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

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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

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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

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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

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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.

486   POSTER

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

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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%.

Results: Tumor PSA levels (median 20 pg/mg protein, range 0–50.000) were significantly associated with young age (p < 0.0001), small tumor size (p < 0.001) and positive PgR status (p < 0.0001), but not with nodal status and grade. PSA levels were not associated with relapse rate. A positive association of PSA with an improved overall survival (p = 0.009) disappeared after correction for age. In 434 patients with recurrent disease a high PSA level was significantly (P < 0.01) related with a poor response to first-line tamoxifen therapy as assessed by response rate, PFS and overall postrelapse survival.

Conclusion: In Cox multivariate analysis PSA had no prognostic value for (relapse-free) survival, but an independent predictive value for response to tamoxifen therapy.

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487   POSTER

The relationship between nm23 gene expression and distal metastasis and prognosis in breast cancer

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Mortality associated with human breast carcinoma is almost entirely due to subsequent metastatic disease, but the micrometastasis is difficult to be detected. Elucidation of the genetic control of metastatic propensity of a tumor is important in determing prognosis and choice of therapy.

The nm23 gene is a putative metastasis suppressor gene originally identified in murine melanoma cells. The purpose of this study was to investigate the relationship of nm23 gene mRNA and protein expression with distant metastasis and prognosis in breast cancer.

We detected nm23 protein expression in 101 patients with primary breast cancer by means of immunohistochemistry. Expression of nm23 gene was inversely associated with lymph node metastasis and distant metastasis (p 0.05). Overall survival was better in patients in whom expression of nm23 was positive than in those in whom it was negative (p 0.05). In patients with negative lymph node, overall survival was better in patients in whom expression of nm23 was positive than in those in whom it was negative. In multivariate analyses using a Cox's proportional-hazard regression model, nm23 showed contribution to patient survival (= 0.4288).

In the mean time, expression of nm23 mRNA and protein in 68 patients with primary breast cancer was detected by means of RT-PCR and immunohistochemistry. The results show consistency with the former one. Within the following two years after the surgery, three patients recurred and one occurred distant metastasis. Expression of nm23 mRNA in all of them was lower.

This study showed that the nm23 gene may perform a independent role in disease prognosis in addition to its participation in breast cancer metastasis.

488   POSTER

New era of treatment in breast cancer – Neoadjuvant therapy without surgery

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Purpose: This study was conducted to investigate the usefulness of using prognostic factors in predicting patients response to neoadjuvant therapy, thus improving the efficacy and decreasing toxic side-effects of therapeutic agents.

Methods: 60 invasive breast cancer patients were treated, patients ranged in age from 25 to 83. All patients received at least four courses of adriamycin, cyclophosphamide and 5-FU, unless tumor growth was observed. Analysis of the tumors for various prognostic factors was done on all patients using immunohistochemistry combined with image analysis.

Results: More than four cycles were given in patients who showed continued tumor dissolution. Primary chemotherapy and tumor markers has identified "responders" who showed consistent tumor ablation to the point of total tumor dissolution. Six patients had no demonstrable tumor at surgery. Four patients had mastectomy and fifty-two had lumpectomy. Four patients had no demonstrable tumor after primary chemotherapy and did not have surgery.

Conclusion: We recommend individualized treatment, based on factors predicting response to chemotherapy, to obtain maximum local control including minimizing or avoiding surgery.

489   POSTER

Lymphocyte subgroups in breast cancer and the effect of tumor removal

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It is known that immune function is effected in cancer patients. However the effect of tumor removal on host immune function is not known.

Fifty-one breast cancer patients who underwent modified radical mastectomy were studied. There were 12 patients with stage I, 16 with stage IIA, 13 with stage IIB and 10 with IIIA. The control group consisted 20 women who underwent either thyroid surgery for benign causes or open cholecystectomy. Preoperative and postoperative (on the seventh day) blood samples were taken for flow-cytometric analysis from the study and control group patients. T lymphocyte, B lymphocyte, Natural killer (NK) cell, T-helper (Th), T-cytotoxic-supressor (Ts), T active (Ta) cell counts and Th/Ts ratios were evaluated. Ts cells of the breast cancer patients were significantly higher than the control group (p < 0.05). Among the breast cancer patients Th cells were higher in early stages (p < 0.05). There were no difference between pre and postoperative lymphocyte profile in the control group. However operation made certain changes in the breast cancer patients. Postoperatively, B lymphocyte, T lymphocyte, Th counts, and Th/Tsor ratios increased (p < 0.05 for each). Ts (p < 0.01) and NK (p < 0.05) counts decreased.

The difference between the immune profiles of the breast cancer and the control groups showed that antigenic stimulus of the tumor influences the parameters of the host immune functions. Operation had no effect in the control group, but had a certain effect in the breast cancer patients. Thus we believe that the removal of the tumor causes a considerable difference in immune parameters.

490   POSTER

Assessment of the response with color-doppler sonography (CDS) in patients affected by breast cancer (BC) in neoadjuvant chemotherapy (NCT)

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NCT is advised for patients with large-sized BC with the aim of reducing the neoplastic mass and increasing the possibility of conducting conservative surgery. The purpose of this study is to test the role o CDS in assessing the response to NCT. From 1/95 to 2/98 CDS has been used to study 32 patients (31 F, 1 M) affected by 3.5 cm average diameter BC (2.5–5 cm), subjected to accelerated NCT with 3 cycles of 120 mg -MQ EPI-ADM and 600 mg/Mg CTX every 2 weeks. CDS assessment was carried out for all patients before beginning treatmend and a re-assessment was made before each new cycle. Diagnosis was always confirmed by cyto-histology and before beginning the NCT the BC was marked with intravital stain. 95% of the BC examined showed an increase in vascularization both peritumoral and intratumoral and about 30% showed anarchic vascularization. After 3 NCT cycles 90% of patients displayed modifications in the nature of the echography of the nodular mammary lesions and 60% of patients showed variations also at the CD with reduction in the vascularization. In Three cases RC of the BC was found. Echography together with CD in BC patients would seem to demonstrate good accuracy in monitoring the response to CT. By providing a semi-quantitative assessment of BC vascularization before and after CT, the CD examination could have predictive value also on the aggressiveness of the disease.

491   POSTER

Prognostic markers in neoadjuvent chemotherapy

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Purpose: To perform immunohistochemistry on breast cancers before and after primary medical treatment to see if there was a particular profile that would predict a good response. A detailed review of the histological feature was also undertaken.

Methods: 15 biopsies from 10 patients were assessed for expression of Ki67, bcl2, p53, oestrogen receptors and progesterone receptors using standard immunohistochemical techniques. The were analysed by a single