therapy. MS SPECT follow-up in the course of combined chemo- and radiation therapy revealed decrease of ^{99m}Tc-MIBI accumulation by 25–45%, supporting usage of the technique for control of non-surgical treatment.

Groups of lymph nodes	Axillar	Subclavicular	Supraclavicular
Detected by ^{99m}Tc-MIBI mammascintigraphy	28	9	5
Verified pathologically	31	12	7
Sensitivity of ^{99m}Tc-MIBI	90.3%	75%	71.3%

Hencefore we conclude the SPECT mammascintigraphy with ^{99m}Tc-MIBI provides correct data on the extent of metastatic spread in breast cancer and can be used for both design of therapy and also for dynamic follow-up.

P23 Monitoring the efficacy of primary chemotherapy for breast cancer using breast scintigraphy and immunocytochemical bone marrow screening

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Primary chemotherapy is indicated for inflammatory breast cancer, primary metastatic breast cancer, and to decrease tumor size to allow lumpectomy instead of mastectomy. To date, conventional monitoring of chemotherapy success includes mammography, ultrasound, and sometimes tumor marker level. These methods are unsuitable to monitor inflammatory breast cancer.

In this pilot-study, breast scintigraphy with Tc-99m-Sestamibi, an established method for tumor differentiation, was used as an alternative method of therapy monitoring in inflammatory breast cancer. Additionally, bone marrow aspirates were obtained from each patient to screen for breast cancer micrometastases before and after chemotherapy, using the pancytokeratin monoclonal antibody A45-B/B3 for tumor cell detection. Up to now ten patients were examined with breast scintigraphy and bone marrow aspiration before and after primary chemotherapy for inflammatory breast cancer. In six patients a clinical regression of disease could be observed.- Parallel a dimished tumor perfusion could be detected by scintigraphy and previously positive micrometastasis in bone marrow aspiration changed to a negative result. Four patients did not respond to chemotherapy and did not show changes in diagnostic results as well.

We conclude that breast scintigraphy and bone marrow screening might be a promising approach to monitor therapeutic efficacy in cases where conventional monitoring fails to predict the clinical outcome

P24 Scintimammography & MR mammography in assessing palpable breast masses and recurrent tumour

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The early detection of recurrent tumour during adjuvant therapy is important in planning management including second-line therapy. We compared prospectively TC-99m tetrofosmin scintimammography (TSM) with MR mammography (MRM) in 47 patients of mean age 51 (26–79) with palpable breast lumps. A remote history of carcinoma in the affected breast was present in 11 patients. All patients had TSM, contrast-enhanced MRM and plain-film mammography (PFM) (age >35) performed on the same day. Al lesions had biopsy or aspiration cytology within two weeks of imaging and the pathology and imaging results were correlated. Claustrophobia in three patients lead to discontinuation of MRM – of the 44 remaining patients the pathology was malignant in 21 and benign in 23. The overall sensitivity of PRM was 81%, with a specificity of 82.4%, a positive predictive value (PPV) of 85% and a negative predictive value (NPV) of 77.8%. The sensitivity of TSM was 95.24%, specificity 91.3%, PPV 90.9% and NPV 95.45%. The sensitivity of MRM was 90.5%, specificity 91.3%, PPV 90.5%, and NPV 91.3%.

Four of the 11 patients with a history of breast cancer had recurrent tumour. In 2 of these 4 patients, PFM failed to detect recurrent carcinoma while suggesting tumour recurrence in 2 of 7 patients with postoperative fibrosis alone. TSM was positive in all 4 patients with recurrent disease and negative in all 7 cases of benign scar tissue. MRM correctly characterised 7 of the 9 lesions with one false positive and one false negative result.

In conclusion, TSM and MRM are both accurate in differentiating benign from malignant breast lesions but TSM is more accurate in evaluating the post-operative and post radiotherapy breast. Because of lower cost, wider availability and high patient acceptance, TSM is superior for the non-invasive characterisation of breast masses, including tumour recurrence and may also have a role in monitoring adjuvant therapy.

P25 Tc-99m-sestamibi scintimammography for the evaluation of breast malignancies

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We evaluated the efficacy of Tc-99-sestamibi (MIBI) scintimammography for the detection of breast cancer in 351 patients. In two-hundred and twenty five patients with breast abnormalities, the scans were confirmed by histological or cytological results. The other patients who did not have pathological results, were examined because they belonged to high-risk groups, had dense fibroglandular breast or were scanned before starting radiotherapy after having breast lumpectomy.

The mean age of the patients was: 49.8 years (range was: 17–84 years).

The results demonstrated among patients with pathological results, positive scan in 125 women: 86 scans were true positive, while 39 examinations were false positive. In 101 patients scintimammography was negative: 94 examinations were true negative, while in 7 cases the result was false, and the patients suffered of malignant tumor of the breast. Six out of seven false negative results were obtained in patients with non-palpable tumor. Among those patients with pathological results, the obtained sensitivity, specificity, positive and negative predictive values were 92.3%, 70.7%, 68.8% and 93.1% respectively. Total accuracy was: 80%.

Our conclusion from the present study is that MIBI scintimammography is a sensitive and accurate method for the detection of breast malignancies and may be part of the available armamentarium for this purpose.

P26 Evaluation of breast cancer utilizing proton magnetic resonance spectroscopy (MRS)

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This prospective study is to evaluate the response to chemo irradiation in breast cancer utilizing the noninvasive proton MRS. Fortyone patients of infiltrating duct carcinoma of breast were investigated using bilateral breast surface coil. MR image guided in vivo localized NMR spectra were obtained from the tumours and non-tumours portion of the breast of the patients using STEAM RF pulse sequence. The spectra were obtained in pre and post chemo-therapy and radiotherapy settings. Localized proton MR spectra of the unaffected contralateral breast of these patients are dominated by resonances arising from fat and are similar to the breast tissue from normal (control) volunteers, while in the malignant breast tissues the water resonance dominates. Elevated water/fat ratios are measured in malignant tissues, compared with the contralateral unaffected breast tissue of the patients. Statistical analysis of the MRS data demonstrates a decrease in the water/fat ratio in patients receiving full course of chemotherapy compared to the pre-therapy ratio ($p < 0.04$). The observed trend in W/F ratio suggests an attractive marker for diagnosis, prognosis and therapeutic follow-up of breast carcinoma. Further, the water suppressed proton MR spectra of malignant breast tissue reveal several metabolite resonances of low concentration including the choline peak around 3.2 ppm and other minor resonances in the region of 8.5 ppm due to protons of purine and pyrimidine nucleotides, thus providing additional useful markers.

P27 The determination of tissue polypeptide antigen (TPA) in follow-up of breast cancer

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Breast cancer is one of the most serious diseases in women both in its incidence and death rate. Tumormarker are playing an important role in the follow-up of breast cancer. Giron et al described, that the concentration of TPA in tumor cell cytosol is a good indicator of prognosis (1). Cancer antigen 15-3 (CA 15-3), Carcinoembryonic antigen (CEA) and Tissue polypeptide antigen (TPA) were measured in 464 sera of breast cancer patients and in 71 sera of women without breast cancer. The tumormarkers were determined using immunoluminometric assays (ILMA) manufactured by Buick-Sangtec Diagnostica, Dietzenbach. The assays are characterised by an Interassay-Variance and Intraassay-Variance <4%. The breast cancer patients were staged according to the TNM classification stage 0–IV (by UICC). Median and range of each stage were investigated (2). The cut-off values (95. percentile of tumor-free control group) of CA 15-3, CEA and TPA were determined: specificity, sensitivity, positive, negative predictive value (PV) and efficiency were investigated for these cut-offs and the receiver-operating-characteristic (ROC)-curves were calculated.

Results: The CA 15-3 and TPA median values are measured higher by about 30 percent in patients with stage 0 + 1 than in patients of the tumor-free control

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.