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Comparison of Nottingham Prognostic Index and Adjuvant Online prognostic tools in young women with breast cancer: Review of a single-institution experience

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Keywords:
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ABSTRACT

Objective: Accurately predicting the prognosis of young breast cancer patients (<40 years) is uncertain since the literature suggests they have a higher mortality and that age is an independent risk factor. We considered two prognostic tools; Nottingham Prognostic Index and Adjuvant Online (Adjuvant!), in a group of young patients, comparing their predicted prognosis with their actual survival.

Setting: North West England

Participants: Data was prospectively collected from the breast unit at a Hospital in Grimsby between January 1998 and December 2007. A cohort of 102 young primary breast cancer patients was identified and actual survival data was recorded. The Nottingham Prognostic Index and Adjuvant! scores were calculated and used to estimate 10-year survival probabilities. Pearson's correlation coefficient was used to demonstrate the association between the Nottingham Prognostic Index and Adjuvant! scores. A constant yearly hazard rate was assumed to generate 10-year cumulative survival curves using the Nottingham Prognostic Index and Adjuvant! predictions.

Results: Actual 10-year survival for the 92 patients who underwent potentially curative surgery for invasive cancer was 77.9% (CI: 69.3 – 86.5%). There was no significant difference between the actual survival and the Nottingham Prognostic Index and Adjuvant! 10-year estimated survival, which was 77.3% and 82.1% respectively. The Nottingham Prognostic Index and Adjuvant results demonstrated strong correlation and both predicted cumulative survival curves accurately reflected the actual survival in young patients.

Conclusions: The Nottingham Prognostic Index and Adjuvant! are widely used to predict survival in breast cancer patients and now have been shown to be statistically robust when compared to the actual survival of a group of young breast cancer patients.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- Based at a single institution leading to high level of standardization. All patients were discussed at multi-disciplinary team meeting attended to by the same team during the study period and the same team of surgeons carried out all surgery. Histopathology reporting was also a constant through out the study.
- The study population in North England including the areas around Scunthorpe and Grimsby contain a very static and the population demographic is constant.
- The Adjuvant online (Adjuvant) and Nottingham Prognostic Index (NPI) have not previously been compared in a sample of young women with breast cancer.
- Long follow-up period of participants in comparison to other published studies. Our median follow up time was 91 months compared to an average of 73 across other studies.
- No missing data or participants lost to follow-up.

Limitations

- Study sample may not be representative of the entire UK population.
- Relatively small sample size leading to low power, which meant a statistical difference between the NPI and Adjuvant was not demonstrated.
- The HER 2 data was not readily available for the majority of study participants. It is now used widely as guide to recommending treatment, however, it is currently not included in either the NPI or Adjuvant! calculations.

INTRODUCTION

Will I live? This is the question that many patients directly or indirectly ask when given the diagnosis of breast cancer. This question is particularly difficult to answer in “younger patients” since breast cancer in young patients is often considered to be a more biologically aggressive disease with a poorer prognosis compared with older women.[1-3] The definition of “young” also varies between different studies with most authors identifying the upper age limit ranging from <35 years,[4,5] to ≤40 years.[6-9]

Since screening is unlikely to ever include women under the age of 40, for the purposes of this study we defined “young” as patients presenting at <40 years of age. In the UK, breast cancer is the most common female cancer. The incidence of women < 40 years of age varies from 4% in Belfast,[8] 6.2% in Italy,[2] and 7% in USA.[6]

There are two widely accepted clinical tools used to calculate an individual’s prognosis, the Nottingham Prognostic Index (NPI) and the Adjuvant Online (Adjuvant!). The NPI combines nodal status, tumour size and histological grade in a simple formula. Its advantage in prognostic discrimination has been validated by various studies and it is used widely in clinical practice.[10-12] Lee & Ellis suggested that the NPI could be used for counseling patients with regard to their prognosis but this has not been validated specifically in younger patients.[13]

Adjuvant! (http://www.adjuvantonline.com) is a web based risk-assessment programme that was developed in a population from North America. The software uses similar factors to the NPI but also includes; patient age, hormone receptor status and comorbidity level.[14] These variables are used to calculate the patients estimated 10-year survival probabilities, risk of relapse and the expected benefit of adjuvant therapy. A large population based study of Canadian women of all ages with early breast cancer has validated the Adjuvant! model.[15]

The objective of this study was to initially identify the actual survival data for a cohort of young breast cancer patients treated in the UK. We then compared these results with the calculated survival as assessed by both the NPI and Adjuvant! This enabled us to evaluate the predictive power and accuracy of these prognostic tools in young breast cancer patients.

MATERIALS AND METHODS

This is a single-centre study, which prospectively collected information over ten years from January 1998 to December 2007. The database included all primary breast cancer patients diagnosed and treated in the Grimsby Breast Unit from 1998 to 2002 and the South Bank Breast Unit, which was the amalgamated service of the breast clinics in Grimsby and Scunthorpe increasing the population base from 200,000 to 420,000 people in 2003-2007.

Patients

There was a cohort of 102 primary breast cancer patients who were less than 40 years of age at the time of presentation. This equaled 5% of all breast cancers treated during the 10-year study period in this unit. Patients were excluded from the study if they were diagnosed with "pure" ductal carcinoma in-situ (DCIS) [n=5] or if they had metastasis at presentation [n=5]. There were 92 women with invasive disease and who had undergone potentially curative surgery in this study. Their age range was 26-39 years. Overall survival was defined as the time between first diagnosis of cancer and death from any cause, regardless of recurrence events. Patients who had neoadjuvant chemotherapy were not excluded because there is evidence that the NPI retains its prognostic value after this form of treatment.[16]

The case records of all patients were surveyed and the following details recorded: Age at presentation, tumour size as measured at histology, tumour grade, oestrogen receptor status and the number of positive lymph nodes. These factors were then used to calculate both an NPI score and the 10-year survival probability using Adjuvant!. To use the Adjuvant! tool it is necessary to input other factors including the patient's comorbidity level, oestrogen receptor status and age. All the patients in this study were fit, so comorbidities defined as 'average for age.' Oestrogen receptor (ER) positivity was determined using the Allred score. At the time of study, if the Allred score was greater than three, the oncologists would offer anti-hormone treatment.

Actual survival data was recorded using the continuously updated hospital electronic records system. These figures were documented at the beginning of 2012, which allowed a follow-up period of between four and fourteen years. No individuals were lost during the follow-up period, which meant all 92 women contributed to the overall survival.

Treatment

All women involved in the study received treatment for breast cancer with what was considered the best practice and in accordance with network and national guidelines at the time of diagnosis. Surgery involved either breast conserving surgery followed by radiotherapy or a simple mastectomy with or without immediate reconstruction. Only six patients received neoadjuvant chemotherapy following multi-disciplinary team (MDT) discussion. The main treatment differences over the study period of 1998-2007 was the increasing use of chemotherapy in Grade 2 and 3 cancers, in lymph node positive patients regardless of tumour grade and the use of Herceptin in HER2 positive patients. Patients who were ER positive were offered Tamoxifen since all were premenopausal although almost half the patients subsequently had a prophylactic oophorectomy and were converted to an Aromatase Inhibitor. All patients were assessed at an MDT and further surgery was undertaken if any of the surgical margins were incomplete defined as a radial margin of less than 2mm as per network guidelines.

Prognostic tools

The calculation for the NPI is (0.2 x tumour size in cm) + lymph node stage (1-3) + tumour grade. There were no tumours larger than 5cm recorded in this current study, therefor the range of NPI is 2.04 -6.99. The NPI scores correspond to five groups

ranging from a poor prognostic group to an excellent prognostic. Adjuvant! data is continuous, on a scale from zero to 100%. In order to accurately compare the NPI and Adjuvant!, the NPI groupings were converted to their equivalent 10-year survival figures which have been validated by previous studies and are shown in Table 1.[17]

NPI Group	NPI score	10-year survival (%)
Excellent prognostic group (EPG)	≤2.40	96
Good prognostic group (GPG)	2.41-3.40	93
Moderate prognostic group 1 (M1PG)	3.41-4.40	81
Moderate prognostic group 2 (M2PG)	4.41-5.40	74
Poor prognostic group (PPG)	5.41-6.40	55

Table 1: Nottingham Prognostic Index details with equivalent 10-year survival figures.[17]

Statistical analysis

To study the correlation between the actual NPI values and Adjuvant! 10-year expected survival each individual's predicted survival was plotted and Pearson's correlation coefficient used to analyze the similarity between these two prognostic indices. The observation time for the study was defined as the time between the date of diagnosis and an event, which was defined as death. Subjects alive at the end of follow up (September 2012) were censored. The overall 10-year survival curve for the group was calculated using the Kaplan-Meier method. Predicted 10-year cumulative survival curves were calculated using the NPI and Adjuvant! scores, this was achieved by assuming a constant yearly hazard rate. These graphs were then directly compared to the actual cumulative survival for the entire group of women. All analysis was carried out in PASW statistics 18.0 and probability values of <0.05 were considered statistically significant.

RESULTS

The average age of the 92 women involved in this study was 36.27 years. The median follow-up time was 85.20 months (range 11-120 months) and at the end of follow-up period 72 (78.3%) patients were alive. The mean and median follow-up time for those patients that died was 37.75 and 39.00 months respectively and for those that were alive at the end of follow-up it was 98.37 and 105.00 months respectively. The main clinically measurable parameters are shown in Table 2. Over 90% of young women presented with a breast lump and the mean tumour size was 2.07cm (SD ±0.92).

Parameter	All patients	
	N = 92	%
Age at diagnosis		
≤35	25	27.2
36-39	67	72.8
Symptoms		

Lump	84	91.3
Deformity of breast shape/skin puckering	5	5.4
Nipple inversion/blood discharge	1	1.1
Inflammation	1	1.1
Incidental imaging finding	1	1.1
Tumour size (cm)		
0.1-1.0	11	12.0
1.1-2.0	41	44.6
2.1-3.0	28	30.4
3.1-5.0	12	13.0
Lymph node status		
0	53	57.6
1-3	25	27.2
>3	14	15.2
Tumour grade		
Grade I	16	17.4
Grade II	25	27.2
Grade III	51	55.4
Histology		
Ductal	88	95.7
Lobular	0	0.0
Other	4	4.3
Oestrogen receptor status		
Positive	73	79.3
Negative	19	20.7
HER-2 receptor status		
Positive	6	6.5
Negative	33	35.9
Unknown	53	57.6
Vascular invasion		
Present	40	43.5
Not present	52	56.5
Surgery		
Overall mastectomy rate	46	50.0
Mastectomy without reconstruction	20	21.7
Mastectomy & immediate reconstruction	26	28.3
Breast conserving surgery	46	50.0
Neoadjuvant chemotherapy		
Yes	6	6.5
No	86	93.5
NPI		
Excellent	12	13.0
Good	14	15.2
Moderate 1	25	27.2
Moderate 2	20	21.7

Poor	21	22.8

Table 2: The main pathological, clinical and treatment parameters within the study population of 92 young patients with invasive breast cancer.

Directly comparing the actual survival with both NPI and Adjuvant! 10-year survival prognosis, confirms that there is a strong linear correlation between these two clinical tools (Figure 1). This is further demonstrated by Pearson's correlation coefficient, which was 0.873 (CI: 0.835-0.901).

Kaplan-Meier actual survival analysis of young women, diagnosed with breast cancer in this study revealed that the 5-year and 10-year survival results were 79.3% (CI: 71.1–87.5) and 77.9% (CI: 69.3–86.5) respectively. The Kaplan-Meier survival plot in Figure 2 indicates that patients, who survived the first five years after diagnosis, had a high probability of surviving to ten years.

Figure 3 illustrates the overall 10-year survival rate for the study population and compares it to the NPI and Adjuvant! predicted survival rates. The NPI predicted survival shows a stronger resemblance to the actual survival curve. A higher survival rate was recorded using the Adjuvant! scores. However, there was no statistically significant difference between survival figures generated by the prognostic tools and the actual survival (Table 3).

	10-year survival (%)
Overall survival	77.9 (CI: 69.3 – 86.5)
NPI prediction	77.3
AOL prediction	82.1

Table 3: Overall survival of young patients after 10-years of follow-up determined using the Kaplan-Meier method. This figure is compared to the NPI and AOL 10-year predicted survival at the time of diagnosis. The predictions are equivalent to the mean values calculated from the prognostic scores for each individual.

DISCUSSION

In the literature young patients with breast cancer are usually said to have a poor prognosis.[7-9] This is often attributed to their higher incidence of grade 3 tumours, more lymph node involvement and less oestrogen positive tumours. These results are usually compared with older patient groups defined as >50 or >60 years.[2,5,7] There is ongoing controversy as to whether age is a risk factor independent of the above biological factors.[1,3,5] McAree et al. found in a series of 57 young breast cancer patients that nearly 16% of their patients fulfilled the NICE guidelines for genetic testing but only 1.8% actually carried the gene.[8]

The aim of this study was to assess the mortality in young patients (< 40 years of age at presentation) during a 10 year follow up period then compare the figures with the NPI and Adjuvant! in order to assess there accuracy at predicting survival in young patients. Over the last few years, both the NPI and Adjuvant! have been

accepted as accurate predictors of survival in older patients and a guide to choice of treatment but their value in young patients is either not established or disputed.[18]

While our series is modest, it is similar in size to other studies reflecting the limited experience worldwide in young breast cancer patients, but unlike other studies our data is complete with no patients lost to follow-up. Our population study has similar tumour size, incidence of grade 3 cancers, oestrogen receptor and lymph node involvement to the literature and our overall survival results are also similar as demonstrated in table 4. This illustrates that similar results have been recorded in studies in Northern Ireland,[8] Sweden,[5,7,9] Australia,[3,19] and Italy.[2]

The data in this study was prospectively collected at the weekly MDT meeting. All histology was first reported by a member of a dedicated group of breast histopathologists, one of who was also the unit's MDT dedicated breast histopathologist. This ensured the histopathology was accurate and the data complete. In particular there was consensus reporting of the tumour grade, which is a very important component in both the NPI and Adjuvant! calculations. A further strength of the present study is that this population is relatively static. Unfortunately the HER 2 was not readily available for much of the study. Although it is now used widely as guide to recommending treatment, it is currently not included in either the NPI or Adjuvant! calculations. To add this parameter would need at least a re-validation of the NPI calculation.[13]

Adjuvant! was developed in the USA using data from the Surveillance, Epidemiology and End-Results (SEER) tumour registry.[14] The biological variables; tumour size, grade and lymph node involvement are included in the Adjuvant! calculation with additional inclusions of the patients' general fitness and the oestrogen status. The score weighting given for each of these factors is not known when applied in the Adjuvant! computer calculation. In a Canadian study to validate the Adjuvant! the authors found the 10 year predicted and overall outcomes were within 1% for overall survival, however Adjuvant! overestimated overall survival in patients under 35 years old by 8.6%.[15] The Adjuvant! has also been validated by a Dutch study which found that it accurately predicted 10 year outcomes in their population overall but it was less reliable in the sub set of young patients. Currently a correction factor of 1.5 is applied to the score for oestrogen receptor positive patients under 35 years. Despite this Mook et al. concluded that the correction was insufficient and an additional correction was required for patients between 35-40 years with oestrogen receptor positive tumours.[18] A British study in Oxford reported a statistically significant difference of 5.54% in predicted and observed overall survival using the Adjuvant! but made no specific reference to young patients.[20]

In the current study, the NPI and Adjuvant! predicted similar survival outcomes for young breast cancer patients with direct linear correlation ($p<0.01$). The large variability between the NPI and Adjuvant! 10-year survival rates within the 'poor' NPI group (Figure 1) were insignificant. It is suggested that this variability is cause by the heterogeneity of the group with between one to 22 lymph nodes involved and some patients likely having already developed micro metastasis. Neither prognostic tool is designed to predict metastasis at presentation.

The NPI appears to maintain its accuracy in young women diagnosed with invasive breast cancer. One of the many benefits of the NPI tool is its simplicity and the fact no computer is needed to perform the calculation. Other studies have validated the accuracy of the NPI within young breast cancer populations by showing that the mortality rate is no different from what would be expected according to the NPI.[10]

The present study showed no statistical difference between the accuracy of the NPI or Adjuvant! However, the impression that the current Adjuvant! appears to overestimate the prognosis by 5% has been identified by other studies in the Netherlands and Canada.[15,18] More recently a single-institute in Ireland reported that the Adjuvant was a significant predictor of both disease free survival and overall survival. However, there was a trend for underestimation of actual survival.[21] These variations have been suggested to correlate with changes in ethnicity and age distribution in populations outside the US where the Adjuvant! was developed.

The survival data from studies that have specifically investigated young breast cancer patients is shown in Table 4. The overall impression is that few papers in the literature have explored the value of the NPI or adjuvant in this group of patient. In one study of 107 patients the analysis demonstrated that if the NPI was between 3.4 and 5.39 the mortality rate was only 24% during the 10-year study period. Concluding, that the NPI was a valuable tool when counseling young breast cancer patients in agreement with the current results.[7]

	Patient numbers	Average tumour size (mm)	Grade 3 tumours (%)	Lymph node involved (%)	Oestrogen receptor negative (%)	HER-2 receptor positive (%)	Overall survival at 5yrs (%)	Overall survival at 10yrs (%)	Median follow-up (months)
McAree et al. (2010)	57	21.3	40.7	40.0	23.8	30.0	77.0	-	52.7
Karihtala et al. (2010)	269	-	46.0	52.4	33.5	15.2	80.0	71.0	74.0
Jaysinghe et al. (2005)	47	-	31.9	53.2	-	-	60.0	49.0	-
Sidoni et al. (2003)	50	22.8	38.0	53.0	46.0	48.0	-	-	-
Gillett et al. (1997)	58	23.0	40.0	34.0	-	-	90.0 [a]	-	31.0
Sundquist et al. (2002)	107	-	64.0	37.0	-	-	72.0	58-63 [b]	134.0
Fredholm et al. (2009)	1329	-	21.0 [c]	46.0	26.0 [c]	-	83.8	-	-
Current study	92	20.1	55.4	42.5	20.7 [d]	6.5	79.3	77.9	91.0

[a] 16% of patients were pure DCIS. [b] 2 figures recorded depending on study period. [c] Data missing for the tumour grade in 60% and oestrogen receptor status in 18% of patients. [d] Oestrogen receptor +ve if Allred score was greater than 3/8.

Table 4: Comparing the data and results from seven similar studies that have investigated invasive breast cancer within a population of young women.

CONCLUSIONS

This study looked at the mortality of young breast cancer patients (<40 years old) treated in a single breast unit with an average follow up of 7.1 years. The results revealed that the 5-year and 10-year survival was 78.5% and 76.6% respectively between 1998 and 2007. The NPI seemed to be more accurate whereas AOL over predicted survival by around 5% although the study had insufficient power to statistically define the difference. This study provides a platform from which future research can further investigate the results highlighted here and whether these findings are reproducible across the UK. The NPI and Adjuvant appear to be precise methods for predicting 10-year survival in young women with breast cancer.

COMPETING INTERESTS

The authors have no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTORSHIP

All authors contributed to the planning, conduct and reporting of this study. Dr BJ Hearne was responsible for the overall content as guarantor.

DATA SHARING

No additional data is available.

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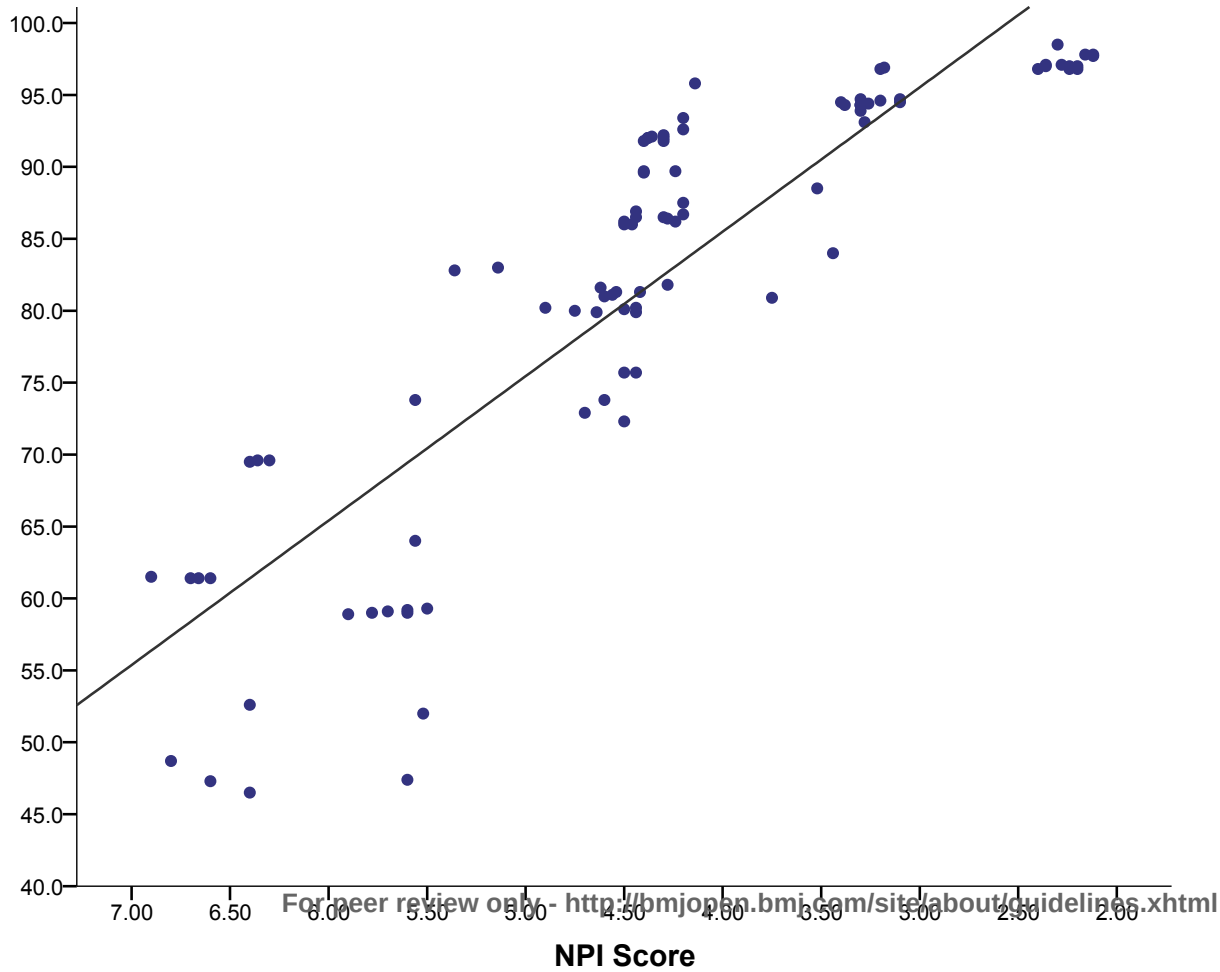
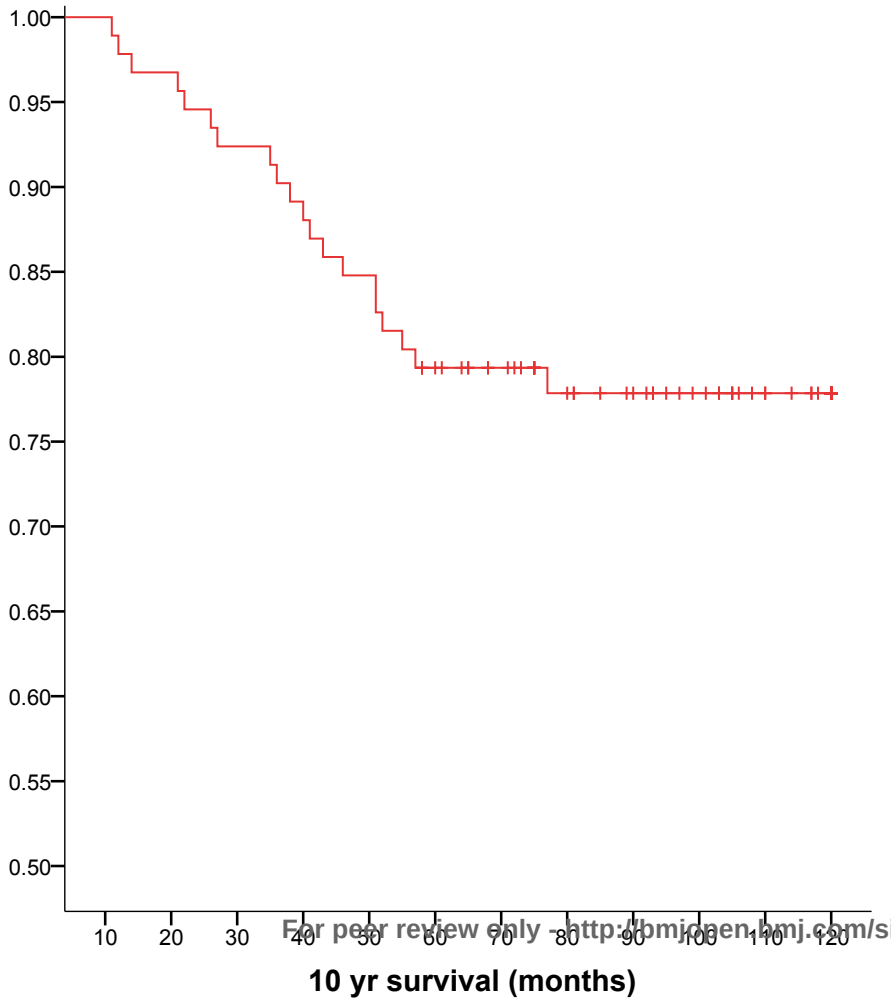
FIGURE LEGENDS

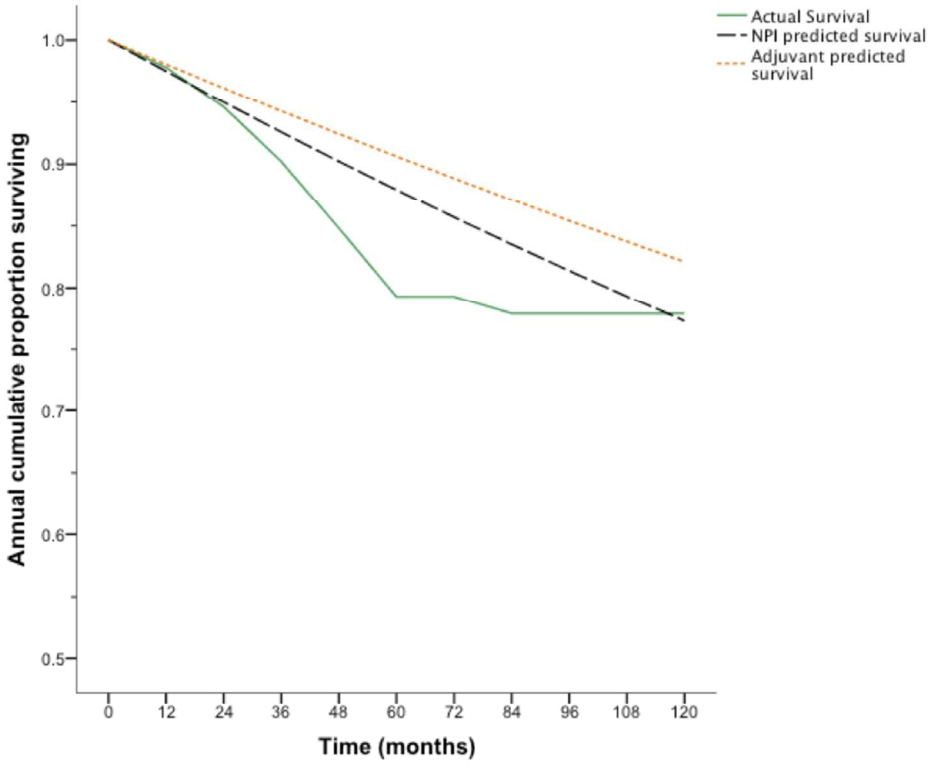
Figure 1: The 10-year survival probability at the time of diagnosis for individual young women aged <40 years between 1998 and 2007. The distribution of survival figures calculated using the NPI compared to those calculated using the AOL model.

Figure 2: Kaplan-Meier curve of overall survival for 92 young women diagnosed with primary invasive breast cancer that underwent potentially curative surgery (Crosses represent censored cases).

Figure 3: The actual survival curve for the group demonstrating the percentage survival after each year over a 10-year follow-up period. The predicted curves generated from the individual NPI and AOL scores are shown for comparison.







The actual survival curve for the group demonstrating the percentage survival after each year over a 10-year follow-up period. The predicted curves generated from the individual NPI and AOL scores are shown for comparison.
159x128mm (150 x 150 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Comparison of Nottingham Prognostic Index and Adjuvant Online prognostic tools in young women with breast cancer: Review of a single-institution experience

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Comparison of Nottingham Prognostic Index and Adjuvant Online prognostic tools in young women with breast cancer: Review of a single-institution experience

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ABSTRACT

Objective: Accurately predicting the prognosis of young breast cancer patients (<40 years) is uncertain since the literature suggests they have a higher mortality and that age is an independent risk factor. We considered two prognostic tools; Nottingham Prognostic Index and Adjuvant Online (Adjuvant!), in a group of young patients, comparing their predicted prognosis with their actual survival.

Setting: North West England

Participants: Data was prospectively collected from the breast unit at a Hospital in Grimsby between January 1998 and December 2007. A cohort of 102 young primary breast cancer patients was identified and actual survival data was recorded. The Nottingham Prognostic Index and Adjuvant! scores were calculated and used to estimate 10-year survival probabilities. Pearson's correlation coefficient was used to demonstrate the association between the Nottingham Prognostic Index and Adjuvant! scores. A constant yearly hazard rate was assumed to generate 10-year cumulative survival curves using the Nottingham Prognostic Index and Adjuvant! predictions.

Results: Actual 10-year survival for the 92 patients who underwent potentially curative surgery for invasive cancer was 77.2% (CI: 68.6-85.8). There was no significant difference between the actual survival and the Nottingham Prognostic Index and Adjuvant! 10-year estimated survival, which was 77.3% (CI: 74.4-80.2) and 82.1% (CI: 79.1-85.1) respectively. The Nottingham Prognostic Index and Adjuvant results demonstrated strong correlation and both predicted cumulative survival curves accurately reflected the actual survival in young patients.

Conclusions: The Nottingham Prognostic Index and Adjuvant! are widely used to predict survival in breast cancer patients and now have been shown to be statistically robust when compared to the actual survival of a group of young breast cancer patients.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- Based at a single institution leading to high level of standardization. All patients were discussed at multi-disciplinary team meeting attended to by the same team during the study period and the same team of surgeons carried out all surgery. Histopathology reporting was also a constant through out the study.
- The study population in North England including the areas around Scunthorpe and Grimsby contain a very static population demographic, which likely remained very constant throughout the study period.
- The Adjuvant online (Adjuvant) and Nottingham Prognostic Index (NPI) have not previously been compared in a sample of young women with breast cancer.
- Long follow-up period of participants in comparison to other published studies. Our median follow up time was 113.5 months compared to an average of 73 across other studies.
- No missing data or participants lost to follow-up.

Limitations

- Study sample may not be representative of the entire UK population.
- Relatively small sample size leading to low power, which meant a statistical difference between the NPI and Adjuvant was not demonstrated.
- The HER 2 data was not readily available for the majority of study participants. It is now used widely as guide to recommending treatment, however, it is currently not included in either the NPI or Adjuvant! calculations.

INTRODUCTION

What is my prognosis? This is the question that many patients directly or indirectly ask when given the diagnosis of breast cancer. This question is particularly difficult to answer in "younger patients" since breast cancer in young patients is often considered to be a more biologically aggressive disease with a poorer prognosis compared with older women.[1-3] The definition of "young" also varies between different studies with most authors identifying the upper age limit ranging from <35 years,[4,5] to ≤40 years.[6-9]

Since screening is unlikely to ever include women under the age of 40, for the purposes of this study we defined "young" as patients presenting at <40 years of age. Breast cancer is the most common cancer in women aged under 40. In the UK around 1,300 women are diagnosed with breast cancer between the ages of 35-39 each year. The incidence of the disease in young women varies from 4% in the UK, [8,10] 6.2% in Italy,[2] and 7% in USA.[6]

There are two widely accepted clinical tools used to calculate an individual's prognosis, the Nottingham Prognostic Index (NPI) and the Adjuvant Online (Adjuvant!). The NPI combines nodal status, tumour size and histological grade in a simple formula. Its advantage in prognostic discrimination has been validated by various studies and it is used widely in clinical practice.[11-13] Lee & Ellis suggested that the NPI could be used for counseling patients with regard to their prognosis but this has not been validated specifically in younger patients.[14]

Adjuvant! (http://www.adjuvantonline.com) is a web based risk-assessment programme that was developed in a population from North America. The software uses similar factors to the NPI but also includes; patient age, hormone receptor status and comorbidity level.[15] These variables are used to calculate the patients estimated 10-year survival probabilities, risk of relapse and the expected benefit of adjuvant therapy. A large population based study of Canadian women of all ages with early breast cancer has validated the Adjuvant! model.[16]

The objective of this study was to initially identify the actual survival data for a cohort of young breast cancer patients treated in the UK. These results were then compared with the calculated survival as assessed by both the NPI and Adjuvant! This enabled evaluation of the predictive power and accuracy of these prognostic tools in young breast cancer patients.

MATERIALS AND METHODS

This is a single-centre study, which prospectively collected information over ten years from January 1998 to December 2007. The database included all primary breast cancer patients diagnosed and treated in the Grimsby Breast Unit from 1998 to 2002 and the South Bank Breast Unit, which was the amalgamated service of the breast clinics in Grimsby and Scunthorpe increasing the population base from 200,000 to 420,000 people in 2003-2007.

Patients

There was a cohort of 102 primary breast cancer patients who were less than 40 years of age at the time of presentation. This equaled 5% of all breast cancers treated during the 10-year study period in this unit. Patients were excluded from the study if they were diagnosed with "pure" ductal carcinoma in-situ (DCIS) [n=5] or if they had metastasis at presentation [n=5]. There were 92 women with invasive disease and who had undergone potentially curative surgery in this study. Their age range was 26-39 years. Overall survival was defined as the time between first diagnosis of cancer and death from any cause, regardless of recurrence events. Patients who had neoadjuvant chemotherapy were not excluded because there is evidence that the NPI retains its prognostic value after this form of treatment.[17]

The case records of all patients were surveyed and the following details recorded: Age at presentation, tumour size as measured at histology, tumour grade, oestrogen receptor status and the number of positive lymph nodes. These factors were then used to calculate both an NPI score and the 10-year survival probability using Adjuvant!. To use the Adjuvant! tool it is necessary to input other factors including the patient's comorbidity level, oestrogen receptor status and age. All the patients in this study were fit, so comorbidities defined as 'average for age.' Oestrogen receptor (ER) positivity was determined using the Allred score. At the time of study, if the Allred score was greater than three, the oncologists would offer anti-hormone treatment.

Actual survival data was recorded using the continuously updated hospital electronic records system. These figures were documented at the end of 2014, which allowed a follow-up period of between seven and seventeen years. No individuals were lost during the follow-up period, which meant all 92 women contributed to the overall survival.

Treatment

All women involved in the study received treatment for breast cancer with what was considered the best practice and in accordance with network and national guidelines at the time of diagnosis. Surgery involved either breast conserving surgery followed by radiotherapy or a simple mastectomy with or without immediate reconstruction. Only six patients received neoadjuvant chemotherapy following multi-disciplinary team (MDT) discussion. The main treatment differences over the study period of 1998-2007 was the increasing use of chemotherapy in Grade 2 and 3 cancers, in lymph node positive patients regardless of tumour grade and the use of Herceptin in HER2 positive patients. Patients who were ER positive were offered Tamoxifen since all were premenopausal although almost half the patients subsequently had a prophylactic oophorectomy and were converted to an Aromatase Inhibitor. All patients were assessed at an MDT and further surgery was undertaken if any of the surgical margins were incomplete, defined as a radial margin of less than 2mm as per network guidelines.

Prognostic tools

The calculation for the NPI is (0.2 x tumour size in cm) + lymph node stage (1-3) + tumour grade. There were no tumours larger than 5cm recorded in this current study,

therefore the range of NPI was 2.04 -6.99. The NPI scores correspond to five groups ranging from a poor to excellent prognostic group. The numbers presented in Table 1 are those reported by Blamey et al. For all NPI scores within each group only a single summary 10-year survival figure is reported which has been validated by previous studies. [18] Adjuvant! data is continuous, on a scale from zero to 100%. The mean of the Adjuvant! and NPI scores were then compared. The groupings in Table 1 were used to predict the 10-year survival for each women in the cohort and then those predicted survival times were averaged to calculate the mean NPI score.

NPI Group	NPI score	10-year survival (%)
Excellent prognostic group (EPG)	≤2.40	96
Good prognostic group (GPG)	2.41-3.40	93
Moderate prognostic group 1 (M1PG)	3.41-4.40	81
Moderate prognostic group 2 (M2PG)	4.41-5.40	74
Poor prognostic group (PPG)	5.41-6.40	55

Table 1: Nottingham Prognostic Index details with equivalent 10-year survival figures.**[18]**

Statistical analysis

To study the correlation between the actual NPI values and Adjuvant! 10-year expected survival each individual's predicted survival was plotted and Pearson's correlation coefficient used to analyze the similarity between these two prognostic indices. The observation time for the study was defined as the time between the date of diagnosis and an event, which was defined as death from any cause. Subjects alive at the end of follow up (September 2014) were censored. The overall 10-year survival curve for the group was calculated using the Kaplan-Meier method. Predicted 10-year cumulative survival curves were calculated using the NPI and Adjuvant! scores, this was achieved by assuming a constant yearly hazard rate. These graphs were then directly compared to the actual cumulative survival for the entire group of women. All analysis was carried out in SPSS statistics 22 and probability values of <0.05 were considered statistically significant.

RESULTS

The average age of the 92 women involved in this study was 36.27 years. The median follow-up time was 113.5 months (range 11-120 months) and at the end of follow-up period 71 (77.2%) patients were alive. The median follow-up time for those patients that died was 40.0 months and for those that were alive at the end of follow-up it was 120.0 months. The main clinically measurable parameters are shown in Table 2. Over 90% of young women presented with a breast lump and the mean tumour size was 2.07cm (SD ±0.92).

Parameter	All patients	
	N = 92	%
Age at diagnosis		

≤35	25	27.2
36-39	67	72.8
Symptoms		
Lump	84	91.3
Deformity of breast shape/skin puckering	5	5.4
Nipple inversion/blood discharge	1	1.1
Inflammation	1	1.1
Incidental imaging finding	1	1.1
Tumour size (cm)		
0.1-1.0	11	12.0
1.1-2.0	41	44.6
2.1-3.0	28	30.4
3.1-5.0	12	13.0
Lymph node status		
0	53	57.6
1-3	25	27.2
>3	14	15.2
Tumour grade		
Grade I	16	17.4
Grade II	25	27.2
Grade III	51	55.4
Histology		
Ductal	88	95.7
Lobular	0	0.0
Other	4	4.3
Oestrogen receptor status		
Positive	73	79.3
Negative	19	20.7
HER-2 receptor status		
Positive	6	6.5
Negative	33	35.9
Unknown	53	57.6
Vascular invasion		
Present	40	43.5
Not present	52	56.5
Surgery		
Overall mastectomy rate	46	50.0
Mastectomy without reconstruction	20	21.7
Mastectomy & immediate reconstruction	26	28.3
Breast conserving surgery	46	50.0
Neoadjuvant chemotherapy		
Yes	6	6.5
No	86	93.5
NPI		

Excellent	12	13.0
Good	14	15.2
Moderate 1	25	27.2
Moderate 2	20	21.7
Poor	21	22.8

Table 2: The main pathological, clinical and treatment parameters within the study population of 92 young patients with invasive breast cancer.

Directly comparing the actual survival with both NPI and Adjuvant! 10-year survival prognosis, confirms that there is a strong linear correlation between these two clinical tools (Figure 1). This is further demonstrated by Pearson's correlation coefficient, which was 0.873 (CI: 0.835-0.901).

Kaplan-Meier actual survival analysis of young women, diagnosed with breast cancer in this study revealed that the 5-year and 10-year survival rates were 79.3% (CI: 71.1–87.5) and 77.2% (CI: 68.6-85.8) respectively. The Kaplan-Meier survival plot in Figure 2 indicates that patients, who survived the first five years after diagnosis, had a high probability of surviving to ten years.

Figure 3 illustrates the overall 10-year survival rate for the study population and compares it to the NPI and Adjuvant! predicted survival rates. The NPI predicted survival shows a stronger resemblance to the actual survival curve. A higher survival rate was recorded using the Adjuvant! scores. However, there was no statistically significant difference between survival figures generated by the prognostic tools and the actual survival (Table 3).

	10-year survival (%)
Overall survival	77.2 (CI: 68.6 – 85.8)
NPI prediction	77.3 (CI: 74.4 – 80.2)
Aduvant! prediction	82.1 (CI: 79.1 – 85.1)

Table 3: Overall survival of young patients after 10-years of follow-up determined using the Kaplan-Meier method. This figure is compared to the NPI and Adjuvant! 10-year predicted survival at the time of diagnosis. The predictions are equivalent to the mean values calculated from the prognostic scores for each individual.

DISCUSSION

In the literature young patients with breast cancer are usually said to have a poor prognosis.[7-9] This is often attributed to their higher incidence of grade 3 tumours, more lymph node involvement and less oestrogen positive tumours. These results are usually compared with older patient groups defined as >50 or >60 years.[2,5,7] There is ongoing controversy as to whether age is a risk factor independent of the above biological factors.[1,3,5] McAree et al. found in a series of 57 young breast cancer patients that nearly 16% of their patients fulfilled the NICE guidelines for genetic testing but only 1.8% actually carried the gene.[8]

The aim of this study was to assess the mortality in young patients (< 40 years of age at presentation) during a 10 year follow up period then compare the figures with the NPI and Adjuvant! in order to assess there accuracy at predicting survival in young patients. Over the last few years, both the NPI and Adjuvant! have been accepted as accurate predictors of survival in older patients and a guide to choice of treatment but their value in young patients is either not established or disputed.[19]

While our series is modest, it is similar in size to other studies reflecting the limited experience worldwide in young breast cancer patients, but unlike other studies our data is complete with no patients lost to follow-up. Our population study has similar tumour size, incidence of grade 3 cancers, oestrogen receptor and lymph node involvement to the literature and our overall survival results are also similar as demonstrated in table 4. This illustrates that similar results have been recorded in studies in the United Kingdom,[8,20] Sweden,[5,7,9] Australia,[3,21] and Italy.[2]

Neoadjuvant chemotherapy is now widely used and recognized as a treatment modality for locally invasive breast cancer especially in young patients. The Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) reports between 2000-2008 15.6% of young women had neoadjuvant chemotherapy compared to 6.5% in the current study which demonstrates the increased acceptance of this form of treatment over the past decade.[20]

The data in this study was prospectively collected at the weekly MDT meeting. All histology was first reported by a member of a dedicated group of histopathologists, one of whom was also the unit's MDT dedicated breast histopathologist. This ensured the histopathology was accurate and the data complete. In particular there was consensus reporting of the tumour grade, which is a very important component in both the NPI and Adjuvant! calculations. A further strength of the present study is that this population is relatively static. Unfortunately the HER 2 was not readily available for much of the study. Although it is now used widely as guide to recommending treatment, it is currently not included in either the NPI or Adjuvant! calculations. To add this parameter would need at least a re-validation of the NPI calculation.[14]

Adjuvant! was developed in the USA using data from the Surveillance, Epidemiology and End-Results (SEER) tumour registry.[15] The biological variables; tumour size, grade and lymph node involvement are included in the Adjuvant! calculation with additional inclusions of the patients' general fitness and the oestrogen status. The score weighting given for each of these factors is not known when applied in the Adjuvant! computer calculation. In a Canadian study to validate the Adjuvant! the authors found the 10 year predicted and overall outcomes were within 1% for overall survival, however Adjuvant! overestimated overall survival in patients under 35 years old by 8.6%.[16] The Adjuvant! has also been validated by a Dutch study which found that it accurately predicted 10 year outcomes in their population overall but it was less reliable in the sub set of young patients. Currently a correction factor of 1.5 is applied to the score for oestrogen receptor positive patients under 35 years. Despite this Mook et al. concluded that the correction was insufficient and an additional correction was required for patients between 35-40 years with oestrogen receptor positive tumours.[19] A British study in Oxford reported a statistically

significant difference of 5.54% in predicted and observed overall survival using the Adjuvant! but made no specific reference to young patients.[22]

In the current study, the NPI and Adjuvant! predicted similar survival outcomes for young breast cancer patients with direct linear correlation ($p<0.01$). The large variability between the NPI and Adjuvant! 10-year survival rates within the 'poor' NPI group (Figure 1) were insignificant. It is suggested that this variability is caused by the heterogeneity of the group with between one to 22 lymph nodes involved and some patients likely having already developed micro metastasis. Neither prognostic tool is designed to predict metastasis at presentation.

The NPI appears to maintain its accuracy in young women diagnosed with invasive breast cancer. One of the many benefits of the NPI tool is its simplicity and the fact no computer is needed to perform the calculation. Other studies have validated the accuracy of the NPI within young breast cancer populations by showing that the mortality rate is no different from what would be expected according to the NPI.[11]

The present study showed no statistical difference between the accuracy of the NPI or Adjuvant! However, the impression that the current Adjuvant! appears to overestimate the prognosis by 5% has been identified by other studies in the Netherlands and Canada.[16,19] The accuracy of the Adjuvant! appears to be population specific as a recent study in Ireland demonstrated that the Adjuvant! actually underestimated the overall 10-year survival of a cohort of 77 women.[23] These variations have been suggested to correlate with changes in ethnicity and age distribution in populations outside the US where the Adjuvant! was developed.

The survival data from studies that have specifically investigated young breast cancer patients is shown in Table 4. The overall impression is that few papers in the literature have explored the value of the NPI or adjuvant in this group of patient. In one study of 107 patients the analysis demonstrated that if the NPI was between 3.4 and 5.39 the mortality rate was only 24% during the 10-year study period. Concluding, that the NPI was a valuable tool when counseling young breast cancer patients in agreement with the current results.[7]

	Patient numbers	Average tumour size (mm)	Grade 3 tumours (%)	Lymph node involved (%)	Oestrogen receptor negative (%)	HER-2 receptor positive (%)	Overall survival at 5yrs (%)	Overall survival at 10yrs (%)	Median follow-up (months)
McAree et al. (2010)	57	21.3	40.7	40.0	23.8	30.0	77.0	-	52.7
Karihtala et al. (2010)	269	-	46.0	52.4	33.5	15.2	80.0	71.0	74.0
Jaysinghe et al. (2005)	47	-	31.9	53.2	-	-	60.0	49.0	-
Sidoni et al. (2003)	50	22.8	38.0	53.0	46.0	48.0	-	-	-

Gillett et al. (1997)	58	23.0	40.0	34.0	-	-	90.0 [a]	-	31.0
Sundquist et al. (2002)	107	-	64.0	37.0	-	-	72.0	58-63 [b]	134.0
Fredholm et al. (2009)	1329	-	21.0 [c]	46.0	26.0 [c]	-	83.8	-	-
Copson et al. (2013)	2956	22.0	58.9	50.6	33.7	24.3	81.9	-	60
Current study	92	20.1	55.4	42.5	20.7 [d]	6.5	79.3	77.2	113.5

[a] 16% of patients were pure DCIS. [b] 2 figures recorded depending on study period. [c] Data missing for the tumour grade in 60% and oestrogen receptor status in 18% of patients. [d] Oestrogen receptor +ve if Allred score was greater than 3/8.

Table 4: Comparing the data and results from eight similar studies that have investigated invasive breast cancer within a population of young women.

CONCLUSIONS

This study looked at the mortality of young breast cancer patients (<40 years old) treated in a single breast unit with an average follow up of 9.5 years. The results revealed that the 5-year and 10-year survival was 79.3% and 77.2% respectively between 1998 and 2007. The NPI seemed to be more accurate whereas Adjuvant! over predicted survival by around 5% although the study had insufficient power to statistically define the difference. This study provides a platform from which future research can further investigate the results highlighted here and whether these findings are reproducible across the UK. The NPI and Adjuvant appear to be precise methods for predicting 10-year survival in young women with breast cancer.

COMPETING INTERESTS

The authors have no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTORSHIP

All authors contributed to the planning, conduct and reporting of this study. Dr BJ Hearne was responsible for the overall content as guarantor.

DATA SHARING

No additional data is available.

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FIGURE LEGENDS

Figure 1: The 10-year survival probability at the time of diagnosis for individual young women aged <40 years between 1998 and 2007. The distribution of survival

figures calculated using the NPI compared to those calculated using the Adjuvant! model.

Figure 2: Kaplan-Meier curve of overall survival for 92 young women diagnosed with primary invasive breast cancer that underwent potentially curative surgery (Crosses represent censored cases).

Figure 3: The actual survival curve for the group demonstrating the percentage survival after each year over a 10-year follow-up period. The predicted curves generated from the individual NPI and Adjuvant! scores are shown for comparison.

Comparison of Nottingham Prognostic Index and Adjuvant Online prognostic tools in young women with breast cancer: Review of a single-institution experience

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ABSTRACT

Objective: Accurately predicting the prognosis of young breast cancer patients (<40 years) is uncertain since the literature suggests they have a higher mortality and that age is an independent risk factor. We considered two prognostic tools; Nottingham Prognostic Index and Adjuvant Online (Adjuvant!), in a group of young patients, comparing their predicted prognosis with their actual survival.

Setting: North West England

Participants: Data was prospectively collected from the breast unit at a Hospital in Grimsby between January 1998 and December 2007. A cohort of 102 young primary breast cancer patients was identified and actual survival data was recorded. The Nottingham Prognostic Index and Adjuvant! scores were calculated and used to estimate 10-year survival probabilities. Pearson's correlation coefficient was used to demonstrate the association between the Nottingham Prognostic Index and Adjuvant! scores. A constant yearly hazard rate was assumed to generate 10-year cumulative survival curves using the Nottingham Prognostic Index and Adjuvant! predictions.

Results: Actual 10-year survival for the 92 patients who underwent potentially curative surgery for invasive cancer was 77.2% (CI: 68.6-85.8). There was no significant difference between the actual survival and the Nottingham Prognostic Index and Adjuvant! 10-year estimated survival, which was 77.3% (CI: 74.4-80.2) and 82.1% (CI: 79.1-85.1) respectively. The Nottingham Prognostic Index and Adjuvant results demonstrated strong correlation and both predicted cumulative survival curves accurately reflected the actual survival in young patients.

Conclusions: The Nottingham Prognostic Index and Adjuvant! are widely used to predict survival in breast cancer patients and now have been shown to be statistically robust when compared to the actual survival of a group of young breast cancer patients.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- Based at a single institution leading to high level of standardization. All patients were discussed at multi-disciplinary team meeting attended to by the same team during the study period and the same team of surgeons carried out all surgery. Histopathology reporting was also a constant through out the study.
- The study population in North England including the areas around Scunthorpe and Grimsby contain a very static population demographic, which likely remained very constant throughout the study period.
- The Adjuvant online (Adjuvant) and Nottingham Prognostic Index (NPI) have not previously been compared in a sample of young women with breast cancer.
- Long follow-up period of participants in comparison to other published studies. Our median follow up time was 113.5 months compared to an average of 73 across other studies.
- No missing data or participants lost to follow-up.

Limitations

- Study sample may not be representative of the entire UK population.
- Relatively small sample size leading to low power, which meant a statistical difference between the NPI and Adjuvant was not demonstrated.
- The HER 2 data was not readily available for the majority of study participants. It is now used widely as guide to recommending treatment, however, it is currently not included in either the NPI or Adjuvant! calculations.

INTRODUCTION

What is my prognosis? This is the question that many patients directly or indirectly ask when given the diagnosis of breast cancer. This question is particularly difficult to answer in "younger patients" since breast cancer in young patients is often considered to be a more biologically aggressive disease with a poorer prognosis compared with older women.[1-3] The definition of "young" also varies between different studies with most authors identifying the upper age limit ranging from <35 years,[4,5] to ≤40 years.[6-9]

Since screening is unlikely to ever include women under the age of 40, for the purposes of this study we defined "young" as patients presenting at <40 years of age. Breast cancer is the most common cancer in women aged under 40. In the UK around 1,300 women are diagnosed with breast cancer between the ages of 35-39 each year. The incidence of the disease in young women varies from 4% in the UK, [8,10] 6.2% in Italy,[2] and 7% in USA.[6]

There are two widely accepted clinical tools used to calculate an individual's prognosis, the Nottingham Prognostic Index (NPI) and the Adjuvant Online (Adjuvant!). The NPI combines nodal status, tumour size and histological grade in a simple formula. Its advantage in prognostic discrimination has been validated by various studies and it is used widely in clinical practice.[11-13] Lee & Ellis suggested that the NPI could be used for counseling patients with regard to their prognosis but this has not been validated specifically in younger patients.[14]

Adjuvant! (http://www.adjuvantonline.com) is a web based risk-assessment programme that was developed in a population from North America. The software uses similar factors to the NPI but also includes; patient age, hormone receptor status and comorbidity level.[15] These variables are used to calculate the patients estimated 10-year survival probabilities, risk of relapse and the expected benefit of adjuvant therapy. A large population based study of Canadian women of all ages with early breast cancer has validated the Adjuvant! model.[16]

The objective of this study was to initially identify the actual survival data for a cohort of young breast cancer patients treated in the UK. These results were then compared with the calculated survival as assessed by both the NPI and Adjuvant! This enabled evaluation of the predictive power and accuracy of these prognostic tools in young breast cancer patients.

MATERIALS AND METHODS

This is a single-centre study, which prospectively collected information over ten years from January 1998 to December 2007. The database included all primary breast cancer patients diagnosed and treated in the Grimsby Breast Unit from 1998 to 2002 and the South Bank Breast Unit, which was the amalgamated service of the breast clinics in Grimsby and Scunthorpe increasing the population base from 200,000 to 420,000 people in 2003-2007.

Patients

There was a cohort of 102 primary breast cancer patients who were less than 40 years of age at the time of presentation. This equaled 5% of all breast cancers treated during the 10-year study period in this unit. Patients were excluded from the study if they were diagnosed with "pure" ductal carcinoma in-situ (DCIS) [n=5] or if they had metastasis at presentation [n=5]. There were 92 women with invasive disease and who had undergone potentially curative surgery in this study. Their age range was 26-39 years. Overall survival was defined as the time between first diagnosis of cancer and death from any cause, regardless of recurrence events. Patients who had neoadjuvant chemotherapy were not excluded because there is evidence that the NPI retains its prognostic value after this form of treatment.[17]

The case records of all patients were surveyed and the following details recorded: Age at presentation, tumour size as measured at histology, tumour grade, oestrogen receptor status and the number of positive lymph nodes. These factors were then used to calculate both an NPI score and the 10-year survival probability using Adjuvant!. To use the Adjuvant! tool it is necessary to input other factors including the patient's comorbidity level, oestrogen receptor status and age. All the patients in this study were fit, so comorbidities defined as 'average for age.' Oestrogen receptor (ER) positivity was determined using the Allred score. At the time of study, if the Allred score was greater than three, the oncologists would offer anti-hormone treatment.

Actual survival data was recorded using the continuously updated hospital electronic records system. These figures were documented at the end of 2014, which allowed a follow-up period of between seven and seventeen years. No individuals were lost during the follow-up period, which meant all 92 women contributed to the overall survival.

Treatment

All women involved in the study received treatment for breast cancer with what was considered the best practice and in accordance with network and national guidelines at the time of diagnosis. Surgery involved either breast conserving surgery followed by radiotherapy or a simple mastectomy with or without immediate reconstruction. Only six patients received neoadjuvant chemotherapy following multi-disciplinary team (MDT) discussion. The main treatment differences over the study period of 1998-2007 was the increasing use of chemotherapy in Grade 2 and 3 cancers, in lymph node positive patients regardless of tumour grade and the use of Herceptin in HER2 positive patients. Patients who were ER positive were offered Tamoxifen since all were premenopausal although almost half the patients subsequently had a prophylactic oophorectomy and were converted to an Aromatase Inhibitor. All patients were assessed at an MDT and further surgery was undertaken if any of the surgical margins were incomplete, defined as a radial margin of less than 2mm as per network guidelines.

Prognostic tools

The calculation for the NPI is (0.2 x tumour size in cm) + lymph node stage (1-3) + tumour grade. There were no tumours larger than 5cm recorded in this current study,

therefore the range of NPI was 2.04 -6.99. The NPI scores correspond to five groups ranging from a poor to excellent prognostic group. The numbers presented in Table 1 are those reported by Blamey et al. For all NPI scores within each group only a single summary 10-year survival figure is reported which has been validated by previous studies. [18] Adjuvant! data is continuous, on a scale from zero to 100%. The mean of the Adjuvant! and NPI scores were then compared. The groupings in Table 1 were used to predict the 10-year survival for each women in the cohort and then those predicted survival times were averaged to calculate the mean NPI score.

NPI Group	NPI score	10-year survival (%)
Excellent prognostic group (EPG)	≤2.40	96
Good prognostic group (GPG)	2.41-3.40	93
Moderate prognostic group 1 (M1PG)	3.41-4.40	81
Moderate prognostic group 2 (M2PG)	4.41-5.40	74
Poor prognostic group (PPG)	5.41-6.40	55

Table 1: Nottingham Prognostic Index details with equivalent 10-year survival figures. **[18]**

Statistical analysis

To study the correlation between the actual NPI values and Adjuvant! 10-year expected survival each individual's predicted survival was plotted and Pearson's correlation coefficient used to analyze the similarity between these two prognostic indices. The observation time for the study was defined as the time between the date of diagnosis and an event, which was defined as death from any cause. Subjects alive at the end of follow up (September 2014) were censored. The overall 10-year survival curve for the group was calculated using the Kaplan-Meier method. Predicted 10-year cumulative survival curves were calculated using the NPI and Adjuvant! scores, this was achieved by assuming a constant yearly hazard rate. These graphs were then directly compared to the actual cumulative survival for the entire group of women. All analysis was carried out in SPSS statistics 22 and probability values of <0.05 were considered statistically significant.

RESULTS

The average age of the 92 women involved in this study was 36.27 years. The median follow-up time was 113.5 months (range 11-120 months) and at the end of follow-up period 71 (77.2%) patients were alive. The median follow-up time for those patients that died was 40.0 months and for those that were alive at the end of follow-up it was 120.0 months. The main clinically measurable parameters are shown in Table 2. Over 90% of young women presented with a breast lump and the mean tumour size was 2.07cm (SD ±0.92).

Parameter	All patients	
	N = 92	%
Age at diagnosis		

≤35	25	27.2
36-39	67	72.8
Symptoms		
Lump	84	91.3
Deformity of breast shape/skin puckering	5	5.4
Nipple inversion/blood discharge	1	1.1
Inflammation	1	1.1
Incidental imaging finding	1	1.1
Tumour size (cm)		
0.1-1.0	11	12.0
1.1-2.0	41	44.6
2.1-3.0	28	30.4
3.1-5.0	12	13.0
Lymph node status		
0	53	57.6
1-3	25	27.2
>3	14	15.2
Tumour grade		
Grade I	16	17.4
Grade II	25	27.2
Grade III	51	55.4
Histology		
Ductal	88	95.7
Lobular	0	0.0
Other	4	4.3
Oestrogen receptor status		
Positive	73	79.3
Negative	19	20.7
HER-2 receptor status		
Positive	6	6.5
Negative	33	35.9
Unknown	53	57.6
Vascular invasion		
Present	40	43.5
Not present	52	56.5
Surgery		
Overall mastectomy rate	46	50.0
Mastectomy without reconstruction	20	21.7
Mastectomy & immediate reconstruction	26	28.3
Breast conserving surgery	46	50.0
Neoadjuvant chemotherapy		
Yes	6	6.5
No	86	93.5
NPI		

Excellent	12	13.0
Good	14	15.2
Moderate 1	25	27.2
Moderate 2	20	21.7
Poor	21	22.8

Table 2: The main pathological, clinical and treatment parameters within the study population of 92 young patients with invasive breast cancer.

Directly comparing the actual survival with both NPI and Adjuvant! 10-year survival prognosis, confirms that there is a strong linear correlation between these two clinical tools (Figure 1). This is further demonstrated by Pearson's correlation coefficient, which was 0.873 (CI: 0.835-0.901).

Kaplan-Meier actual survival analysis of young women, diagnosed with breast cancer in this study revealed that the 5-year and 10-year survival rates were 79.3% (CI: 71.1–87.5) and 77.2% (CI: 68.6-85.8) respectively. The Kaplan-Meier survival plot in Figure 2 indicates that patients, who survived the first five years after diagnosis, had a high probability of surviving to ten years.

Figure 3 illustrates the overall 10-year survival rate for the study population and compares it to the NPI and Adjuvant! predicted survival rates. The NPI predicted survival shows a stronger resemblance to the actual survival curve. A higher survival rate was recorded using the Adjuvant! scores. However, there was no statistically significant difference between survival figures generated by the prognostic tools and the actual survival (Table 3).

	10-year survival (%)
Overall survival	77.2 (CI: 68.6 – 85.8)
NPI prediction	77.3 (CI: 74.4 – 80.2)
Aduvant! prediction	82.1 (CI: 79.1 – 85.1)

Table 3: Overall survival of young patients after 10-years of follow-up determined using the Kaplan-Meier method. This figure is compared to the NPI and Adjuvant! 10-year predicted survival at the time of diagnosis. The predictions are equivalent to the mean values calculated from the prognostic scores for each individual.

DISCUSSION

In the literature young patients with breast cancer are usually said to have a poor prognosis.[7-9] This is often attributed to their higher incidence of grade 3 tumours, more lymph node involvement and less oestrogen positive tumours. These results are usually compared with older patient groups defined as >50 or >60 years.[2,5,7] There is ongoing controversy as to whether age is a risk factor independent of the above biological factors.[1,3,5] McAree et al. found in a series of 57 young breast cancer patients that nearly 16% of their patients fulfilled the NICE guidelines for genetic testing but only 1.8% actually carried the gene.[8]

The aim of this study was to assess the mortality in young patients (< 40 years of age at presentation) during a 10 year follow up period then compare the figures with the NPI and Adjuvant! in order to assess there accuracy at predicting survival in young patients. Over the last few years, both the NPI and Adjuvant! have been accepted as accurate predictors of survival in older patients and a guide to choice of treatment but their value in young patients is either not established or disputed.[19]

While our series is modest, it is similar in size to other studies reflecting the limited experience worldwide in young breast cancer patients, but unlike other studies our data is complete with no patients lost to follow-up. Our population study has similar tumour size, incidence of grade 3 cancers, oestrogen receptor and lymph node involvement to the literature and our overall survival results are also similar as demonstrated in table 4. This illustrates that similar results have been recorded in studies in the United Kingdom,[8,20] Sweden,[5,7,9] Australia,[3,21] and Italy.[2]

Neoadjuvant chemotherapy is now widely used and recognized as a treatment modality for locally invasive breast cancer especially in young patients. The Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) reports between 2000-2008 15.6% of young women had neoadjuvant chemotherapy compared to 6.5% in the current study which demonstrates the increased acceptance of this form of treatment over the past decade.[20]

The data in this study was prospectively collected at the weekly MDT meeting. All histology was first reported by a member of a dedicated group of histopathologists, one of whom was also the unit's MDT dedicated breast histopathologist. This ensured the histopathology was accurate and the data complete. In particular there was consensus reporting of the tumour grade, which is a very important component in both the NPI and Adjuvant! calculations. A further strength of the present study is that this population is relatively static. Unfortunately the HER 2 was not readily available for much of the study. Although it is now used widely as guide to recommending treatment, it is currently not included in either the NPI or Adjuvant! calculations. To add this parameter would need at least a re-validation of the NPI calculation.[14]

Adjuvant! was developed in the USA using data from the Surveillance, Epidemiology and End-Results (SEER) tumour registry.[15] The biological variables; tumour size, grade and lymph node involvement are included in the Adjuvant! calculation with additional inclusions of the patients' general fitness and the oestrogen status. The score weighting given for each of these factors is not known when applied in the Adjuvant! computer calculation. In a Canadian study to validate the Adjuvant! the authors found the 10 year predicted and overall outcomes were within 1% for overall survival, however Adjuvant! overestimated overall survival in patients under 35 years old by 8.6%.[16] The Adjuvant! has also been validated by a Dutch study which found that it accurately predicted 10 year outcomes in their population overall but it was less reliable in the sub set of young patients. Currently a correction factor of 1.5 is applied to the score for oestrogen receptor positive patients under 35 years. Despite this Mook et al. concluded that the correction was insufficient and an additional correction was required for patients between 35-40 years with oestrogen receptor positive tumours.[19] A British study in Oxford reported a statistically

significant difference of 5.54% in predicted and observed overall survival using the Adjuvant! but made no specific reference to young patients.[22]

In the current study, the NPI and Adjuvant! predicted similar survival outcomes for young breast cancer patients with direct linear correlation ($p<0.01$). The large variability between the NPI and Adjuvant! 10-year survival rates within the 'poor' NPI group (Figure 1) were insignificant. It is suggested that this variability is caused by the heterogeneity of the group with between one to 22 lymph nodes involved and some patients likely having already developed micro metastasis. Neither prognostic tool is designed to predict metastasis at presentation.

The NPI appears to maintain its accuracy in young women diagnosed with invasive breast cancer. One of the many benefits of the NPI tool is its simplicity and the fact no computer is needed to perform the calculation. Other studies have validated the accuracy of the NPI within young breast cancer populations by showing that the mortality rate is no different from what would be expected according to the NPI.[11]

The present study showed no statistical difference between the accuracy of the NPI or Adjuvant! However, the impression that the current Adjuvant! appears to overestimate the prognosis by 5% has been identified by other studies in the Netherlands and Canada.[16,19] The accuracy of the Adjuvant! appears to be population specific as a recent study in Ireland demonstrated that the Adjuvant! actually underestimated the overall 10-year survival of a cohort of 77 women.[23] These variations have been suggested to correlate with changes in ethnicity and age distribution in populations outside the US where the Adjuvant! was developed.

The survival data from studies that have specifically investigated young breast cancer patients is shown in Table 4. The overall impression is that few papers in the literature have explored the value of the NPI or adjuvant in this group of patient. In one study of 107 patients the analysis demonstrated that if the NPI was between 3.4 and 5.39 the mortality rate was only 24% during the 10-year study period. Concluding, that the NPI was a valuable tool when counseling young breast cancer patients in agreement with the current results.[7]

	Patient numbers	Average tumour size (mm)	Grade 3 tumours (%)	Lymph node involved (%)	Oestrogen receptor negative (%)	HER-2 receptor positive (%)	Overall survival at 5yrs (%)	Overall survival at 10yrs (%)	Median follow-up (months)
McAree et al. (2010)	57	21.3	40.7	40.0	23.8	30.0	77.0	-	52.7
Karihtala et al. (2010)	269	-	46.0	52.4	33.5	15.2	80.0	71.0	74.0
Jaysinghe et al. (2005)	47	-	31.9	53.2	-	-	60.0	49.0	-
Sidoni et al. (2003)	50	22.8	38.0	53.0	46.0	48.0	-	-	-

Gillett et al. (1997)	58	23.0	40.0	34.0	-	-	90.0 [a]	-	31.0
Sundquist et al. (2002)	107	-	64.0	37.0	-	-	72.0	58-63 [b]	134.0
Fredholm et al. (2009)	1329	-	21.0 [c]	46.0	26.0 [c]	-	83.8	-	-
Copson et al. (2013)	2956	22.0	58.9	50.6	33.7	24.3	81.9	-	60
Current study	92	20.1	55.4	42.5	20.7 [d]	6.5	79.3	77.2	113.5

[a] 16% of patients were pure DCIS. [b] 2 figures recorded depending on study period. [c] Data missing for the tumour grade in 60% and oestrogen receptor status in 18% of patients. [d] Oestrogen receptor +ve if Allred score was greater than 3/8.

Table 4: Comparing the data and results from eight similar studies that have investigated invasive breast cancer within a population of young women.

CONCLUSIONS

This study looked at the mortality of young breast cancer patients (<40 years old) treated in a single breast unit with an average follow up of 9.5 years. The results revealed that the 5-year and 10-year survival was 79.3% and 77.2% respectively between 1998 and 2007. The NPI seemed to be more accurate whereas Adjuvant! over predicted survival by around 5% although the study had insufficient power to statistically define the difference. This study provides a platform from which future research can further investigate the results highlighted here and whether these findings are reproducible across the UK. The NPI and Adjuvant appear to be precise methods for predicting 10-year survival in young women with breast cancer.

COMPETING INTERESTS

The authors have no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTORSHIP

All authors contributed to the planning, conduct and reporting of this study. Dr BJ Hearne was responsible for the overall content as guarantor.

DATA SHARING

No additional data is available.

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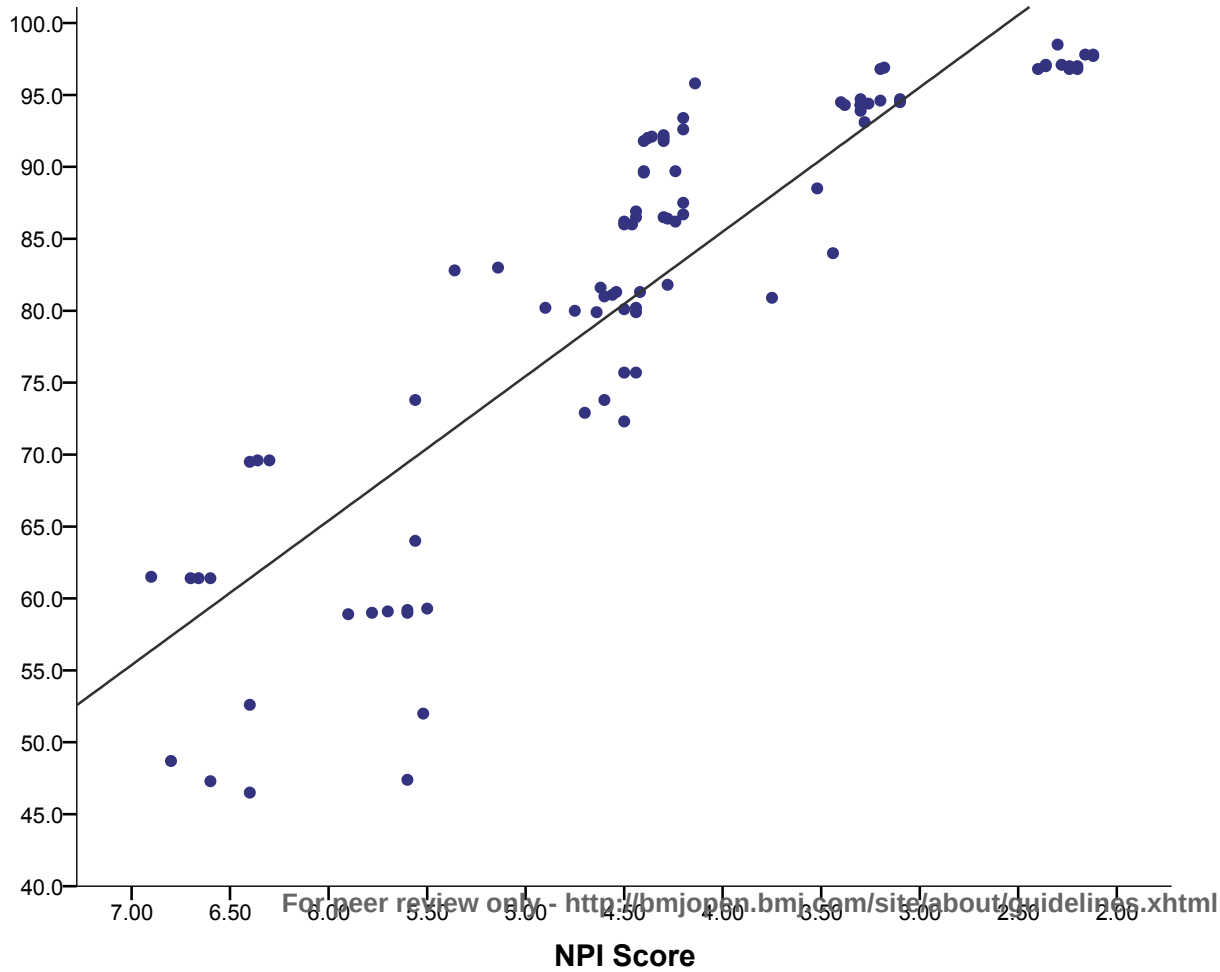
FIGURE LEGENDS

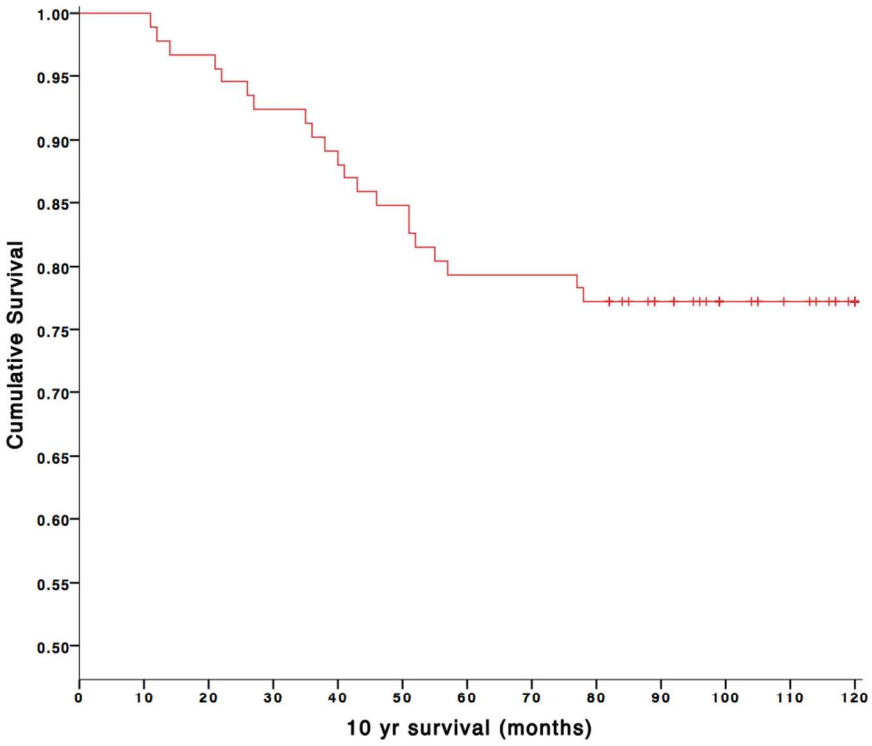
Figure 1: The 10-year survival probability at the time of diagnosis for individual young women aged <40 years between 1998 and 2007. The distribution of survival

figures calculated using the NPI compared to those calculated using the Adjuvant! model.

Figure 2: Kaplan-Meier curve of overall survival for 92 young women diagnosed with primary invasive breast cancer that underwent potentially curative surgery (Crosses represent censored cases).

Figure 3: The actual survival curve for the group demonstrating the percentage survival after each year over a 10-year follow-up period. The predicted curves generated from the individual NPI and Adjuvant! scores are shown for comparison.





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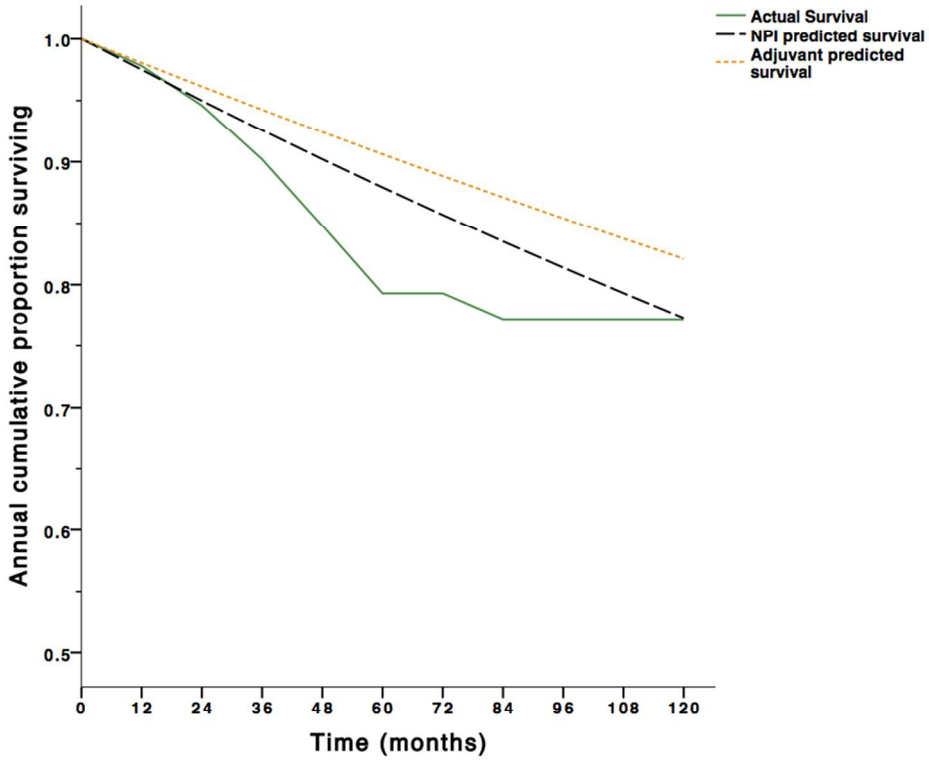

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Comparison of Nottingham Prognostic Index and Adjuvant Online prognostic tools in young women with breast cancer: Review of a single-institution experience

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Comparison of Nottingham Prognostic Index and Adjuvant Online prognostic tools in young women with breast cancer: Review of a single-institution experience

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ABSTRACT

Objective: Accurately predicting the prognosis of young breast cancer patients (<40 years) is uncertain since the literature suggests they have a higher mortality and that age is an independent risk factor. In this cohort study we considered two prognostic tools; Nottingham Prognostic Index and Adjuvant Online (Adjuvant!), in a group of young patients, comparing their predicted prognosis with their actual survival.

Setting: North West England

Participants: Data was prospectively collected from the breast unit at a Hospital in Grimsby between January 1998 and December 2007. A cohort of 102 young primary breast cancer patients was identified and actual survival data was recorded. The Nottingham Prognostic Index and Adjuvant! scores were calculated and used to estimate 10-year survival probabilities. Pearson's correlation coefficient was used to demonstrate the association between the Nottingham Prognostic Index and Adjuvant! scores. A constant yearly hazard rate was assumed to generate 10-year cumulative survival curves using the Nottingham Prognostic Index and Adjuvant! predictions.

Results: Actual 10-year survival for the 92 patients who underwent potentially curative surgery for invasive cancer was 77.2% (CI: 68.6-85.8). There was no significant difference between the actual survival and the Nottingham Prognostic Index and Adjuvant! 10-year estimated survival, which was 77.3% (CI: 74.4-80.2) and 82.1% (CI: 79.1-85.1) respectively. The Nottingham Prognostic Index and Adjuvant! results demonstrated strong correlation and both predicted cumulative survival curves accurately reflected the actual survival in young patients.

Conclusions: The Nottingham Prognostic Index and Adjuvant! are widely used to predict survival in breast cancer patients. In this study no statistically significant difference was shown between the predicted prognosis and actual survival of a group of young breast cancer patients.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- Based at a single institution leading to high level of standardization. All patients were discussed at multi-disciplinary team meeting attended to by the same team during the study period and the same team of surgeons carried out all surgery. Histopathology reporting was also a constant through out the study.
- The study population in North England including the areas around Scunthorpe and Grimsby contain a very static population demographic, which likely remained very constant throughout the study period.
- The Adjuvant Online (Adjuvant!) and Nottingham Prognostic Index (NPI) have not previously been compared in a sample of young women with breast cancer.
- Long follow-up period of participants in comparison to other published studies. Our median follow up time was 113.5 months compared to an average of 60 across other studies.
- No missing data or participants lost to follow-up.

Limitations

- Study sample may not be representative of the entire UK population.
- Relatively small sample size leading to low power, which meant a statistical difference between the NPI, Adjuvant! and actual survival was not demonstrated.
- The HER 2 data was not readily available for the majority of study participants. It is now used widely as guide to recommending treatment, however, it is currently not included in either the NPI or Adjuvant! calculations.

INTRODUCTION

What is my prognosis? This is the question that many patients directly or indirectly ask when given the diagnosis of breast cancer. This question is particularly difficult to answer in "younger patients" since breast cancer in young patients is often considered to be a more biologically aggressive disease with a poorer prognosis compared with older women.[1-3] The definition of "young" also varies between different studies with most authors identifying the upper age limit ranging from <35 years,[4,5] to ≤40 years.[6-9]

Since screening is unlikely to ever include women under the age of 40, for the purposes of this study we defined "young" as patients presenting at <40 years of age. Breast cancer is the most common cancer in women aged under 40. In the UK around 1,300 women are diagnosed with breast cancer between the ages of 35-39 each year. The incidence of the disease in young women varies from 4% in the UK, [8,10] 6.2% in Italy,[2] and 7% in USA.[6]

There are two widely accepted clinical tools used to calculate an individual's prognosis, the Nottingham Prognostic Index (NPI) and the Adjuvant Online (Adjuvant!). The NPI combines nodal status, tumour size and histological grade in a simple formula. Its advantage in prognostic discrimination has been validated by various studies and it is used widely in clinical practice.[11-13] Lee & Ellis suggested that the NPI could be used for counseling patients with regard to their prognosis but this has not been validated specifically in younger patients.[14]

Adjuvant! (http://www.adjuvantonline.com) is a web based risk-assessment programme that was developed in a population from North America. The software uses similar factors to the NPI but also includes; patient age, hormone receptor status and comorbidity level.[15] These variables are used to calculate the patients estimated 10-year survival probabilities, risk of relapse and the expected benefit of adjuvant therapy. A large population based study of Canadian women of all ages with early breast cancer has validated the Adjuvant! model.[16]

The objective of this study was to initially identify the actual survival data for a cohort of young breast cancer patients treated in the UK. These results were then compared with the calculated survival as assessed by both the NPI and Adjuvant! This enabled evaluation of the predictive power and accuracy of these prognostic tools in young breast cancer patients.

MATERIALS AND METHODS

This is a single-centre study, which prospectively collected information over ten years from January 1998 to December 2007. The database included all primary breast cancer patients diagnosed and treated in the Grimsby Breast Unit from 1998 to 2002 and the South Bank Breast Unit, which was the amalgamated service of the breast clinics in Grimsby and Scunthorpe increasing the population base from 200,000 to 420,000 people in 2003-2007.

Patients

There was a cohort of 102 primary breast cancer patients who were less than 40 years of age at the time of presentation. This equaled 5% of all breast cancers treated during the 10-year study period in this unit. Patients were excluded from the study if they were diagnosed with "pure" ductal carcinoma in-situ (DCIS) [n=5] or if they had metastasis at presentation [n=5]. There were 92 women with invasive disease and who had undergone potentially curative surgery in this study. Their age range was 26-39 years. Overall survival was defined as the time between first diagnosis of cancer and death from any cause, regardless of recurrence events. Patients who had neoadjuvant chemotherapy were not excluded because there is evidence that the NPI retains its prognostic value after this form of treatment.[17]

The case records of all patients were surveyed and the following details recorded: Age at presentation, tumour size as measured at histology, tumour grade, oestrogen receptor status and the number of positive lymph nodes. These factors were then used to calculate both an NPI score and the 10-year survival probability using Adjuvant!. To use the Adjuvant! tool it is necessary to input other factors including the patient's comorbidity level, oestrogen receptor status and age. All the patients in this study were fit, so comorbidities defined as 'average for age.' Oestrogen receptor (ER) positivity was determined using the Allred score. At the time of study, if the Allred score was greater than three, the oncologists would offer anti-hormone treatment.

Actual survival data was recorded using the continuously updated hospital electronic records system. These figures were documented at the end of 2014, which allowed a follow-up period of between seven and seventeen years. No individuals were lost during the follow-up period, which meant all 92 women contributed to the overall survival.

Treatment

All women involved in the study received treatment for breast cancer with what was considered the best practice and in accordance with network and national guidelines at the time of diagnosis. Surgery involved either breast conserving surgery followed by radiotherapy or a simple mastectomy with or without immediate reconstruction. Only six patients received neoadjuvant chemotherapy following multi-disciplinary team (MDT) discussion. The main treatment differences over the study period of 1998-2007 was the increasing use of chemotherapy in Grade 2 and 3 cancers, in lymph node positive patients regardless of tumour grade and the use of Herceptin in HER2 positive patients. Patients who were ER positive were offered Tamoxifen since all were premenopausal although almost half the patients subsequently had a prophylactic oophorectomy and were converted to an Aromatase Inhibitor. All patients were assessed at an MDT and further surgery was undertaken if any of the surgical margins were incomplete, defined as a radial margin of less than 2mm as per network guidelines.

Prognostic tools

The calculation for the NPI is (0.2 x tumour size in cm) + lymph node stage (1-3) + tumour grade. There were no tumours larger than 5cm recorded in this current study,

therefore the range of NPI was 2.04 -6.99. The NPI scores correspond to five groups ranging from a poor to excellent prognostic group. The numbers presented in Table 1 are those reported by Blamey et al. For all NPI scores within each group only a single summary 10-year survival figure is reported which has been validated by previous studies. [18] Adjuvant! data is continuous, on a scale from zero to 100%. The mean of the Adjuvant! and NPI scores were then compared. The groupings in Table 1 were used to predict the 10-year survival for each women in the cohort and then those predicted survival times were averaged to calculate the mean NPI score.

NPI Group	NPI score	10-year survival (%)
Excellent prognostic group (EPG)	≤2.40	96
Good prognostic group (GPG)	2.41-3.40	93
Moderate prognostic group 1 (M1PG)	3.41-4.40	81
Moderate prognostic group 2 (M2PG)	4.41-5.40	74
Poor prognostic group (PPG)	5.41-6.40	55

Table 1: Nottingham Prognostic Index details with equivalent 10-year survival figures.**[18]**

Statistical analysis

To study the correlation between the actual NPI values and Adjuvant! 10-year expected survival each individual's predicted survival was plotted and Pearson's correlation coefficient used to analyze the similarity between these two prognostic indices. The observation time was defined as the time between the date of diagnosis and an event, which was defined as death from any cause. No subjects were lost to follow-up and those alive at the end of the study period (September 2014) were censored. The overall 10-year survival curve for the group was calculated using the Kaplan-Meier method. Predicted 10-year cumulative survival curves were calculated using the NPI and Adjuvant! scores, this was achieved by assuming a constant yearly hazard rate. These graphs were then directly compared to the actual cumulative survival for the entire group of women. All analysis was carried out in SPSS statistics 22 and probability values of <0.05 were considered statistically significant.

RESULTS

The average age of the 92 women involved in this study was 36.27 years. The median follow-up time was 113.5 months (range 11-120 months) and at the end of follow-up period 71 (77.2%) patients were alive. The median follow-up time for those patients that died was 40.0 months and for those that were alive at the end of follow-up it was 120.0 months. The main clinically measurable parameters are shown in Table 2. Over 90% of young women presented with a breast lump and the mean tumour size was 2.07cm (SD ±0.92).

Parameter	All patients	
	N = 92	%

Age at diagnosis		
≤35	25	27.2
36-39	67	72.8
Symptoms		
Lump	84	91.3
Deformity of breast shape/skin puckering	5	5.4
Nipple inversion/blood discharge	1	1.1
Inflammation	1	1.1
Incidental imaging finding	1	1.1
Tumour size (cm)		
0.1-1.0	11	12.0
1.1-2.0	41	44.6
2.1-3.0	28	30.4
3.1-5.0	12	13.0
Lymph node status		
0	53	57.6
1-3	25	27.2
>3	14	15.2
Tumour grade		
Grade I	16	17.4
Grade II	25	27.2
Grade III	51	55.4
Histology		
Ductal	88	95.7
Lobular	0	0.0
Other	4	4.3
Oestrogen receptor status		
Positive	73	79.3
Negative	19	20.7
HER-2 receptor status		
Positive	6	6.5
Negative	33	35.9
Unknown	53	57.6
Vascular invasion		
Present	40	43.5
Not present	52	56.5
Surgery		
Overall mastectomy rate	46	50.0
Mastectomy without reconstruction	20	21.7
Mastectomy & immediate reconstruction	26	28.3
Breast conserving surgery	46	50.0
Neoadjuvant chemotherapy		
Yes	6	6.5
No	86	93.5

NPI		
Excellent	12	13.0
Good	14	15.2
Moderate 1	25	27.2
Moderate 2	20	21.7
Poor	21	22.8

Table 2: The main pathological, clinical and treatment parameters within the study population of 92 young patients with invasive breast cancer.

Directly comparing the actual survival with both NPI and Adjuvant! 10-year survival prognosis, confirms that there is a strong linear correlation between these two clinical tools (Figure 1). This is further demonstrated by Pearson's correlation coefficient, which was 0.873 (CI: 0.835-0.901).

Kaplan-Meier actual survival analysis of young women, diagnosed with breast cancer in this study revealed that the 5-year and 10-year survival rates were 79.3% (CI: 71.1–87.5) and 77.2% (CI: 68.6-85.8) respectively. The Kaplan-Meier survival plot in Figure 2 indicates that patients, who survived the first five years after diagnosis, had a high probability of surviving to ten years.

Figure 3 illustrates the overall 10-year survival rate for the study population and compares it to the NPI and Adjuvant! predicted survival rates. The NPI predicted survival shows a stronger resemblance to the actual survival curve. A higher survival rate was recorded using the Adjuvant! scores. However, there was no statistically significant difference between survival figures generated by the prognostic tools and the actual survival (Table 3).

	10-year survival (%)
Overall survival	77.2 (CI: 68.6 – 85.8)
NPI prediction	77.3 (CI: 74.4 – 80.2)
Adjuvant! prediction	82.1 (CI: 79.1 – 85.1)

Table 3: Overall survival of young patients after 10-years of follow-up determined using the Kaplan-Meier method. This figure is compared to the NPI and Adjuvant! 10-year predicted survival at the time of diagnosis. The predictions are equivalent to the mean values calculated from the prognostic scores for each individual.

DISCUSSION

In the literature young patients with breast cancer are usually said to have a poor prognosis.[7-9] This is often attributed to their higher incidence of grade 3 tumours, more lymph node involvement and less oestrogen positive tumours. These results are usually compared with older patient groups defined as >50 or >60 years.[2,5,7] There is ongoing controversy as to whether age is a risk factor independent of the above biological factors.[1,3,5] McAree et al. found in a series of 57 young breast cancer patients that nearly 16% of their patients fulfilled the NICE guidelines for genetic testing but only 1.8% actually carried the gene.[8]

The aim of this study was to assess the mortality in young patients (< 40 years of age at presentation) during a 10 year follow up period then compare the figures with the NPI and Adjuvant! in order to assess there accuracy at predicting survival in young patients. Over the last few years, both the NPI and Adjuvant! have been accepted as accurate predictors of survival in older patients and a guide to choice of treatment but their value in young patients is either not established or disputed.[19]

While our series is modest, it is similar in size to other studies reflecting the limited experience worldwide in young breast cancer patients, but unlike other studies our data is complete with no patients lost to follow-up. Our population study has similar tumour size, incidence of grade 3 cancers, oestrogen receptor and lymph node involvement to the literature and our overall survival results are also similar as demonstrated in table 4. This illustrates that similar results have been recorded in studies in the United Kingdom,[8,20] Sweden,[5,7,9] Australia,[3,21] and Italy.[2]

Neoadjuvant chemotherapy is now widely used and recognized as a treatment modality for locally invasive breast cancer especially in young patients. The Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) reports between 2000-2008 15.6% of young women had neoadjuvant chemotherapy compared to 6.5% in the current study which demonstrates the increased acceptance of this form of treatment over the past decade.[20]

The data in this study was prospectively collected at the weekly MDT meeting. All histology was first reported by a member of a dedicated group of histopathologists, one of whom was also the unit's MDT dedicated breast histopathologist. This ensured the histopathology was accurate and the data complete. In particular there was consensus reporting of the tumour grade, which is a very important component in both the NPI and Adjuvant! calculations. A further strength of the present study is that this population is relatively static. Unfortunately the HER 2 was not readily available for much of the study. Although it is now used widely as guide to recommending treatment, it is currently not included in either the NPI or Adjuvant! calculations. To add this parameter would need at least a re-validation of the NPI calculation.[14]

Adjuvant! was developed in the USA using data from the Surveillance, Epidemiology and End-Results (SEER) tumour registry.[15] The biological variables; tumour size, grade and lymph node involvement are included in the Adjuvant! calculation with additional inclusions of the patients' general fitness and the oestrogen status. The score weighting given for each of these factors is not known when applied in the Adjuvant! computer calculation. In a Canadian study to validate the Adjuvant! the authors found the 10 year predicted and overall outcomes were within 1% for overall survival, however Adjuvant! overestimated overall survival in patients under 35 years old by 8.6%.[16] The Adjuvant! has also been validated by a Dutch study which found that it accurately predicted 10 year outcomes in their population overall but it was less reliable in the sub set of young patients. Currently a correction factor of 1.5 is applied to the score for oestrogen receptor positive patients under 35 years. Despite this Mook et al. concluded that the correction was insufficient and an additional correction was required for patients between 35-40 years with oestrogen receptor positive tumours.[19] A British study in Oxford reported a statistically

significant difference of 5.54% in predicted and observed overall survival using the Adjuvant! but made no specific reference to young patients.[22]

In the current study, the NPI and Adjuvant! predicted similar survival outcomes for young breast cancer patients with direct linear correlation ($p<0.01$). The large variability between the NPI and Adjuvant! 10-year survival rates within the 'poor' NPI group (Figure 1) were insignificant. It is suggested that this variability is caused by the heterogeneity of the group with between one to 22 lymph nodes involved and some patients likely having already developed micro metastasis. Neither prognostic tool is designed to predict metastasis at presentation.

The NPI appears to maintain its accuracy in young women diagnosed with invasive breast cancer. One of the many benefits of the NPI tool is its simplicity and the fact no computer is needed to perform the calculation. Other studies have validated the accuracy of the NPI within young breast cancer populations by showing that the mortality rate is no different from what would be expected according to the NPI.[11]

The present study showed no statistical difference between the accuracy of the NPI or Adjuvant! However, the impression that the current Adjuvant! appears to overestimate the prognosis by 5% has been identified by other studies in the Netherlands and Canada.[16,19] The accuracy of the Adjuvant! appears to be population specific as a recent study in Ireland demonstrated that the Adjuvant! actually underestimated the overall 10-year survival of a cohort of 77 women.[23] These variations have been suggested to correlate with changes in ethnicity and age distribution in populations outside the US where the Adjuvant! was developed.

The main limitation of this study was the sample size was too small to demonstrate a statistically significant difference between the prognostic tools and the actual survival. If the Adjuvant! over prediction is a true result then a larger study will need to be performed to investigate this. A retrospective calculation using 77.2% as the true survival rate indicates that reducing the width of the 95% confidence interval to 10% would require a sample of 273 patients. This figure for the 95% confidence interval would exclude the Adjuvant! predicted value of 82.1%. The results emphasise the need for a national study to further scrutinise the accuracy of the Adjuvant! and NPI in young women with breast cancer.

The survival data from studies that have specifically investigated young breast cancer patients is shown in Table 4. The overall impression is that few papers in the literature have explored the value of the NPI or Adjuvant! in this group of patient. The current data should be interpreted as an establishment of information on this topic in a UK population. In one study of 107 patients the analysis demonstrated that if the NPI was between 3.4 and 5.39 the mortality rate was only 24% during the 10-year study period. Concluding, that the NPI was a valuable tool when counseling young breast cancer patients in agreement with the current results.[7]

	Patient numbers	Average tumour size (mm)	Grade 3 tumours (%)	Lymph node involved (%)	Oestrogen receptor negative (%)	HER-2 receptor positive (%)	Overall survival at 5yrs (%)	Overall survival at 10yrs (%)	Median follow-up (months)
McAree et al. (2010)	57	21.3	40.7	40.0	23.8	30.0	77.0	-	52.7
Karihtala et al. (2010)	269	-	46.0	52.4	33.5	15.2	80.0	71.0	74.0
Jaysinghe et al. (2005)	47	-	31.9	53.2	-	-	60.0	49.0	-
Sidoni et al. (2003)	50	22.8	38.0	53.0	46.0	48.0	-	-	-
Gillett et al. (1997)	58	23.0	40.0	34.0	-	-	90.0 [a]	-	31.0
Sundquist et al. (2002)	107	-	64.0	37.0	-	-	72.0	58-63 [b]	134.0
Fredholm et al. (2009)	1329	-	21.0 [c]	46.0	26.0 [c]	-	83.8	-	-
Copson et al. (2013)	2956	22.0	58.9	50.6	33.7	24.3	81.9	-	60
Current study	92	20.1	55.4	42.5	20.7 [d]	6.5	79.3	77.2	113.5

[a] 16% of patients were pure DCIS. [b] 2 figures recorded depending on study period. [c] Data missing for the tumour grade in 60% and oestrogen receptor status in 18% of patients. [d] Oestrogen receptor +ve if Allred score was greater than 3/8.

Table 4: Comparing the data and results from eight similar studies that have investigated invasive breast cancer within a population of young women.

CONCLUSIONS

This study looked at the mortality of young breast cancer patients (<40 years old) treated in a single breast unit with an average follow up of 9.5 years. The results revealed that the 5-year and 10-year survival was 79.3% and 77.2% respectively between 1998 and 2007. The NPI seemed to be more accurate whereas Adjuvant! over predicted survival by around 5% although the study had insufficient power to statistically define the difference. This study provides a platform from which future research can further investigate the results highlighted here and whether these findings are reproducible across the UK. The NPI and Adjuvant! appear to be precise methods for predicting 10-year survival in young women with breast cancer.

COMPETING INTERESTS

The authors have no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the

submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTORSHIP

All authors contributed to the planning, conduct and reporting of this study. Dr BJ Hearne was responsible for the overall content as guarantor.

DATA SHARING

No additional data is available.

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FIGURE LEGENDS

Figure 1: The 10-year survival probability at the time of diagnosis for individual young women aged <40 years between 1998 and 2007. The distribution of survival figures calculated using the NPI compared to those calculated using the Adjuvant! model.

Figure 2: Kaplan-Meier curve of overall survival for 92 young women diagnosed with primary invasive breast cancer that underwent potentially curative surgery (Crosses represent censored cases).

Figure 3: The actual survival curve for the group demonstrating the percentage survival after each year over a 10-year follow-up period. The predicted curves generated from the individual NPI and Adjuvant! scores are shown for comparison.

Comparison of Nottingham Prognostic Index and Adjuvant Online prognostic tools in young women with breast cancer: Review of a single-institution experience

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ABSTRACT

Objective: Accurately predicting the prognosis of young breast cancer patients (<40 years) is uncertain since the literature suggests they have a higher mortality and that age is an independent risk factor. In this cohort study we considered two prognostic tools; Nottingham Prognostic Index and Adjuvant Online (Adjuvant!), in a group of young patients, comparing their predicted prognosis with their actual survival.

Setting: North West England

Participants: Data was prospectively collected from the breast unit at a Hospital in Grimsby between January 1998 and December 2007. A cohort of 102 young primary breast cancer patients was identified and actual survival data was recorded. The Nottingham Prognostic Index and Adjuvant! scores were calculated and used to estimate 10-year survival probabilities. Pearson's correlation coefficient was used to demonstrate the association between the Nottingham Prognostic Index and Adjuvant! scores. A constant yearly hazard rate was assumed to generate 10-year cumulative survival curves using the Nottingham Prognostic Index and Adjuvant! predictions.

Results: Actual 10-year survival for the 92 patients who underwent potentially curative surgery for invasive cancer was 77.2% (CI: 68.6-85.8). There was no significant difference between the actual survival and the Nottingham Prognostic Index and Adjuvant! 10-year estimated survival, which was 77.3% (CI: 74.4-80.2) and 82.1% (CI: 79.1-85.1) respectively. The Nottingham Prognostic Index and Adjuvant! results demonstrated strong correlation and both predicted cumulative survival curves accurately reflected the actual survival in young patients.

Conclusions: The Nottingham Prognostic Index and Adjuvant! are widely used to predict survival in breast cancer patients. In this study no statistically significant difference was shown between the predicted prognosis and actual survival of a group of young breast cancer patients.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- Based at a single institution leading to high level of standardization. All patients were discussed at multi-disciplinary team meeting attended to by the same team during the study period and the same team of surgeons carried out all surgery. Histopathology reporting was also a constant through out the study.
- The study population in North England including the areas around Scunthorpe and Grimsby contain a very static population demographic, which likely remained very constant throughout the study period.
- The Adjuvant Online (Adjuvant!) and Nottingham Prognostic Index (NPI) have not previously been compared in a sample of young women with breast cancer.
- Long follow-up period of participants in comparison to other published studies. Our median follow up time was 113.5 months compared to an average of 60 across other studies.
- No missing data or participants lost to follow-up.

Limitations

- Study sample may not be representative of the entire UK population.
- Relatively small sample size leading to low power, which meant a statistical difference between the NPI, Adjuvant! and actual survival was not demonstrated.
- The HER 2 data was not readily available for the majority of study participants. It is now used widely as guide to recommending treatment, however, it is currently not included in either the NPI or Adjuvant! calculations.

INTRODUCTION

What is my prognosis? This is the question that many patients directly or indirectly ask when given the diagnosis of breast cancer. This question is particularly difficult to answer in "younger patients" since breast cancer in young patients is often considered to be a more biologically aggressive disease with a poorer prognosis compared with older women.[1-3] The definition of "young" also varies between different studies with most authors identifying the upper age limit ranging from <35 years,[4,5] to ≤40 years.[6-9]

Since screening is unlikely to ever include women under the age of 40, for the purposes of this study we defined "young" as patients presenting at <40 years of age. Breast cancer is the most common cancer in women aged under 40. In the UK around 1,300 women are diagnosed with breast cancer between the ages of 35-39 each year. The incidence of the disease in young women varies from 4% in the UK, [8,10] 6.2% in Italy,[2] and 7% in USA.[6]

There are two widely accepted clinical tools used to calculate an individual's prognosis, the Nottingham Prognostic Index (NPI) and the Adjuvant Online (Adjuvant!). The NPI combines nodal status, tumour size and histological grade in a simple formula. Its advantage in prognostic discrimination has been validated by various studies and it is used widely in clinical practice.[11-13] Lee & Ellis suggested that the NPI could be used for counseling patients with regard to their prognosis but this has not been validated specifically in younger patients.[14]

Adjuvant! (http://www.adjuvantonline.com) is a web based risk-assessment programme that was developed in a population from North America. The software uses similar factors to the NPI but also includes; patient age, hormone receptor status and comorbidity level.[15] These variables are used to calculate the patients estimated 10-year survival probabilities, risk of relapse and the expected benefit of adjuvant therapy. A large population based study of Canadian women of all ages with early breast cancer has validated the Adjuvant! model.[16]

The objective of this study was to initially identify the actual survival data for a cohort of young breast cancer patients treated in the UK. These results were then compared with the calculated survival as assessed by both the NPI and Adjuvant! This enabled evaluation of the predictive power and accuracy of these prognostic tools in young breast cancer patients.

MATERIALS AND METHODS

This is a single-centre study, which prospectively collected information over ten years from January 1998 to December 2007. The database included all primary breast cancer patients diagnosed and treated in the Grimsby Breast Unit from 1998 to 2002 and the South Bank Breast Unit, which was the amalgamated service of the breast clinics in Grimsby and Scunthorpe increasing the population base from 200,000 to 420,000 people in 2003-2007.

Patients

There was a cohort of 102 primary breast cancer patients who were less than 40 years of age at the time of presentation. This equaled 5% of all breast cancers treated during the 10-year study period in this unit. Patients were excluded from the study if they were diagnosed with "pure" ductal carcinoma in-situ (DCIS) [n=5] or if they had metastasis at presentation [n=5]. There were 92 women with invasive disease and who had undergone potentially curative surgery in this study. Their age range was 26-39 years. Overall survival was defined as the time between first diagnosis of cancer and death from any cause, regardless of recurrence events. Patients who had neoadjuvant chemotherapy were not excluded because there is evidence that the NPI retains its prognostic value after this form of treatment.[17]

The case records of all patients were surveyed and the following details recorded: Age at presentation, tumour size as measured at histology, tumour grade, oestrogen receptor status and the number of positive lymph nodes. These factors were then used to calculate both an NPI score and the 10-year survival probability using Adjuvant!. To use the Adjuvant! tool it is necessary to input other factors including the patient's comorbidity level, oestrogen receptor status and age. All the patients in this study were fit, so comorbidities defined as 'average for age.' Oestrogen receptor (ER) positivity was determined using the Allred score. At the time of study, if the Allred score was greater than three, the oncologists would offer anti-hormone treatment.

Actual survival data was recorded using the continuously updated hospital electronic records system. These figures were documented at the end of 2014, which allowed a follow-up period of between seven and seventeen years. No individuals were lost during the follow-up period, which meant all 92 women contributed to the overall survival.

Treatment

All women involved in the study received treatment for breast cancer with what was considered the best practice and in accordance with network and national guidelines at the time of diagnosis. Surgery involved either breast conserving surgery followed by radiotherapy or a simple mastectomy with or without immediate reconstruction. Only six patients received neoadjuvant chemotherapy following multi-disciplinary team (MDT) discussion. The main treatment differences over the study period of 1998-2007 was the increasing use of chemotherapy in Grade 2 and 3 cancers, in lymph node positive patients regardless of tumour grade and the use of Herceptin in HER2 positive patients. Patients who were ER positive were offered Tamoxifen since all were premenopausal although almost half the patients subsequently had a prophylactic oophorectomy and were converted to an Aromatase Inhibitor. All patients were assessed at an MDT and further surgery was undertaken if any of the surgical margins were incomplete, defined as a radial margin of less than 2mm as per network guidelines.

Prognostic tools

The calculation for the NPI is (0.2 x tumour size in cm) + lymph node stage (1-3) + tumour grade. There were no tumours larger than 5cm recorded in this current study,

therefore the range of NPI was 2.04 -6.99. The NPI scores correspond to five groups ranging from a poor to excellent prognostic group. The numbers presented in Table 1 are those reported by Blamey et al. For all NPI scores within each group only a single summary 10-year survival figure is reported which has been validated by previous studies. [18] Adjuvant! data is continuous, on a scale from zero to 100%. The mean of the Adjuvant! and NPI scores were then compared. The groupings in Table 1 were used to predict the 10-year survival for each women in the cohort and then those predicted survival times were averaged to calculate the mean NPI score.

NPI Group	NPI score	10-year survival (%)
Excellent prognostic group (EPG)	≤2.40	96
Good prognostic group (GPG)	2.41-3.40	93
Moderate prognostic group 1 (M1PG)	3.41-4.40	81
Moderate prognostic group 2 (M2PG)	4.41-5.40	74
Poor prognostic group (PPG)	5.41-6.40	55

Table 1: Nottingham Prognostic Index details with equivalent 10-year survival figures.**[18]**

Statistical analysis

To study the correlation between the actual NPI values and Adjuvant! 10-year expected survival each individual's predicted survival was plotted and Pearson's correlation coefficient used to analyze the similarity between these two prognostic indices. The observation time was defined as the time between the date of diagnosis and an event, which was defined as death from any cause. No subjects were lost to follow-up and those alive at the end of the study period (September 2014) were censored. The overall 10-year survival curve for the group was calculated using the Kaplan-Meier method. Predicted 10-year cumulative survival curves were calculated using the NPI and Adjuvant! scores, this was achieved by assuming a constant yearly hazard rate. These graphs were then directly compared to the actual cumulative survival for the entire group of women. All analysis was carried out in SPSS statistics 22 and probability values of <0.05 were considered statistically significant.

RESULTS

The average age of the 92 women involved in this study was 36.27 years. The median follow-up time was 113.5 months (range 11-120 months) and at the end of follow-up period 71 (77.2%) patients were alive. The median follow-up time for those patients that died was 40.0 months and for those that were alive at the end of follow-up it was 120.0 months. The main clinically measurable parameters are shown in Table 2. Over 90% of young women presented with a breast lump and the mean tumour size was 2.07cm (SD ±0.92).

Parameter	All patients	
	N = 92	%

Age at diagnosis		
≤35	25	27.2
36-39	67	72.8
Symptoms		
Lump	84	91.3
Deformity of breast shape/skin puckering	5	5.4
Nipple inversion/blood discharge	1	1.1
Inflammation	1	1.1
Incidental imaging finding	1	1.1
Tumour size (cm)		
0.1-1.0	11	12.0
1.1-2.0	41	44.6
2.1-3.0	28	30.4
3.1-5.0	12	13.0
Lymph node status		
0	53	57.6
1-3	25	27.2
>3	14	15.2
Tumour grade		
Grade I	16	17.4
Grade II	25	27.2
Grade III	51	55.4
Histology		
Ductal	88	95.7
Lobular	0	0.0
Other	4	4.3
Oestrogen receptor status		
Positive	73	79.3
Negative	19	20.7
HER-2 receptor status		
Positive	6	6.5
Negative	33	35.9
Unknown	53	57.6
Vascular invasion		
Present	40	43.5
Not present	52	56.5
Surgery		
Overall mastectomy rate	46	50.0
Mastectomy without reconstruction	20	21.7
Mastectomy & immediate reconstruction	26	28.3
Breast conserving surgery	46	50.0
Neoadjuvant chemotherapy		
Yes	6	6.5
No	86	93.5

NPI		
Excellent	12	13.0
Good	14	15.2
Moderate 1	25	27.2
Moderate 2	20	21.7
Poor	21	22.8

Table 2: The main pathological, clinical and treatment parameters within the study population of 92 young patients with invasive breast cancer.

Directly comparing the actual survival with both NPI and Adjuvant! 10-year survival prognosis, confirms that there is a strong linear correlation between these two clinical tools (Figure 1). This is further demonstrated by Pearson's correlation coefficient, which was 0.873 (CI: 0.835-0.901).

Kaplan-Meier actual survival analysis of young women, diagnosed with breast cancer in this study revealed that the 5-year and 10-year survival rates were 79.3% (CI: 71.1–87.5) and 77.2% (CI: 68.6-85.8) respectively. The Kaplan-Meier survival plot in Figure 2 indicates that patients, who survived the first five years after diagnosis, had a high probability of surviving to ten years.

Figure 3 illustrates the overall 10-year survival rate for the study population and compares it to the NPI and Adjuvant! predicted survival rates. The NPI predicted survival shows a stronger resemblance to the actual survival curve. A higher survival rate was recorded using the Adjuvant! scores. However, there was no statistically significant difference between survival figures generated by the prognostic tools and the actual survival (Table 3).

	10-year survival (%)
Overall survival	77.2 (CI: 68.6 – 85.8)
NPI prediction	77.3 (CI: 74.4 – 80.2)
Adjuvant! prediction	82.1 (CI: 79.1 – 85.1)

Table 3: Overall survival of young patients after 10-years of follow-up determined using the Kaplan-Meier method. This figure is compared to the NPI and Adjuvant! 10-year predicted survival at the time of diagnosis. The predictions are equivalent to the mean values calculated from the prognostic scores for each individual.

DISCUSSION

In the literature young patients with breast cancer are usually said to have a poor prognosis.[7-9] This is often attributed to their higher incidence of grade 3 tumours, more lymph node involvement and less oestrogen positive tumours. These results are usually compared with older patient groups defined as >50 or >60 years.[2,5,7] There is ongoing controversy as to whether age is a risk factor independent of the above biological factors.[1,3,5] McAree et al. found in a series of 57 young breast cancer patients that nearly 16% of their patients fulfilled the NICE guidelines for genetic testing but only 1.8% actually carried the gene.[8]

The aim of this study was to assess the mortality in young patients (< 40 years of age at presentation) during a 10 year follow up period then compare the figures with the NPI and Adjuvant! in order to assess there accuracy at predicting survival in young patients. Over the last few years, both the NPI and Adjuvant! have been accepted as accurate predictors of survival in older patients and a guide to choice of treatment but their value in young patients is either not established or disputed.[19]

While our series is modest, it is similar in size to other studies reflecting the limited experience worldwide in young breast cancer patients, but unlike other studies our data is complete with no patients lost to follow-up. Our population study has similar tumour size, incidence of grade 3 cancers, oestrogen receptor and lymph node involvement to the literature and our overall survival results are also similar as demonstrated in table 4. This illustrates that similar results have been recorded in studies in the United Kingdom,[8,20] Sweden,[5,7,9] Australia,[3,21] and Italy.[2]

Neoadjuvant chemotherapy is now widely used and recognized as a treatment modality for locally invasive breast cancer especially in young patients. The Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) reports between 2000-2008 15.6% of young women had neoadjuvant chemotherapy compared to 6.5% in the current study which demonstrates the increased acceptance of this form of treatment over the past decade.[20]

The data in this study was prospectively collected at the weekly MDT meeting. All histology was first reported by a member of a dedicated group of histopathologists, one of whom was also the unit's MDT dedicated breast histopathologist. This ensured the histopathology was accurate and the data complete. In particular there was consensus reporting of the tumour grade, which is a very important component in both the NPI and Adjuvant! calculations. A further strength of the present study is that this population is relatively static. Unfortunately the HER 2 was not readily available for much of the study. Although it is now used widely as guide to recommending treatment, it is currently not included in either the NPI or Adjuvant! calculations. To add this parameter would need at least a re-validation of the NPI calculation.[14]

Adjuvant! was developed in the USA using data from the Surveillance, Epidemiology and End-Results (SEER) tumour registry.[15] The biological variables; tumour size, grade and lymph node involvement are included in the Adjuvant! calculation with additional inclusions of the patients' general fitness and the oestrogen status. The score weighting given for each of these factors is not known when applied in the Adjuvant! computer calculation. In a Canadian study to validate the Adjuvant! the authors found the 10 year predicted and overall outcomes were within 1% for overall survival, however Adjuvant! overestimated overall survival in patients under 35 years old by 8.6%.[16] The Adjuvant! has also been validated by a Dutch study which found that it accurately predicted 10 year outcomes in their population overall but it was less reliable in the sub set of young patients. Currently a correction factor of 1.5 is applied to the score for oestrogen receptor positive patients under 35 years. Despite this Mook et al. concluded that the correction was insufficient and an additional correction was required for patients between 35-40 years with oestrogen receptor positive tumours.[19] A British study in Oxford reported a statistically

significant difference of 5.54% in predicted and observed overall survival using the Adjuvant! but made no specific reference to young patients.[22]

In the current study, the NPI and Adjuvant! predicted similar survival outcomes for young breast cancer patients with direct linear correlation ($p<0.01$). The large variability between the NPI and Adjuvant! 10-year survival rates within the 'poor' NPI group (Figure 1) were insignificant. It is suggested that this variability is caused by the heterogeneity of the group with between one to 22 lymph nodes involved and some patients likely having already developed micro metastasis. Neither prognostic tool is designed to predict metastasis at presentation.

The NPI appears to maintain its accuracy in young women diagnosed with invasive breast cancer. One of the many benefits of the NPI tool is its simplicity and the fact no computer is needed to perform the calculation. Other studies have validated the accuracy of the NPI within young breast cancer populations by showing that the mortality rate is no different from what would be expected according to the NPI.[11]

The present study showed no statistical difference between the accuracy of the NPI or Adjuvant! However, the impression that the current Adjuvant! appears to overestimate the prognosis by 5% has been identified by other studies in the Netherlands and Canada.[16,19] The accuracy of the Adjuvant! appears to be population specific as a recent study in Ireland demonstrated that the Adjuvant! actually underestimated the overall 10-year survival of a cohort of 77 women.[23] These variations have been suggested to correlate with changes in ethnicity and age distribution in populations outside the US where the Adjuvant! was developed.

The main limitation of this study was the sample size was too small to demonstrate a statistically significant difference between the prognostic tools and the actual survival. If the Adjuvant! over prediction is a true result then a larger study will need to be performed to investigate this. A retrospective calculation using 77.2% as the true survival rate indicates that reducing the width of the 95% confidence interval to 10% would require a sample of 273 patients. This figure for the 95% confidence interval would exclude the Adjuvant! predicted value of 82.1%. The results emphasise the need for a national study to further scrutinise the accuracy of the Adjuvant! and NPI in young women with breast cancer.

The survival data from studies that have specifically investigated young breast cancer patients is shown in Table 4. The overall impression is that few papers in the literature have explored the value of the NPI or Adjuvant! in this group of patient. The current data should be interpreted as an establishment of information on this topic in a UK population. In one study of 107 patients the analysis demonstrated that if the NPI was between 3.4 and 5.39 the mortality rate was only 24% during the 10-year study period. Concluding, that the NPI was a valuable tool when counseling young breast cancer patients in agreement with the current results.[7]

	Patient numbers	Average tumour size (mm)	Grade 3 tumours (%)	Lymph node involved (%)	Oestrogen receptor negative (%)	HER-2 receptor positive (%)	Overall survival at 5yrs (%)	Overall survival at 10yrs (%)	Median follow-up (months)
McAree et al. (2010)	57	21.3	40.7	40.0	23.8	30.0	77.0	-	52.7
Karihtala et al. (2010)	269	-	46.0	52.4	33.5	15.2	80.0	71.0	74.0
Jaysinghe et al. (2005)	47	-	31.9	53.2	-	-	60.0	49.0	-
Sidoni et al. (2003)	50	22.8	38.0	53.0	46.0	48.0	-	-	-
Gillett et al. (1997)	58	23.0	40.0	34.0	-	-	90.0 [a]	-	31.0
Sundquist et al. (2002)	107	-	64.0	37.0	-	-	72.0	58-63 [b]	134.0
Fredholm et al. (2009)	1329	-	21.0 [c]	46.0	26.0 [c]	-	83.8	-	-
Copson et al. (2013)	2956	22.0	58.9	50.6	33.7	24.3	81.9	-	60
Current study	92	20.1	55.4	42.5	20.7 [d]	6.5	79.3	77.2	113.5

[a] 16% of patients were pure DCIS. [b] 2 figures recorded depending on study period. [c] Data missing for the tumour grade in 60% and oestrogen receptor status in 18% of patients. [d] Oestrogen receptor +ve if Allred score was greater than 3/8.

Table 4: Comparing the data and results from eight similar studies that have investigated invasive breast cancer within a population of young women.

CONCLUSIONS

This study looked at the mortality of young breast cancer patients (<40 years old) treated in a single breast unit with an average follow up of 9.5 years. The results revealed that the 5-year and 10-year survival was 79.3% and 77.2% respectively between 1998 and 2007. The NPI seemed to be more accurate whereas Adjuvant! over predicted survival by around 5% although the study had insufficient power to statistically define the difference. This study provides a platform from which future research can further investigate the results highlighted here and whether these findings are reproducible across the UK. The NPI and Adjuvant! appear to be precise methods for predicting 10-year survival in young women with breast cancer.

COMPETING INTERESTS

The authors have no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the

submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTORSHIP

All authors contributed to the planning, conduct and reporting of this study. Dr BJ Hearne was responsible for the overall content as guarantor.

DATA SHARING

No additional data is available.

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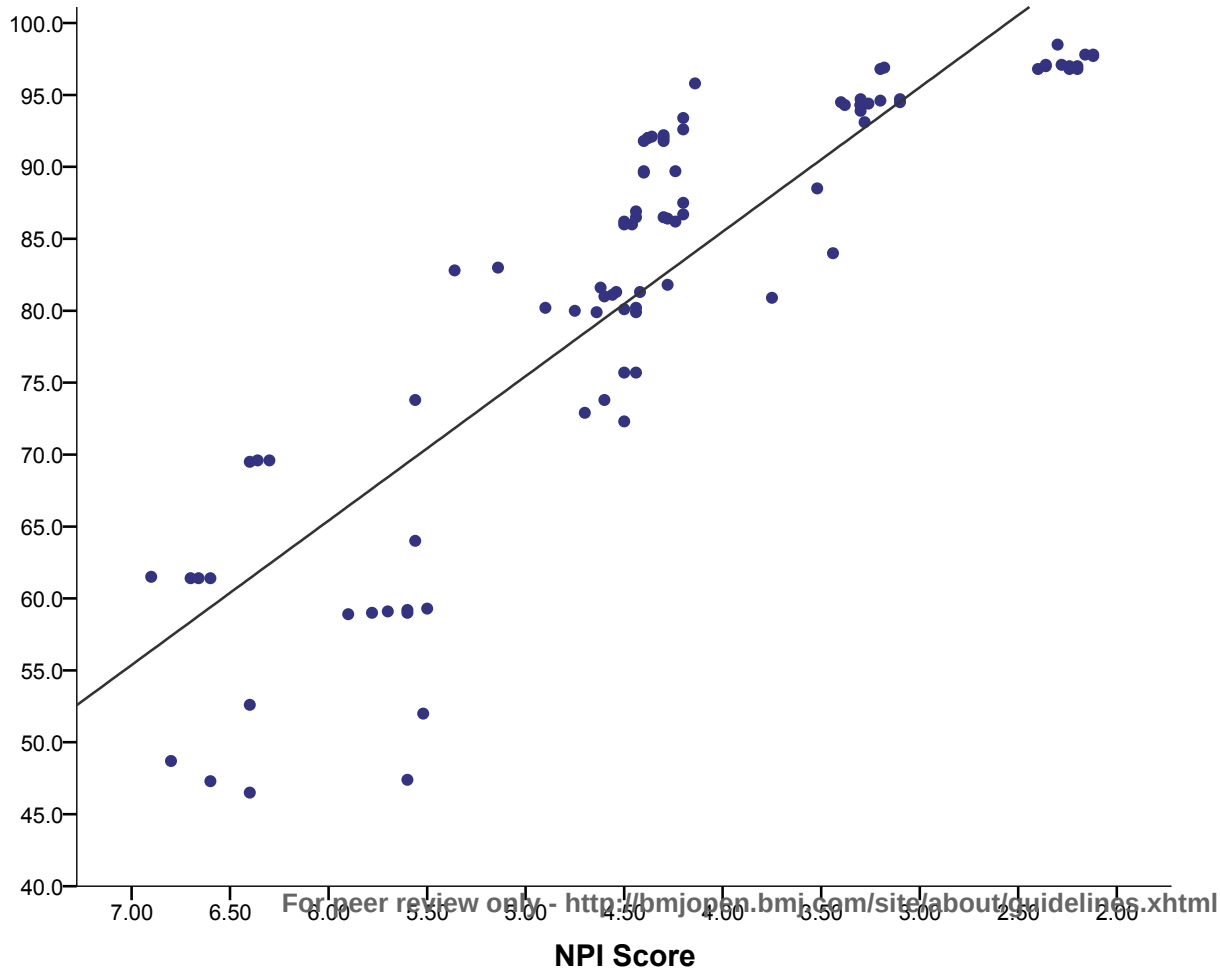
23 Quintyne KI, Woulfe B, Coffey JC, *et al.* Correlation Between Nottingham Prognostic Index and Adjuvant! Online Prognostic Tools in Patients With Early-Stage Breast Cancer in Mid-Western Ireland. *Clinical Breast Cancer* 2013;**13**:233–8. doi:10.1016/j.clbc.2013.02.011

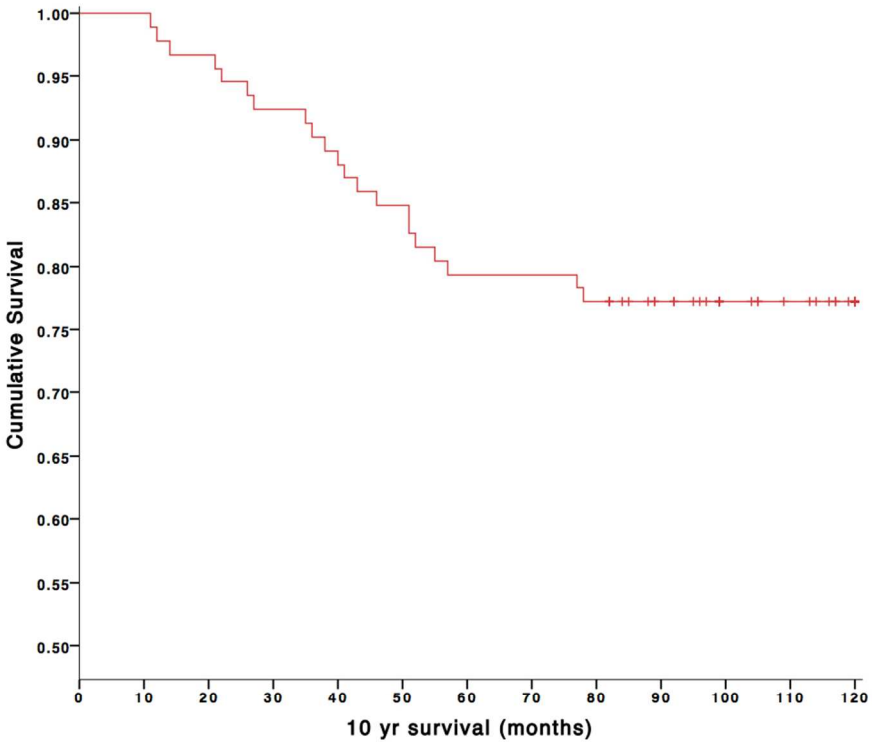
FIGURE LEGENDS

Figure 1: The 10-year survival probability at the time of diagnosis for individual young women aged <40 years between 1998 and 2007. The distribution of survival figures calculated using the NPI compared to those calculated using the Adjuvant! model.

Figure 2: Kaplan-Meier curve of overall survival for 92 young women diagnosed with primary invasive breast cancer that underwent potentially curative surgery (Crosses represent censored cases).

Figure 3: The actual survival curve for the group demonstrating the percentage survival after each year over a 10-year follow-up period. The predicted curves generated from the individual NPI and Adjuvant! scores are shown for comparison.





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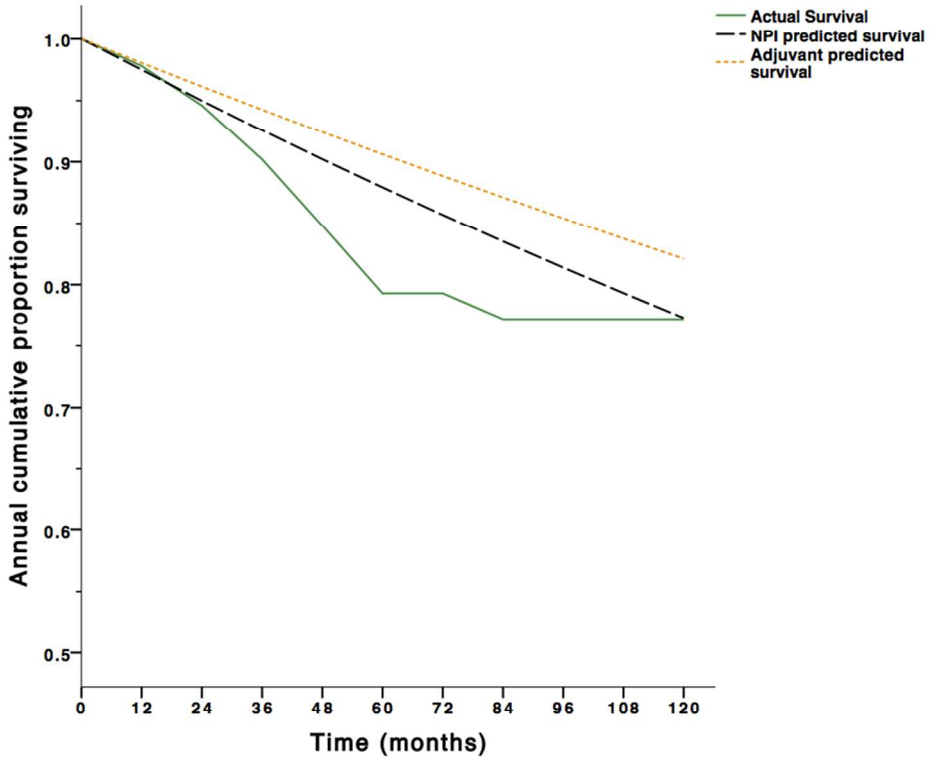

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8 (Table 2)
		(b) Indicate number of participants with missing data for each variable of interest	No missing data
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.