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Prognostic factors in breast cancer: the predictive value of the Nottingham Prognostic Index in patients with a long-term follow-up that were treated in a single institution

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Abstract

The Nottingham Prognostic Index (NPI) is an index, derived from a retrospective multivariate study, that is able to predict survival in patients with breast cancer. The index is based on tumour size, lymph node stage and histological grade and allows the stratification of patients into three different prognostic groups. The aim of this study was to verify, according to our experience with a long-term follow-up, the effect of some prognostic variables on survival and to establish the independent influence of each of them by means of a survival regression analysis. Then we applied the NPI to the same group of patients in order to assess the predictive power and reproducibility of the index. 402 patients treated from January 1979 to December 1987 were evaluated. In multivariate analysis (Cox proportional hazard model), only size, lymph node involvement and histological grade remained independent prognostic factors. The survival curves obtained after applying the NPI are similar to those for the factors with independent prognostic significance derived from our multivariate analysis. Our improved survival rates may be attributed to the administration of adjuvant therapies to a larger number of patients. The NPI allow us to accurately predict prognosis and we advocate its more common use.

Keywords: Prognostic index; Breast cancer; Histological grade; Size; Lymph node status; Prognosis

1. Introduction

Prognostic factors influence the design, conduct and analysis of clinical trials of breast cancer. Such factors might be used to discriminate patients likely to have recurrences after their primary tumour has been treated from those at little risk for recurrence, and those likely to benefit from adjuvant therapy from those likely to have disease that is resistant to treatment [1]. Historically, nodal status, tumour size and histological grade have been used to determine the threshold of risk. The standard prognostic factors in common use today are lymph node status, tumour size, histological grade, histological type, nuclear grade, oestrogen (ER) and progesterone receptor (PR) status, and patient's age. More recently, DNA ploidy and S-phase fraction (SPF, a measure of tumour proliferation) measured by flow cytometry have been proposed as candidates to join this list. During the past several years, biochemical and genetic markers, such as growth factors, oncogenes and oncogene products, have been continuously discovered and investigated [2]. Although the evaluation of such prognostic factors is quite expensive and the results have rarely justified the outlay of such costs.

Some prognostic factors have been used to propose a prognostic index and in particular, in 1982, Haybittle and colleagues [3] advanced a prognostic index, the Nottingham Prognostic Index (NPI), derived from a retrospective, multivariate study of prognostic factors in 387 patients with primary, operable (clinical size less than 5 cm) breast cancer. The index, predicting survival, was calculated: NPI = Size (cm) × 0.2 + grade (I–III) + lymph node score (1–3 according to stage A–C) as subsequently modified by sampling of four lower axillary nodes together with internal mammary node sampling

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for medially located tumours only. Stage A denoted no involvement of regional nodes; stage B denoted involvement of $\leqslant 3$ axillary nodes or involvement of the internal mammary node; stage C denoted >3 axillary nodes or both internal mammary and axillary node involvement [4].

The aim of this study was to verify, according to our experience with a long-term follow-up, the effect of some prognostic variables on survival and to establish the independent influence of each of them by means of a survival regression analysis. Then we applied the NPI to the same group of patients in order to assess the predictive power and reproducibility of the index.

2. Patients and methods

At the Institute of Surgical Semeiotics of the University of Bari (Italy) 504 patients with breast cancer underwent surgical treatment from January 1979 to December 1987. Only 402 patients were evaluated; 102 were excluded from the study due to the occurrence of one of the following conditions: age >70 years, tumour size >5 cm, synchronous or metachronous neoplasias, presence of metastatic disease or *in situ* ductal carcinoma histology. The mean age was 52.3 years (range 31–70 years).

Variables evaluated for the analysis of prognostic significance were: age, menopausal status, tumour size, kind of surgery, histological type, histological grade, ER status and peritumoral lymphatic invasion (PLI).

All patients underwent surgery (quadrantectomy, axillary lymphadenectomy and radiotherapy; radical or modified radical mastectomy) and a complete axillary clearance was carried out with a mean of 22 (range 6–39) lymph nodes removed.

Patients who were axillary node-negative were not treated with adjuvant systemic chemotherapy or hormonal manipulation. Premenopausal patients with nodal involvement ($\leqslant 3$) were treated with systemic chemotherapy using cyclophosphamide, methotrexate and 5-fluorouracil (CMF) for 6 months and those that were ER-positive with tamoxifen for 5 years. Postmenopausal patients who were ER-negative were treated with CMF for 6 months and those who were ER-positive with tamoxifen for 5 years.

A more aggressive cytotoxic regimen was used in patients with substantial lymph node involvement (>3). These patients, if premenopausal, were treated with doxorubicin (4 months) + CMF (6 months) + tamoxifen (5 years) and if postmenopausal with CMF (6 months) + tamoxifen (5 years).

Tumour diameter was measured by the pathologist after surgical dissection. It was reclassified according to the recently recommended TNM of the American Joint Committee on Cancer (AJCC) [5].

Histological type was classified as follows: ductal/lobular infiltrating versus medullar/mucinous/papillar/others versus tubular.

Histological grade was evaluated by a limited number of experienced pathologists and revised according to the criteria (grade I, II, III) described by Elston and Ellis [6].

The presence of receptors for steroid hormones was routinely evaluated from 1980 using the charcoal-dextran method; ER values of more than 10 fmol/mg were considered positive.

The presence or absence of PLI was assessed according to the methods proposed by Pinder and coworkers [7] for the assessments of lymphatic and blood vessel invasion. Lymphatic invasion was definite only if tumour cell emboli were noted within a lymphatic space. Nevertheless, differentiating lymphatic channels from blood vessels is particularly difficult and so we admit, according to Pinder, that lymphatic and blood vessel invasion should be designated as vascular invasion.

The NPI was calculated, according to the equation described above, for each patient, who was then assigned to one of three prognostic groups: Good ($I \leqslant 3.4$), Moderate ($3.4 < I \leqslant 5.4$) and Poor ($I > 5.4$).

The follow-up was completed for all patients by the end of December 1998, with a median follow-up of 15 years (range 11–19 years).

2.1. Statistical methods

We estimated the survival function by the product limit method (also called the Kaplan–Meier method) [8] and the Log-rank test was used to compare the curves.

Prognostic factors found to be significant in the univariate analysis were entered in to the multivariate analysis of survival based on the Cox proportional hazard model [9].

Survival was calculated, from the date of first observation, by counting as breast cancer deaths only those women who died with known metastases of their disease or until the date the patient, if still alive, was last evaluated in the clinic.

3. Results

Actuarial survival for all patients at 10 and 16 years was 68 and 63%, respectively (Fig. 1).

In Table 1, we report a summary of the variables considered in the univariate analysis: age, menopausal status, ER status and kind of surgery did not significantly affect survival.

A significant difference in actuarial survival was demonstrated for tumour size (Fig. 2), lymph node involvement (Fig. 3) and histological grade (Fig. 4). Patients with a ductal and lobular infiltrating histological

type had a poor prognosis compared with those with a medullary, papillar or tubular histological type ($P = 0.002$ Log-rank test). The presence of PLI was strongly related to a poor prognosis ($P = 0.003$ Log-rank test).

Only significant P variables ($P < 0.05$) were included in the multivariate analysis (equivalent to the Cox proportional hazard model) and of all these only size, lymph node involvement and histological grade remained independent prognostic factors of statistical significance. Histological type and PLI were not independent prognostic indicators (Table 2).

When we applied the NPI to our cases, each patient was assigned to one of three prognostic groups: Good ($I \leqslant 3.4$), Moderate ($3.4 < I \leqslant 5.4$) and Poor ($I > 5.4$). 110 (27%) patients were in the good prognostic group, 198 (49%) in the moderate prognostic group and 94 (23%) in the poor prognostic group. Actuarial survival curves for each of three prognostic groups are plotted in Fig. 5.

Table 1
Summary of variables entered into univariate analysis ($n = 402$)

Variable	n (%)	P (Log-rank test)
Age		
⩽40	60 (15)	0.48
>40	342 (85)	
Menopausal state		
Premenopausal	163 (41)	0.59
Postmenopausal	239 (59)	
Size		
T1a–b	51 (13)	0.0006
T1c	181 (45)	
T2	170 (42)	
Nodal involvement		
0	156 (39)	0.0001
1–3	124 (31)	
>3	122 (30)	
Histological type		
1. Ductal, lobular infiltrating	344 (86)	0.002
2. Medullar, mucinous, papillar, others	48 (12)	
3. Tubular	9 (2)	
Histological grade		
GI	81 (20)	0.0001
GII	143 (36)	
GIII	178 (44)	
ER		
Positive	285 (71)	0.37
Negative	117 (29)	
PLI		
Present	60 (15)	0.003
Absent	342 (85)	
Kind of surgery		
Quadrantectomy	37 (9)	0.42
Radical mastectomy	229 (57)	
Modified radical mastectomy	136 (34)	

ER, oestrogen receptor. PLI, peritumoral lymphatic invasion.

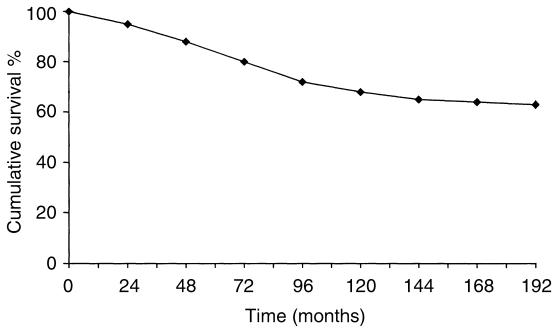

Fig. 1. Actuarial survival for all patients ($n = 402$).

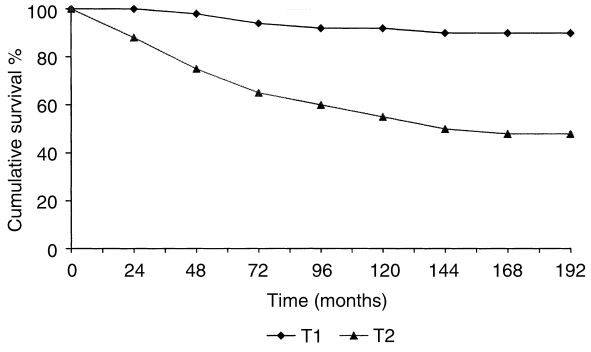

Fig. 2. Actuarial survival according to tumour size T1 = 232, T2 = 170 ($P = 0.0006$ Log-rank test) (95% CI: 1.91–4.32).

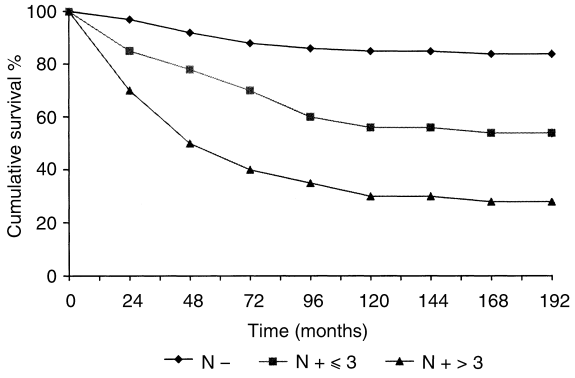

Fig. 3. Actuarial survival according to lymph node involvement N– = 156, N+ </= 3 = 124, N+ > 3 = 122 ($P = 0.0001$ Log-rank test) (95% CI: 2.31–6.20).

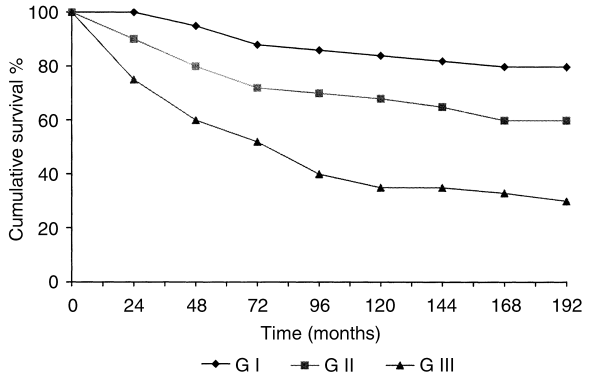

Fig. 4. Actuarial survival according to histological grade GI = 81, GII = 143, GIII = 178 ($P = 0.0001$ Log-rank test) (95% CI: 2.40–5.91).

Table 2
Results of Cox multivariate analysis

Variable	β value	SEM	*P* coefficient
Size			
1. T1a–b	2.11	0.05	0.0001
2. T1c	1.42	0.12	
3. T2	0.91	0.19	
Nodal involvement			
1. 0	2.85	0.02	< 0.0001
2. 1–3	1.90	0.10	
3. > 3	1.12	0.12	
Histological type			
1	0.20	0.32	0.3
2	0.51	0.25	
3	0.82	0.21	
Histological grade			
I	2.42	0.01	< 0.0001
II	1.55	0.08	
III	0.98	0.14	
PLI			
Presence	0.95	0.24	0.09
Absence	0.21	0.14	

SEM, standard error of the mean. PLI, peritumoral lymphatic invasion.

The 10 and 16 years survival rates were 88 and 85%, respectively, in the good prognostic group, 70 and 65%, respectively, in the moderate prognostic group, 40 and 34%, respectively, in the poor prognostic group ($P < 0.0001$ Log-rank test).

4. Discussion

The need to devise a prognostic index able to help predict the prognosis of patients with breast cancer has recently become the focus of many studies and many proposals have been made with different prognostic factors [10–12].

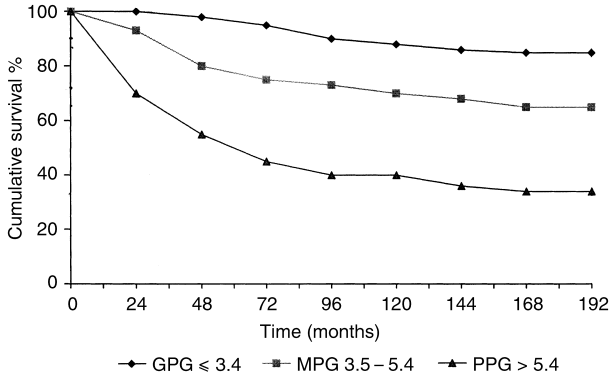

Fig. 5. Actuarial survival for the three prognostic groups according to Nottingham Prognostic Index (NPI) GPG = 110, MPG = 198, PPG = 94 ($P < 0.0001$ Log-rank test) (95% CI: 2.85–6.53).

The Nottingham City Hospital Study Group must be given credit for having been one of the first to advance, in 1982, a prognostic index derived from a multivariate analysis of nine factors. The NPI has afterwards been revised by the same authors [13]: for surgeons who favour axillary clearance an alternative is to number of axillary nodes involved (A = none, B = 1–3, C = 4 or more). In addition, many others have recently proposed to change or complete the NPI using, for example, additional prognostic factors [14], young age and very high ER values which have all been associated with worse prognosis [15]. The prognostic contribution of oestrogen and progesterone status to the NPI has been tested [16] and a temporary index (Kalmar Prognostic Index, KPI) has been derived and normalised to the NPI for comparison [17].

Considering the high predictive value of the NPI for survival, we have applied it to our patients with breast cancer. The survival curves obtained are similar to those for the factors with independent prognostic significance in our multivariate analysis.

For example, the 10 years survival of the good prognostic group was 88%. Indeed, a patient assigned to the good prognostic group usually has a small sized tumour (T1a–b) ($\leqslant 1$ cm), with a low grade and without axillary metastatic nodes and her 10 year survival rates, in our experience, were, for example 96, 84 and 85% with respect to each prognostic factor examined. There was not a significant difference between the mean (88.3%) of survival reported above and the survival derived from applying the NPI (88%).

In our univariate analysis, significant prognostic factors for survival were: size, nodal involvement, histological type, histological grade and the presence of PLI.

In multivariate analysis, only size, nodal involvement and histological grade remained independent prognostic factors, in accordance with the results of Nottingham Study Group analysis.

According to Rosen and coworkers [18], in patients with invasive ductal or lobular carcinoma, the risk of recurrence was significantly higher than in those with less common histological types such as tubular, mucinous and papillary carcinomas. In our series, the tumour type showed, in univariate analysis, a statistically significant prognostic validity. However, this significance was not found in the multivariate analysis.

The presence of PLI showed a very high prognostic significance in our experience ($P = 0.003$). Many authors have already considered PLI as a very important prognostic factor [19–21]. PLI was found to be positive in these series in 8–33% of cases. Clemente and colleagues [22] reported on the evaluation of PLI: when it was routinely determined the incidence was estimated to be 6.9%: if a histopathological review was performed and attention was primarily drawn to the presence of PLI, its incidence rose to 20% of patients. These data

indicate the need for a specific search for PLI in order to identify patients with a higher risk of relapse.

In our experience, PLI was present in 60 (15%) of patients and 9 (15%) of these later developed local recurrence: in the flap after mastectomy and in the breast after quadrantectomy. When PLI was included in the multivariate analysis, it was not significant probably because of its relationship to the stronger factors of lymph node stage and grade. PLI was not an independent prognostic factor for survival, but rather covaries with the other factors and that suggests it might be a predictor of local recurrence. That is confirmed by other authors: where PLI does appear to be a powerful factor in the assessment of the risk of local recurrence [13].

Our results showed a better 16 year survival rate especially in the moderate prognostic group (65%) and the poor prognostic group (34%) compared with those of Nottingham study (15 years survival of the moderate prognostic group of 42% and the poor prognostic group of 13%). These improved survival rates may be attributed to the exclusion of the 102 patients who did not meet the study requirements or may be attributed to the administration of adjuvant therapies (CMF and/or tamoxifen) to patients in the moderate prognostic group and the more aggressive cytotoxic regimen (CMF±doxorubicin + tamoxifen) to those in the poor prognostic group. Patients of the Nottingham Study were not routinely given adjuvant systemic therapy before October 1988, thereafter systemic therapy was given to all patients with an NPI > 5.4 (poor prognostic group) [23]. The authors in the current protocol offered adjuvant systemic therapy to all patients in the medium and poor prognostic groups

If the use of NPI in the selection of patients for adjuvant therapy (moderate prognostic group and poor prognostic group) is well proven and recommended, its greater clinical application lies in the selection of patients in the good prognostic group. In this group falls a relative small number of patients with a long-term survival and therefore so-called excellent prognostic group with a NPI $\leqslant$ 2.4. The chance of a patient in the excellent prognostic group relapsing is very small and so the benefit of adjuvant systemic therapy is negligible and not recommended. The NPI allows us to select this group. Effectively, it might be possible in these patients to avoid performing an axillary clearance, which we routinely perform.

Our current study in small breast cancers using sentinel lymph node biopsy, identified by lymphoscintigraphy or blue dye, enables the selection of patients with non-metastatic sentinel lymph nodes and consequent negativity of the remaining axillary nodes. These patients are presently not undergoing the surgical intervention of axillary clearance. Thus, this approach avoids the morbidity associated with a complete lymphadenectomy.

In conclusion, the use of the NPI, that we now routinely use, allows us to accurately predict the prognosis of patients with breast cancer and therefore to carry out surgical and systemic adjuvant procedures that are appropriate for the individual patient in order to improve survival and also quality of life. Finally, we advocate the common use of the NPI with the aim to increase the comparability of groups of patients receiving different treatments.

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