Survival of invasive breast cancer according to the
Nottingham Prognostic Index in cases diagnosed in
1990–1999

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ARTICLE INFO

Article history:
Received 24 August 2006
Received in revised form 12 January 2007
Accepted 15 January 2007
Available online 26 February 2007

Keywords:
Breast cancer
Prognosis
Prognostic Index
Case survival
Improved surgery

ABSTRACT

The Nottingham Prognostic Index (NPI) is a well established and widely used method of predicting survival of operable primary breast cancer.

Aims: Primary: To present the updated survival figures for each NPI Group. Secondary: From the observations to suggest reasons for the reported fall in mortality from breast cancer.

Methods: The NPI is compiled from grade, size and lymph node status of the primary tumour. Consecutive cases diagnosed and treated at Nottingham City Hospital in 1980–1986 (n = 892) and 1990–1999 (n = 2238) are compared. Changes in protocols towards earlier diagnosis and better case management were made in the late 1980s between the two data sets.

Results: Case survival (Breast Cancer Specific) at 10 years has improved overall from 55% to 77%. Within all Prognostic groups there are high relative and absolute risk reductions. The distribution of cases to Prognostic groups shows only a small increase in the numbers in better groups.

Conclusion: The updated survival figures overall and for each Prognostic group for the NPI are presented.

1. Introduction

A great many prognostic factors in breast cancer have been described, but few when placed in multivariate analysis retain independent significance. Prognosis is multifactorially determined and the best discrimination is achieved by integrating independently significant factors. A widely used method of integration is the Nottingham Prognostic Index (NPI), for which integration of prognostic factors was devised in 1978 and the NPI described in 1982. It is the only Index to have prospective validation, both intra- and inter-centre. Although new prognostic methods are being sought, the only published comparison of the NPI with cDNA microarray analysis has shown no advantage in prognostic discrimination to the latter (and measurement of the NPI is much easier and at least 100 times cheaper!).

The NPI has satisfied the criteria which should be applied to all claimed methods for prognostic prediction, namely ability

1. To separate patients into groups with significantly differing survival chances.
2. To achieve wide separation, i.e. to recognise a ‘cured’ group and a group with poor survival.

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0959-8049/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.ejca.2007.01.016
3. To place a sufficient percentage of cases into each group.
4. To be applicable to all operable breast cancers, i.e. small,9
screen detected10 as well as symptomatic and those in
patients of young age.11
5. To have been prospectively validated intra-centre in a new
tumour set from that on which it was derived3 and inter-
centre and internationally.4–7
6. To be capable of measurement in all units and
inexpensive.

Mortality from breast cancer has fallen over the last years in
the Western World.12–14 Allied to that, case survival has risen.
As the NPI is widely used in clinical practice,15 in the estimation
of causation in legal reports and as the best present gold stan-
dard as a basis of comparison for new prognostic methods,8
there has been a good deal of demand for figures based on mod-
day diagnosis and case management to be provided.

Updated survival figures on the whole Nottingham-Teno-
vus series (1973–2000) and on cancers treated in 1990–1999
were reported in an invited paper over-viewing the NPI in
2002.16

The primary objective of this paper is to report the im-
proved figures within all NPI groups in women treated for pri-
mary breast cancer in the 1990s, brought about by modern
day treatment protocols. Comparison is also made with the
situation in the early to mid-1980s.

2. Patients and methods

The analyses undertaken were of consecutive women diag-
nosed with and treated for primary operable invasive breast
breast cancer at Nottingham City Hospital, aged 70 years or less,
with tumours of less than 5 cm diameter on clinical measure-
ment and/or on operative histology, in 1980–1986 inclusive
(n = 892) and 1990–1999 inclusive (n = 2238).

Women aged over 70 were not included because of the in-
creased confounding factor of death from other causes and
because primary treatment protocols for patients of that age
often differed from those for younger women, principally in
the use of Tamoxifen as the sole primary therapy.17

The majority of women with tumours of greater than 5 cm
diameter (locally advanced primary tumours) were also trea-
ted by different protocols, again by primary endocrine therapy
or irradiation before any surgery18; these measures alter the
factors used for the NPI, nullifying its use after eventual sur-
gery: therefore they have not been included in the present
study.

Cases in the 1980–1986 set came under the care of a single
surgeon (RWB), with pathology by a single pathologist (CWE)
and in the 1990s set were under the care of the integrated
Breast Team at Nottingham City Hospital. Cases referred after
an initial operation for diagnosis or following treatment car-
ried out elsewhere were excluded.

Cases diagnosed in the years 1987–1989 have not been in-
cluded because major changes in diagnosis and treatment
were made in those years: the introduction of population
screening, of expertise in radiology, case management by a
team of breast specialists in all disciplines, strict criteria for
selection for breast conserving therapy, the introduction of
selective local, regional and systemic adjuvant therapies.

Median follow-up from the 1980 to 1986 series is 21 years
(19–25) and for the 1990–1999, 8.3 years (5–15).
All cases had histological assessment of node sampling,
histological grade19 and tumour size. These were the only fac-
tors recognised to have independent significance in the origi-
nal multivariate analysis from which the Index was constructed1,2
and in the first intra-centre prospective verification.3

The NPI is calculated as previously described2,16: lymph
node (LN) stage (1–3) + Grade (1–3) + maximum diameter
(cm · 0.2), giving an observed range of NPI from 2.08 (LN neg-
ative, grade 1, 0.4 cm) to 6.8 (LN Stage 3, grade 3, size 4.9 cm).
The earlier studies2,3,7 divided patients into three NPI groups;
in the present report six NPI groups are recognised: an Excel-
\[\text{lient Prognostic group (EPG)}\] with an observed NPI range of
2.08–2.4, Good (GPG) 2.42 to ≤3.4; Moderate I (MPG I) 3.42 to
≤4.4, Moderate II (MPG II) 4.42 to ≤5.4, Poor (PPG) 5.42 to
≤6.4 and very poor (VPG) 6.5–6.8.

Life table survival curves have been constructed using
SPSS version 13, for both breast cancer specific and all
causes of death and for both time sets. Comparison of
curves between neighbouring NPI groups and between the
different time sets in each prognostic group has been made
using Wilcoxon–Gehan statistics. Analysis has also been
carried out on absolute numbers of cases entered and of
events.

All patients have been followed up regularly and indefi-
nitely in the hospital Primary Breast Clinic (PBC) and data
on survival and recurrence recorded. At death the hospital
notes are examined and deaths allocated to ‘With/from breast
cancer’ or to ‘Without known breast cancer’. Patients with
diagnosed distant metastatic spread are allocated to the for-
mer, even if the disease appears to be in complete remission;
women dying without having any known distant recurrence,
even if they have suffered prior local or regional recurrence
of which no trace remains on or after treatment, are allocated
to the latter (unless a post-mortem study indicates other-
wise). Although in the early reports of the NPI, survival was
from all causes of death, in this paper the survival curves
have provisionally been constructed for death from breast
cancer although some comparisons have been made with
curves for all causes of death.

3. Results

Fig. 1 shows the breast cancer specific survival for all cases
diagnosed in 1980–1986 inclusive and of cases diagnosed in
1990–1999 inclusive and the overall survival for all causes of
death for the two time periods. Survival is considerably and
significantly better in cases treated in the latter time period.
The relative risk reduction of death remains constant at 5,
2.08–2.4, Good (GPG) 2.42 to ≤3.4; Moderate I (MPG I) 3.42 to
≤4.4, Moderate II (MPG II) 4.42 to ≤5.4, Poor (PPG) 5.42 to
≤6.4 and very poor (VPG) 6.5–6.8.

Table 2 shows the percentage distribution of cases to prog-
nostic groups in 1980–1986 and 1990–1996 and the distribu-
tions by age. In 1990–1999, 4% more lie in the better 2 NPI
groups (EPG and GPG) and 1% less in the bottom two (PPG
and VPG have been combined for this illustration). There were
no significant differences in age distribution across the prog-
nostic groups in each time series: the mean ages diminishing
in rank order from 55.5% in the EPG to 51.5% in the PPG in the
1990s set. There were no significant differences between the two sets in age distribution.

The breast cancer specific survivals (Life Table) for each prognostic group are shown in Figs. 2 (1980–1986) and 3 (1990–99). Survival is seen to have greatly improved in each prognostic group in the 1990–1999 series.

Table 3 shows the 1990–1999 (breast cancer specific) 10 years survivals and standard errors for each prognostic group and the significances of the difference between the curves of adjacent prognostic groups. There are significant differences between all neighbouring groups, with the exception of the Excellent and Good groups, in which numbers of events are very low.

There is an excellent curvilinear inverse correlation between NPI and tumour specific survival (see Fig. 4). This function summarises a broad relativity between the NPI value and 10 year survival.

An internal validation was carried out by dividing the data set into ‘odds’ and ‘evens’, as entered consecutively on the

**Table 1 – Overall survival in the 1980–1986 and 1990–1999 series at 5, 10 and 15 years of follow-up**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>73</td>
<td>88</td>
<td>0.56</td>
</tr>
<tr>
<td>10 years</td>
<td>55</td>
<td>80</td>
<td>0.56</td>
</tr>
<tr>
<td>15 years</td>
<td>46</td>
<td>78</td>
<td>0.59</td>
</tr>
</tbody>
</table>

**Table 2 – Distribution of cases to prognostic groups and distribution by age**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EPG</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>GPG</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>MPG I</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>MPG II</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>PPG</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>VPG</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>53.1</td>
<td>9.6</td>
<td>27–70</td>
</tr>
<tr>
<td>53.6</td>
<td>10.2</td>
<td>27–70</td>
</tr>
<tr>
<td>52.9</td>
<td>10.5</td>
<td>26–70</td>
</tr>
<tr>
<td>52.1</td>
<td>10.3</td>
<td>25–69</td>
</tr>
<tr>
<td>50.0</td>
<td>12.0</td>
<td>25–68</td>
</tr>
<tr>
<td>55.0</td>
<td>9.3</td>
<td>31–69</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>55.5</td>
<td>7.9</td>
<td>31–70</td>
</tr>
<tr>
<td>55.7</td>
<td>8.6</td>
<td>34–70</td>
</tr>
<tr>
<td>54.5</td>
<td>9.7</td>
<td>27–70</td>
</tr>
<tr>
<td>52.9</td>
<td>10.6</td>
<td>28–70</td>
</tr>
<tr>
<td>52.9</td>
<td>11.2</td>
<td>18–70</td>
</tr>
<tr>
<td>51.3</td>
<td>11.0</td>
<td>29–70</td>
</tr>
</tbody>
</table>

Fig. 1 – Overall survival breast cancer specific and for all causes of death, consecutive operable primary breast cancer treated in 1980–1986 and 1990–1999.
Fig. 2 – 1980–1986 series. Breast Cancer Specific Survival (Log Rank) by NPI group. EPG, excellent prognostic group, G, good, MPG1, moderate 1, MPG2, moderate 2, PPG, poor, VPG, very poor.

Fig. 3 – 1990–1999 series. Breast Cancer Specific Survival (Log Rank) by NPI group.
database. Fitted polynomial curves were constructed from the raw data for ‘odds’ and ‘evens’ in each prognostic group (Fig. 4). In order to revalidate the curves produced, odd values were applied to the evens series and vice-versa. Predictions from the curves were compared with the actual values; the differences ranged between 1.56% and 9.65% and between 0.79% and 12.9% (the greatest differences lying in the very poor prognosis group (VPG)).

The 10 year breast cancer specific survivals calculated by the life table method, in each NPI group for the two data sets, are compared in Table 4, together with significances of the improvement in survival, the relative risk reduction and the absolute increase in survival achieved in the 1990s within each prognostic group. The survival increase in the 1990s is highly significant in every group, with the exception of the EPG (p = 0.025), for which survival in both time periods was excellent and therefore numbers of events very small. The magnitude of improvement within the groups is seen to lie between a relative risk reduction of 31% and 75% (greatest in the better prognostic groups and smallest in the poorer).

Table 5 shows the Breast Cancer Specific Survival for each prognostic group with the expected number of extra deaths for all causes (obtained from the Office of National Statistics for England and Wales) subtracted. This is compared with the observed ‘all causes’ survival and the figures differ by a maximum of 2%, verifying the recording of the cause of death in this series.

4. Discussion

Overall survival is much better in the 1990s tumour set at 77% 10 years (Breast Cancer Specific), compared to the patients

<table>
<thead>
<tr>
<th>% 10 year survival</th>
<th>±2SE</th>
<th>Wilcoxon–Gehan</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPG 96</td>
<td>2</td>
<td>1.2</td>
<td>0.272</td>
</tr>
<tr>
<td>GPG 93</td>
<td>2</td>
<td>25.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MPGI 81</td>
<td>4</td>
<td>14.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MPGII 74</td>
<td>4</td>
<td>25.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPG 50</td>
<td>6</td>
<td>10.2</td>
<td>0.001</td>
</tr>
<tr>
<td>VPG 38</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL 80</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 – Survival (BCS): 1990–1999
with tumours in the 1980s tumour set at 55%, a 22% absolute increase at 10 years.

Improved case survival with time is not a new phenomenon. Buchanan\textsuperscript{20} studied cohorts from the Mercy Hospital of Pittsburgh, showing 10 year survivals of 12% in 1895–1920, rising to 58% in 1971–1987. In the UK study of Brinkley and Haybittle,\textsuperscript{21} stages I and II cases diagnosed in Addenbrooke’s Hospital, Cambridge in 1947–1950 had a 10 year survival of

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**Table 4 – Survival (BCS): 1980–1986 and 1990–1999**

<table>
<thead>
<tr>
<th></th>
<th>1980–1986 % survival</th>
<th>1990–1999 % survival</th>
<th>Wilcoxon Gehan</th>
<th>P</th>
<th>PRR</th>
<th>% ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPG</td>
<td>88 ± 6</td>
<td>96 ± 2</td>
<td>4.990</td>
<td>0.025</td>
<td>0.67</td>
<td>8</td>
</tr>
<tr>
<td>GPG</td>
<td>72 ± 8</td>
<td>93 ± 2</td>
<td>48.974</td>
<td>&lt;0.001</td>
<td>0.75</td>
<td>21</td>
</tr>
<tr>
<td>MPG I</td>
<td>61 ± 6</td>
<td>81 ± 4</td>
<td>34.747</td>
<td>&lt;0.001</td>
<td>0.51</td>
<td>20</td>
</tr>
<tr>
<td>MPG II</td>
<td>42 ± 6</td>
<td>74 ± 4</td>
<td>59.898</td>
<td>&lt;0.001</td>
<td>0.55</td>
<td>32</td>
</tr>
<tr>
<td>PPG</td>
<td>15 ± 8</td>
<td>55 ± 8</td>
<td>47.836</td>
<td>&lt;0.001</td>
<td>0.48</td>
<td>41</td>
</tr>
<tr>
<td>VPG</td>
<td>12 ± 10</td>
<td>38 ± 12</td>
<td>12.377</td>
<td>&lt;0.001</td>
<td>0.29</td>
<td>26</td>
</tr>
<tr>
<td>All</td>
<td>55 ±</td>
<td>80 ± 2</td>
<td>186.029</td>
<td>&lt;0.001</td>
<td>0.56</td>
<td>25</td>
</tr>
</tbody>
</table>

PRR is simply calculated as number of deaths: \( \frac{E - O}{c} \times 100 \). ARR is \( E - O \) is % survival.

---

**Table 5 – 10 year survival (BCS) minus expected death from other causes compared with observed all causes survival 1990–1999**

<table>
<thead>
<tr>
<th></th>
<th>Obs BCS survival</th>
<th>Expec extra dead</th>
<th>Exp % survival</th>
<th>Observed % survival (all causes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPG</td>
<td>320</td>
<td>6</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>GPG</td>
<td>475</td>
<td>9</td>
<td>87</td>
<td>86</td>
</tr>
<tr>
<td>MPG I</td>
<td>634</td>
<td>8</td>
<td>76</td>
<td>78</td>
</tr>
<tr>
<td>MPG II</td>
<td>489</td>
<td>7</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>PPG</td>
<td>233</td>
<td>3</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>VPG</td>
<td>86</td>
<td>2</td>
<td>36</td>
<td>32</td>
</tr>
</tbody>
</table>

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**Fig. 5 – Overall (breast cancer specific) survival in 5 year cohorts between 1974 and 1999: improvements in survival are seen in all successive cohorts together.**
around 42%. An analysis of operable cases treated at Nottingham City Hospital shows the overall improvement in survival in sequential 5 year cohorts of cases presenting over a 25 year span (Fig. 5), rising from 49% in the 1970s to over 80% in the 1990s; survival in the first of these cohorts (1973–1978) was at a comparable level with the last of the Buchanan cohorts (1971–1987).

There were considerable changes in both the diagnosis and management of breast cancer at Nottingham City Hospital between the two sets. Population screening for women aged 50–64, as part of the UK NHS Breast Screening Programme (NHSBSP), was introduced in 1988 with the prevalent round completed in 1993.

Neither local (radiotherapy to mastectomy flaps), nor regional prophylaxes (radiotherapy or surgical clearance to axillary nodes) nor systemic adjuvant therapies, were used at all in the 1980s tumour set; instead after surgery a ‘watch policy’ was used, following the results of the UK Cancer Research Campaign Trial, selection criteria for breast conserving surgery were less strict with clear margins not a requirement, resulting in a high rate of uncontrollable local recurrence. Case management protocols introducing criteria in the late 1990s for breast conserving surgery, axillary prophylaxis for lymph node positive cancers and selection for adjuvant systemic therapies resulted in dramatic falls in local and regional recurrences, which may have translated into improved survival.

A relatively small part of the overall improvement in case survival is from better prognostic factors at diagnosis in that there are only a few more cases lying in the better prognostic groups in the 1990s (Table 2). There is a major improvement in case survival in every prognostic group (Figs. 2 and 3 and Table 4). Improved survival within NPI groups must come from improved case management. Much of the improvement is likely to lay in the use of adjuvant systemic therapies, as anticipated from the results of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) Overview Analyses, but not all the increase may be attributed to this, since women in the EPG and the great majority in the GPG were not selected for adjuvant therapies and yet improved survival was observed within these groups.

This paper presents the survival according to the NPI group in which the patient lies, to be expected from present-day case management protocols. This report is of importance and is overdue and much demanded, because the NPI is frequently used in decisions on adjuvant therapy in individual cases. NPI is also used as the basis for calculating loss of life expectancy in medico-legal cases. For both uses the breast cancer specific survival is the basis of the calculation; in addition it is known that natural life expectancy has greatly increased in recent decades and consideration of breast cancer specific survival thereby becomes more relevant. The NPI is also used to provide a basis for the assessment of newly designed methods for prognostication in breast cancer, such as by microarray techniques. The stratification provided by the NPI has allowed audit of the performance of units in screening and has been used to select cases for clinical trials, e.g. the British Association of Surgical Oncology BASO II trial of breast conserving surgery in excellent prognosis cases.

Conflict of interest statement

None.

REFERENCES