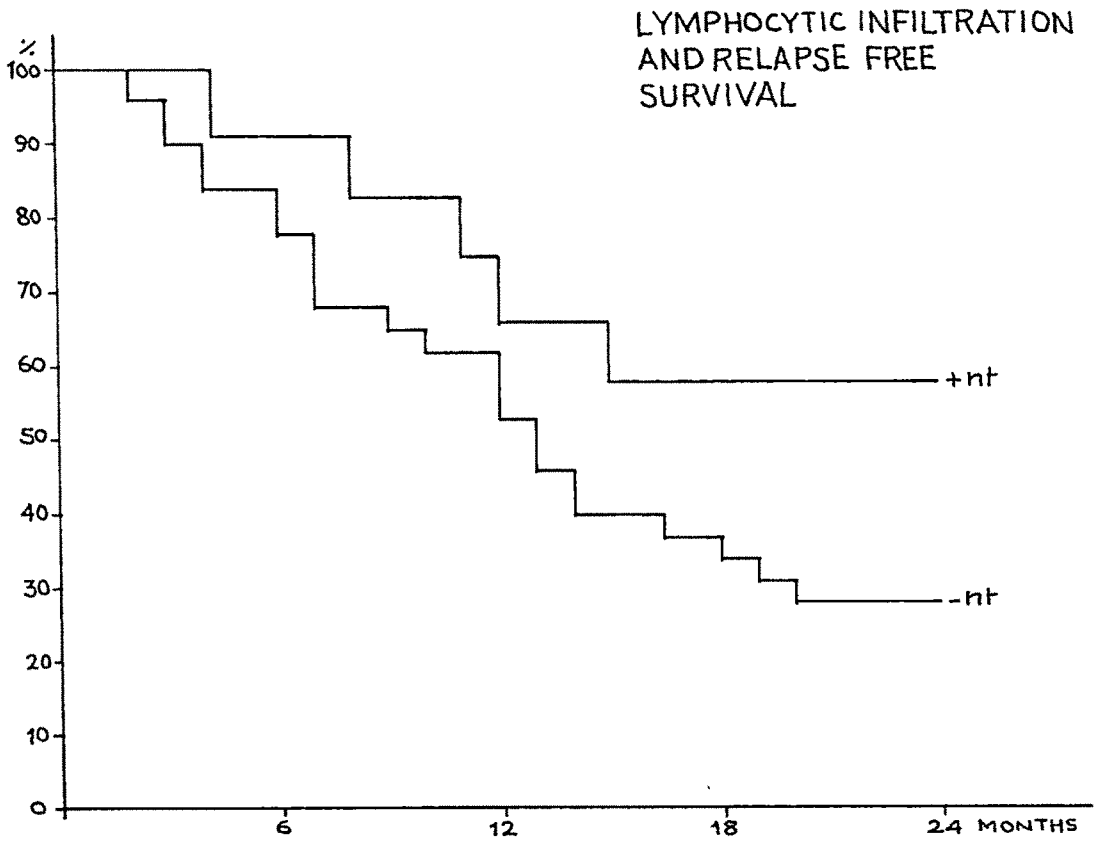
LYMPHOCYTIC INFILTRATION
AND RELAPSE FREE
SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS
+nt
-nt

Fig. 18

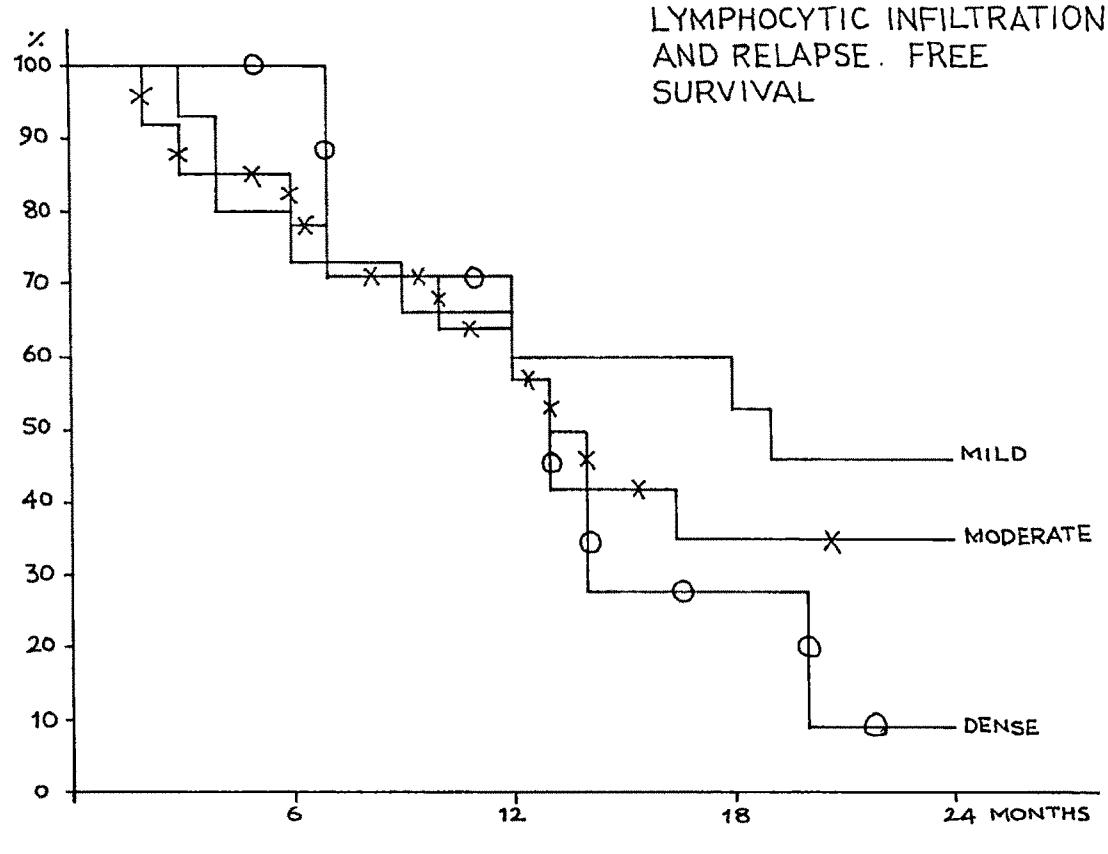
LYMPHOCYTIC INFILTRATION
AND RELAPSE. FREE
SURVIVAL
%
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24 MONTHS
MILD
MODERATE
DENSE

Fig. 19