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Familiar history in breast conservative treatment of breast cancer a good prognostic factor?

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In the Twente-Achterhoek region we do breast conservative treatment since 1984 for patients with T1 and T2 ≤ 3 cm breast carcinoma. Since 1990 we register and follow-up consequently our known and new breast cancer patients with a breast conservative treatment. Until now we have treated more than 1350 patients with breast conservative treatment, all according to the same protocol.

The family history of breast cancer is registered as none, 1 first degree relative (F.D.R) or ≥ 2 F.D.R. This is an analysis of 1071 patients treated up to and including 1995. The follow-up ranged from 3–159 months with a mean of 60 and a median of 55 months.

The age ranged from 27–89 years with a median age of 56 years. According to the TNM classification we had 644 T1N0, 205 T1N1, 103 T2N0 and 97 T2N1 patients.

The familiar history of breast cancer showed 15% (161 pat.) with one F.D.R and 2.7% (29 pat.) with ≥ 2 F.D.R.

We looked at the influence of the family history on the pathological T and N stage, the incidence of local recurrence, metastasis and on the survival.

There was no difference in pT between the patients with none, one or ≥ 2 F.D.R. There was less pN1 in 1 or more F.D.R., 30 vs. 24.5 vs. 21%.

Local recurrence was comparable for none and 1 F.D.R. 3.9 and 4.4%, but no local recurrence for ≥ 2 F.D.R. Also for distant metastasis there was a striking difference 14 and 12.5% vs. 3.5%.

Looking at the corrected, for intercurrent dead, survival 9% of the patients with none or 1 F.D.R. died of tumour. No patients with > 2 F.D.R. died of tumour (p = 0.002).

Considering the patients with ≥ 2 F.D.R. as the most important group with an almost certain hereditary breast cancer, we were surprised to see no local recurrences and only one patients with metastasis. The corrected survival for those patients was 100%. Taking together all patients with F.D.R., we still see a significant better survival for this group (p = 0.004).

Conclusion: Patients with F.D.R. seem to have a better prognosis.

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Differential impact of high steroid hormone receptor concentrations on overall survival (OS) in primary breast cancer subgroups

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Purpose: Occasional reports have suggested an unfavorable effect of high estrogen receptor (ER) concentrations in primary breast cancer. In a population-based study we identified a subgroup explicitly exhibiting this seemingly paradoxical effect. We excluded a similar phenomenon for the progesterone receptor (PgR).

Methods: ER and PgR were prospectively measured in a single laboratory by multiple point DCC assay. The relative risk of death in relation to the concentration of the interval-scaled variables ER and PgR was continually estimated by serial Cox-Regression analyses. Thus, we circumvented loss of information due to primary categorization and avoided assumptions about relations between factor and risk.

Results: Based on 2035 consecutively accrued primary breast cancer cases (median follow-up 56 months) we identified node-negative patients up to 60 years of age as the relevant subpopulation. High (≥300 fmol/mg protein) ER concentrations exhibited an even more unfavorable impact (p < 0.02) on OS than ER concentrations below 10 fmol/mg protein. The well-known association of age and ER concentration was definitely excluded as underlying biological cause for the increased risk. Differences in the distribution of other prognostic factors (HER-2/neu, Ki-67, DNA ploidy) were also excluded. As we observed a preponderance of pT2 tumors in the high ER group, we repeated the analysis, selectively focusing on pT2 tumors in the relevant subgroup, but the effect remained unchanged. In contrast, node-positive patients adjusted for age significantly (p = 0.02) profited from high ER concentrations as compared to the ER negative group. We excluded a comparable phenomenon for age-matched node-negative patients regarding PgR.

Conclusions: As the phenomenon did not occur in node-positive patients receptor defects in the high ER group seem unlikely. Contrarily, we suspect that ER overexpressing tumor cells are hypersensitive to even low levels of estrogens. Once they have sneaked past local barriers prior to primary surgery they may cause early death in the absence of appropriate adjuvant endocrine therapy.

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Analysis of variables associated with recurrence/metastasis in breast cancer tumor of ≤1 cm

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Purpose: To individualize variables predicting recurrence/metastasis in small breast cancer tumor.

Methods: A group of 344 patients with breast invasive tumor of ≤1 cm amongst a cohort of 3198 patients (T0 T1 T2 > 3 cm) seen consecutively between 1975 et 1996, operable and treated with primary surgery and axillary nodal dissection.

Results: The univariate analysis showed that vascular invasion (p = 0.009) and ER (p = 0.02) were significant factors for recurrence, whereas axillary nodal invasion (p = 0.08) and modified SBR (p = 0.07) were of marginal significance.

Multivariate analyses selected only modified SBR as the independant factor for overall survival (OS); modified SBR and negative ER for metastasis free survival (MFS); and vascular invasion and negative ER for disease free survival (DFS).

With a median follow-up of 77 months, ten year DFS is 85.4% for the whole cohort of 344 patients. One hundred and sixty three patients, who were all node negative, with mSBR 1, no vascular invasion and postive ER had a 10 year DFS of 97.5%

Conclusion: In small (≤1 cm) primary tumors, histobiological factors appear to be more potent prognostic indicators than axillary nodal involvement. The prognosis for tumors measuring ≤1 cm is excellent and women in this category (about half the group) should not be considered as candidates for systemic adjuvant therapy.

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Does prior pregnancy influence breast cancer outcome in young women?

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Purpose: To determine the impact of prior pregnancy on breast cancer outcome in young women.

Methods: Tumor and patients characteristics and outcome were compared according to prior pregnancy in 577 young women (less than or equal to 35 years) with breast cancer treated between 1963 and 1990. 163 patients (28%) had no prior pregnancy, 21 patients (4%) had concurrent pregnancy. Last delivery had occurred between 0 and 12 months before diagnosis of breast cancer in 75 patients (13%), between 13 and 24 months in 43 patients (7%) or from more than 24 months in 275 patients (48%).

Results: Median follow-up was 12 years. Tumor stage (T, N, pN) was significantly higher in patients with concurrent pregnancy or interval from delivery ≤ 2 years. Survival was shorter in these two groups than in other patients. When adjusted to tumor stage as well as to age or clinical and biological factors, relative risks of metastasis and death were 1.5 times higher when last delivery occurred ≤ 2 years before breast cancer (p = 0.01). These findings persisted after adjusting for systemic treatment.

Conclusion: This study, limited to patients less than or equal to 35 years, shows that pregnancy influences clinical characteristics of breast cancer up to 2 years following delivery. These patients did worse than patients with interval less than or equal to 2 years from last delivery or than patients who had no prior pregnancy. The interval between last delivery and diagnosis of breast cancer should therefore be taken into account when defining treatment strategies in young women with breast cancer.

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Expression of the apoptosis-related genes *c-myc, p53* and *bcl2* in breast carcinomas from operable patients. Only *bcl2* expression is associated with a lower risk of death

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Purpose: To investigate the prognostic value of the expression of apopto-

sis-related genes *c-myc*, *p53* and *bcl2* in breast cancers (BC) in association with the main prognotic markers after a long-term follow-up.

Methods: Total RNAs and paraffin-embedded tissue sections were obtained from 175 primary tumors and analysed for *c-myc* transcripts by Northern blot and *p53* and *bcl-2* proteins by immunohistochemistry. All patients were treated by surgery and by adjuvant therapy according to their clinicobiological characteristics. The risk of death associated with the expression of these genes was evaluated by multivariate analysis taking into account the main prognostic factors, namely, tumor size, histoprognostic grade (HG), hormonal receptors (HR) and nodes, after a mean follow-up of 9.5 ± 2 yrs.

Results: *c-myc* overexpression was observed in 35% of BC and *p53* and *bcl2* overexpression was found in 23 and 63% of BC, respectively. A strong association between *c-myc* overexpression and positive nodes ($p = 0.0005$), *p53* expression and both high HG ($p = 0.0001$) and HR-negative tumors ($p = 0.0003$) was shown. In contrast, *bcl-2* expression was found to be associated with favorable prognostic factors including HR-positive tumors ($p = 0.0001$). Multivariate analysis showed that only positive nodes ($p = 0.0001$) and *bcl-2* expression ($p = 0.008$) were independent factors correlated to a higher or lower risk of death, respectively.

Conclusion: Both *c-myc* and *p53* genes favor the development of more aggressive BC. In contrast, the anti-apoptotic function of *bcl2* seems to be most hypothetical in BC. Expression of *bcl2* identifies a particular phenotype of BC with a favorable long-term prognosis and thus may be a useful marker.

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Prognostic significance of p53 mutations in the zinc-binding domains (L2/L3) in lymph node-positive breast cancer patients

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Purpose: Mutations of the p53 tumor suppressor gene have been shown to be of prognostic significance in the node-negative breast cancer population. We investigated the prognostic value of p53 mutations in the functionally important L2/L3 zinc-binding domains in lmph node-positive breast cancer patients.

Methods: For detection of p53 mutations we used in vitro amplification by polymerase chain reaction and consecutively performed temperature gradient gel electrophoresis (PCR-TGGE). We evaluated if mutations in the L2/L3 domains provide prognostic information for node-positive breast cancer patients.

Results: Out of 213 tumor samples we found p53 mutations in 48 cases (23%). About a third of the p53 mutations ($n = 17$) were located in the L2/L3 domains. Univariate analysis revealed that patients with p53 mutated tumors had a statistically significant shorter relapse free survival (RFS) ($p = 0.034$). However, in multivariate analysis no significant correlation between p53 mutated tumors and reduced RFS could be detected. We could not detect any significant difference regarding RFS and overall survival (OS) for patients with p53 mutations in the L2/L3 domains.

Conclusion: p53 mutations in the L2/L3 domains in node-positive breast cancer patients do not provide information regarding the clinical outcome of these patients.

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mRNA determination of estrigen receptor, progestin receptor, pS2. PAI-1 by competitive reverse transcription-PCR in human breast cancer

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Purpose: Estrogen receptor (ER) and progestin receptor (PR) are important regulators of growth and differentiation of the mammary gland as well as in the development of malignant tumors. pS2 is an estrogen inducible protein, which is supposed to be involved in tissue differentiation. Urokinase inhibitor-1 (PAI-1) inhibits the activity of urokinase-type plasminogen activator (uPA) which contributes to the degradation of the extracellular matrix in tumor invasion and metastasis. ER, PR, pS2 and PAI-1 have been reported to be prognostoic parameters in primary breast cancer. We developed a competitive RT-PCR system to allow simultaneous quantitative determinations of ER, PR, pS2 and PAI-1 mRNA in tissue samples. We evaluated 100 breast cancer specimen for mRNA expression. Results were compared with protein status and with clinical data.

Results: We found a statistically significant correlation between mRNA and protein levels of ER ($p < 0.00001$), PR ($p < 0.00001$), pS2 ($p < 0.00001$) and PAI-1 ($p < 0.0147$), respectively. ER, PR, pS2, and PAI-1 showed a statistically significant correlation to each other except to the mRNA expression of PAI-1. Furthermore the mRNA data of ER and PR showed an inverse correlation to tumor size and histological grade.

Conclusion: Our data are in agreement with reports about ER, PR concerning tumor size and grade. We did not find any correlation to lymph node involvement. We did not find any association of pS2 mRNA to the clinical data. PAI-1 was found to be independent of tumor size, grade or lymph node involvement. The present study shows, cRT-PCR is an appropriate method for the simultaneous determination of prognostic factors in breast cancer specimen, requiring small amounts of total RNA.

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Medullary breast carcinoma. Ten-year results in 108 patients treated in a single center

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Purpose: To analyse clinical presentation and outcome of patients with medullary breast carcinoma treated at the Institut Curie between 1981 and 1996.

Methods: 108 cases of medullary carcinoma (0.7%) were retrospectively identified in the breast cancer database. All charts were reviewed. All 108 patients were female. Median age was 50 years (24–82 yrs.). 64 pts. (59%) were premenopausal. Median clinical tumor size was 3 cm (0–15). There were 35 T1 (32%), 51 T2 (47%), and 22 T3T4 (20%); 57 were NO (53%), 47 N1 (43%) and 4 N2 (4%). Treatments varied according to tumor sizes. 62 pts. (58%) had a wide tumor excision and radiotherapy (mean tumor size: 2.4 cm), 24 pts. (22%) received irradiation alone (mean size: 6.4 cm) and 22 pts. (20%) had a mastectomy (mean size: 3.8 cm). Overall, 86/108 pts. (80%) had a breast-conserving treatment. 32 pts. (30%) received chemotherapy, either before (13 pts.) or after local treatment (19 pts. Treatment outcome was determined using Kaplan-Meier estimates.

Results: Median followup was 116 months (8–205). Ten-year survival and metastasis-free interval rates were 81% and 79%, respectively. 13 breast recurrences occurred and 8 contralateral breast cancer. 10-year breast recurrence rate was 17%. The 10-year overall breast conservation rate was 66%. It was 83% in patients who had an initial breast-conserving procedure. Survival and metastasis-free interval were similar in patients treated with mastectomy, or breast conservation.

Conclusion: This retrospective study of 108 patients with 10 year follow-up confirms that medullary breast cancer seems to carry a better prognosis than invasive ductal carcinoma. Medullary breast cancer seems very sensitive to chemotherapy and radiotherapy, which allow breast preservation in patients with large tumors. Biological characterization of this particular form of breast cancer is ongoing.

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Anti-apoptotic phenotype is associated with decreased loco-regional recurrence rate in breast cancer

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Purpose: Tumour and nodal status are the most important factors predicting loco-regional recurrence in breast cancer. We wanted to investigate the predictive value of some new molecular genetic markers, for the occurrence of a loco-regional recurrence in order to improve the selection of patients for loco-regional adjuvant therapy.

Methods: Bcl-2, p53, MIB-1, pS2, PCNA and CD44v6 were determined immunohistochemically on formalin-fixed and paraffin embedded tumour tissues of 163 patients treated by modified radical mastectomy between 1982 and 1987. Postoperative irradiation was given to only few patients. Node-positive patients had been given CAF adjuvant chemotherapy. A multivariate analysis was performed on a number of potential prognostic factors. The risk for loco-regional recurrence was estimated using the competing risk approach.

Results: After a median period of 7.5 years 28 patients developed a loco-regional recurrence. The cumulative incidence of loco-regional recurrence at 10 years was 17%. Bcl-2 and p53 were found to be independent