Proffered papers

Breast cancer—diagnostic and prognostic factors

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BREAST CANCER SURVIVAL AFTER ORAL CONTRACEPTIVE USE

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The aim of our study was to investigate the influence of a positive history of OC use on survival of breast cancer. The prognostic effect of an antecedent OC use was investigated in 471 breast cancer patients recruited between 1982 and 1986 as contribution to the WHO Collaborative Study of Neoplasia and Steroid Contraceptives using univariate (Kaplan-Meier/ logrank test)- and multivariate (Cox model) survival analyses.

297 (63%) patients had ever used OCs and 202 (43%) were long-term users. Sixty months after diagnosis OC users had a significantly increased overall survival ($P = 0.037$). The effect persisted after adjustment for other prognostic factors and was mainly attributed to women who had taken OCs four years or longer ($P = 0.025$). Comparing the survival dependent on duration of OC use (never, 1–48 months, $\geqslant$ 49 months) the most significant influence on survival was observed among long-term users with a rather expected worse prognosis.

These results suggest an effect of OC use on tumor biology during the preclinical course of the disease.

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PROGNOSTIC VALUE OF BONE MARROW BIOPSY IN OPERABLE BREAST CANCER PATIENTS AT THE TIME OF INITIAL DIAGNOSIS: RESULTS OF A 19-YEAR MEDIAN FOLLOW-UP

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From May 1975 until May 1980, 128 operable breast cancer patients clinical stage I–II had a core bone marrow biopsy (BMB) from the posterior iliac crest as a part of the routine diagnostic work-up at the time of initial diagnosis. The mean age of the patients was 56 years, range 26–93. Prior to this study, in 10 patients BMB (7.8%) were positive for tumor cells and in 118 negative by conventional histopathology. In 1995 we reexamined all BMB separately at two laboratories, using monoclonal antibodies against cytokeratins AE1–AE3, KL 1, CAM 5-2 (DPG), and DC10, BA17 (MCI). Micrometastases were detected totally in 17 patients (13.3%) at MCI and in 16 patients at DPG. Moreover, at MCI another 8 patients were classified as suspicious. Median follow-up was 19 years. All tumor cell-positive patients relapsed and deceased within 6 years of disease progression with evident osseous metastases. There were 3 survivors of the 8 patients with suspicious BMB: 2 with evident osseous and skin metastases, time to relapse 19 and 20 years respectively, and one patient was disease-free after 15 years of follow-up. The median overall survival was significantly shorter in tumor-cell positive patients being 1.9 years compared to 11.7 years in the BMB negative and BMB suspicious groups ($P < 0.0001$). BMB is useful in predicting the prognosis in patients with breast cancer clinical stage I–II.

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PROGNOSTIC SIGNIFICANCE OF UPA AND PAI-1 IN RELATION TO OTHER PROGNOSTICATORS FOR THE CLINICAL OUTCOME OF BREAST CANCER

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In a retrospective study, uPA and PAI-1 were assayed by enzyme-linked immunosorbent assay (ELISA) in detergent extracts prepared from 400 primary breast tumours. The patients were followed for a median of 9 years and for all patients relevant clinical findings were recorded.

We found a correlation between uPA/PAI-1 and classical prognostic factors such as number of lymph nodes involved, grade, tumour size, hormone receptor status and histology, but no correlation according to menopause or age.

Disease-free (DFS) and over-all survival (OS) were analyzed using a Cox's proportional hazard model. As cut-off point the median uPA and PAI-1 values were used. Breast cancer patients with high content of PAI-1 (>11.0 ng/mg protein) have an increased risk of relapse and death (RR: 1.74 (1.27–2.39), while high uPA (>4.3 ng/mg protein) had no impact.

Despite PAI-1's correlation to other prognosticators, PAI-1 retained its independent significance in the Cox-model in contrast to uPA.

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PROTEIN TYROSINE KINASE ACTIVITY IN 350 T1/T2, N0/N1 BREAST CANCER. PRELIMINARY RESULTS

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Protein tyrosine kinases (PTKs) play a major role in the transduction of the mitogenic signal and have been reported to be involved in cell proliferation, differentiation and transformation. PTKs can be subdivided into two major families: membrane associated PTKs consisting essentially of growth factor receptors (receptor tyrosine kinases or RTKs) and cytosolic PTKs involved in the transduction of mitogenic and differentiation signals. From January 1988 to January 1992, PTK activity was assayed in cytosolic fractions prepared from 350 T1–T2, N0–N1 M0, breast carcinomas. Enzymatic activity was measured using ^{32}P-ATP and poly-Glu-Tyr as an artificial substrate. According to our previously reported pilot study, we chose a cut-off value of 12 pmol ^{32}P incorporated min^{-1} mg^{-1} protein, corresponding to median value. We found positive PTK levels ($\geqslant$12 pmol/min/mg) to be correlated with the loss of differentiation according to Scarff-Bloom grade ($P < 0.001$), negative PR ($P = 0.003$) and ER status ($P = 0.004$). With a median follow-up of 30 months (0–90), patients with a positive PTK level and a positive axillary status presented a significantly smaller 3 year disease-free survival than the PTK negative ($\leqslant$12 pmol/min/mg) ones ($P = 0.07$). In Cox multivariate analysis including pT, pN, Scarff-Bloom grade, PR and ER, PTK activity does however not emerge as a prognostic factor.

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MEDULLARY CARCINOMA OF THE BREAST, HISTOPATHOLOGICAL AND CLINICAL CHARACTERISTICS

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We characterized 110 medullary breast cancers (MC), diagnosed according to a new definition, recently proposed by us. The criteria are: (1) predominantly syncytial growth pattern and no tubular component,

(2) diffuse stromal infiltration with mononuclear cells and (3) sparse (<25%) necrosis. The tumors are further characterized by high histological grade (96% gr. III) and by predominance of estrogen receptor negativity (67%). Both factors normally indicate poor prognosis. However, this group of tumors has a significantly better overall survival and recurrence-free survival compared with a control group of infiltrating ductal carcinomas (IDC). Classical risk factors for breast cancer have a significantly different distribution and only minor prognostic importance in the group of MC compared with the control group of IDC.

According to the proposed definition, MC is biologically unique and the results indicate that the risk factors presently used for selecting breast cancer patients for systemic adjuvant treatment probably should be modified in MC.

651 ORAL

APOPTOSIS ACCOUNTS FOR THE NECROSIS SEEN IN DCIS

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The biology of DCIS is poorly understood and treatment highly controversial. Apoptosis, a genetically triggered death program has been described in the normal breast, possibly as a regulator of tissue homeostasis. To evaluate the presence of apoptosis in DCIS, we studied 25 cases of DCIS accessioned in 1993 and 1994. 10 patients presented with comedo DCIS, 9 with cribriform DCIS with intraductal necrosis, and 6 with cribriform or micropapillary DCIS without intraductal necrosis. All cases were stained for presence of apoptosis using the terminal transferase assay (TUNEL) staining free DNA ends. In all 19 cases with necrosis, TUNEL stain was positive. The 6 DCIS cases that lacked intraductal necrosis displayed no intraductal apoptosis by TUNEL assay. p53 analysis suggests that this apoptosis is independent of p53. For 2 additional cases with synchronous invasive cancer and DCIS with intraductal apoptosis, not included in this series, apoptosis was restricted to the DCIS tumor.

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THE RELATION OF EXTENSIVE INTRADUCTAL CARCINOMA COMPONENT (EIC) WITH PROGNOSIS AND TREATMENT RESULTS OF PATIENTS (PTS) WITH PRIMARY BREAST CANCER

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Within the context of a large retrospective study on a broad scale of prognostic factors we studied the clinical significance of EIC. In a series of 1064 primary infiltrating ductal breast carcinomas, 133 tumors appeared to contain EIC (>25% of the tumor being DCIS) as described in the pathology report. In general no significant differences in stage were found between the groups with and without EIC. Of the 133 pts with EIC 48 underwent breast conserving therapy (BCT) and 85 modified mastectomy (MM Patey). Of the 931 pts without EIC 462 underwent BCT and 469 MM Patey. After a follow-up of 7 years the 85 pts with EIC treated with MM Patey showed a better disease-free survival (DFS) than the 48 patients treated with BCT (difference 17.5%; $P = 0.07$). Within the whole group of 510 pts treated with BCT the 48 pts with EIC tended to show a worse prognosis as compared with pts without EIC (difference 9.5%; n.s.). The opposite was observed in the group of 554 pts treated with MM Patey, indicating that the 85 pts with EIC had a clearly better DFS (difference 27.9%; $P < 0.01$). With respect to overall survival only pts treated with MM Patey showed a better overall survival for pts with EIC as compared to pts without EIC (difference 31.5%; $P < 0.01$).

In conclusion: the results of this retrospective study suggest that modified mastectomy might be a safer treatment modality in patients with EIC (this study is supported by the Dutch Cancer Society, project DDHK 92-04).

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CHANGES IN PROLIFERATION IN PRIMARY BREAST CANCERS DURING CHEMOENDOCRINE THERAPY

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The proliferation markers Ki67 and S-phase fraction (SPF) are important biological variables in determining the course of malignant disease. Changes in these variables may provide additional prognostic information.

We have studied changes in Ki67 (measured by immunocytochemistry using the Mib 1 antibody) and SPF (by flow cytometry) on samples obtained by FNA from patients with early breast cancer.

In a control group of 25 patients repeat FNAs were taken 2 weeks apart, with no intervening treatment, in order to determine the normal variation. For Ki67 the median % +ve for the first sample was 3.0% (range 0–23%) and the second was 4.0% (range 0–23%). For SPF the median for the first sample was 7.8% (range 1.5–21.8%) and for the second 10.3% (range 0.8–22.5%). This demonstrates (i) the good reproducibility of the technique and (ii) that FNA itself does not affect subsequent measurement of proliferation in the same tumour. In 24 patients repeat FNA was performed at 10 or 21 days after chemoendocrine therapy (CET) with Mitozantrone, Methotrexate and tamoxifen. Pre-CET the median Ki67 was 12.9% (range 1–37.7%) and post-CET 5.5% (range 0–14.7%), $P < 0.05$. Pre-CET the median SPF was 4.1% (range 0.9–27.7%) and the post-CET 3.2% (range 0.4–19.2%), P = NS.

These changes in Ki67 may be used as an intermediate marker of response to evaluate the effectiveness of different therapeutic agents in groups of patients. For individual patients change in relation to response to therapy needs to be evaluated with more patients. Additional quantitative measurement of apoptosis might enhance the biological and clinical significance of these measurements.

654 POSTER

HORMONAL-METABOLIC STATUS IN SMOKING AND NON-SMOKING BREAST CANCER (BC) PATIENTS WITH NORMAL (N) AND EXCESSIVE (E) BODY MASS: POSSIBLE PROGNOSTIC SIGNIFICANCE

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Survival is decreased in smokers and obese patients with BC. We compared indices of hormonal-metabolic status in 118 pts with BC, 35 of whom smoked and 43 have had Quetelet index $\gg$32. PreMP BC pts with E demonstrated greater than postMP pts increase in body fat content, LBM, waist/hip ratio, blood glucose and free cortisol excretion in relation to these values in pts with N. In postMP obese pts increase in reactive insulinemia and triglyceridemia was expressed more than in corresponding group of preMP pts. Smoking increased waist/hip ratio and decreased ER content in tumor tissue in greater degree in pre- and postMP pts with N than with E. The lowest level of FSH and LH and highest of estradiol in blood was discovered in smokers with E. Thus, different hormonal-metabolic mechanisms can mediate devastating effect of body mass excess and smoking on prognosis in pre- and postMP type of BC.

655 POSTER

COMPUTER ANALYSIS OF BREAST CANCER CELL POPULATIONS IN ER AND PR POSITIVE AND NEGATIVE TUMOURS

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The ER and PR status are known to be one of the most significant prognostic factors for selection of adjuvant hormone and/or chemotherapy. It is regarded as the indicator of the malignancy of the tumour cell population. Therefore the cell population characteristics in tumors with positive or negative ER and PR is of utmost importance, allowing morphological prediction of possible malignancy of the process and prognosis of the survival of the cancer patients.

We have investigated routine stained cytological imprint slides from 34 breast cancer specimens obtained during operation. In the slide we