Method: TS levels were measured within tumors by TS binding assays in 47 female primary breast cancer patients excluding stage IV patients operated on from July 1993 to October 1995. TS levels were compared between patients with early recurrence and disease free patients within three years. These patients were classified into two groups by TS levels (high TS group vs low TS group). Disease free survival rates were compared between these groups statistically.

Result: TS levels ranged from 1.0 pmol/g to 30.8 pmol/g (mean:10.3 pmol/g). TS levels in twelve patients with early recurrence were significantly higher (17.7 ± 7.4 pmol/g) than those in 35 disease free patients (7.3 ± 6.1 pmol/g) ($p = 0.0002$). The high TS group (TS ≥ 10 pmol/g) and the low TS group (TS < 10 pml/g) consisted of 17 and 30 patients respectively. Age, TNM stage, histological characteristics, nodes status and ER status were not significantly different between these groups. The three year disease free survival rate of the high TS group was significantly poorer than that of the low TS group (47% vs 90%, $p < 0.0001$). Moreover in 22 patients with four or more positive nodes, the high TS group's survival rate was significantly poorer than the low TS group. In 19 advanced patients who had received adjuvant chemotherapy such as CMF or CEF, the mean TS level of six patients with cancer recurrence was 14.5 pmol/g which was higher than that of 13 patients with no recurrence (8.2 pmol/g).

Conclusion: The TS level is an important indicator for early prognosis in patients with breast cancer. The outcome of adjuvant chemotherapy in advanced patients will be expected for patients in the low TS group.

478 POSTER

A proposed prognostic factor for node-negative invasive breast carcinomas: Evaluation based on the intraductal component, particularly the presence of comedo-type necrosis

H. Yagata[1], K. Harigaya[2], M. Suzuki[1], M. Oshida[1], T. Nagashima[1], H. Hashimoto[1], T. Shishikura[1], G. Ishii[2], N. Nakajima[1], A. Mikata[2]. *[1]First Department of Surgery, First Department of Pathology; [2]University School of Medicine, Chiba, Japan*

Purpose: Node-negative invasive breast carcinomas relatively have a good prognosis with some exception. The aim of this study was to correlate their prognoses with some morphological features based on the intraductal component.

Methods: Ninety-four patients with node-negative invasive breast carcinoma with the intraductal component were classified into two types: the com () type included tumors which showed little or none of necrosis in the intraductal component, and the com (+) type included tumors which had a significant comedo-type necrosis. The Kaplan-Meier method was used to calculate disease-free survival. Moreover, in tumor specimens from 82 patients, the expression of p53, c-erbB-2, and Ki-67 protein was examined by immunohistochemistry.

Results: Disease-free survival was significantly poorer in the com (+) type than in the com () type ($p = 0.007$). The expression of p53 and c-erbB-2 was found in only 2 (4.2%) and 1 (2.1%) of 47 com () cases, respectively, whereas it was observed in 16 (45.7%) and 15 (42.9%) of 35 com (+) cases, respectively. High expression of MIB-1 was seen in 20 (42.4%) of 47 com () cases and 28 (80%) of 35 com (+) cases. The chi-square test showed a significant correlation between com type and each expression of p53, c-erbB-2 and MIB-1 ($p < 0.0001$, $p < 0.0001$, $p = 0.0015$).

Conclusion: These results suggest that the presence of comedo-type necrosis is associated with a biologically aggressive phenotype, and thus the subclassification of com (+) or com (−) types can be useful as a prognostic factor in node-negative invasive breast carcinoma.

479 POSTER

Relationship between tumor shrinkage and changes kinetic cell activity after primary chemotherapy (PC) in breast cancer (BC) patients

A. Bottini, A. Berruti, A. Bersiga, M.P. Brizzi, A. Brunelli, E. Betri, L. Filippini, G. Bertoli, L. Alquati, P. Dogliotti. *Centro di Senologia, Istituti Ospitalieri, Cremona; Dipartimanto di Scienze Cliniche e Biologisch, Università degli Studi di Torino, Oncologia Medica, Azienda Ospedaliera San Luigi di Orbassano, Torino, Italy*

Ki67 labelling index (LI) was evaluated immunohistochemically in tumor specimens obtained before and after PC in 145 patients with T2-4, N0-1, M0 primary BC submitted to a median of 3 cycles of either CMF regimen (days 1,8 every 28) or single agent epirubicin (120 mg/m2, every 21 days). Tumor shrinkage greater than 50% was obtained in 112 patients (72.8%), 38 of them being complete responders (24.7%). PC significantly decreased the Ki67 LI: median 16% (range 1–90%), 7% (0–55%), before and after PC respectively. More than 50% decrease in Ki67 expression significantly correlated with tumor response (either complete or partial) both in univariate and multivariate analysis. Changes in cell kinetic activity, however, did not parallel with tumor regression in 22 patients. In addition a great proliferation activity (>15% of Ki67 positive cells) have been observed in 19 residual tumor of responding patients. Elevated KI67 LI at post-chemotherapy residual BC was found to be significantly related with short disease free interval (65% vs 85% DFI at 5 years). To conclude reduction in kinetic cell activity as a whole correlated but did not always match with the clinical response. Elevated kinetic cell activity after PC was related to poor prognosis. All these data suggest that the proliferation activity may be a useful toll that in addition with tumor response can discriminate early BC patients who would benefit from the cytotoxic treatment from those who would not.

480 POSTER

Relationship between estrogen receptor (ER) status in primary breast cancer (BC) specimens and serum CA 15-3 levels at first relapse of disease

M. Tampellini, G. Gorzegno, G.M. Sarobba, A. Durando, P. Arese, E. Manzin, F. Castiglione, A. De Matteis, F. Nuzzo, L. Dogliotti. *On behalf of the Ca 15-3 Italian Study Group; Ospedale S. Luigi Gonzaga, Dipartimento di Scienze Cliniche e Biologiche, Regione Gonzole, 10, I-10043 Orbassano, Italy*

It has been shown a strict relationship between CA 15-3 concentration and ER expression in the cytosol of both primary and metastatic BC specimens. In newly diagnosed (BC), CA 15-3 serum levels are influenced by the disease extent (DE). We recorded data from 430 BC patients between October,88 and April, 97.260 patients (61%) were ER+ at diagnosis. At relapse, 278 (65%) had 1 organ involved, 118 (27%) 2 organs involved, and 34 (8%) >2; dominant sites of recurrence were 26% in liver, 32% in lung, 28% in bone and 14% in soft tissue. CA 15-3 overall sensitivity was 61%. Supranormal CA 15-3 levels were found in 183/260 patients (70%) with ER+ primary BC as compared to 78/170 patients (46%) with ER− ones (X2 $p < .0001$). CA 15-3 sensitivity parallelled the DE (assessed according to Swenerton, 1979). However, in patients with limited DE, elevated CA 15-3 levels were found in 71/123 (58%) with ER+ primary BC and in 18/70 (26%) with ER− primary tumors (X2 $p < .0001$), the corresponding percentages were 84% vs 57% ($p < .001$) in patients with intermediate overall tumor load and 84% vs 58% (p = n.s.) in those with elevated DE. ER status, DE and the presence of pleural effusion were independent variables predicting for CA 15-3 supranormal values according to a multivariate logistic regression analysis. The relationship between CA 15-3 supranormal rate at first relapse of disease and ER expression at diagnosis suggests that the steroid hormone receptor status might be a stable phenotype in BC patients. These data also suggest that the capability of CA 15-3 to early detect the disease relapse might be confined to patients with ER+ primary BC.

481 POSTER

Prognosis of 56 male breast cancers – Comparison with females

K. Herman, A. Stelmach, J. Mitús, P. Skotnicki, T. Kusy. *Cancer Centre, Kraków, Poland*

Purpose: Due to a very low incidence rate of male breast cancer the prognostic factors are not so clear. Sometimes poorer than in females prognosis is suspected.

Methods: A study of 56 male and 952 female breast cancers was carried out and survivals were assessed in uni-, and multivariate analysis.

Results: Overall 5 and 10-year survivals of males treated by radical surgery were 71.6% and 38.9% (respectively). Lymph node status hardly influenced prognosis (81.5% NO patients survived 5 years compared with 65% N+ patients). In multivariate Cox analysis only grading and lymph node status were independent factors which influenced males' survival. Relative risk of death was over 4 times higher for grade III tumours and near 3 times higher for males with metastatic axillary lymph nodes. An additional comparison of identical male and female breast cancer groups (pNO) showed marginally significant ($p = 0.08$) differences in survival. At 5th and 10th year, 82.3% and 69.1% (respectively) women were alive compared with 54.1% and 45% men. When multivariate Cox analysis was performed in the whole breast cancer group of patients, sex did not predict survival,

and the relative risk of death depended only on lymph node status (RR = 1.99), tumour grading (RR = 1.32), and size (RR = 1.17) – $p < 0.005$.

Conclusion: Although sex seems to play a limited role in breast cancer prognosis, the data showed in unilateral analysis had some influence on survival. There is great need for further study of this phenomena.

482 POSTER

Prognosticators in axillary node negative breast cancer

W.E. Fiets[1], M.A. Blankenstein[3], J.W.R. Nortier[1], H.M. Rultenberg[2], D.H. Rutgers[4], A. Hennipman[5], C.H.F. Gimbrere[6], H. Strulkmans[4]. *[1]Departments of Internal Medicine; [2]Pathology, Diaconess Hospital, Utrecht; Departments of [3]Biochemistry; [4]Radiation Oncology; [5]Surgery, University Hospital Utrecht; [6]Comprehensive Cancer Centre Midden-Nederland, The Netherlands*

Introduction: Ultimately 30% of all axillary node negative (ANN) breast cancer patients will relapse and die of their disease. Prognostic factors are, therefore, needed to identify high risk patients.

Methods: 221 ANN (median number of 13 nodes examined), T1–3, breast cancer patients were studied. Initial therapy consisted of mastectomy in 71, and breast-conservation-therapy in 150 patients. None of the patients received adjuvant systemic therapy. Prognostic significance of: age, tumour size, estrogen- (ER) and progesterone-receptor (PR) both immunocytochemically (ICA) and by enzyme immuno assay (EIA), mitotic activity index (MAI), DNA-index (DI), S-phase fraction, cathepsin-D, PS2, urokinase plasminogen activator (uPA), and plasminogen activator inhibitor (PAI-1) was prospectively investigated. Disease free survival (DFS) was determined after a median follow up of 61 (range 40 – 88) months. It should be noted that we analysed both local, regional en distant metastases. Continuous and categorical variables were analysed using Cox regression analysis and logrank test, respectively.

Results: The overall 5 year DFS was 85% (38 patients relapsed). Only the following prognosticators: ER-ICA (negative vs positive, n = 149, p = 0.05), DI (diploid vs aneuploid, n = 193, p = 0.05), MAI (cut-off 5 mitoses/10 HPF, n = 152, p = 0.03), uPA (n = 98, p = 0.02) and PAI-1 (n = 98, p = 0.01) are significant prognostic indicators for DFS ($p < 0.05$). ER-ICA and ER-EIA were significantly correlated (t-test for equality of means p = 0.004), ER-EIA showed no prognostic significance, though.

Conclusion: High risk for relapses is associated with MAI > 5, high PAI-1 and uPA, aneuploidy, and a negative ER-ICA score. Prognostic significance was noted for: ER-ICA, while in contrast ER-EIA showed no significance. MAI was significant only with a cut off point of 5 (instead of 10) mitoses per 10 HPF.

483 POSTER

Functional intravital assay of anticancer drug efflux transporters in breast cancer biopsy specimens

T. Bogush, G. Smirnova, E. Koldaeva, E. Bogush, V. Kirsanov, D. Komov, V. Khailenko. *Blokhin Cancer Research Center RAMS, Moscow, Russia*

The main task of the investigation is the functional assay of multidrug resistance-related (MDR) anticancer drug transporters in intact breast cancer specimens for prediction of disease prognosis, tumor sensitivity to the MDR drugs and determination of transporters' type. Doxorubicin (DOX) is used as a model MDR drug. The new methodology developed by us previously was used for intravital determination of intratumor uptake and intracellular DOX accumulation in terms of kinetics of DOX fluorescence decrease in medium of incubation of intact tumor specimen with DOX as well as the changes of the index after modifier action. Two modifiers were studied in this investigation: verapamil (VP)-specific inhibitor of P-glycoprotein and MDR-associated protein transporters, as well as sodium azide (SA)-inhibitor of all energy-dependent (ATP-dependent) transporters. The following types of transporters were shown in 30 breast cancer tumor specimens investigated: 1) VP-sensitive transporters only (the effect of SA is comparable to that seen with VP); 2) VP and non-VP-sensitive transporters (the effect of SA is much greater than that of VP); 3) non-VP-sensitive transporters only (there is a modifying effect of SA and no effect of VP). No VP- and SA-sensitive transporters extruding DOX out of the cells were shown in about 30% of the specimens (there is no modifying effect of VP and SA). We believe that exactly this type of the tumors has to be mostly sensitive to MDR-anticancer drugs and disease prognosis according to this index has to be the best among the patients investigated. Supported by Russian State Committee of Science and Technology.

484 POSTER

Depression as prognostic factor in breast cancer

T. Jørgensen[1], E. Olsen[2], N. Keiding[2], H. Mouridsen[3], P.B. Mortensen[4], K. Hjerl[1]. *[1]Centre of Preventive Medicine, Glostrup; [2]Department of Biostatistics; [3]Department of Oncology, Rigshospitalet, University of Copenhagen; [4]Department of Psychiatric Demography, University Hospital of Århus, Denmark*

Purpose: To test the hypothesis that women with primary invasive breast cancer and previous affective or neruotic disorders have a poorer prognosis compared to other women with breast cancer.

Methods: All 36,422 women registered in The Danish Breast Cancer Cooperation Group during the period 1978–1995 comprised the study population. By cross-linkage to the nation-wide Danish Psychiatric Central Register, 939 women admitted with a previous affective or neurotic disorder in psychiatric departments were identified. We used survival analyses, controlled for all the well-documented prognostic factors and analysed for deaths of natural and unnatural causes of death.

Results: Low risk breast cancer patients with a previous affective or neurotic disorders suffered a marginal increased rate of recurrence and a significant increased mortality rate compared to the other women. This could be explained by an increased mortality rate due to unnatural causes. In high risk breast cancer patients the same trends were seen but the results could not be explained by an increased mortality rate due to unnatural causes.

Conclusion: A previous psychiatric admission with affective or neurotic disorder seems to be only a weak negative prognostic factor in breast cancer.

485 POSTER

Loco-regional recurrence in randomized trial of breast cancer TNM stage II. Prognostic factors

L. Tennvall-Nittby[1], I. Tengrup[2], L. Anagnostaki[3]. *[1]Departments of oncology; [2]Department of surgery; [3]Department of pathology, Malmö University Hospital, Sweden*

Material and Methods: Loco-regional recurrence (LR) was studied in a material of 1153 patients with breast cancer TNM stage II and randomized into 6 adjuvant treatment groups including RTR (4 groups) and/or Cyclophophamide or tamoxifen. p53 expression and c-erbB-2 oncoprotein were analysed immunohistochemically. Median observation time was 12 years.

Results: Recurrence occurred in 460 patients, 129 of whom had LR ± distant metastasis. The LRs were identical histologically with the primary tumours. p53 expression was observed in 1/3 of the cases with LR as was c-erbB-2 oncoprotein and in 10% both p53 and c-erbB-2. 19% of the 58 patients without RTR had LR and 6% of these showed p53 compared with 8% and 2% respectively of the 71 patients with LR receiving RTR.

Conclusion: No tumour progression was seen histopathologically between the primary tumour and the LR. Among patients with LR not given RTR three times as many cases showed p53 and c-erbB-2 as the corresponding patients given RTR. The results may indicate that RTR in cases with p53 expression results in fewer LR. Further studies have been initiated on oncogenes in the primary tumours in relation to adjuvant therapy and LR.

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The significance of prostate specific antigen (PSA) in breast cancer

J.G.M. Klijn, E.P. Diamandis[1], H. Yu[2], M.P. Look, M.E. Meijer-van Gelder, W.L.J. van Putten, J.A. Foekens. *Department of Medical Oncology, Rotterdam Cancer Institute (Dr. Daniel den Hoed Kliniek) and University Hospital Rotterdam, The Netherlands; [1]Mount Sinai Hospital and University of Toronto, Canada; [2]Diagnostic Systems Laboratories, Webster, Texas, USA*

Purpose: The serine protease PSA has been found in breast and some other non-prostatic cancers. The expression of PSA is regulated by steroid hormones. In the present study we have determined PSA levels by ELISA in 1516 primary breast tumors, and have correlated PSA levels with tumor characteristics and clinical outcome.

Methods: The tumors were derived from 1516 patients with primary breast cancer: median age 56 yr (range 24–89 yr), 59% postmenopausal, median follow-up 85 months (13–202 m), relapse rate 47%, deaths 38%.