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EPIDERMAL GROWTH FACTOR RECEPTOR (EGFr) AS A MARKER FOR POOR PROGNOSIS IN NODE-NEGATIVE BREAST CANCER PATIENTS: NEU AND TAMOXIFEN FAILURE

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Summary—Analysis of EGFr and ER was performed on tumour samples from 231 patients with operable breast cancer followed for up to 6 yr after surgery. The median duration of follow-up in patients still alive at the time of analysis was 45 months.

Thirty-five percent of patients (82) had tumours greater than 10 fmol/mg ^{125}I–EGF binding ($EGFr^+$) and 47% (109) had cystolic ER concentration >5 fmol/mg (ER^+), with a marked inverse relationship between EGFr and ER ($P < 0.00001$). EGFr was second only to axillary node status as a prognostic marker for all patients both in terms of relapse-free and overall survival ($P < 0.001$, logrank $EGFr^+$ vs $EGFr^-$).

For patients with histologically negative axillary nodes EGFr was superior to ER in predicting relapse and survival ($P < 0.01$ and $P < 0.005$, respectively, compared to $P < 0.1$ and $P < 0.1$, logrank). In a multivariate (Cox model) analysis only EGFr, out of EGFr, ER, size and grade, was predictive for either relapse-free or overall survival for patients with node-negative disease ($P = 0.052$ and $P = 0.026$, respectively).

The correlation of neu expression with response to tamoxifen in patients with recurrent diesase was assessed immunochemically. Response rate was reduced in the presence of neu from 50 to 17% for ER^+ cases and from 26 to 0% for ER^- cases.

INTRODUCTION

The histological status of the axillary lymph nodes, specifically the absolute number of nodes involved, remains the most potent prognostic marker for patients with operable breast cancer [1, 2]. Tumour recurrence and death due to breast cancer, however, affects a significant proportion of patients with node-negative disease [3, 4], suggesting the need for a marker for patients at high risk of recurrence and death. Tumour oestrogen receptor (ER) content has been proposed as a marker but there is disagreement about its value [5, 6].

Several reports describe the presence of specific, high affinity receptors for epidermal growth factor (EGFr) on membranes prepared from primary human breast carcinoma [7, 8]. These studies showed a marked inverse relationship between expression of EGFr and ER. Tumours which overexpressed EGFr were associated with a poor overall prognosis [9, 10]. Continued prospective patient follow-up and increased patient numbers now allows examination of the prognostic value of EGFr, particularly in node-negative patients.

There was a policy of first line treatment with tamoxifen for relapsing patients without immediate life-threatening visceral disease. In 61 such patients, immunochemical assessment of neu expression was carried out. Previously we have shown EGFr expression is related to poor response to tamoxifen in the same patients [11].

PATIENTS AND METHODS

Two hundred and thirty one patients with operable breast cancer and no biochemical or radiological evidence of distant metastases were treated by simple mastectomy ($n = 181$) or wide local excision and post-operative radiotherapy by external beam and irridium wire implants ($n = 50$). Axillary nodes were sampled if palpable at surgery ($n = 129$, 56%). In patients treated by mastectomy adjuvant radiotherapy was given to the ipsilateral axilla if the nodes

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Table 1. EGFr vs ER

		EGFr −	EGFr +	Total
ER	−	55	67	122
	+	94	15	109
		149	82	231

$\chi^2 = 40.808$, dof = 1, $P < 0.00001$.

were involved. No systemic adjuvant treatment was given.

Samples were analysed for EGFr and ER as previously described [12].

Immunochemistry for neu was carried out as reported [13].

Statistics

Analysis of patient and tumour characteristics within subgroups was performed using χ^2 contingency tables. Survival data was analysed using the logrank method [14] and the Cox proportional hazards regression model [15].

RESULTS

Relationship of EGFr to other prognostic indicators

There was a marked inverse relationship between EGFr and ER ($P < 0.00001$, Table 1).

In the 213 patients with ductal carcinomas there was a significant association between increasing tumour grade and expression of EGFr ($P < 0.025$, Table 2).

EGFr and survival

After a median follow-up of 45 months for patients still alive at the time of analysis, 125 patients (54%) have recurred and there have been 80 breast cancer related deaths (35%). Fifty-five patients out of 82 with EGFr positive tumours have recurred and 41 have died ($P < 0.001$, logrank for recurrence-free and overall survival (Fig. 1A, B). In a univariate analysis of prognostic factors in all 231 patients EGFr was second only to axillary node status considering all patients (Table 3A) or those with known axillary node status (Table 3B).

The effect of EGFr overexpression in specific patient subgroups is shown in Table 4. In the 50

Table 2. EGFr vs grade

		−	+	Total
Bloom and Richardson	I	23	4	27
	II	49	24	73
	III	63	50	113
		135	78	213

$\chi^2 = 8.805$, dof = 2, $P < 0.025$.

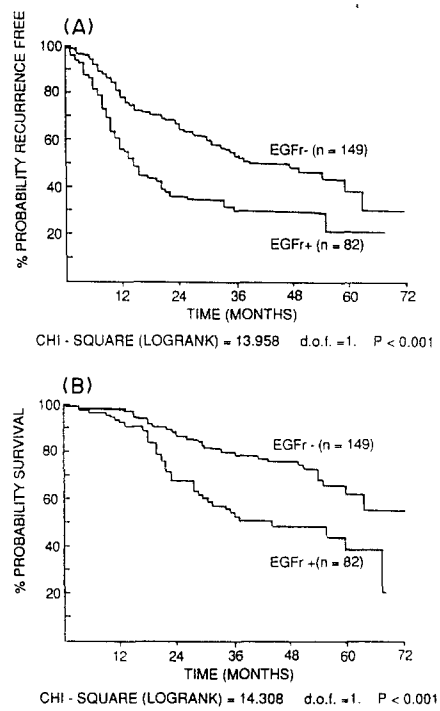

Fig. 1. Survival of patients with operable breast cancer stratified by tumour EGFr expression: (A) relapse-free; and (B) overall survival.

patients with histologically examined and negative axillary nodes EGFr expression was associated with a significant reduction in recurrence-free and overall survival ($P < 0.01$ and < 0.005, respectively, Fig. 2A, B). Similarly in patients with lower grade tumours (Grades I and II) there was a reduction in recurrence-free and overall survival for those with EGFr positive tumours.

Multivariate analysis of survival data

Five factors were assesssed in this analysis: axillary node status, tumour grade, tumour size (analysed as a continuous variable), EGFr and ER. This allowed, therefore, analysis of only the 213 pateints (92%) with ductal carcinomas. Axillary node status was either positive (histologically proven) or not positive (histologically negative and unsampled). In this analysis EGFr

Table 3. Univariate analysis of survival data (logrank)

	Factor	Disease-free	Overall survival
A	Axillary nodes	$P < 0.005$	$P < 0.001$
	EGFr	$P < 0.001$	$P < 0.001$
	ER	$P < 0.01$	$P < 0.01$
	Tumour grade	NS	$P < 0.025$
	Size	NS	$P < 0.1$
B	Lumph node status	$P < 0.005$	$P < 0.001$
	EGFr	$P < 0.01$	$P < 0.01$
	ER	NS	$P < 0.1$
	Tumour grade	NS	NS
	Size	NS	NS

Table 4. Effect of EGFr expression on different sub-groups (log rank)

	Disease-free	Overall survival
Axillary node negative	$P < 0.01$	$P < 0.005$
Bloom and Richardson		
Grade I	$P < 0.1$	$P < 0.005$
Grade II	$P < 0.005$	$P < 0.001$
ER^+	$P < 0.05$	$P < 0.05$
ER^-	$P < 0.1$	$P < 0.05$

expression is second only to lymph node status in prediction of death (P 0.005 vs P 0.059) and neither ER nor tumour grade were significant.

In a separate analysis patients with axillary node-negative (histologically confirmed), ductal carcinomas ($N = 49$) were assessed. Only EGFr was significant for overall survival ($P = 0.026$, grade, ER, size NS).

Neu and response to hormone therapy

Thirty of the 61 tumours were ER^+, 31 negative. There was a higher response rate (including stable disease for 6 months) in the former, 45 vs 25%. Coexpression of neu markedly reduced the response rate of both ER^+ and ER^- tumours (Table 5). None of the tumours expressing EGFr and neu responded to tamoxifen.

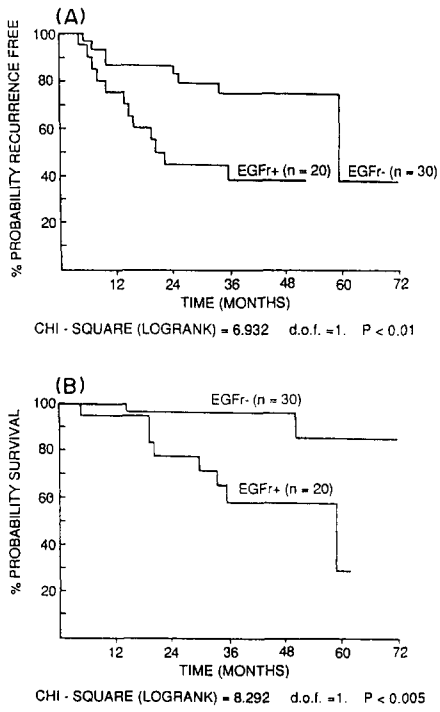

Fig. 2. Survival of patients with histologically negative axillary nodes stratified by tumour EGFr expression; (A) relapse-free; and (B) overall survival.

Table 5. Neu and tamoxifen response

	Neu − ER^+	Neu − ER^-	Neu + ER^+	Neu + ER^-
None responders	12	17	5	8
Responders	12	6	1	0

DISCUSSION

This study has demonstrated that overexpression of EGFr in tumours of patients with operable breast cancer is associated with a poor overall porognosis and that EGFr status is second only to axillary lymph node status in its prognostic power. In subgroups which would otherwise have been considered to have a good prognosis (axillary node-negative and low tumour grade) overexpression of EGFr led to a significant reduction in both relapse-free and overall survival. Similarly, patients whose tumours coexpressed EGFr and ER had survival patterns similar to those expressing EGFr alone, suggesting that overexpression of EGFr conferred a growth potential on a tumour which obviated its requirement for oestrogen.

These results, and those which have shown a failure of response to endocrine therapy associated with overexpression [11, 16], suggest that EGFr may be a clinically useful prognostic marker in patients with axillary node-negative breast cancer capable of identifying a poor prognosis subgroup which may benefit from systemic adjuvant chemotherapy.

The association of neu expression with failure to respond to tamoxifen suggests that neu may bypass oestrogen-regulated growth. Alternatively neu may normally be down regulated by oestrogen and its elevation in the presence of ER suggests non-functional ER. This would only apply to cases with high neu, but without gene amplification. Nevertheless, high neu expression may suggest the early introduction of chemotherapy even in ER positive cases and opens the possibility of anti-neu therapy for this poor prognosis group of relapsed patients.

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