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Reading the prognosis of the individual with breast cancer

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ABSTRACT

Aim: To obtain better survival estimates for the individual than is provided by placement in an NPI group.

Method: Consecutive primary operable breast cancers treated at Nottingham City Hospital 1990–1999. Ten year % actuarial survivals plotted for 10 ranges of NPI from 2.0 to 6.9. There is an excellent inverse correlation between median NPI value for each range and survival at 10 years. To enable estimation of survival for all individual values of NPI, a curve fitting technique applied to these results (by G.B.) gave the formula to estimate survival from the individual's NPI score: 10 year % survival for the individual = $-3.0079 \times \text{NPI}^2 + 12.30 \times \text{NPI} + 83.84$. This gave an r^2 of 0.98.

Results and conclusion: Greater accuracy in individual survival prediction is obtained by dividing women into 10 groups by NPI scores than in the originally described six groups; rank order of survival in relation to NPI score is preserved. A curve fitting technique has been applied to these data to give a formula for the prediction of 10 year survival for every 0.1 value of NPI.

1. Introduction

The Nottingham Prognostic Index (NPI) is widely used for the estimation of prognosis of primary breast cancers. The Index integrates independently significant prognostic factors recognised in multivariate analysis and satisfies the criteria for a method of good prognostic discrimination: accurate recognition of groups with significantly differing survival chances and small confidence intervals; placement of sufficient percentages of cases into each group; prospective validation in other tumour sets both – intra[1] and inter centre,[2–5] application to young women[6]; to pre- and post-menopausal women; to small tumours[7]; to cases detected at screening as well as presenting symptomatically[8]; ease and low cost of evaluation.

At present the Index is used to stratify to six groups and the prognosis for the individual is given as that of the group in which the patient lies. This represents an average, for the group covering a range of NPI values of 1.0. This paper describes a method for the allocation of the survival chance for an individual NPI score.

2. Materials and methods

The derivation of the NPI,[9] verification and methods for measurement and calculation[10] have been previously described. The NPI is calculated as Grade (measured 1–3) + Lymph Node (LN) Stage (measured 1–3) and Size (0.2 × maximum diameter in cm). The higher the NPI the worse the outcome (Fig. 1); the range of values of NPI is from 2.04 to 6.98; the range of 10 year survival estimates is between 33% for the Very Poor Prognostic Group and 95% for the Excellent Prognostic Group.

The survival of breast cancers has improved since the 1980s, when the NPI was first described and survival figures for NPI groups have been updated by analysis of cases treated in 1990–1999.[11]

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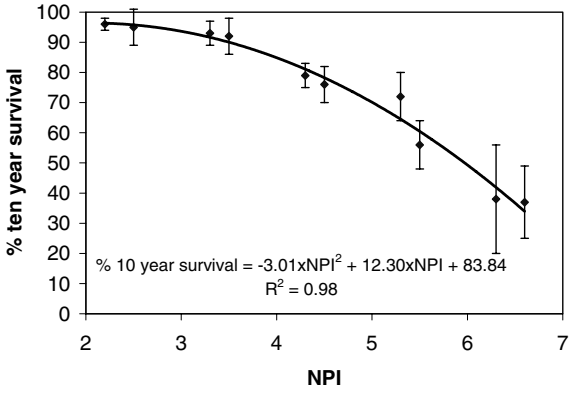

Fig. 1 – Median NPI values within each 0.5 NPI value range plotted against 10 year % survival for that range (breast cancer specific, 1990–1999 tumour set) with plot of best fit by second-order polynomial function: individual 10 year survival = $-3.0079 \times NPI^2 + 12.295 \times NPI + 83.84$.

2.1. *Patients*

The data set is consecutive cases of primary operable (tumour diameter <5 cm) invasive breast cancer, in women aged 70 or less, undergoing surgery at Nottingham City Hospital in 1990–1999 (inclusive), originally under the care of a single surgeon (RWB) and later under the care of the multidisciplinary Nottingham Breast Unit ($n = 2261$).

Adjuvant systemic therapies were protocolled according to the NPI group in which the patient lay. Systemic therapy was prescribed to the Excellent and Good Prognostic Groups. The Moderate I group received hormonal therapy for ER positive tumours. The Moderate II, Poor and Very Poor Groups received hormone therapy for ER positive tumours and cytotoxic therapy for ER negative.

All patients have been followed up regularly in the hospital Primary Breast Clinic (PBC) and data on survival and recurrence recorded. At death, the hospital notes are examined and deaths allocated to 'With or from breast cancer' or to 'Without known breast cancer'. Patients with previously diagnosed distant metastatic spread, even if in complete remission are allocated the former; women dying without prior distant recurrence and without uncontrolled local or regional recurrence, are allocated the latter (unless a post-mortem study indicates otherwise). The survival curves may then be constructed for both breast cancer specific and for death from all causes.

Median follow-up is 8.3 years to May 2005.

3. Results

For the 1990–1999 tumours 10 year life table based survivals (breast cancer specific) have been examined (Kaplan–Meier) for 10 ranges of NPI from 2.0 upwards (Table 1); survival descends in rank order from 96% in the 2–2.4 NPI range to 37% at 6.41–7.0; 95% confidence limits are also shown.

Fig. 1 shows the plot of these percentage 10 year survivals, against the median NPI for each range. Superimposed is the line of best-fit obtained using a second-order polynomial function ($r^2 = 0.98$). Other curvilinear functions were tested but showed lower regression coefficients (data not presented).

Table 1 – Actuarial 10 year percentage survival in NPI ranges of 0.5 intervals

NPI range	*n*	Median NPI	10 year % Survival (BCS)	±95% CL
2.00–2.40	321	2.2	96	2
2.41–3.00	32	2.5	95	6
3.01–3.40	441	3.3	93	4
3.41–4.00	134	3.5	92	6
4.01–4.40	504	4.3	79	4
4.41–5.00	316	4.5	76	6
5.01–5.40	170	5.3	72	8
5.41–6.00	203	5.5	56	8
6.01–6.40	33	6.3	38	18
6.41–7.00	86	6.6	37	12

The expected 10 year breast cancer specific survival for an individual NPI value is obtained by applying the formula: $-3.0079 \times NPI^2 + 12.295 \times NPI + 83.84$.

Interpolation models using continuous NPI, NPI-squared and NPI-cubed covariates were also developed (NPI scale = 0.1). These models had r^2-values of 0.60, 0.61, and 0.61, respectively. The line of best fit equations were %10 year survival = $-4.07NPI^2 + 22.96NPI + 56.97$, %10 year survival = $-0.04\ (NPI^2)^2 + 0.22\ NPI^2 + 88.56$ and %10 year survival = $-0.00042(NPI^3)^2 - 0.097NPI^3 + 90.17$, respectively. These showed significantly poorer performance than the interpolation model using higher resolution.

Cox regression was not conducted on these variables as the purpose of this paper was to evaluate the existing NPI derived from Cox regression on new data and not to derive a new NPI.

To investigate the validity of the fitted response curves summarising the relationship between NPI and % 10 year survival, the data were divided into two groups (odds and evens on the data base of cases entered consecutively), for which curves were plotted using second-order polynomial function (Fig. 2). Data were applied reciprocally between one curve and the other to predict survival as if on blind data. The results of the analysis indicate a general concordance between the two graphs and no significant difference as identified by the confidence intervals of the points. The greatest

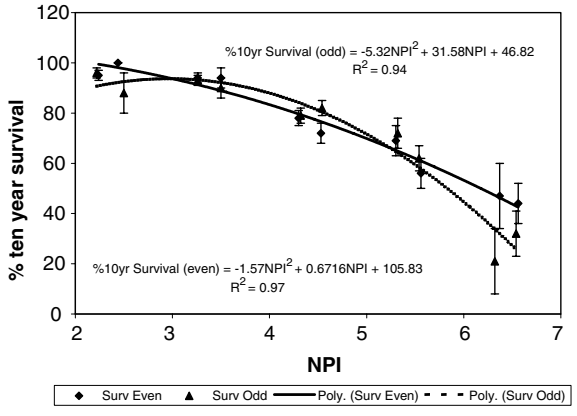

Fig. 2 – Data divided to two groups for validation showing general concordance between the two graphs and no significant difference as identified by confidence limits of the points.

Table 2 – Under and over estimates of survival when NPI group values (Kaplan–Meier) are used for estimating the survival of an individual rather than individual values from the polynomial function

NPI Group	Individual NPI	10 % Survival according to	
		NPI Group In which individual NPI lies (Kaplan–Meier)	Individual NPI from Polynomial function
EPG	2.0	96 ± 2	96
	2.4		96
	2.5	93 ± 4	96
	3.4		91
MPG I	3.5	82 ± 4	90
	4.4		80
	4.5	75 ± 4	78
	5.4		63
PPG	5.5	53 ± 8	60
	6.4		39
	6.5	39 ± 12	37
	7.0		23

differences between the curves occurred at the high NPI values where the confidence limits were greatest.

Table 2 shows the maximum over or underestimate of survival when the NPI group survival is used rather than individual values: the individual NPI values shown are those for the top and bottom of the range of each NPI group.

4. Discussion

A prognostic estimate is given for any individual with primary breast cancer. Although the group value is usually a good enough estimate in clinical work, in certain cases the individual estimate is better. Internal validation for individual values is impossible without a very large series, since numbers are only high enough for validating the NPI group predictions. Internal validation by splitting patients to 10 ranges of NPI retaining rank order of survival (Table 1) and the assumption that this would be preserved on splitting to more groups and finally to individual values seem reasonable. The fitted polynomial curves show no significant differences between the two halves of the split set.

As examples of cases in which the individual values appear to reflect predicted outcome better than by using the NPI groups (Table 2):

1. Two patients with NPI's differing little, of 5.4 and 5.5 lie in different NPI groups (Moderate II and Poor), giving estimated breast cancer specific 10 year survivals of 75% and 53%, respectively, a 22% difference. Calculation for the individual from the formula for the individual NPI values gives their survivals as 63% and 60% respectively, only a 3% difference.
2. Two patients have NPI's of 4.5 and 5.4; they both lie in MPG II therefore giving no apparent difference in their estimated 10 year group survivals of 75%. However, from the formula, their individualised survivals are 78% and 63% respectively, a 15% difference.

Whilst the relative risk reduction from adjuvant therapies is well known, the potential absolute gain is the important knowledge for patient and clinician. Knowledge of the predicted 10 year survival is essential in estimating the magnitude of absolute gain to the individual from adjuvant therapies and in explaining the importance of these therapies.[12]

The individual estimate is also likely to be of particular use in estimation of loss of life expectancy in medico-legal cases, for which because of the shape of the survival curves, a 10% difference in 10 year survival transforms to a very large difference in life expectancy.

The method of prognostic prediction presented here gives greater accuracy in assessing the survival chance for the individual than that obtained for the NPI group in which the patient lies.

Conflict of interest statement

None declared.

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