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The Nottingham Prognostic Index in primary breast cancer

Marcus H. Galea, Roger W. Blamey, Christopher E. Elston, Ian O. Ellis
Nottingham City Hospital, Nottingham, U.K.

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Summary

In 1982 we constructed a prognostic index for patients with primary, operable breast cancer. This index was based on a retrospective analysis of 9 factors in 387 patients. Only 3 of the factors (tumour size, stage of disease, and tumour grade) remained significant on multivariate analysis. The index was subsequently validated in a prospective study of 320 patients. We now present the results of applying this prognostic index to all of the first 1,629 patients in our series of operable breast cancer up to the age of 70. We have used the index to define three subsets of patients with different chances of dying from breast cancer: 1) good prognosis, comprising 29% of patients with 80% 15-year survival; 2) moderate prognosis, 54% of patients with 42% 15-year survival; 3) poor prognosis, 17% of patients with 13% 15-year survival. The 15-year survival of an age-matched female population was 83%.

Introduction

Lymph node status has been regarded for many years, and often still is regarded, as the main indicator of prognosis; certainly in the guidance of therapy it is the only factor taken into account in many centres and is the only factor used to stratify the majority of clinical trials. Lymph node involvement seemed to be such an important factor when radical lymph node surgery was perceived as a curative measure in breast cancer [1]; the clinical trials of the 1970's showed that prophylactic attack on the lymph nodes did not improve survival [2,3]. The channel of lymph node spread is not now regarded as the essential route for metastases, but rather as a useful marker as to whether blood stream spread has occurred. Lymph node status is a time-dependent prognostic factor — the longer the tumour has been growing the more likely it is to have spread to lymph nodes. Taken alone, lymph node stage is incapable of defining either a 'cured' group of patients or a group with a close to 100% mortality from breast cancer (Figure 1).

Prognosis depends not only upon the presence of distant metastases but also upon their virulence. The virulence of a tumour depends on a number of intrinsic biological factors — some measurable, such as growth rate or response to hormone therapies, and some not yet so, such as invasiveness or power of tissue destruction.

If real power of prognostication is required,

Address for offprints: Marcus H. Galea, City Hospital, Nottingham NG5 1PB, U.K.

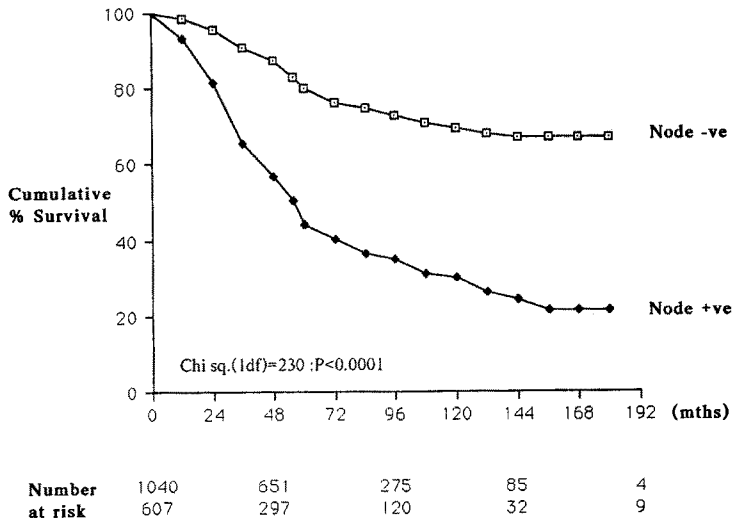

Figure 1. Patient survival by lymph node status: Nottingham series, 1976-1989

then an index must be used which makes use not only of Time-Dependent Factors, such as lymph node involvement, but also of Biological Factors.

The Nottingham Prognostic Index

In 1982 [4] we advanced a prognostic index derived from a retrospective, multivariate study of nine factors in 387 patients with primary, operable (clinical size less than 5 cm) breast cancer. All had undergone triple lymph node biopsy (low axilla, apical axillary, and internal mammary) [5]. Histological grading had been carried out by CWE [6]. Although a number of factors were related to survival in univariate analysis, only three remained significant on multivariate analysis (Table 1). The ß values in the multivariate analysis show the contribution of each factor to the estimation of survival. Thus, using the ß value for weighting, an index predicting survival was calculated:

> Nottingham Prognostic Index (NPI) =
> Size (cm) x 0.2 Stage (lymph node, 1-3 by level) + Grade (1-3: good, moderate, poor)

The higher the index the worse the prognosis.

Curves of survival by life table analysis methods showed excellent separation of patient groups depending on the index level, but since the index had been derived on these patients this was a self-fulfilling prophesy. The index was therefore tested prospectively in a further 320 patients [7] and an extremely good confirmation showed in the survival curves. The late extension of this study is shown in Figure 2.

Figure 3 shows the analysis on all of the first 1,629 patients in our series of operable breast cancer up to the age of 70. The index reproduc-

Table 1. Cox's multivariate analysis: data from 351 patients with primary operable breast cancer 1976-1981. Results used to derive the NPI.

Factors	Original analysis	
	β	Z
Menopause	0.5	1.5
Tumour size	0.17	2.92
Lymph node stage	0.76	5.29
Tumour grade	0.82	4.56
ER content	-0.34	-1.72
Longest survival	6 years	

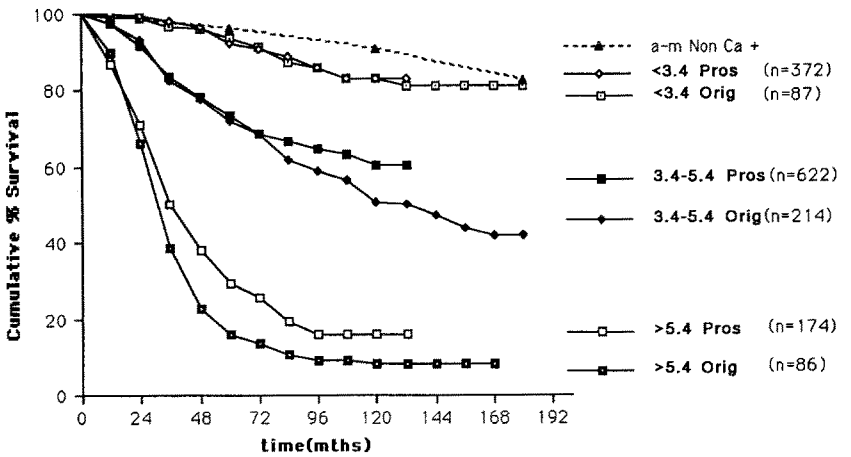

Figure 2. Prospective confirmation of the Nottingham Prognostic Index (log-rank analyses). Good prognostic group, < 3.4; moderate prognostic group, 3.4-5.4; poor prognostic group, > 5.4. Orig: original series, n = 387, 1976-1981; Pros: prospective series, n = 1168, 1981-1989; a-m Non ca: age-matched women, non breast cancer related deaths.

ibility defined groups of women who differ in their chances of dying from breast cancer and in their survival at 15 years after surgery. We have found the use of three groups useful — good (GPG), moderate (MPG), and poor (PPG) prognostic groups (Table 2, Figure 3).

The percentages of patients falling into each group shown in Table 2 are based on the situation prior to the introduction of breast cancer screening. Mammographic screening, which has been introduced on a three yearly basis, has changed the percentages falling into the groups in the 50-65 year age group. Of the invasive cancers detected at screening, around 40% fall into a so-called excellent prognosis group (EPG, NPI ≤ 2.4 and expected 15-year survival of 87%)

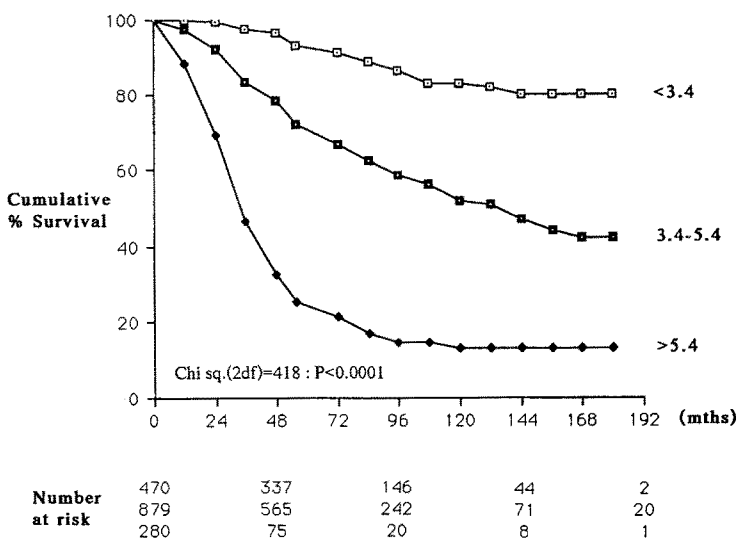

Figure 3. Patient survival: whole Nottingham series (n = 1629), 1976-1989

Table 2. The Nottingham Prognostic Index scores in 1629 cases of operable breast cancer, showing the numbers and percentage in each prognostic group, the expected 15-year survival for the 3 groups, and for comparison the expected survival of age-matched females from life-table statistics.

NPI	n	%	15-year survival
Age-matched female population			83%
GPG (< 3.4)	470	29%	80%
MPG (3.4-5.4)	879	54%	42%
PPG (> 5.4)	280	17%	13%

(Table 3), and at least 1 in 2 of all breast cancers occurring in this age group are detected at screening examinations.

Clinical application of the NPI

The different outlooks that may be ascribed to these patients require different therapeutic strategies. For example, a woman in the PPG has a very poor survival chance (only 40% by 3 years). This is comparable to survival in locally advanced breast cancer (stage III or tumours greater than 5 cm diameter). Several groups are now evaluating aggressive cytotoxic regimens as the initial treatment for locally advanced breast cancers; the only present possibility of improving survival in the PPG would seem to be to follow this line. Certainly patients in this group require adjuvant systemic therapy, usually cytotoxic.

An example at the other end of the scale lies in the women in the EPG. Such cancers are frequently detected by breast cancer screening: small (≤ 2 cm), well-differentiated, and often of special histological type (tubular or tubular-mixed) and node-negative; they may be regarded as cured by the initial surgery. There is little chance of the patient developing signs of distant spread and therefore adjuvant systemic therapy is not required. The definition of such a group has been the target of many studies — each trying to add a single factor to lymph node negativity. No such study has matched the NPI in the definition of a 'cured' group who do not require adjuvant systemic therapy.

In the screened population a substantial number of EPG cancers are detected. The proportion of EPG cancers in the unscreened population is low (Table 3). The next question regarding adjuvant cytotoxic therapy is whether the group who do not need such therapy may be extended beyond the EPG. The good prognostic group (GPG) has a very good survival at 15 years in comparison with age-matched women in the population at large. However, inspection of Figure 3 shows that the curves of these two groups diverge a little before coming together. The chance of dying of breast cancer is higher in the GPG women than in the population at large — some 10% will die from breast cancer. Tamoxifen adjuvant therapy is successful in giving a small extension of disease-free interval and of life in women who die from breast cancer [8]. However, the gain is small and only 1 in 10 women in this group stand to benefit. Although tamoxifen is largely without serious side effects, there are some (menopausal symptoms in premenopausal women, uterine atypia and risk of uterine cancer, rare hepatic problems, retinopathy, loss of libido). Also the women in the GPG have largely ER positive tumours and are likely to be those responding best if metastatic disease presents [9]. It therefore seems reasonable overall to withhold

Table 3. The distribution of 134 cancer detected in the prevalent round of mammographic screening (Nottingham), by prognostic index. Comparison is made with the frequency distribution by prognostic index in the unscreened population.

NPI Group	Screened		Unscreened
	n	%	%
EPG	59	44%	13%
GPG	102	76%	29%
MPG	27	20%	54%
PPG	5	4%	17%

hormonal adjuvant therapy in the GPG. The very small potential benefit for the group as a whole means that cytotoxic therapy is contradicted in this group.

The GPG is composed of node-negative, grade II tumours and node-positive, grade I tumours. The arguments on the application of systemic adjuvant therapy have largely revolved around node-negative patients, but it should be noted that here is a node-positive subgroup in which the need for this treatment is at least debatable.

A summary of how the NPI can be used to guide therapy is shown in Table 4.

The factors comprising the Index

The index depends for its power on the synergism between Time-Dependent Factors and Biological Factors. The three factors to remain significant in the NPI after multivariate analysis were two time-dependent factors, size and lymph node stage, and the biological factor histological grade.

Primary tumour size

Both clinical and pathological tumour size have been shown to be useful independent prognostic factors [10-12]. The decreasing survival associated with increasing tumour size (pathological) is illustrated well by data from over 1,600 primary operable breast cancer patients treated on the Nottingham Unit; patients with tumours ≤ 2 cm had a 65% chance of being alive at ten years compared to 24% in those patients with tumours of 4-5 cm.

Lymph node involvement

Node-positive patients have significantly worse prognoses than node-negative patients and many publications describe this finding [11,13-14]. Data from this unit has already been illustrated in Figure 1.

Apart from the prognostic information afforded by the simple distinction between positive and negative nodes, the number of nodes involved and the level of nodal involvement are important. Fisher [15], reporting on 505 node-positive patients, noted a five-year survival of 73% for 1-3 nodes involved, dropping to 48% if 4-12 nodes were positive.

The prognostic importance of the level of nodal metastases was first reported by Adair [16], who showed a five-year survival of 65% for patients with level I involvement, 45% for level II involvement, and 28% for level III. This association of prognosis and level of nodal metastases holds true for tumours of any given size [17,18]. In Nottingham the level of node involvement has been used to further subdivide the lymph node positive patients [4]. Combining the number of positive nodes and the level of involvement in one analysis, Smith [19] and Barth [20] both report that survival is more closely related to total number of metastatic nodes than level of involvement.

The internal mammary chain of nodes has also been biopsied in Nottingham. Analysis of this data by du Toit [21] showed that only 6% of patients would have been understaged by the omission of internal mammary node sampling, although this procedure appears useful in medial tumours. This analysis also showed that when both chains of nodes were involved the prognosis was equivalent to that of high (apical) node

Table 4. Simplified therapeutic guide by NPI.

NPI Group	Initial treatment	Axillary irradiation	Systemic adjuvant
EPG	CE[a] only	No	No
GPG	CE + RT[b]	No	No
MPG	CE + RT	No	Hormonal
PPG	Mastectomy	Yes	Cytotoxic

[a] CE = complete excision.
[b] RT = radiotherapy.

involvement.

Tumour size and lymph node status have above been discussed as separate factors but, as expected for time-dependent factors, a direct relationship exists between the two. The contribution of tumour size is proportionately higher in patients with low grade node-negative tumours than it is in patients with high grade node-positive tumours.

Histological grade

The correlation of grade with prognosis has been confirmed by many reports [22-27]. Despite this considerable body of evidence, histological grade has not been widely accepted because of apparent high inter and intra-observer variability [28-30]. In many units it is still not regarded as an important procedure in routine diagnostic breast pathology. These deficiencies have been addressed by Elston [6], who has defined clear criteria for semi-quantitative measurement of these components scored 1 to 3 in a manner that should be comparable between centres.

Improvement of the Index

Improvement depends upon making the time-dependent and intrinsic factors more accurate.

Time-dependent factors

Lymph node staging. Obviously the more nodes removed the more accurate the staging, but the constraint on this approach is the morbidity of axillary clearance. Chetty [31] has shown that axillary sampling — in which at least four nodes were taken — is as accurate as clearance in staging simply to node-positive or -negative.

Micrometastases in lymph nodes. Serial lymph node sectioning with conventional histochemical staining or routine sectioning with immunohistochemical staining have been used to identify micrometastases. Conversion rates of between 9-14% are reported [32,34], but only the study from the International (Ludwig) Breast Cancer Study Group [35] found this to be of prognostic significance. More specifically, it appears that if the micrometastasis is ≤ 2 mm, it does not carry a significantly worse prognosis in comparison with node-negative patients [36,37]. In our own study using monoclonal antibodies CAM 5.2 (specific for low molecular weight cytokeratin) and NCRC-11 (specific for epithelial mucin antigen), positive immunohistochemical staining for occult lymph node metastases was seen in 9% of apparently node-negative patients; deposits were under 2 mm, with one exception, and the finding appears to have made no significant difference to their prediction of survival [38].

Vasculo-lymphatic invasion (VI). This is a poor prognostic sign [39-41]. Not surprisingly, VI correlates with node stage (Table 5) but also to some extent with grade.

Table 5. Cross-tabulation of vascular invasion with node status.

	Node-negative	Node-positive
VI-negative	970	285
VI-positive	207	287

Chi-square = 242 (1 d.f.); $p < 0.0001$

Table 6. Multivariate analysis of most recent analysis of Nottingham data (n = 1475), entering tumour size, histological grade, lymph node status, vasculo-lymphatic invasion (VI), and tumour type (TT).

	β	Z
Grade	0.70	8.4
Node status	0.74	12.9
Size	0.14	4.7
VI	0.19	3.8
TT	0.23	3.4

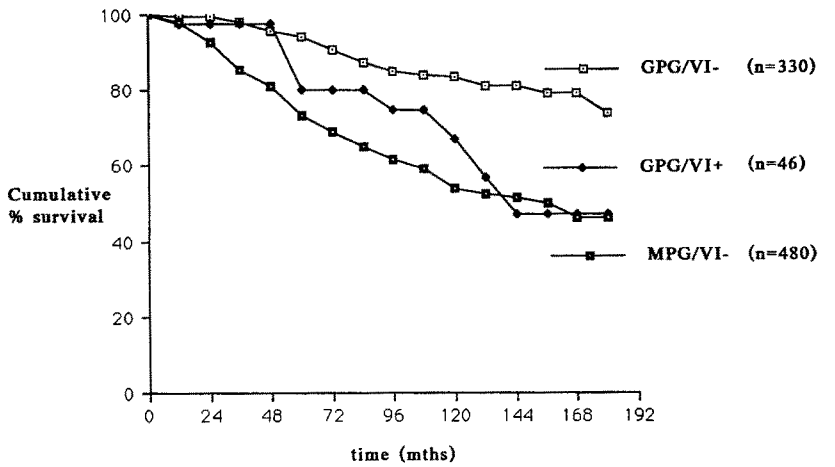

Figure 4. The influence of vascular invasion (VI) on cases in the good prognostic group

In multivariate analysis of the Nottingham series, VI is nearly eliminated by its relation to the stronger factors of stage and grade (Table 6), but retains a small independent power despite this. The hazard is not proportional to the other factors, and patients in the GPG with VI have a survival more akin to that of the MPG (Figure 4).

Where VI does appear to be a powerful factor is in the assessment of risk of local recurrence. In Nottingham, of 721 patients who received simple (total) mastectomy alone, 216 had VI and 35% of these later developed local (in-flap) recurrence [42]. VI also codes strongly for local (in breast) recurrence after treatment by tumourectomy with intact breast irradiation [43,44].

Intrinsic biological factors

These represent features of tumour biology which appear to change little in the tumour lifetime. They reflect the biological aggressiveness of tumours and the cellular functions.

New intrinsic factors. Over the years many biological prognostic factors have been assessed in Nottingham. These include histological grade [6], tumour type [45], ER status [9], binding of epithelial mucin antibodies [46], DNA index and SPF fraction [47], c-erbB-2 [48], c-myc [49], and *Helix pomatia* lectin binding [50]. Each relates to prognosis but also to grade, and in multivariate analysis, grade consistently emerges as the most powerful (and after its inclusion, the only) significant prognostic factor.

Many of these factors have been the subject of encouraging reports in the world literature. It is worth observing that although some show excellent prognostic separation at perhaps two years, any significant difference may be eliminated by 5-10 years. Ploidy, ER, and possibly EGFR are clear examples of this: ER shows by eighteen months a 15% mortality in the positive group and a 30% mortality in the negative — a 100% difference in mortality but only a 5% difference in case survival. By 10 years the mortality is the same. Analysis too early has lead to many misleading publications on the value of individual prognostic factors.

Some factors, however, have prognostic importance not strictly related to survival; ER for example predicts hormone responsiveness after primary treatment failure [9] and also in the adjuvant situation [8].

Tumour type. In the absence of histological grade, tumour type is a strong intrinsic factor (Table 7). Despite its relation to grade, typing does provide a little extra to the multivariate estimation of survival (Table 6).

Making the Index usable by other centres

Objective measurements of grades

Grade is the paramount intrinsic factor. The objections regarding its reproducibility have in part been answered but are dependent upon the individual enthusiasm of the pathologist. Because of this problem we have recently looked to using machine technology to derive an objective grading, equivalent in its power and usefulness to histological grade and measurable by a technical officer. The approach adopted was to try to identify objective and reproducible surrogate measurements, made by a technical officer, of the components of grade: nuclear pleomorphism, mitosis, and tubule formation. The morphometric variable of standard deviation of nuclear size (OBSZSD) was found to be the best morphometric measure of nuclear pleomorphism and was measured by image analysis (CAS 200, Becton Dickinson); proliferative index (PI, the sum of G2M and SPF) was taken to replace mitotic rate and was measured by flow cytometry (FACS Analyser, Becton Dickinson), staining with NCRC-11 (anti epithelial mucin antibody), which on immunohistochemistry shows the strongest staining in cells lining tubules, was assessed as a measure of tubule formation; NCRC-11 binding was measured by flow cytometry, and ER status and c-erbB-2 expression were added as measures of functional differentiation. In a stepwise regression analysis (n = 331) controlling for histological grade, only OBSZSD and PI showed independent association. Combining these two variables a grade equivalent 'Score' was derived. Strong association of Score is seen with histological grade (Table 8). However, it is not yet as good as histological grade in picking out the very good and very poor prognostic tumours, as shown by survival curves.

Table 7. Frequency of each histological type and 10 year survival in the Nottingham series.

Type of carcinoma	Relative frequency %	10-year survival %
Ductal NST	49.0	47
Lobular	16.0	54
Tubular	2.5	90
Tubular mixed	14.2	69
Cribriform	0.8	91
Mucinous	0.9	80
Medullary	2.8	51
Atypical medullary	4.9	55
Mixed ductal & lobular	5.0	40
Mixed ductal & special type	2.6	64
Miscellaneous	1.3	60

Alternative scoring of stage

Stage was scored in Nottingham from single node biopsies and using level of involvement. Our latest analysis uses: Stage A = confined to breast, Stage B = confined to low axilla (or) internal mammary node only, Stage C = both axillary and IM chains involved (or) apical node (adjacent to axillary vein at first rib) involved.

An alternative is to use the number of axillary nodes involved, having biopsied at least four, i.e. A = none, B = 1-3, C = 4 or more. This is of

Table 8. Cross tabulation of histological grade and equivalent 'Score' ranges.

	GRADE		
SCORE	1	2	3
< 33	28	22	16
33 - 52	25	77	25
> 52	7	34	97

Chi-square = 92.3 (4 d.f.); $p < 0.0001$

obvious applicability to those surgeons who favour axillary clearance.

Relevant work from other centres

Chevallier in an analysis of 379 patients identified young age, tumour size, and histological grade as factors which added to lymph node stage in the prediction of recurrence. These factors were combined to divide lymph node negative patients into three prognostic groups [51].

The factors of size, lymph node stage, and mitotic index emerged as having independent significance in a series of 281 patients from The Netherlands [52]. These factors were combined to produce an index which provided good prognostic separation.

Following the work on the Nottingham index, a group from Melbourne looked for similar factors. They did not have reproducible histological grading and therefore used steroid receptors as their intrinsic factor. An index of prognosis was constructed using age, size, lymph node stage, and ER value [53]. This gave good separation into three prognostic groups.

One of the strengths of the NPI is that it has been verified prospectively. A recent study by the Yorkshire Breast Group has now verified the NPI in another centre: each of the prognostic groups in this set has actuarial survival at 10 years within 1% of the survival of the Nottingham patients [54].

Discussion

The outlook at the diagnosis of breast cancer differs widely; from death within one year, to a personal cure of the disease with the patient alive and well 30 years later. In those women who develop symptomatic distant spread the pattern is equally variable; some with bone metastases respond well to endocrine therapy, while others with visceral metastases are unresponsive to anything.

These events are not random and may be predicted from analysis of the primary tumour. The Nottingham Prognostic Index results from such an analysis, and gives an excellent indication of prognosis. A group of patients comprising one quarter of all operable breast cancers is selected in which the prognosis is good; the chance of dying from breast cancer over the next 15 years is around 10%, while by 15 years the chance of overall survival is little short of the age-matched female population at large. Another group of one fifth of the operable breast cancers is selected with a very poor outlook.

The NPI has a greater power for this selection than other prognostic methods, such as the combination of a single factor, e.g. c-erbB-2, with lymph node status. The biological factor used in the NPI is histological grade. This reflects a number of other factors and has consistently outscored them in comparative analyses within our own series. The possibility of replacing histological grade, which is measured semi-quantitatively by Elston's method in Nottingham [6], with the objectively measured 'Score' has been described above, but as yet 'Score' is less powerful than grade.

The use of the NPI in selection for adjuvant therapy has been commented on above. Indeed, a described index having the power to select a group in which the great majority will be long term survivors, should make redundant the 'industry' which at present is responsible for the numerous publications which seek to add one factor to lymph node negativity to make this prediction.

The index, however, has other clinical uses. The predictive power described amounts to, for example, a 90% sensitivity and a 50% specificity in the selection of long term survivors. Expensive and time consuming techniques, such as isotope bone scanning and marrow aspiration, show the presence of undetected metastases; the NPI does just this, but with much greater accuracy and

much more simply.

In addition to adjuvant systemic therapy, selection is required for adjuvant radiotherapy to lymph nodes and flaps after mastectomy. Overall, if neither irradiation nor axillary clearance are carried out, some 40% of patients will develop loco-regional recurrence [55,56]. To carry out prophylactic irradiation on all of these would mean that 60% received this treatment unnecessarily. The challenge is to select those women who would develop loco-regional recurrence and to treat them only. We have showed that such recurrence is largely confined to women in the PPG [56], and have subsequently shown in a randomised trial that adjuvant irradiation of this group significantly reduced loco-regional recurrence [57].

The index may be applied for the indication of suitability for treatment of the primary tumour with breast conservation. Patients in the EPG have been treated with wide local excision without subsequent radiotherapy. Although follow-up is only up to 2 years in this group, we have treated 57 such patients with only one local recurrence. Patients outside this group are treated with the addition of intact breast irradiation but without very wide excision (such as quadrantectomy as described by Veronesi [58]). Local recurrence within the treated breast occurred in some 20% in our initial series [43]. We identified the factors responsible for local recurrence — patients in the PPG in general fared badly. However, in this series, as in that from the Institute Curie [44], factors with the greatest power of prediction of local recurrence were Vascular Invasion, Young Age, and Size. We altered our criteria for the selection of patients suitable for treatment with wide local excision and irradiation according to these factors and now have achieved a low rate of local recurrence without very wide, cosmetically poor, excision. Again we see the use of predictive factors, this time combined into a somewhat different index for a different prediction.

The NPI also has uses in counselling the individual patient. For example, a young woman with breast cancer may well ask whether she can have another pregnancy. Her NPI value shows her chance of survival: a woman in the PPG is clearly ill advised to have further children since they will almost certainly be motherless in a few years, while women in the GPG (and certainly in the EPG) should be encouraged to look upon themselves as cured and to live a normal life.

Decisions on follow-up may be guided by the NPI. Women in the GPG perhaps do not need regular follow-up in a breast clinic — the chance of a problem arising in subsequent years is small. Their main threat may be the occurrence of a new cancer in the opposite breast; they do require screening of this breast. Women in the PPG have an annual interval probability of distant and of local recurrence of around 30%; they must therefore be followed at relatively short intervals. There might be a case for using tumour markers such as CA 15-3 in the follow-up of this group [59]; however, regular mammographic screening of the opposite breast is ineffective as there is little point in the early detection of a second breast cancer in a woman programmed to die from her first.

In this paper we have demonstrated the power and reproducibility of the NPI. Important decisions for the individual patient are based on this index. Even now papers appear [60,61] stating that if a reliable index of prognosis existed, decisions as to whether a woman should or should not receive adjuvant therapy would be made on a national basis. Such an index does exist in the Nottingham Prognostic Index.

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