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Predictors of recurrence in stage I invasive breast carcinoma

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Background. *The aim of the retrospective study was to determine whether 6 classical prognostic factors might predict a disease-free survival (DSF) in stage I breast carcinoma.*
Patients and methods. *We analysed 181 patients who were operated on from 1991 through 1995. Measurements were made to find the association between the incidence of recurrence and prognostic features (size; histological subtype; lymphatic/vascular invasion (LVI); histological grade; hormone receptor status; age).*
Results. *There were 4 cases with locoregional recurrences (2.2 %), 6 with locoregional and distant metastases (3.3 %) and 13 women with distant metastases (7.2 %). In univariate analysis, the following prognostic factors were significantly related to DSF: tumour size, age and LVI. In the multivariate analysis age ($p = 0.007$) and LVI ($p = 0.00001$) remained firmly associated with DSF, although the tumour size ($p = 0.067$) lost its significance.*
Conclusions. *Our experience indicates that the combined use of the tumour size, LVI and age may be a better predictor of recurrence in T1N0M0 breast cancer.*

Key words: breast neoplasms, stage I breast carcinoma; prognosis, prognostic factors; recurrence

Introduction

The last decade has witnessed changing trends in the presentation and primary treatment of, and adjuvant therapy for women with early breast carcinoma. Patient awareness and mammographic screening have resulted in earlier detection of the disease.[1,2]

Women with breast cancer-lacking evidence of regional lymph node metastases and systemic disease (stage I) fare significantly better than those in whom nodal but not systemic involvement (stage II) occurs. Disease-free survival (DFS) of the former has been estimated to be approximately 93.8 % for 5 years and 79.3-81 % for 18-20 years following surgical treatment.[3-5]

The literature discussed various prognostic factors of T1 (≤ 2 cm) tumours for their association with the likelihood of locoregional and distant recurrences. This study for stage

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I breast cancer was performed to determine whether 6 classical clinical and histological features might predict DSF and also be used to identify patients who have increased or decreased risk of relapse.

Patients and methods

A total of 181 patients with T1 lesions were initially examined at the University Centre of Oncology in Pleven from 1991 through 1995. They all underwent axillary node dissection (complete or levels I and II) as part of their treatment for breast carcinoma and those who had an adequate follow-up were included into the study. The women's age range was 24-75 years (median 58.8 years).

None of them had any known regional or distant metastases at the time of initial diagnosis and, according to the International Union Against Cancer (UICC) classification, they were presented as patients with pT1N0M0 deasise.[6] Invasive carcinomas were classified using the largest dimension of the invasive component to determine the size: 5 mm or less, T1a; 6-10 mm, T1b; 11-20 mm, T1c. The axillary contents were dissected fresh; all identified lymph nodes (10-24, median 12.9) were sectioned through the hilum and examined histologically.

Pathologic characteristics of the primary tumour (size, histological type and grade, lymphatic/vascular channel invasion (LVI) by tumour emboli) were evaluated on the routine haematoxylin and eosin slides. Oestrogen receptor (ER) and progesterone receptor (PR) status were determined by radioimmunoassay.

The patients were treated with a modified radical mastectomy (81 %) or breast-conserving surgery and radiation therapy (19 %). Of 181 patients with ER or PR positive cases, 121 women received adjuvant hormonal treatment with Tamoxifen for 5 years. Seven node-negative T1c patients with high risk of recurrence (age < 40 years, ER/PR negative) received six courses of cyclophosphamide, methotrexate and 5-fluorouracil (classical adjuvant CMF), repeated every 4 weeks.

The cases of recurrence were defined separately as locoregional (after mastectomy) and distant metastases. The median follow-up duration of patients was 7 years (range 5-9 years).

The log rank test was used to perform the univariate analyses. Multivariate analysis was based on the Cox proportional hazards regression model and included any variable found to be significant in the univariate analysis.

Results

Table 1 illustrates the distribution of various clinical and pathologic features studied. The median tumour size was 14.8 mm. Ten patients (5.5 %) were with T1a tumours, 38 (21 %) were with T1b, and 133 (73.5 %) were with T1c. The majority of tumours (80.7 %) were infiltrating ductal carcinoma, 16 (8.8 %) were of infiltrating lobular type, and 19 (10.5 %) were of "favourable" (mucinous, tubular or papillary) histology. One hundred and forty-four patients (79.6 %) had positive steroid hormone receptor status - oestrogen and/or progesterone receptor positive (> 10 fmol). The majority of cases (86.8 %) had LVI (-) tumours. Within the period of 1991-1995, the histological grading was studied on 80 cases out of 181 patients. In 31 patients (38.7 %), the tumour was well differentiated, and in the remaining 49 women, the tumour was moderately or partly differentiated.

Twenty-three cases (12.7 %) developed the disease recurrence; ten were with locoregional recurrences (5.5 %), and 19 were with distant metastases (10.5 %), four women developed only locoregional, and the other 6 had locoregional and distant recurrence. Thirteen patients with distant metastases (7.2 %) died of the disease.

Table 1. Patients with T1N0M0 breast cancer

Variable	N	(%)
Tumour size (mm)	181	
< 10	48	26.5 %
11-20	133	73.5 %
Histologic type	181	
"Favourable"	19	10.5 %
ductal/lobular	162	89.5 %
Histologic grade	80	
G1	31	38.7 %
GII/GIII	49	61.3 %
Lymphatic/vascular invasion	166	
Absent	143	86.8 %
Present	23	13.2 %
Hormone receptor status	181	
(+) or (+/-)	144	79.6 %
(-)	37	20.4 %
Age (yr)	181	
≥ 60	99	51.9 %
< 60	82	48.1 %

On univariate analysis, variables significantly associated with the disease recurrence were: tumour larger than 1 cm (p = 0.03), presence of LVI (p = 0.00001) and patient's age under 60 years (p = 0.018).

The variables statistically significant at the univariate level entered into a multivariate logistic regression model with backward elimination. Only two variables remained statistically significant as independent predictors in the final model. They were LVI (odds ratio 13.41; p = 0.00001) and age (odds ratio 5.21; p = 0.007) (Table 2).

Among 77 older patients (≥ 60 years) without LVI, the incidence of disease recurrence was observed only in 2 cases (2.6 %). However, 4 patients out of 6 with the two risk factors (LVI positive; age < 60 years) had an incidence of relapse that accounted for 66.7 %.

Table 3 present the relationship of various clinical and pathologic markers to the clinical

Table 2. Statistical associations between recurrences and prognostic variables

Factor	% Recurrences	Univariate p value	Multivariate p value (Odds ratio)
Tumour size (mm)			
≤ 10	4.3 %		0.067 (4.57)
11-20	15.8 %	0.03	NS*
Histological type			
"Favourable"	5.3 %		
Ductal/lobular	13.7 %	0.3	
Histological grade			
G1	6.5 %		
GII/GIII	12.2 %	0.35	
Lymphatic/vascular invasion			
Absent	7.3 %		
Present	43.5 %	0.00001	0.00001 (13.41)
Hormone receptor status			
(+) or (+/-)	11.2 %		
(-)	18.9 %	0.15	
Age (yr)			
≥ 60	7.2 %		
< 60	17.1 %	0.018	0.007 (5.21)

*NS: not significant

Table 3. Pathologic parameters and recurrence at 7 years

Factor	Disease free survival	p value	Distant disease free survival	p value
Tumour size (mm)				
≤ 10	95.8 %		97.9 %	
11-20	84.2 %	0.38	86.5 %	0.026
Histological type				
"Favourable"	94.7 %		94.7 %	
Ductal/lobular	86.4 %	0.45	88.9 %	0.62
Histological grade				
G1	93.5 %		96.8 %	
GII/GIII	87.8 %	0.61	89.8 %	0.44
Lymphatic/vascular invasion				
Absent	92.4 %		93.8 %	
Present	54.5 %	0.000002	63.6 %	0.000048
Hormone receptor status				
(+) or (+/-)	88.9 %		91.0 %	
(-)	81.1 %	0.27	83.8 %	0.28
Age (yr)				
≥ 60	92.6 %		93.6 %	
< 60	81.6 %	0.027	85.1 %	0.06

outcome. By univariate analysis, the tumour size, LVI and age were significant prognostic factors for disease free survival. These factors also showed a trend toward better outcome for distant relapse-free survival, although only LVI and age reached statistical significance.

Discussion

Absence of metastases in the axillary lymph nodes has traditionally been considered as favourable biologic condition for patients with invasive breast cancer. However, all the cases with node-negative breast cancer are at risk for disease recurrence. Intensive efforts to define an individual patient's risk of relapse have produced a plethora of potential prognostic factors, from patient features to histological, biochemical and molecular characteristics of the tumour. The importance of these various prognostic factors has been the subject of controversies.

The frequency of the reported DFS period (83.3 % for 7 years) in 181 patients with the stage I disease is close to that reported by other authors.[3,4]

The most important predictors of DFS, out of the studied 6 ones, are LVI and the patient's age followed by the size of the primary tumour. These results, excluding the histological grading, concur with a number of preceding analyses, demonstrating their extreme prognostic importance. As to the histological grading, the lack of statistic authenticity in our study ($p = 0.35$) can be explained by a limited number of cases with a histological grading defined.[5,7-11]

For the patients with node-negative disease, International Consensus Panel (St. Gallen, 1998) recommends that the tumour size, histological and nuclear grade, steroid hormone receptor status, LVI and age are the

factors considered by the Panel to define groups with differential prognosis for use in treatment selection. For women assumed to be at high risk of recurrence (T > 2 cm; hormone receptor status negative; Grade II-III; age < 35 years) the treatment choice follows an algorithm similar to that for node-positive disease, which has a similar prognosis.[12]

The current multivariate analyses aiming to define the role of the growth rate of the tumour, measuring in terms of S-phase fraction, DNA ploidy, the occurrence of oncogene amplification of the epidermal growth-factor receptor or the c-erb B-2 gene, are going to determine the scope of the routine clinical implementation of these new prognostic factors to estimate the risk of the disease recurrence with the cases of early breast cancer.

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