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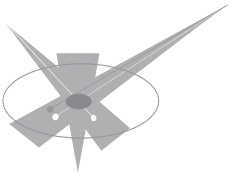

Original Paper

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# Prognostic index in lobular breast cancer

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## Summary

**Background** The topic of this study was lobular carcinoma, the second most frequently diagnosed cancer of the breast, which is less well known and is more problematic, diagnostically.

**Aim** To define a prognostic index for patients with lobular carcinoma of the breast through application of a multivariate analysis, Cox's proportional hazard model.

**Materials/Methods** An immunohistochemistry based analysis was carried out on paraffin embedded materials taken from 75 women who underwent surgery for lobular carcinoma of the breast in the Oncological Surgery Department, Poznań University of Medical Sciences, during the period of 1990–1997.

**Results** A statistically significant relationship was found between the size of tumour (p=0.044), lymph node status (p=0.011), expression of progesterone receptors (p=0.034), and survival time. In support of the above parameters, the multivariate analysis allowed the formulation of a prognostic index: I=T+2N-2PgR, where T (tumour)=tumour size, N (nodulus)=lymph node status, and PgR=expression of progesterone receptors.

**Conclusions** The formulated prognostic index for lobular carcinoma of the breast allows for the differential prognosis of survival time, in representative risk groups. The index may be useful in the process of qualifying patients for adjuvant therapy.

**Key words** **prognostic index • lobular carcinoma**

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## Background

The most common cause of death among patients treated radically for breast cancer is progression of the disease, by metastasis, to remote sites. Effective treatment of breast cancer must take the form of combined therapy. Qualification for treatment depends on the stage of disease and on the analysis of prognostic factors (which allow for a prognosis to be made, regardless of treatment method) and predictive factors (which allow us to foresee the effectiveness of applied therapies) [1–8].

The topic of interest for these authors is lobular carcinoma (carcinoma lobulare), which is the second most frequently diagnosed cancer of the breast, after ductal carcinoma. Invasive lobular carcinoma accounts for 5–20% of all breast cancer diagnoses. It is often diagnosed multifocally or bilaterally and is diagnostically problematic. Frequently it is "silent" in mammography. It is also difficult to assess cytologically, a result of its structure. In their classic form, lobular carcinoma cells are scattered singularly or form barrel shaped clusters, sometimes arranged concentrically. These cells are small, round and regular, with scanty cytoplasm. The number of nuclear polymorphisms is low and figures are of a low scale. Stroma is usually scant and glassy. Infiltration of lymphocytes and plasma cells is seen less frequently than in other forms of cancer of the breast [9–12].

In the case of lobular carcinoma, completion and modification of the histological staging of malignancy, according to Elston and Ellis, requires the grading of three morphological factors: duct formation, nuclear polymorphism of cells and the number of mitoses [13,14].

## Aim

The purpose of the study was to define a prognostic index for patients diagnosed with lobular carcinoma of the breast, using patho-clinical prognostic parameters and immunohistochemical markers verified earlier.

## Materials

An immunohistochemical analysis was performed on materials derived from 75 women, aged from 31 to 84, treated for lobular carcinoma of the breast in the Oncological Surgery Department, Poznań University of Medical Sciences, in the years 1990–1997.

## Methods

Clinical information was obtained from documents in the Oncology Department of Poznań University of Medical Sciences. In the case of patients who died outside the hospital, the date and cause of death were obtained from the Register of Malignant Cancers in the Statistics Department of the Great Poland Cancer Centre in Poznań.

The results of microscopic studies were obtained thanks to the Department of Histopathology, Poznań University of Medical Sciences, where slides were reassessed, verified and graded, with regard to the histological stage of malignancy, according to the Elston scale.

Immunohistochemical tests, using selected markers, were undertaken in the laboratory of the Department of Histopathology.

Nuclear staining reactions were graded for oestrogen receptors (ER), progesterone receptors (PgR), p53 and Ki67. Cytoplasmic reactions were graded for cathepsin D (CD) and MMP-2. Reactions in the cell membranes were graded for HER-2.

The characteristics of the group studied and the results of immunohistochemical tests are presented in Table 1.

A curve showing overall survival was produced using the Kaplan-Meier method. In order to determine relationships between selected factors, we applied Cox's non-parametric proportional hazard regression model.

Useful patho-clinical factors and immunohistochemical markers for lobular carcinoma of the breast have been presented in earlier publications [15].

## Results

After completion of the multi-factor statistical analysis, significant prognostic factors are: tumour size (p=0.044), the presence of metastases to the axillary lymph nodes (p=0.011) and expression of progesterone receptors (p=0.034). The results of the multi-factor analysis are shown in Table 2. The survival curve for patients in our study group is shown in Figure 1.

Based on the parameters of the multi-factor analysis used, the prognostic index was calculated according to the following formula:

**Table 1.** Clinical and pathological characteristics of group.

| Characteristic | Number | % |
|---|---|---|
| Total Number of Patients | 75 | 100 |
| Average age | 56.9 | |
| years (age range) | (31–84) | |
| Standard deviation | 13.42 | |
| Hormonal status | | |
| Premenopausal | 30 | 40.0 |
| Postmenopausal | 45 | 60.0 |
| Deaths during observation period | 21 | 28.0 |
| Observation period (months) – median | 105.9 | |
| Size of tumour | | |
| T 1 | 18 | 24.0 |
| T 2 | 43 | 57.3 |
| T 3 | 8 | 10.7 |
| T 4 | 6 | 8.0 |
| Lymph node status | | |
| N 0 | 16 | 21.3 |
| N 1 | 56 | 74.7 |
| N 2 | 3 | 4.0 |
| p N 1 | 32 | 42.7 |
| Histological grade of malignancy according to the Elston scale | | |
| G 1 | 12 | 16.0 |
| G 2 | 47 | 62.7 |
| G 3 | 7 | 9.3 |
| no data | 9 | 12.0 |
| Markers | | |
| ER (+) | 53 | 72.6 |
| PgR (+) | 61 | 82.4 |
| CD (+) | 49 | 73.1 |
| p53 (+) | 20 | 29.4 |
| Ki 67 (+) | 46 | 71.9 |
| MMP-2 (+) | 37 | 57.8 |
| HER-2 (+3) | 4 | 5.9 |

$$I = \beta \times z + \beta \times z + \beta \times z + \ldots,$$

where β = factor, and z = marker.

The index is $I = 0.7 \times T + 1.5 \times N + (-1.5) \times PgR$.

Taking into consideration the standard deviation, the Cox index was normalised by dividing the sides by 0.8, in order to make the factors into integers.

The final formula for the Cox Index is:

$$I = T + 2N - 2PgR,$$

where T (tumour) = tumour size, N (nodulus) = lymph node status, and PgR = expression of progesterone receptors.

In order to differentiate risk groups, it was necessary to re-write the values of certain parameters. For tumour sizes (T) less than 2 cm we recorded a score of 1, for medium sized tumours from 2 to 5 cm we scored 2, and for tumours larger than 5 cm a score of 3 was recorded. For lymph node status (N) we recorded a score of 0 where no metastasis was found, while a score of 1 was noted if metastasis was detected. In cases where expression of progesterone receptors was not seen, a score of 0 was noted while a score of 1 denoted that expression of progesterone receptors had been detected. The analyzed group of patients, with lobular carcinoma of the breast, was divided into three categories, with regard to their risk of relapse and death. Qualification for these risk groups was based on the following criteria.

Group 1 included patients in the lowest risk category. Qualification for inclusion in this group was as follows:
- diameter of tumour less than 5 cm (T:1 and 2),
- no metastases to the axillary lymph nodes detected (N:0),
- expression of progesterone receptors demonstrated (PgR:1).

Such values were accepted and used in possible combinations for the previously formulated Cox Index. It was found that in the low risk group, the prognostic index is: – 1 or 0.

Patients in the group most at risk of relapse were classified into group 3 as follows:
- metastases to the axillary lymph nodes detected (N:1),
- expression of progesterone receptors could not be demonstrated (PgR:0)

**Table 2.** Correlation between examined factors and overall survival using the Cox proportional hazards regression model of survival.

| **Statistical analysis of survival** | ***Dependency: survival – calculated in months taking into consideration the incomplete observations Size of group 75, incomplete: 54, complete: 21*** **$Chi^2$=25,8689; df=12; p=0.01123 (p<0.05)** | | | |
|---|---|---|---|---|
| **Prognostic factor** | **Beta** | **Standard deviation** | **Exponent beta (risk factor)** | **p** |
| Age of patient | 0.052 | 0.042467 | 1.053683 | |
| Hormonal status | –2.013 | 1.105447 | 0.133636 | |
| Size of tumour T | 0.799 | 0.396986 | 2.223897 | **p<0.05** |
| Metastases to lymph nodes N | 1.536 | 0.606240 | 4.646432 | **p<0.05** |
| Grading G | –0.697 | 0.675556 | 0.498074 | |
| ER | 0.789 | 0.822221 | 2.200582 | |
| PgR | –1.511 | 0.716318 | 0.220671 | **p<0.05** |
| CD | 0.610 | 0.878251 | 1.840912 | |
| p 53 | 0.626 | 0.751286 | 1.870675 | |
| Ki 67 | 0.121 | 0.739315 | 1.128056 | |
| MMP-2 | –0.049 | 0.619147 | 0.952548 | |
| HER-2 | –0.474 | 0.637646 | 0.622719 | |

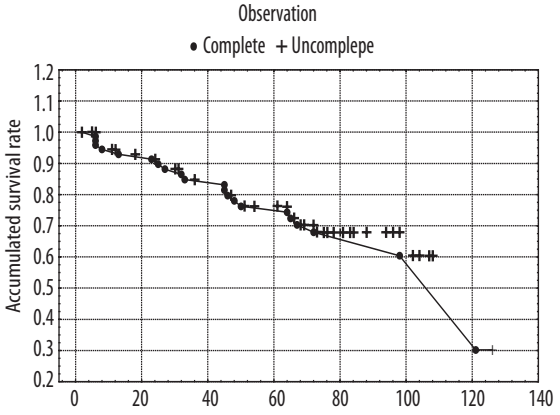


**Figure 1.** Kaplan-Meier's accumulated survival rates for patients with invasive lobular breast cancer.

• irrespective of tumour size (T:1, 2 and 3).

After inserting the values accepted for the group into the formula, the prognostic index for the group was calculated and amounts to: 3, 4 and 5.

The remainder of the patients, who qualified for neither group 1 nor group 3, were deemed to be at medium risk and were categorized into group 2. For such patients, the prognostic index was either 1 or 2, depending on the data put into the Cox Index.

The qualification scheme described above is shown in Figure 2.

Table 3 shows a comparison of survival times for patients in the groups at low, medium and high risk of death. The most numerous group is group 2 – the medium risk group – and is comprised of 31 patients. In this group, 10 deaths were recorded during the observation period, giving a 32.3% risk of death. The second largest group was group 1 – the low risk category. 28 patients qualified for this group, among whom 2 deaths were recorded. Based on this, the likelihood of death in the low risk group may be set at 7.1%. Into group 3 – the high risk group – we classified 16 cases and the risk of death was significantly higher – 56.3%. Figure 3 shows a graphical representation of the chances for survival in each of the risk groups. Differentiation of the course of disease in cases of good, poor or medium prognosis is clearly needed.

## Discussion

In spite of the diagnostic difficulties, which often include such risks as multi-focal changes, bilateral and sometimes disseminated disease, lobular carcinoma can have a better prognosis than ductal carcinoma – the most common cancer of the breast. This can be proved by the fact that the third degree of histological malignancy, G3,

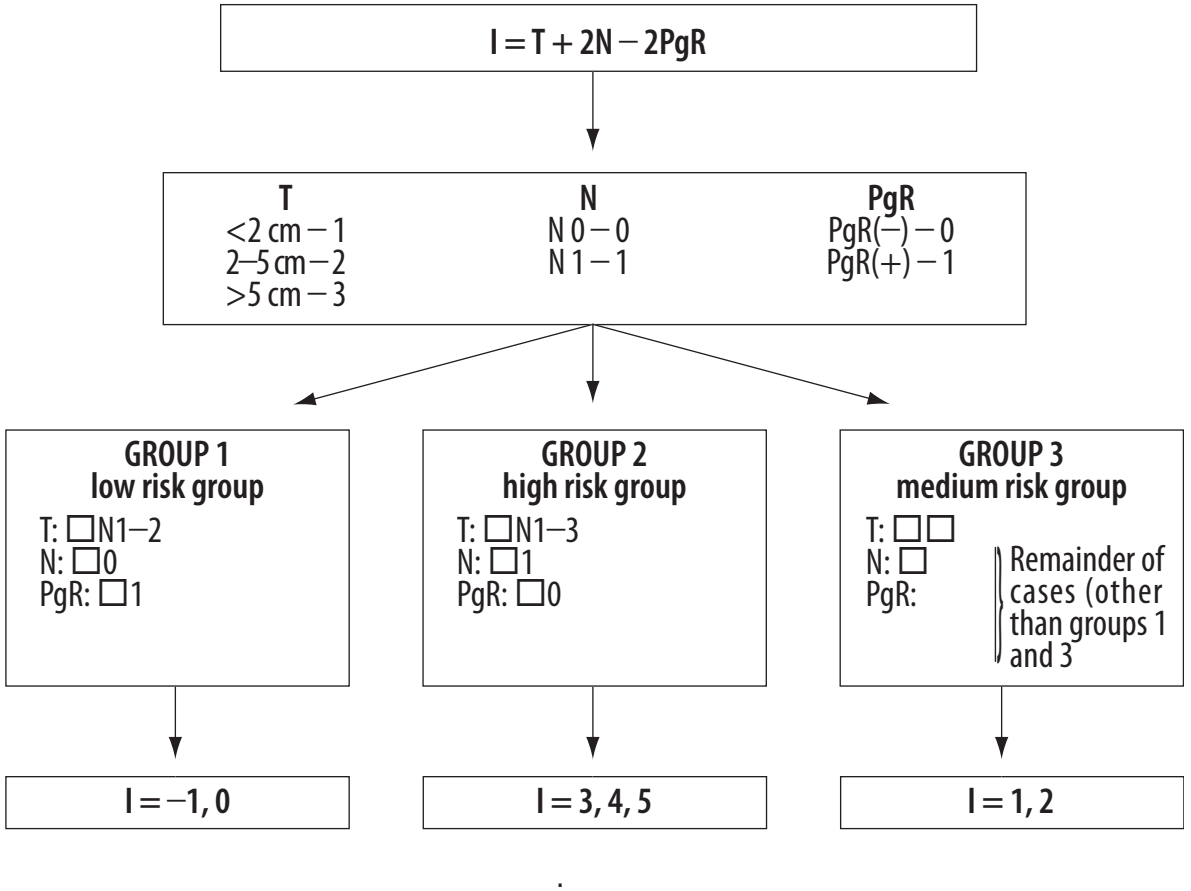


**Figure 2.** Value of prognostic index in each risk group, applying the Cox formula.

**Table 3.** Comparison of survival in low, medium and high risk groups.

| | Descriptive statistics for each group | | | | |
|---|---|---|---|---|---|
| **Group** | **Median** | **Mean** | **Standard deviation** | **Number of deaths in group** | **Number of cases in group** |
| 1. | 67.5 | 59.35714 | 32.98733 | 2 | 28 |
| 2. | 68.0 | 61.64516 | 32.55308 | 10 | 31 |
| 3. | 36.5 | 41.68750 | 33.49969 | 9 | 16 |
| Totals | 65.0 | 56.53333 | 33.40267 | 21 | 75 |

is rarely diagnosed in lobular carcinoma and by the more common finding of expression of ER and PgR, and the over-expression of HER-2, also by the lower percentage of deaths within the observation period. Other authors have also reached the conclusion that lobular carcinoma has a better prognosis [5,7,16–22]. Jeziorski found that lobular carcinoma with metastasis to the lymph nodes is associated with longer periods free from relapse and overall survival than is the case in ductal carcinoma [23]. Furthermore, in a study carried out by Ishige et al. it was found that the presence of a lobular component in ductal carcinoma is associated with a better prognosis. The investigators concluded that the presence of lobular structures could be a new prognostic factor for ductal carcinoma [24].

The classification of patients into groups of cases with good, medium and poor prognosis is a

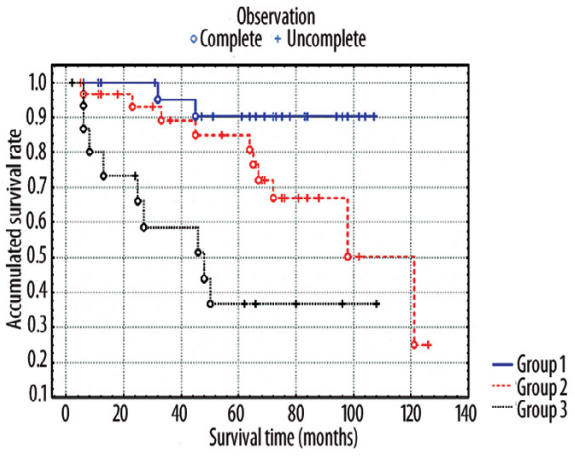


**Figure 3.** Accumulated proportion of survivors – Kaplan-Meier method. Group 1: I=–1.0; Group 2: I=1.2; Group 3: I=3,4,5

matter of the greatest importance for the proper and appropriate planning of patients' treatment. Sundquist and co-workers assert that the Nottingham Prognostic Index allows us to use more exact prognostic data than lymph node status alone – the strongest prognostic factor [25]. Baker et al. suppose that different prognostic factors are of value at each stage in the process of advancement of the neoplasm [26].

In practical oncology, most helpful indices are: The Nottingham Prognostic Index (which includes the size of the tumour, lymph node status and histological degree of malignancy according to the Bloom-Richardson scale) and the Van Nuys Index (which supports the treatment of ductal carcinoma in situ) [25,27–32]. Also cited in the literature is the Adelaide Prognostic Index, in which the diameter of the neoplasm, expression of progesterone receptors and cellular proliferation potential are graded [2].

Our second aim was to define the special prognostic index for lobular carcinoma. After assessing the independent diagnostic factors (T, N & PgR) in the observed group, they were used in a Cox Index in the following stage to create a prognostic index for lobular carcinoma of the breast. More importantly, it allows the definition of qualifying criteria for individual risk groups. Patients with metastases to the lymph nodes and lacking expression of progesterone receptors can therefore be classified into the group with the worst prognosis. Qualification for this group does not require the size of the tumour to be taken into account which, bearing in mind the biology of lobular carcinoma, is an obvious matter.

The group at the highest risk of death, in this study, was the smallest (21.3%), and the likelihood of a 5-year survival amounted to nearly 43%. The next group was that of the best prognosis in cases of lobular carcinoma, into which we included patients with tumours < 5 cm in diameter, without metastases to the lymph nodes and who expressed PgR. This group accounted for 37.3%. The largest group, that of medium risk, was only 4% larger. The likelihood of 5-year survival in the group with the best prognosis amounted to nearly 93% while it only came close to 68% in the medium risk category.

In these days of dynamic growth in the field of genetic sciences we can predict that, after only a few years more, information regarding the course of disease may be obtained by an analysis of the genetic profile. We already know that the "genetic signature" gives prognostic information which is tens of times better than the conventional prognostic factors we have been using up to the current time. Known groups of genes code for information regarding whether or not a tumour is likely to metastasize or not. It is also known that certain groups of genes control the route of metastasis, whether it be via the blood vessels or by the lymphatic system. Such an approach is revolutionising qualification for adjuvant therapy [33,34].

The prognostic index we propose may be used to define the groups of patients at the highest risk of relapse or death in cases of lobular carcinoma. It allows a more precise qualification scheme for adjuvant therapy in the treatment of patients suffering from the second most commonly diagnosed cancer of the breast.

## Conclusions

1. The use of a multi-factor analysis, according to Cox's proportional hazard method, allows the formulation of a prognostic index for lobular carcinoma of the breast.

2. Application of the prognostic index allows for patients to be classified into risk groups such that differential prognosis and total survival time can be more accurately predicted.

3. After further clinical testing in a larger group of patients, the prognostic index for lobular car-

cinoma could be used in the process of qualifying patients for adjuvant therapy.

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