emboli. There was a non significant trend between positive staining and overall survival either in each arm of the trial and in all population. Interestingly, we observed a higher relative risk of local relapse after conservative therapy in the boosted area in the group of mutated p53 (RR = 1.85).

Conclusions: We conclude that, in this node-negative breast tumor population, the alterations of the p53 cannot predict the response to the chemotherapy. However, it may represent a useful marker of risk of local relapse and of radioresistance.

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Clinical significance of urokinase plasminogen activator and its receptor in breast cancer

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Background: Urokinase plasminogen activator (uPA) is a multifunctional protein involved in tissue proteolysis, cellular migration, cellular proliferation and growth factor activation. Most of these actions are mediated while the protease is bound to a membrane receptor, termed uPAR.

Aim: The aim of this project was to study uPA and uPAR in breast cancer and to relate levels of both to patient outcome.

Methods: uPA and uPAR were measured by ELISAs (American Diagnostica).

Results: Initially, different detergents were evaluated for their ability to extract uPA and uPAR. The most effective detergent for the extraction of uPA was n-dodecylmaltoside (nDM) followed by Nonidet P40, CHAPS and Triton X-100. Neither Tween 20 nor digitonin increased the yield of uPA. nDM and CHAPS were the most effective in extracting uPAR followed by Triton and Tween. As for uPA, digitonin had no effect on the release of uPAR. Median levels of uPAR were 2.2-fold higher in primary carcinomas than in benign samples ($p = 0.043$).

However, levels in primary and metastatic cancers were not significantly different. Median levels of uPA were also significantly higher (7.6-fold) in the primary cancers than in the benign samples ($p = 0.0001$) but as with uPAR, levels of uPA were not significantly different in primary and metastatic samples. Using optimum cut-off points, both uPA and uPAR were significant prognostic markers in breast cancer, including in patients with node-negative disease. However, uPA was a stronger indicator of both disease-free interval ($p = <0.005$) and overall survival ($p = <0.005$) than uPAR (disease-free interval $p = <0.05$; overall survival ($p = <0.025$). Our results are consistent with data from model systems suggesting that both uPA and its receptor are involved in cancer spread. We conclude that both uPA and uPAR are of prognostic value in breast cancer.

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Ductal carcinoma in situ of the breast, an evaluation of a new histopathological classification system

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Purpose: New histopathological classification systems for ductal carcinoma in situ of the breast (DCIS) have recently been suggested. We aimed to evaluate the reproducibility for the system proposed by Holland and co-workers and the correlation to the prognosis. The system is based upon cytonuclear differentiation and cellular polarisation. It divides DCIS into three categories, highly differentiated, intermediately- and low differentiated lesions (R1, R2 and R3 respectively).

Methods: The histopathological specimen from 195 consecutive women diagnosed with a primary DCIS 1986–1994 have been reclassified by two separate observers. The relapse-free survival in relation to the histopathological subgroup was calculated for patients treated with breast conserving surgery (BCS). The material was stratified for postoperative radiotherapy.

Findings: The distribution by histopathological subgroup was 7% (R1), 51% (R2) and 42% (R3) respectively. There was an interobserver agreement in 66% of the first 100 reviewed cases and in 93% for the thereafter reviewed 95 cases. There were 32 local recurrences among 149 patients treated with BCS, with a median follow-up time of 59 months. There were no distant recurrences or deaths in breast cancer. No recurrences occurred in the R1 group. The relapse-free survival did not differ appreciably between R2 and R3. This was true also after stratification for radiotherapy.

Conclusion: Holland's classification had a high reproducibility after a short learning period. One group with an excellent prognosis was easily discerned. Further classification into R2 and R3 groups did not help predict local recurrences.

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Immunoreactive detection of parathormone related protein (PTHrP) in primary breast cancers is a good prognostic factor for subsequent bone metastases

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Purpose: Bone metastases in breast cancer patients are frequent. In a prospective study we evaluated, whether tumor associated production of parathormone related protein (PTHrP) is a valuable prognostic factor for subsequent bone metastases.

Methods: Tumors of 216 patients were stained immunocytochemically with MoAb's against PTHrP. Median time of postoperative care was 5 years (6–134 months) including the most critical interval for metastasis.

Results: PTHrP was positive in 124 (56%) patients. After 5 years distant metastases were found in 63 (28%) women. This subcollective contained 42 (19%) cases of isolated bone metastases. 29 (69%) were positive and 13 (31%) were negative for detection of PTHrP. The calculated risk for metastatic bone disease was twice as high for the former patient group. Significant correlation was found between PTHrP and positive tumor cell detection in bone marrow ($P = 0.031$, Fisher's t-test), and between PTHrP and the chronological sequence of skeletal events ($P = 0.026$, Kaplan-Meier-analysis), too.

Conclusion: We could show that PTHrP is a specific prognostic factor, not for screening metastases in general, but to identify high-risk-patients for subsequent osseous metastases. PTHrP increases bone turnover and thereby chemotaxis on tumor cells. However, prophylactic treatment with bisphosphonates could be useful for these patients to reduce their risk of bone metastases.

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A multivariate analysis of tumour biologic factors predicting response to cytotoxic treatment in advanced breast cancer

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Purpose: To identify factors which could predict response to chemotherapy in breast cancer.

Methods: 173 patients with measurable or evaluable metastatic breast cancer were enrolled in a randomized trial between 11/87 and 1/91. The two groups of patients received the same monthly dose of 5-fluorouracil (500 mg/m^2), epirubicin (60 mg/m^2) and cyclophosphamide (500 mg/m^2) either on a weekly or monthly basis as first line cytotoxic treatment. In 103 evaluable patients we performed a multivariate analysis of the tumour biologic factors (grade, ER, PgR, SPF, ploidy, p 53, c-erbB-2, Bcl-2 and Bax) which showed significance in the univariate analysis according to treatment response, time to progression (TTP) or overall survival (OS).

Results: In the univariate analysis only S-phase fraction (SPF), grade and proapoptotic protein Bax showed statistically significant effect on response to cytotoxic treatment. In the multivariate analysis of these factors S-phase fraction had the strongest effect on response; thereafter grade and Bax.

In the univariate analysis grade, PgR, Bax and Bcl-2 had significant effect on TTP, while in the multivariate analysis only Pgr receptor showed statistically significant effect.

In the univariate analysis Pgr and Bax had effect on OS and both remained significant also in the multivariate analysis.

Conclusion: The factors which had significant effect on response to cytotoxic treatment in the univariate analysis i.e. grade, SPF and Bax seemed to be able to predict independently the response to treatment also in the multivariate analysis. Thus they might be of value for the clinician in the decision making of treatment for metastatic breast cancer. TTP could be predicted partly by the same factors i.e. grade, Pgr, Bax, Bcl-2 and OS by Pgr, Bax although the association was quite weak.