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TUMOR PLOIDY AND CLINICAL OUT-COME IN PATIENTS WITH ER+ ADVANCED BREAST CANCER TREATED BY HORMONE THERAPY

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We studied the relationship between flow cytometry (FCM) tumor DNA content and clinical out-come in 43 patients (median age 64 yrs) with ER+ advanced breast cancer treated by homogeneous hormone therapy (TAM 20mg/die). ER and PgR tumor content was analyzed by DCC method on tumor biopsies performed just before starting therapy, whereas Hedley method (Histochem.Cytochem., 1983) with minor modifications has been utilized for FCM ploidy study on archival paraffin embedded material. Biopsies were performed on 27 primary tumors, 12 skin nodules and 4 lymphnodes. PgR+ resulted 28/43 (65%). Aneuploid tumors resulted 20/43 (47%) and 8 were tetraploid. In diploid and aneuploid cases we found similar percentages of PgR+ cases (65% vs 55%), similar ER+ mean content (170 vs 173 fmol/mg prot.cyt.) and in PgR+ mean content (79 vs 183 fmol/mg prot.cyt.). At 26 months median follow-up, percentage of clinical response, median time to progression and median overall survival observed in patients resulted: clinical responses, 74% vs 75%; median time to progression, 10 vs 12 months; median overall survival, not reached vs 26 months, respectively in diploid and aneuploid cases. In spite of preliminary reports, when homogeneous therapy and hormone receptor status patient series were considered, FCM DNA content analyzed on archival paraffin included material does not seem to provide additional information on clinical out-come of patients with ER+ advanced breast cancer treated by hormone therapy.

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BREAST CANCER (BC) CELL KINETICS (CK) COMPARISON OF THE GROWTH FRACTION (GF) BY Ki-67 ANTIBODY WITH THE FLOW CYTOMETRIC (FCM) S-PHASE FRACTIONS (S-PF).

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The development of new methods for a more accurate measurement of CK represents a major area of research in BC. Recently it was claimed that Ki-67 monoclonal antibody recognizes an antigen related to proliferating (prol.) cells in late G_1-S-G_2 and M phases of the cell cycle, but not present in quiescent (G_0) cells. To study the relationship between Ki-67 with the FCM-S-PF, as conventional marker of CK, we compared both the techniques in 98 BC. Eighty-one% of carcinomas were Ki-67+, with a mean value of 15%, of which 33% were classified as high prol. (>15%). With the FCM method the mean value of the S-PF was 14% and 44% of the carcinomas were classified as high prol. (>14%). Using the mean value of distribution as cut-off point no correlation was found between the two methods concerning the classification of tumors into high and low prol. Comparing both the methods with the main markers of tumor differentiation we found a significant correlation between low CK indexes with diploidy and grading I-II. A close inverse relationship was observed between high GF and S-PF values with estrogen-receptor+ while no correlation was observed with the progesterone-receptor. In conclusion, a discrepancy between Ki-67 values and FCM S-PF was observed. Since the major objective for assessing prol. status in BC is to determine the prognosis, it will have to be evaluated with an adequate follow-up, which of the two markers of CK will be of greater prognostic value in BC.

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CATHEPSIN D- AND CA 15-3-CONCENTRATION IN BREAST CANCER CYTOSOL

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In oncology the tumor cytosol is a very important source for investigation of biomarkers such as hormone receptors, tumor markers, proteolytic enzymes etc.. In the last months we began to analyze the concentration of cathepsin D (CATH D) and CA 15-3 by IRMA in addition to the established steroid receptors.
Both kits are provided by CIS and are based on ELSA technique. The kit for measuring CATH D concentration was recently introduced by CIS. The basic research was done by H. ROCHEFORT and colleagues. By this kit the total amount of different forms of CATH D can be quantified. CA 15-3 is well known since some years as breast cancer associated antigen which is mainly assayed in the serum of those patients.
Results: In the cytosols of 38 breast cancer primaries we found different amounts of both biomarkers.The range of CA 15-3 was obviously wider: 0.2 - 370.8 U/mg prot. than the range of CATH D: 1.3 - 117.6 fmol/mg prot.. The mean values of the total group were 27.4 fmol/mg prot. for CATH D and 57.1 U/mg prot. for CA 15-3.After grouping the data by lymph node status - N0, N1,N2 - we found significant differences for CATH D but not for CA 15-3. The corresponding CATH D values were 15, 31 and 41 fmol/mg prot. The CA 15-3 values showed only a trend to higher levels in the N0 group. No significant relation was noticeable to the tumor diameter or receptor status.
Conclusio: The CATH D concentration in the cytosol of breast cancers could be an important indicator of prognosis. Probably this parameter is rather a tumorborn product than a result of host reaction.If this result can be confirmed in larger series, this cytosolic parameter could act as a helpful tool for the decision which node negative patient should receive adjuvant chemotherapy in the treatment of breast cancer.

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PROGNOSTIC VALUE OF TOTAL CATEPSIN D IN BREAST CANCER

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The 52K procathepsin D was first discovered by H.Rochefort. A related protein (34K) was reported by W.McGuire as prognostic factor in node negative breast cancer (BC). We assayed total 52K-cath D and its precursors (34K+48K) (TCD) with the Elisa kit commercialized by CIS International in 278 BC cytosol stored in liquid nitrogen. These samples had been obtained from patients who underwent surgery in our institution between Sept 78 and Sept 83 with a median follow-up of 72.5 mo. 65 related disease deaths and 80 distant metastases occured during the follow-up period. The study population was as follows: T1:65, T2:175, T3-4:38;N-:159, N+:119; Scarff & Bloom histologic grade SBI:84, SBII:113, SBIII:38 (43 pts could not be graded); ER+:206, ER-:72, PR+:202, PR-:76. TCD was found in all tumor specimens but one at levels ranging from 5 to 235 pmol/mg prot. (median 34.2). The optimal cut-off value for predicting overall survival was 35 pmol/mg prot. ($p<0.02$ log Rank test). The distribution of TCD level among the other prognostic parameters such as tumor size, nodal involvement, histologic grade, ER and PR status did not reveal any significant link. Cox multivariate analysis of the survival of the entire population population for the four prognostic factors N, ER, PR and TCD placed TCD ($p=0.006$) immediately after PR ($p=0.00001$) arriving first. TCD level had no influence on the survival of N- pts but splitted the N+ population in TCD low N+ pts warrying a better prognosis than TCD high N+ ($p<0.0004$ log rank test).Furthermore the overall survival of TCD low N+ pts was similar to that of N- pts. Cox multivariate analysis of the metastasis free survival of the entire population for the same prognostic factors placed TCD ($p=0.02$) immediately after nodal involvement. Here also TCD level had no influence on N- and strong influence on N+ BC.
In conclusion TCD is a very powerful new independent prognostic factor in breast cancer, especially in node positive patients.