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The Prognostic Value of Insulin-like Growth Factor-I in Breast Cancer Patients. Results of a Follow-up Study on 126 Patients

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The insulin-like growth factor-I is an important mitogen and has a growth promoting property, especially in breast cancer. This work analyses the prognostic value of the insulin-like growth factor receptor-I (IGFR-I), which belongs to the group of membrane receptors for growth factors. The study included 126 patients. 49 patients (39%) were IGFR positive (≥4.0%). There was a significant correlation between IGFR and oestrogen receptor (ER) status ($P = 0.001$), but not between IGFR and progesterone receptor status (PR; $P = 0.07$). There was no correlation between node status and IGFR. The expression of IGFR had a strong significance in the disease-free analysis ($P = 0.0108$). The IGFR status was not of predictive value in the node-negative subgroup (64 patients). Within the ER-negative group, the disease-free analysis further stratified with IGFR revealed that patients with IGFR-positive and ER-negative cancers are in a worse situation than IGFR-negative ER-negative cancer patients ($P = 0.01$).

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INTRODUCTION

THE INCREASING number of options for the treatment of breast cancer will make the prognostic evaluation of the disease even more important. The histological criteria for grading of the cancer into poorly differentiated and well differentiated, established by Bloom and Richardson [1], correlated a shorter relapse-free survival of patients with poorly differentiated tumours, and a better prognosis for patients with well differentiated tumours. Node positivity has also been found to shorten the disease-free survival rate [2, 3]. The measurement of S phase cells by indirect [^{3}H]thymidine incorporation [4, 5], and the measurement of the DNA content by flow cytometry [6], are well established but complex procedures. The mouse monoclonal antibody, KI-67, introduced by Gerdes and colleagues [7], simplified the measurement of proliferating activity in breast cancer tissue. The ability to grow breast cancer cells *in vitro* has lead to the identification of polypeptide hormones that regulate their growth.

The insulin-like growth factor-I (IGF-I) is an important mitogen, and has growth promoting property in many tumour types, especially breast cancer [8]. The primary role of IGF-I is to act on the skeletal development via the endocrine pathway

along with growth hormone (GH) [9]. IGF-I is synthesised mainly in the liver but also in the lung and the kidney [10]. The hepatic synthesis of IGF-I is regulated by GH, nutritional status and liver function [11]. Type I IGF binds to a transmembrane receptor, IGFR-I, that has a high affinity to IGF-I, two to three times lower affinity to IGF-II, and very low affinity for insulin [12]. The IGFR-I is a tetrameric complex, comprised of extracellular, ligand binding domains, and the intracellular tyrosine kinase domain. The IGF-I type receptor is identified in several breast cancer cell lines by competitive binding and affinity cross-linking studies [13]. The tumour growth stimulating activity of IGF can be mediated from serum or tumour stroma. Particularly in breast cancer with functional IGF receptors, the autocrine and stromal paracrine secretion of IGF may be able to enhance tumour growth [14, 15].

The number of studies on the prognostic value of IGFR expression on relapse-free survival with a longer follow-up time, are limited. Due to a limited amount of follow-up studies and to the different quoting methods, the determination of the cut-off levels for IGFR expression are abitrary. We have used IGFR determination since 1985 in 126 primary operable breast cancers. The aim of our follow-up study was to evaluate the prognostic value of the IGFR expression in breast cancer. The relationship of IGFR was also evaluated according to oestrogen (ER), progesterone (PR), node status, tumour size and age.

PATIENTS AND METHODS

This study included 126 patients with primary breast cancer. The mean follow-up time was 4.2 years (range 60 days–6 years). The mean age was 61.8 years (range 28–89).

Processing of breast tissue was performed as follows: approximately 1 cm^3 samples of tumour tissue were frozen immediately after excision in liquid nitrogen and stored at −80°C until receptor analysis. The tissue was then thawed and cut into small pieces, washed with 0.04 M Tris–HCl, 1.5 mM EDTA, 0.02% NaN_3, pH 7.4 and homogenised with an Ultraturrax homogeniser in the same buffer at 4°C. After centrifugation at 800 *g* for 5 min, the pellet was discharged and the supernatant was further centrifuged at 30 000 *g* for 15 min. The 30 000 *g* supernatant was further centrifuged at 105 000 *g* for 60 min, and the supernatant fraction, designated cytosol fraction, was immediately used for ER and PR determination. The 30 000 *g* pellet was resuspended in 10 mM Tris–HCL, 50 mM NaCl, 0.1% bovine serum albumin, 0.02% NaN_3 (Tris–NaCl buffer) pH 7.4, and was recentrifuged at 30 000 *g*, for 15 min. The pellet was rehomogenised in Tris–NaCl buffer, and its protein content was adjusted to 1.7 mg/ml. These membrane samples were stored at −80°C until IGFR analysis.

A human recombinant IGF-I (Amgen, Thousand Oaks, California, U.S.A.) was iodinated by chloramine T. The specific activity was 50–150 μCi/μg. For IGF receptor determination, a 100 μl membrane suspension was incubated with [^{125}I]IGF-I, 30 000 cpm in the presence or absence of 0.7×10^{-8} M unlabelled IGF-I in a final volume of 250 μl Tris–NaCl buffer, pH 7.6 for 18 h at 4°C. The incubation mixture was layered on top of 300 μl ice-cold Tris–NaCl buffer and centrifuged at 30 000 *g* for 15 min. The supernatant was aspirated and the pellet counted in an autogamma counter. The binding depicting IGFR activity was expressed as specific binding (total [^{125}I]IGF-I binding minus binding in the presence of 0.7×10^{-8} M IGF-I) in the percentage of total [^{125}I]IGF-I added (B/T%), as described by Pekonen and colleagues [16]. At the present time there is no generally specified cut-off level for IGFR positivity. In this study, the cut-off levels were chosen arbitrarily, according to a subdivision of the patients into two groups with clear differences in disease-free survival (DFS), and with nearly equal number of patients. The cut-off point for the IGFR expression was 4.0%. IGFR expression <4% was considered negative (low), and ≥4.0% positive (high). The ER and PR levels were determined as described by Vihko and colleagues, and the receptor content was expressed as fmol/mg cytosol protein [17]. The cut-off point for ER and PR positive was 10 fmol/mg. The degree of histological differentiation was classified as three categories according to the WHO classification; low, intermediate or high. The histological grading was available on 73 patients. The p-TNM status was evaluated on the basis of the pathologist's report. Metastatic disease was confirmed with radiological and clinical examination.

Statistical methods

Analysis of patient and tumour characteristics within the subgroups was performed using χ^2 contingency tables. DFS curves were obtained with the product limit method of Kaplan and Meier [18]. Survival data was analysed using log rank test and the Cox proportional hazards regression model [19].

RESULTS

Ductal carcinoma formed 86% of the breast carcinomas, 5% were lobular, 3% mucinous and the rest papillar, medullar or tubular carcinomas. 49 patients (39%) were IGFR positive (≥4.0%). The ER staining was successful in 120 patients, and the PR staining in 119 patients. The number of ER-positive patients (ER ≥10 fmol/mg) was 79 (66%) and PR-positive patients (PR ≥10 fmol/mg) was 76 (64%) (Table 1). Low grade carcinomas formed 32%, intermediate grade 58% and high grade carcinomas 10%. The rate of node-negative (N0) patients was 51% (64 patients), N1 patients with one to three nodes 42% (53 patients) and above three nodes 7% (9 patients) (Table 1).

Table 1. Patients' characteristics

	IGFR negative	IGFR positive
ER <10 fmol/mg	33 (27%)	8 (7%)
ER ≥10 fmol/mg	39 (33%)	40 (33%)
PR <10 fmol/mg	31 (26%)	12 (10%)
PR ≥10 fmol/mg	42 (35%)	34 (29%)
Nodes 0	41 (33%)	23 (18%)
Nodes 1–3	29 (23%)	24 (20%)
Nodes ≥4	5 (4%)	4 (3%)
T1	38 (31%)	17 (13%)
T2	26 (21%)	27 (21%)
T3–4	13 (10%)	5 (4%)

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The relationship of the IGFR expression with other prognostic factors

There was a significant correlation between IGFR positivity and positive ER status ($P = 0.001$), but not between IGFR positivity and PR positivity ($P = 0.07$), showing that increased oestrogen receptor content is associated with increased IGFR binding. There was no correlation between node status and IGFR. The ratio of N0 patients was 53% (41 patients) among the IGFR-negative patients, and 47% (23 patients) among the IGFR-positive patients. Once node positivity had been reached (nodes 1–3 and ≥4), the distribution between IGFR negative and positive was almost equal (Table 1). There was no statistically significant correlation between IGFR status and age, or between IGFR status and grade of differentiation (data not shown). The correlation between IGFR and tumour size showed no statistical significance, although small tumours were predominantly IGFR negative (Table 1). Both increasing tumour size and ER negativity decreased the relapse-free survival (data not shown).

Relationship of IGFR expression and relapse-free survival

The expression of IGFR had a strong significance in the disease-free analysis ($P = 0.01$). At the end of the average follow-up time, 50 months, 55% of the IGFR-positive patients were disease free compared to 80% in the IGFR-negative group. At the end of the follow-up, the disease-free survival rate among the IGFR-negative patients was 75% and 40% among the IGFR-positive breast cancer patients (Figure 1).

The IGFR status was not of predictive value (Figure 2) in the node-negative subgroup (64 patients). In this N0 subgroup, different cut-off levels for IGFR were tested, and none were significant. Among the node-positive patients (62), the IGFR-positive (26) patients had a worse prognosis compared to IGFR-negative patients (36) ($P = 0.02$) (Figure 3).

The ER and PR content in breast cancer tissue are known to correlate positively with a better prognosis in breast cancer, and are both predictive factors for the hormonal adjuvant therapy in breast cancer. The disease-free analysis for ER-positive breast cancers, i.e. patients with supposedly better prognosis, further stratified by IGFR, shows no statistically significant difference between the two groups (Figure 4). However, within the ER-negative group, i.e. the patients with a worse prognosis, the disease-free analysis, further stratified with IGFR, revealed that patients with IGFR-positive and ER-negative cancers (8 patients) are in a worse situation than IGFR-negative ER-

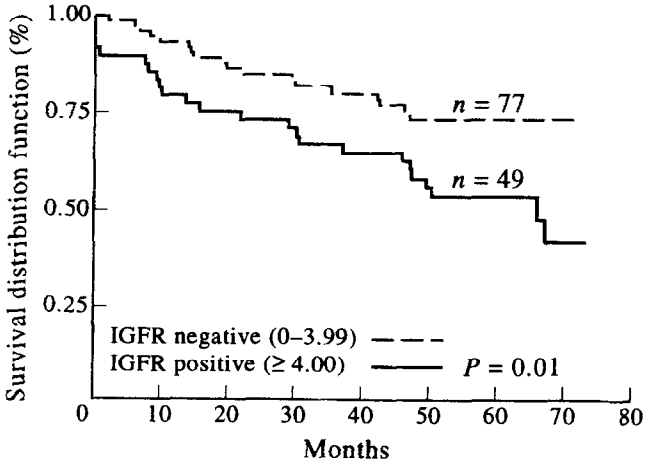

Fig. 1. The disease-free survival according to the IGFR-I status.

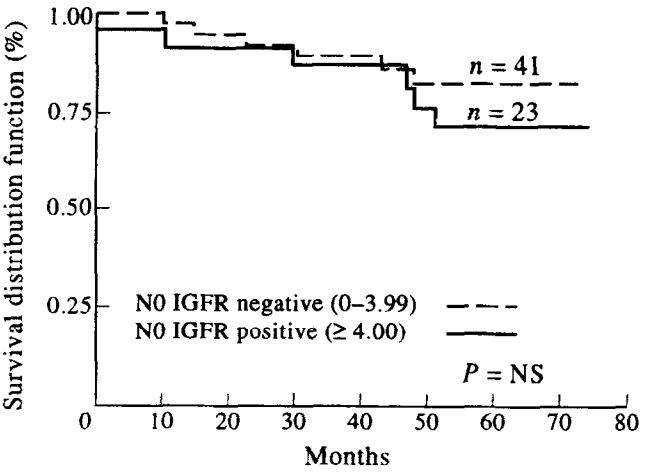

Fig. 2. The disease-free survival in node-negative (N0) patients according to the IGFR-I status.

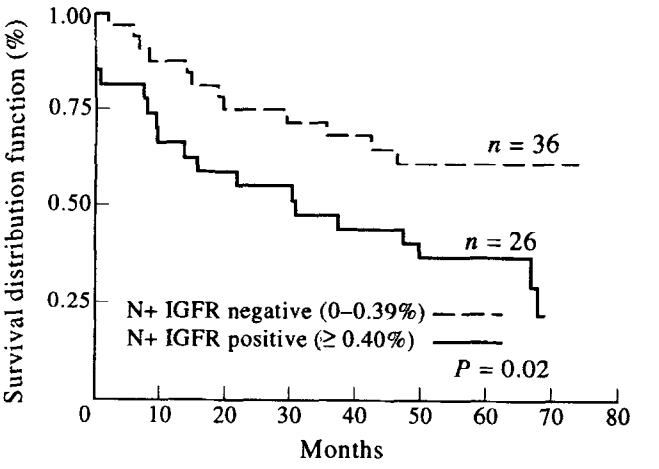

Fig. 3. The disease-free survival in node-positive patients according to the IGFR-I status.

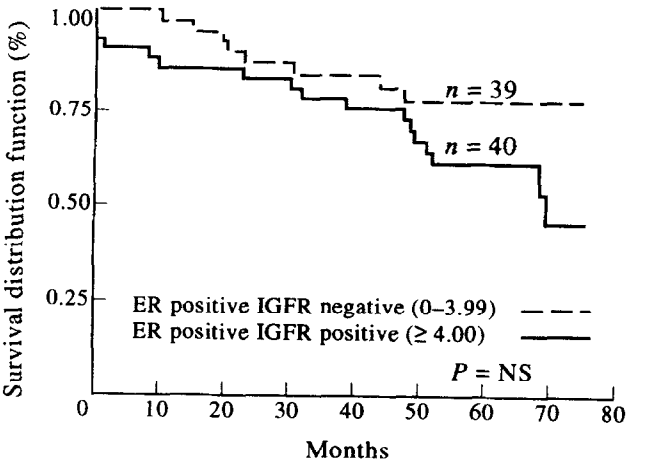

Fig. 4. The disease-free survival in ER-positive patients according to the IGFR-I status.

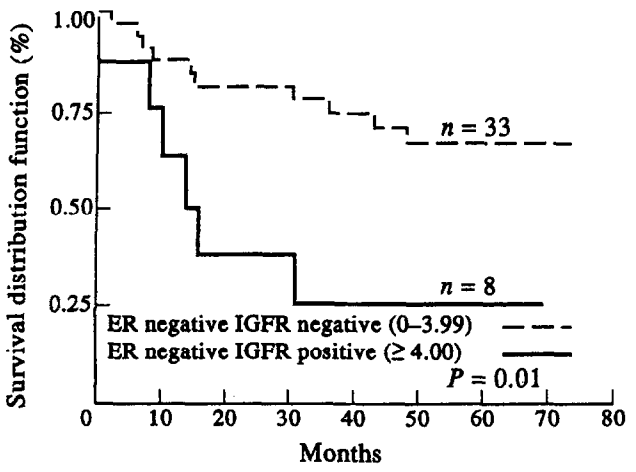

Fig. 5. The disease-free survival in ER-negative patients according to the IGFR-I status.

negative cancer patients (33 patients) (P = 0.01) (Figure 5). At the end of the average follow-up time, the relapse-free rate was only 25% in the IGFR-positive/ER-negative patients compared to 60% in the IGFR-negative/ER-negative patients.

The different prognostic factors were examined according to the Cox proportional hazards regression model (Table 2). The significance of IGFR was obvious (P = 0.015). Node status (P = 0.002) and PR (P = 0.01) were also independent factors. Tumour size was non-significant (P = 0.064). In this Cox model, ER status and age were not significant factors.

DISCUSSION

Studies correlating histological and nuclear differentiation to DSF and overall survival have shown that a histologically poorly differentiated carcinoma correlates with a worse DSF [20]. High thymidine, bromodeoxyuridine labelling index and flow cytometry revealing high percentages of S-phase cells, are prognostic factors in breast cancer [21, 5]. ER-negative and PR-negative (<10 fmol/mg) breast cancer correlates with shorter relapse-free survival [22–24]. Among the immunohistochemical labelling methods, the mouse monoclonal antibody KI-67 labels proliferating cells, and seems to correlate with the percentage of S phase inflow cytometry of breast cancer [25].

Table 2. Cox proportional hazards regression model

Parameters	Univariate analysis P values	Multivariate analysis Classes	RR	P values
IGFR-I	0.011	<4%	1*	—
		≥4%	2.241	0.015
Age	NS			NS
ER	NS			NS
T1-4	0.064 (NS)			NS
PR	0.021	<10 fmol/mg	1*	0.010
		≥10 fmol/mg	0.4255	—
N0-2	<0.001	N0	1*	0.002
		N1	3.045	0.027
		N2	10.95	

* Reference classes. NS, non-significant.

In this study's analysis, the prognostic value of the IGFR, which belongs to the group of membrane receptors for growth factors, has been investigated.

Almost all cultured breast cancer cell lines and fresh tumour biopsies express IGFRs [16, 26]. The mitogenic effects of type I IGF are stronger than the effects of type II or insulin [27]. The binding of the IGFR is stronger in tumour tissue compared to normal adjacent breast tissue. This suggests that the IGFR expression may be linked to the malignant transformation of the breast epithelial cells [16].

The number of studies on the prognostic value of IGFR expression on relapse-free survival are limited. Most of the IGFR studies are based on cultured breast cancer cell lines *in vitro*.

This study included 126 patients with primary operable breast cancer, with a mean follow-up time of 4.2 years. The IGFR assays were expressed as specific binding, the same method used in the series by Foekens and colleagues [28], and Bonneterre and colleagues and Peyrat and colleagues [29, 30]. High IGFR binding was found, on average, in 60% of different tumour grades of ductal breast carcinoma (low 64%, intermediate 67%, high 50%) which is somewhat lower compared to other series [29, 30]. The correlation to ER receptors was significant and consistent with other series [28–30]. The positive correlation of IGFR to ER was strong (P = 0.001), but to PR it was non-significant (P = 0.07). In contrast, IGF-I-like activity has been reported to be higher in ER-negative breast cancer [31]. This indicates that the interaction between IGF and its receptors is probably multifactorial. As reported by others, there was no correlation between the IGFR and node status. Evidence for the correlation of IGFR to tumour differentiation is conflicting. There was no correlation in this study between tumour differentiation and IGFR status. This is in accordance with the results of Foekens and colleagues [28], while Bonneterre and colleagues and Peyrat and colleagues [29, 30], in contrast, showed a positive correlation.

The results of DFS obtained in this series are quite different from three other major series [28–30]. According to Foekens and colleagues, the IGFR status is not a predictor of early recurrence of the breast cancer disease. In the series by Bonneterre and colleagues, a longer relapse-free survival was found in IGFR-positive patients. According to our study, IGFR-positive patients are, on the contrary, facing a worse relapse-free survival. The IGFR status was not able to predict a subgroup of patients with worse prognosis in the node-negative breast cancers. This is similar to the series of Bonneterre and Foekens.

The mean follow-up time is somewhat longer in our material, 4.2 years compared to 3.5 years. In our study, within the ER-negative subgroup of patients, the IGFR-positive patients had a worse DFS, while Bonneterre and colleagues found no differences in the ER-negative subgroup. Moreover, they did find that, among the PR-negative subgroup of patients, the IGFR-positive PR-negative patients showed a better relapse-free interval [29]. In both studies, the IGFR status is a good predictor of relapse, although with different criteria. The reason for these contradictory results concerning the predictive value of IGFR is not clear. As Bonneterre and colleagues stated, it seems paradoxical that tumours containing an excess of IGFR would have a better prognosis than tumours with fewer receptors. Because there are still quite a few series evaluating the predictive value of the IGFR, and the follow-up time in these series is relatively short, it is difficult, as yet, to draw conclusions concerning the real prognostic value of the IGFR status. More studies and longer follow-up times are needed. The difference

between high and low affinity of the tumour specimen to biochemical competitive IGFR labelling is a complex entity. Is the receptor occupied by some inactive IGF? Does this influence the results?

The IGF binding in breast cancer is increased compared to adjacent normal tissue ($P < 0.001$), as shown by Pekonen and colleagues [16], suggesting that IGFR-I is associated with malignant transformation of breast tissue [16]. In addition, the content of insulin-like growth factor binding protein, with a molecular weight of 49000 Mr, is increased in breast cancer tissue and is more abundant in ER-negative tumours [32]. These associations could explain the malignant potential of the IGFR-I in our series, despite its positive correlation to ER content.

Our conclusion is that, in this series, the prognostic value of the IGFR is good, and that it also has the ability to predict the prognosis of a subgroup of patients within ER-negative patients.

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