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HYALURONIDATE RECEPTOR CD44 AND ISOFORMS IN HUMAN BREAST CANCER

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In human breast carcinomas, hyaluronidate receptor CD44 (CD44s) and isoforms generated by alternative splicing of primary RNA (CD44v), especially, those containing exon 6v (CD44-6v) have been discussed to be involved in processes of tumor progression and metastasis. On microwave pretreated paraffin embedded material, 220 cases of invasive carcinomas including 80 lymph node metastasis were analyzed immunohistologically for the expression of CD44s, CD44-9v, -6v, -5v and -3v. Data were compared to classical prognostic factors, to tumor growth patterns, to hormone receptor status as well as to Kaplan-Meier-Survival functions [mean observation: 104 mo.]. Obviously, the occurrence of CD44 isoforms correlates among each other ($P < 0.001$). Weaker correlations were found e.g. for CD44-6v with patients' age, with tubular tumor differentiation, with negative nodal status and with estrogen receptor content. No correlations, however, could be obtained with poor prognostic indicators or with poor clinical outcome. In contrast to previous reports, neither CD44s nor CD44v revealed an adverse prognostic impact or seem to be useful as a "new prognostic factor" indicating a poor outcome in invasive breast cancer. More likely, as normal epithelium is seen to express these adhesion molecules, the function of CD44s/v may be important for cellular differentiation within the human breast.

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DELAY IN DIAGNOSIS AND TREATMENT OF BREAST CANCER IN NORTHERN NORWAY. WHAT IS THE IMPACT?

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Between 1986–94, 173 women with breast cancer were admitted to the Department of Oncology, University Hospital of Tromsø for postoperative radiotherapy. In July 1994 their journals were retrospectively analysed to document delay in diagnosis and treatment.

The median delay from symptom to histological/cytological diagnosis was 2.4 months (0–98.6 months) in 154 evaluable patients. The delay pattern was different in the three counties of northern Norway. A statistically significant delay in Finnmark county compared to Troms was documented ($P = 0.041$). The median delay in Finnmark was 3.1 months (0.3–98.6 months), Troms 2.1 months (0–21.3 months) and Nordland 2.7 months (0–67.9 months). There were no differences in age or stage of disease between the three counties. The median delay from histological/cytological proven cancer to surgical treatment was performed was 7 days (0–523 days). The median delay from surgery to postoperative radiotherapy was 47 days (24–102 days).

Data from the Norwegian Cancer Registry 1983–92 revealed an improved survival of breast cancer in Troms compared to Finnmark and Nordland. The 5-year relative survival was 75% in Norway, 80% in Troms, 73% in Nordland and 66% in Finnmark. We will try to establish whether there is a connection between delay and survival.

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PROGNOSTIC VALUE OF STEROID RECEPTORS AFTER LONG TERM FOLLOW UP OF 2257 OPERABLE BREAST CANCER PATIENTS

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The prognostic value of estradiol receptor (ER) and progesterone receptor (PR) was estimated by a multicentric study of 2257 operable breast cancer patients without any adjuvant treatment, followed up for a median of 8.5 years. The series included 33.3% stage I, 57.1% stage II, 5.7% stage IIIa and 2.4% stage IIIb. At the endpoint of the study were observed 589/2257 (26.1%) metastases and 673/2257 (29.8%) deaths. Receptors were measured by radioligand assay. Of the tumours, 68.8% were ER+ and 54.0% PR+ ($\geq$ 10 fmol/mg cytosol protein).

In univariate analysis, ER and PR status were of prognostic value ($P < 0.001$) for the disease-free interval (DFI), the metastases-free interval (MFI) and the overall survival (OS). The OS after a first metastase was also significantly different between ER+ and ER− tumours ($P < 0.001$).

In multivariate analysis (Cox's proportional hazard model), only the ER status showed a significant difference ($P < 0.01$) between + and − groups for DFI, MFI and OS. By using Cox's non-proportional, time-dependant models, we show that the predictive value of ER status is decreasing by approximately 20% per year, loosing its significance after 8 years of follow-up.

Overall, when compared to the TNM and histological grading, ER and PR status have a small prognostic value, their major interest remaining in the domain of therapeutic decisions.

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NON-PALPABLE BREAST LESIONS: ANALYSIS OF 1264 CASES

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From March 1985 to March 1993, 1264 non palpable breast lesions were operated at National Cancer Institute of Milan. At histological examination 650 (51.4%) cases resulted cancers, 614 (48.6%) benign lesions. The mammographic findings of 650 tumors consisted of 317 (48.8%) clustered microcalcifications, 175 nodular opacities (+95 with microcalcifications) and 63 distortions. 323 out of 650 patients with malignant lesions were ductal infiltrating carcinoma ± DCIS, 74 lobular infiltrating carcinoma ± LCIS. Non infiltrating carcinomas were found in 192 cases (29.5%). Node-positive cases were 81/350 (23.1%). Mammography proved reliable in detecting small cancers: in our series we observed 192 non-invasive carcinomas and 448 tumors 10 mm or smaller at pathologic examination.

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FIRST RESULTS WITH THE ESTROGEN RECEPTOR RADIOLIGAND Z-[I-123]MIVE IN METASTATIC BREAST CANCER PATIENTS

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Z-11β-methoxy-17α-[I-123] iodovinylestradiol-17β (Z-[I-123]MIVE) showed excellent binding properties both *in vitro* and in the rat *in vivo*. In healthy human volunteers Z-[I-123]MIVE showed low lung retention, rapid hepato-biliary excretion, and diffuse uptake in normal breast tissue. This study presents the first results on metastatic breast cancer imaging with Z-[I-123]MIVE in three patients.

Anterior and posterior whole body scans were made at 1, 2, 4, 6 and 24 h after i.v. injection of 150 MBq Z-[I-123]MIVE (specific activity 200 MBq/nmol). Regions of interest were drawn to calculate the geometric mean counts/pixel in the different lesions. The results were expressed as lesion-to-background uptake ratios.

Pathologic accumulation of Z-[I-123]MIVE was detected in radiologically and/or scintigraphically confirmed metastases in the lungs, liver, bone and lymph nodes. The lesion-to-background ratios increased over time, being at 24 h p.i. in the lungs 3.6, abdominal region 4.3, mediastinal lymph nodes 3.8, other lymph nodes 4.0, liver 4.7, sternum 3.3 and os ilium 6.1. In contrast, the normal breast-to-background ratio was 2.3 at 6 h p.i., and decreased to 1.7 at 24 h after injection.

In conclusion, Z-[I-123]MIVE accumulates specifically in breast cancer metastases of bone, liver, lung and lymph nodes. Therefore, Z-[I-123]MIVE promises to be a radioligand for the detection and analysis of both primary and metastatic estrogen receptor positive breast cancer.