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# **PROGNOSTIC VALUE OF CYTOSOLIC THYMIDINE KINASE ACTIVITY AS A MARKER OF PROLIFERATION IN BREAST CANCER**

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Thymidinekinase (TK) is involved in DNA synthesis by the salvage pathway. In this study, thymidine kinase activity (TK) was determined in 290 breast cancer cytosols using a radioenzymatic method. High levels of TK ( $\geq 126$  mU/mg protein) were positively associated with the histological grade in both pre/perimenopausal and postmenopausal patients. In univariate analysis, high levels of TK were strongly associated with shorter overall survival in both pre/perimenopausal ( $P = 0.001$ ) and postmenopausal patients ( $P = 0.02$ ). Pre/perimenopausal patients whose tumours had high levels of TK also had an increased risk of relapse ( $P = 0.001$ ). In multivariate analysis TK status was found to be an independent prognostic factor for recurrence-free survival in pre/perimenopausal patients with a weight similar to that of PgR status. In postmenopausal patients, TK was the only factor selected for overall survival.

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# **THE CLINICAL IMPORTANCE OF KERATIN 18 IN BREAST CANCER**

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This study was performed to determine the prognostic significance and the biological function of the differentiation associated structure protein keratin 18 (K18) in patients with breast carcinoma.

**Materials and Methods:** Paraffin sections from 134 patients with breast carcinoma were examined for the expression of K18 immunohistochemically. The intensity of the expression was compared with clinical follow-up data over 8 years. In addition K18 expression in different human cell lines of breast carcinomas with well defined metastatic behavior were investigated.

**Results:** A marked positive staining was observed in 22 (16.4%) women. Mortality rate in the positive group was 4.5% in comparison to 44.6% in the negative group ( $P < 0.0009$ ). Irrespective of the morphological tumor stage, almost all patients with strong K18 expression were still metastasis-free after 8 years. These findings were supported by corresponding observations in cell cultures.

**Conclusion:** K18 expression was found to be an independent and significant predictor for disease-free survival whereas the down-regulation of this protein seems to favor early metastatic spread.

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# **GAMMA PROBE-GUIDED SENTINEL NODE BIOPSY—OPTIMAL TIMING FOR INJECTION**

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The principle of the sentinel lymph node (SLN) implies that the LN nearest to the primary tumor site on the direct drainage pathway is the most likely site of early metastases. A novel method for SLN identification is by injection of a labeled colloid. We examined the optimal pre-operative timing for this injection. Seven pts with primary tumor were injected with 60 MBq (TcK-17A) <sup>99m</sup>Tc Rhenium Colloid. Scintigraphy was done 30 min and 2, 6 and 24 h postinjection. After the final scan, the pt went to surgery where the SLN was localized with a gamma detecting probe (Neoprobe 1000) at a ratio of 15:1 (LN/bd of resection). SLN excision was followed by regional LN dissection. Scintigraphy visualized the SLN in all 7 pts by the 2-hr scan and remained identifiable at the 24-hr scan. Pathology showed one positive LN and was the only involved LN in this patient. In all other 6 pts, neither the SLNs nor the regional LNs were involved. Thus, 24-hrs before surgery was found to

be the optimal time for injection, and is being used in further study of the SLN concept.

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# **VALUE OF NEW PROGNOSTIC FACTORS IN LYMPH NODE—NEGATIVE BREAST CANCER**

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In 216 breast cancer patients the prognostic value of current biological factors (c-erbB-2, EGF-receptor, p53, PCNA-proliferative fraction) was compared with that of conventional histomorphologic features (histologic type, histologic grade, tumor size, hormonal receptor status). After a 66 (6–109) months median follow-up survival was significantly correlated with histological grade ( $P = 0.014$ ) and PCNA-proliferative activity ( $P = 0.015$ ). The prognostic influence of estrogen receptor (ER)- and progesterone receptor (PR)-status achieved borderline significance (ER/ $P = 0.07$ , PR/ $P = 0.05$ ). Neither c-erbB-2, EGF-R, p53 nor any of the other factors showed any correlation to survival. In the multivariate analysis histological grade was revealed as the only independent prognostic factor. The prognostic value of PCNA was second to histological grade and if grade was excluded from the analysis, PCNA-expression became the only independent factor. Thus, in individual cases the PCNA-proliferative fraction could help the clinician decide on therapy.

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# **CA 15-3 PREDICTS OUTCOME IN BREAST CANCER PATIENTS**

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Serial values of circulating CA 15-3 were recorded from 563 patients with breast cancer over a 10-year period. A fall in CA 15-3 of at least 20% between preoperative and postoperative measurements was observed in 60% of patients ( $P < 0.05$ ). Patient outcome deteriorates as CA 15-3 increases between 10 u/ml and 45 u/ml. At a cut-off of 25 u/ml postoperative CA 15-3 discriminates between patient groups with 44% and 70% five-year disease-free survival ( $P < 0.001$ ). Postoperative CA 15-3 values predict outcome better than preoperative values. CA 15-3 values also predict outcome in patient subgroups identified by nodal status, tumour size and oestrogen-receptor status. We conclude that circulating CA 15-3 values reflect total tumour burden in breast cancer patients; after resection of a primary tumour CA 15-3 values reflect the extent of occult metastases.

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# **PROGNOSTIC VALUE OF CA 15-3 IN ADVANCED BREAST CANCER (BC) PATIENTS: RELATIONSHIP WITH THE DISEASE EXTENT (DE)**

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The prognostic value of CA 15-3 in BC patients at first relapse of disease may be ascribed to the correlation of marker levels with DE or with the tumor differentiation and aggressiveness (*Eur J Cancer*, 1994). From Oct. 1988 to Sept. 1994 we recorded data from 293 BC patients. CA 15-3 serum levels and DE were separately evaluated before treatment onset. The DE of visceral metastases (mts) was assessed considering the percentage of organ involvement (no mts,  $< 25\%$ ,  $25\%$ – $50\%$  or  $> 50\%$ ). Bone tumor load was defined as the number of skeletal segments positive at scintigraphy. Pleural effusion and lymphangitis were separately considered. Serum CA 15-3 was higher in patients with visceral involvement and with pleural effusion than in those with bone or soft tissue mts. CA 15-3 significantly correlated with liver, pulmonary and bone DE but not with soft tissue DE. Only liver and bone DE demonstrated to be independent variables at multiple regression analysis. Elevated CA 15-3 levels predicted poor survival either in overall patients or in those with visceral involvement. Performance status, menopause, DE in liver and in bone were found to be independence prognostic factors when Cox regression analysis was performed, while CA 15-3 failed to enter the model. To conclude, all these data suggest that the prognostic role of CA 15-3 is linked to the extent of disease.