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Predictive value of vascular endothelial growth factor (VEGF) for overall survival in estrogen receptor positive breast carcinoma

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Purpose: VEGF has been reported as a independent predictor of overall survival (OS) in primary breast cancer. This study was conducted in order to evaluate correlation to other prognostic factors and how that might influence the predictive value of VEGF.

Methods: VEGF was measured with a quantitative enzyme immunoassay on cytosols of primary tumors from 878 consecutive primary breast cancer patients without distant metastasis.

Results: An inverse correlation was found between VEGF content and ER content ($p < 0.001$). Relationships were also found between VEGF and grade ($p = 0.008$) and tumor size ($p = 0.014$). No correlation was found between VEGF and number of axillary metastasis ($p = 0.756$), nor between VEGF and clinical stage ($p = 0.360$). Univariate analysis in ER positive patients ($n = 645$) showed VEGF as a predictor for OS, both when using the median level in this group 1.88 pg/ug DNA ($p = 0.0243$) and when using the median level among all patients 2.40 pg/ug DNA ($p = 0.0272$) as cut-off values. VEGF did not have any predictive value in ER negative tumors, neither when using the median level in this group 4.87 pg/ug DNA as cut-off value ($p = 0.4678$) nor when using 2.40 pg/ug DNA ($p = 0.1806$). A multivariate analysis in ER positive patients showed nodal status ($p = 0.008$), grade (0.0172) as independent prognostic factors, VEGF showed a boarder line value ($p = 0.0606$) (CI = 0.976–3.055) while tumor size and age failed.

Conclusion: Despite an inverse correlation to estrogen receptor content the predictive value of VEGF for overall survival was restricted to ER positive patients. VEGF could be suggested as a strong additional prognostic factor to receptor status in primary breast carcinoma.

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Importance of tissue-infiltrating macrophage activation in breast cancer progression

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Tissue-infiltration of monocytic cells is thought to be one of crucial events for the progression of solid tumors. We have analyzed the accumulation of CD68 positive macrophages and its activation in 229 primary breast cancer tissues. The macrophages density in 1 mm2 microscopic field at the most accumulated area varied from a few to more than 200 counts. There was no significant correlation between macrophage count and conventional clinicopathological factors. In the survival analysis, no prognostic significance of macrophage count was found, however, activated macrophage count assessed by staining with thymidine phosphorylase (TP), which is known to be unregulated by various stimuli including TNF-α, IFNγ, IL-1 and hypoxia, showed a significant prognostic value. Tumors with high TP-positive count were significantly poor prognostic compared to those with low TP-positive count ($P < 0.001$). A multivariate analysis confirmed that macrophage TP status was an independent prognostic indicator. In addition, tumors with both high TP-positive count and high microvessel density exhibited a markedly poor prognosis. It was suggested that macrophage activation probably caused by the alteration of intratumoral microenvironmental conditions including cytokine concentrations and hypoxia plays crucial roles in breast cancer progression.

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The higher local recurrence rate after breast conserving therapy in young patients explained by larger tumour size, incomplete excision at first attempt and smaller excision volume?

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Purpose: Age less than 40 years is one of the major factors related to higher local recurrence rate after breast conserving therapy. The aim of this study is to identify patient- and treatment-related factors associated with young age which could be related to the risk of recurrence after breast conserving therapy.

Methods: In the "boost versus no boost" trial 22881 of the EORTC, 5569 stage I or II breast cancer patients have been included; 5318 patients were randomised between no boost or a boost of 15 Gy; 251 patients having a microscopically incomplete excision were randomised between a boost dose of 10 or 25 Gy. All patients first underwent tumorectomy and axillary dissection followed by tangential irradiation of the breast up to a dose of 50 Gy in 5 weeks with 2 Gy per fraction. In the whole patient population 155 patients were younger than 35 years and 312 patients were aged between 36 and 40 years.

Results: The local recurrence rate after breast conserving therapy was significantly increased in women of under 40 years of age and in patients who underwent a microscopically incomplete excision ($p = 0.0001$ and $p = 0.0095$ resp.). The tumour size was significantly larger in younger patient group; especially non-palpable lesions were more often seen in older patients. A re-excision was more often performed in the younger patient group; also a microscopically incomplete excision at first attempt occurred more frequently. The total volume of breast tissue removed at tumorectomy was also smaller in the younger patient group, even after including the volume removed during the re-excision. The number of examined and involved lymph nodes was similar in both age groups. The oestrogen receptor was more often negative in the young patients, while no significant difference was seen for the progesterone receptor values. No differences were seen in the histological types in the different age groups.

Discussion and Conclusion: This large EORTC trial with breast conserving therapy for stage I and II breast cancer showed again that age less than 40 years is associated with a higher local recurrence rate. The younger patient had on average a larger tumour and despite more re-excisions in this group, the excised volume of breast tissue removed remained smaller. A microscopically incomplete excision at first attempt was also more frequently observed. These findings suggest that a better pre-operative estimation and marking of the tumour extension followed, for example, by ultrasound-guided surgery could ensure a higher probability of tumour-free margins.

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Evaluation of biological prognostic factors in relation to local recurrence after breast conserving therapy

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Purpose: To evaluate the levels of cathepsin-D (catD), urokinase-type plasminogen activator (uPA), plasminogen activator inhibitor-1 (PAI-1) and steroid hormone receptors, in relation to developing *a)* local recurrence (LR) after breast-conserving therapy (BCT) and *b)* distant metastases (DM) after LR.

Methods: We studied 1630 Dutch breast cancer patients treated with BCT and radiotherapy between 1980–1992. Levels of the biological factors were available from 1260 primary tumors and 65 LR tissues. LR was defined as renewed tumor growth in the treated breast as first event at least 3 months after surgery. The 5-year survival rate after LR was 64%.

Results: As first event 171 LR, 70 local regional relapses (LRR), 363 DM and 81 contralateral breast carcinomas were observed. Biological factors were not associated with LR, but high levels of catD, uPA and PAI-1 were strong prognostic factors for LRR and DM ($p < .001$). Age, extensive intraductal component and multifocality were risk factors for LR. In the Cox multivariable analysis the time elapsed from surgery to LR, skin involvement of the LR and uPA status of the primary tumor were independent prognostic factors for developing distant metastasis after LR.

Conclusion: There was no relation between tumor levels of biological factors and LR after BCT. Risk factors for distant metastasis after LR were shorter relapse-free interval, skin involvement, and high levels of uPA in the primary tumor. An aggressive systemic therapy could be of benefit to women with these risk factors.

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