group. The median of CEA is increasing by patients with higher stage. The cut-off values were determined for CA 15-3 by 32.7 U/ml, CEA by 3.5 ng/ml and TPA by 80 U/l. We determined no differences in specificity (0.92), positive PV (0.95) and negative PV (0.17) for all three tumor marker. We found a higher sensitivity and efficiency for our investigated patient group for TPA; (CA 15-3/CEA/TPA): sensitivity (0.33/0.26/0.38); efficiency (0.41/0.32/0.43). The ROC curves analysis shows a higher discriminatory capacity of TPA between CA 15-3 and CEA. In the follow-up of breast cancer the combination of CA15-3 with TPA is considered as suitable (3).

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[2] Findeisen R, et al: Eur J Clin Chem Clin Biochem 1997; 35: A105
[3] Nekulova M, et al: Neoplasma 1994; 41: 113–8

P28 Determination of c-erbB-2 protein in sera from primary breast cancer patients

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The level of c-erbB-2 protein was determined in sera from 162 primary breast cancer patients using sandwich enzyme immunoassay between 1996 and 1997. The level of c-erbB-2 protein was calculated from a standard curve constructed with the use of recombinant c-erbB-2 (Nichirei, Tokyo). The cut-off level was set at 5.4 ng/ml for female in healthy blood donor. Firstly, serum levels at preoperative diagnosis were analyzed in 44 cases of stage I–III B. The range and median value of c-erbB-2 protein in sera were from 2.3 to 32.3 ng/ml and 4.9 ng/ml. The positive rate was 44%. Serum levels of c-erbB-2 protein were significantly associated with clinical stage and nodal status, but not with menopausal status, histologic grade, hormonal receptor status and other tumor marker levels (CEA and CA15-3). Secondly, serum levels of c-erbB-2 protein in addition to CEA and CA15-3 were monitored in 118 cases during postoperative periods. The range and median value of c-erbB-2 protein in sera were from 1.8 to 87.6 ng/ml and 4.4 ng/ml. For 107 cases free of relapse, false positive rates of serum c-erbB-2 protein, CEA, and CA15-3 were 12%, 5%, and 1%, respectively. For 11 cases relapsed, however, sensitivities of these markers were 81%, 36%, and 18%. These results suggest that serum c-erbB-2 protein is useful as a novel tumor marker to detect early relapse as well as a prognostic indicator.

Thursday, February 26, 1998 9.00–18.00

Prognostic and Predictive

P29 Tumor proliferative activity evaluated with thymidine labelling index predicts response to adjuvant chemotherapy

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In order to find a factor able to predict response of Breast Cancer (BC) to chemotherapy (CT) we retrospectively analyzed data on tumor proliferative activity evaluated by means of Thymidine Labelling Index (TLI) in a series of patients (pts) entered a trial of adjuvant CT. We evaluated the ability of TLI to predict the effectiveness of the addition of perioperative chemotherapy (periop CT) to conventional treatment of primary BC. 600 pts entered a randomized protocol as follows: N– pts: 1 cycle of periop CT versus no therapy; N+ pts: 1 cycle of periop CT + 11 cycles of CT at conventional times versus 12 cycles of CT at conventional times. The periop CT consisted of Cyclophosphamide 600 mg/sm, Epidoxorubicin 60 mg/sm and Fluorouracil 600 mg/sm (CEF). Overall results show only marginal advantages for periop CT. The evaluation of TLI was performed in 197 cases. Pts were grouped as high or low TLI on the basis of a cut-off value established on previous large series. At a follow-up of ten years Relapse Free Survival (RFS) and Overall Survival (OS) are similar in pts with high and low TLI. Different outcomes of the periop CT were observed according to TLI. The observed/expected ratio (o/e) observed was: 1. OS of N+/N– high TLI pts: 13/11.6 (control) vs 11/12.3 (periop CT); p = 0.5. 2. RFS of N+/N– high TLI pts: 18/15.6 (control) vs 17/19.3 (periop CT); p = 0.4. 3. OS of N+/N– low TLI pts: 9/11.6 (control) vs 12/9.3 (periop CT); p = 0.2. 4. RFS of N+/N– low TLI pts:17/16.5 (control) vs 14/14.4 (periop CT); p = 0.8 5. OS of N– high TLI pts: 7/3.7 (control) vs 2/5.2 (periop CT); p = 0.03. 6. RFS of N– high TLI pts: 10/5.9 (control) vs 6/10.1 (periop CT); p = 0.03 7. OS of N– low TLI pts: 4/6.2 (control) vs 8/5.7 (periop CT); p = 0.1. 8. RFS of N– low TLI pts: 9/8.3 (control vs 8/8.6 (periop CT).

In this study TLI predicted the effectiveness of periop CT in reducing the relapse and death rate of N-patients. Supported by CNR, PF ACRO, Rome.

P30 A different P53 genotype predicts major response to antracycline or paclitaxel based neoadjuvant therapy in breast cancer

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Effect of anticancer therapies has been recognized to be rather based on apoptosis induction than targeting rapidly proliferating cells. Intact p53 seems to be crucial for the induction of the apoptotic effect of DNA damaging agents (e.g. antracyclins). In contrast, drug potency of substances acting in M-phase (e.g. paclitaxel) might be reduced by normal p53 via inducing cell cycle arrest and preventing tumor cells entering S-phase.

In a retrospective study we evaluated weather a distinct p53 genotype is associated to response to neoadjuvant regimen with different modes of cytotoxic mechanism. 52 patients with inflammatory or T4 breast cancer were entered into the study. 29 received paclitaxel monotherapy preoperatively, 23 were treated with an antracycline based combination therapy consisting of Fluorouracil, Epirubicin and Cyclophosphamide. P53 genotype was assessed by complete direct sequencing (exon 2–11). PCR amplification was carried out from total tumor DNA extracted from pretherapeutical biopsies. Tumor diameter was assessed bidimensionally at time of presentation and at regular intervals by taking together information from mammography, ultrasound, magnetic resonance and clinical examination. Clinical response was classified according to UICC criteria.

Antracycline based combination treatment with FEC resulted in partial remission in 12/23 patients who exhibited all wild type p53 in their tumors. p53 mutations were detected in 11/23 tumors of patients experiencing stable and progressive disease. *Paclitaxel treatment* resulted in stable disease in 19/29 patients exhibiting a normal p53 status including three patients with silent p53 point mutations. P53 alterations being present in 10/23 tumors appeared to be associated with complete and partial remission in 9/29 patients and with stable disease per definition in one patient (tumor shrinkage from 9 × 9 cm to 8 × 5 cm).

Our data suggest that the p53 genotype could be predictive for response to neoadjuvant therapy in breast cancer patients. The prior knowledge of the p53 status could probably increase the rate of treatment responses and save patients from inefficient chemotherapy. In this study we present clinical data underlining the paradoxical effect of wild type p53, showing that functionally active p53 is associated with major response to neoadjuvant treatment with antracyclins but is related to complete failure of preoperative paclitaxel treatment in breast cancer patients.

P31 Prognostic significance of vascular tumor emboli in 1518 breast carcinoma patients with small tumor size (≤3 cm)

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The aim of this study was to assess retrospectively the prognostic value of vascular tumor emboli on local recurrence, survival without metastases and overall survival in a prospectively followed (median, 7 years) cohort of 1518 patients with T0, T1, T2 ≤3 cm N0 M0 breast carcinoma. All the patients were treated with tumorectomy and postoperative radiotherapy. 1048 patients had axillary dissection with the tumorectomy, 328 (31%) had lymph node metastases. 470 patients had tumorectomy alone followed by breast and axillary irradiation. The patient's age, tumor size, nodal status, estrogen (ER) and progesterone receptor status, histology, tumor grade and the presence of tumor emboli were studied using univariate and Cox multivariate analyses. The overall local relapse rate was 10%, overall metastasis rate was 17%, overall death rate was 13%. Vascular tumor emboli were observed in 6.2% of the patients and were significantly associated with larger tumor size (>2 cm), higher tumor grade, negative estrogen receptor status and positive nodes. At univariate analysis, tumor emboli were a significant prognostic factor. At multivariate analysis, age ≤35 years and ER- were significantly associated with local recurrence, tumor size, metastatic nodes, high tumor grade, ER- and tumor emboli (p = 0.03) were associated with appearance of metastases. Tumor size, high tumor grade and ER – were associated with poor overall survival. In an univariate subgroup study of the 720 patients without nodes metastases, vascular tumor emboli were significantly associated with appearance of metastases. This significance disappeared at multivariate analysis. In conclusion, tumor emboli are an independent prognostic factor in small breast carcinoma and further studies are mandatory in node negative patients.