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

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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[1] and the NPI described in 1982.[2] It is the only Index to have prospective validation, both intra- and inter-centre.[3–7] Although new prognostic methods are being sought, the only published comparison of the NPI with cDNA microarray analysis[8] 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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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 detected[10] 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 derived[3] 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 standard as a basis of comparison for new prognostic methods,[8] there has been a good deal of demand for figures based on modern day diagnosis and case management to be provided.

Updated survival figures on the whole Nottingham-Tenovus 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 improved figures within all NPI groups in women treated for primary 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 diagnosed with and treated for primary operable invasive breast cancer at Nottingham City Hospital, aged 70 years or less, with tumours of less than 5 cm diameter on clinical measurement 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 increased 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 treated by different protocols, again by primary endocrine therapy or irradiation before any surgery[18]; these measures alter the factors used for the NPI, nullifying its use after eventual surgery: 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 carried out elsewhere were excluded.

Cases diagnosed in the years 1987–1989 have not been included 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 grade[19] and tumour size. These were the only factors recognised to have independent significance in the original multivariate analysis from which the Index was constructed[1,2] and in the first intra-centre prospective verification.[3]

The NPI is calculated as previously described[2,16]: lymph node (LN) stage (1–3) + Grade (1–3) + maximum diameter (cm × 0.2), giving an observed range of NPI from 2.08 (LN negative, grade 1, 0.4 cm) to 6.8 (LN Stage 3, grade 3, size 4.9 cm). The earlier studies[2,3,7] divided patients into three NPI groups; in the present report six NPI groups are recognised: an Excellent Prognostic group (EPG) with an observed NPI range of 2.08–2.4, Good (GPG) 2.42 to $\leqslant$3.4; Moderate I (MPG I) 3.42 to $\leqslant$4.4, Moderate II (MPG II) 4.42 to $\leqslant$5.4, Poor (PPG) 5.42 to $\leqslant$6.4 and very poor (VPG) 6.5–6.8.

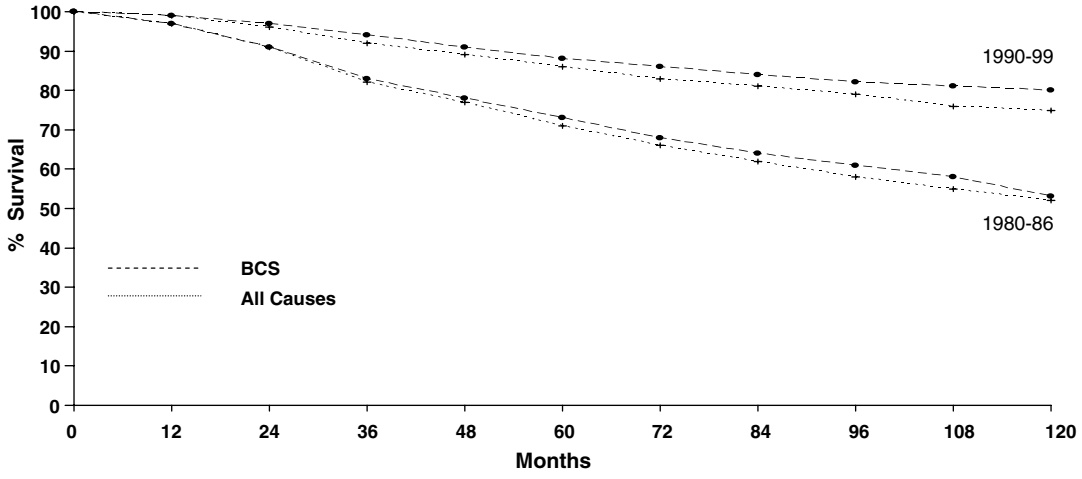
Life table survival curves have been constructed using SPSS version 13, for both breast cancer specific and all causes of death and for both time sets. Comparison of curves between neigbhouring NPI groups and between the different time sets in each prognostic group has been made using Wilcoxon–Gehan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

All patients have been followed up regularly and indefinitely 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 former, 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 otherwise). 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, 10 and 15 years of follow up (Table 1).

Table 2 shows the percentage distribution of cases to prognostic groups in 1980–1986 and 1990–1996 and the distributions 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 prognostic 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



1990-99											
BCS	n at risk	2225	2188	2108	2001	1812	1564	1297	1054	826	628
	Events	18	57	56	17	46	38	30	23	12	9
ACS	n at risk	2232	2195	2115	2008	1817	1568	1301	1056	832	631
	Events	31	68	70	83	56	47	37	28	24	14
1980-86											
BCS	n at risk	889	857	802	721	670	615	565	527	490	460
	Events	27	50	72	41	49	41	29	30	22	26
ACS	n at risk	890	858	803	724	672	616	566	529	491	462
	Events	30	52	75	46	53	43	32	34	25	30

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.

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.

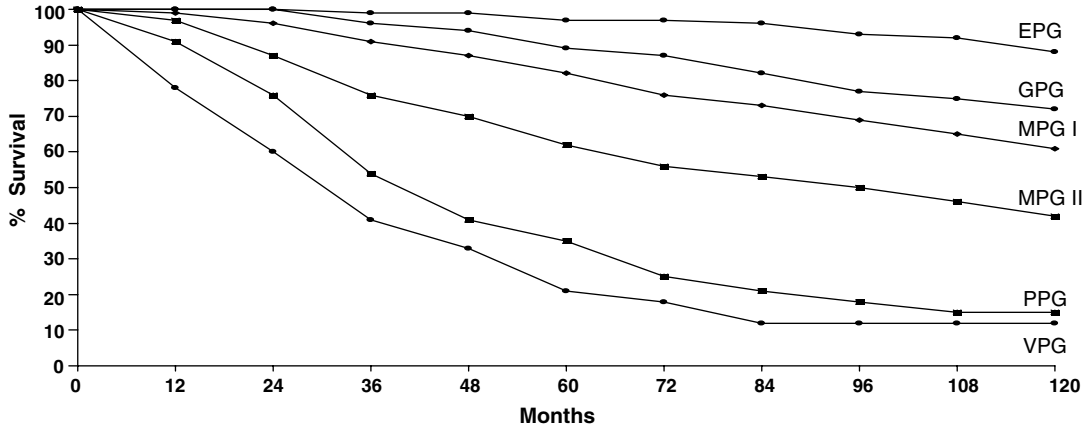
An internal validation was carried out by dividing the data set into 'odds' and 'evens', as entered consecutively on the

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

% Survival at:	1980–1986	1990–1999	Proportional risk reduction
5 years	73	88	0.56
10 years	55	80	0.56
15 years	46	78	0.59

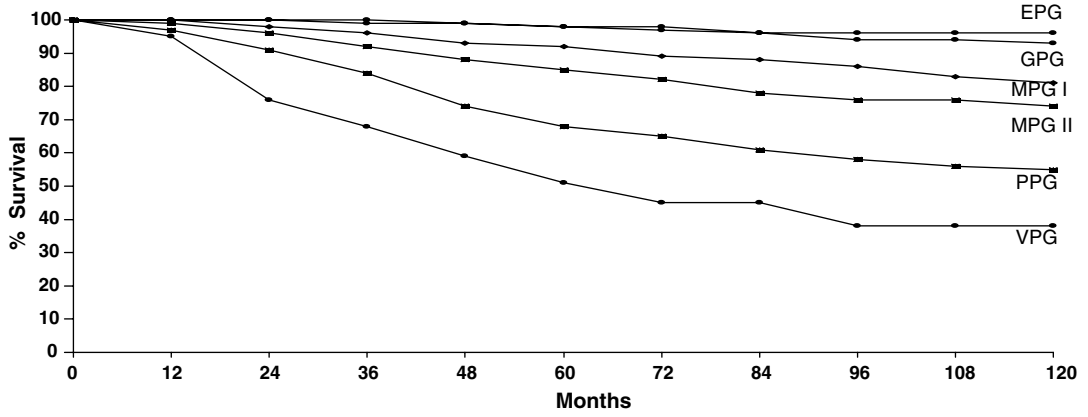
Table 2 – Distribution of cases to prognostic groups and distribution by age

	% in NPI groups		Age distribution at diagnosis					
	1980–1986	1990–1999	1980–1989			1990–1999		
			Mean	SD	Range	Mean	SD	Range
EPG	12	15	53.1	9.6	27–70	55.5	7.9	31–70
GPG	19	21	53.6	10.2	27–70	55.7	8.6	24–70
MPG I	29	28	52.9	10.5	26–70	54.5	9.7	27–70
MPG II	24	22	52.1	10.3	25–69	52.9	10.6	28–70
PPG	11	10	50.0	12.0	25–68	52.9	11.2	18–70
VPG	5	4	55.0	9.3	31–69	51.3	11.0	29–70



EPG	n at risk	106	106	105	103	103	100	8	96	91	89
	n events	0	0	2	0	3	1	1	5	2	6
GPG	n at risk	173	172	171	163	157	145	141	131	123	117
	n events	1	0	7	5	11	3	8	8	5	5
MPGI	n at risk	258	256	244	230	217	202	182	172	160	148
	n events	2	10	12	11	13	17	7	10	8	11
MPGII	n at risk	215	208	187	161	145	128	115	106	98	90
	n events	7	20	25	14	16	12	9	7	8	8
PPG	n at risk	97	86	72	51	39	33	24	19	16	14
	n events	11	14	21	12	6	9	5	3	2	0
VPG	n at risk	40	31	23	15	11	7	6	4	4	4
	n events	9	8	8	4	4	1	2	0	0	0

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.



EPG	n at risk	319	316	312	306	292	261	227	195	165	138
	n events	1	0	0	1	3	1	4	0	0	1
GPG	n at risk	473	467	461	446	412	362	304	249	197	150
	n events	1	1	2	2	3	4	3	4	1	1
MPGI	n at risk	632	626	611	587	533	461	389	330	261	192
	n events	1	9	14	19	8	12	6	8	8	4
MPGII	n at risk	486	476	454	424	381	328	256	188	136	98
	n events	5	16	16	20	13	13	11	4	1	2
PPG	n at risk	230	223	207	186	155	125	100	75	57	42
	n events	6	14	17	21	13	5	6	4	2	1
VPG	n at risk	86	81	65	55	41	29	23	18	11	9
	n events	4	16	7	7	6	3	0	3	0	0

Fig. 3 – 1990–1999 series. Breast Cancer Specific Survival (Log Rank) by NPI group.

Table 3 – Survival (BCS): 1990–1999

	% 10 year survival	±2SE	Wilcoxon–Gehan	*p*
EPG	96	2	1.2	0.272
GPG	93	2	25.4	<0.001
MPGI	81	4	14.4	<0.001
MPGII	74	4	25.7	<0.001
PPG	50	6	10.2	0.001
VPG	38	12		
ALL	80	2		

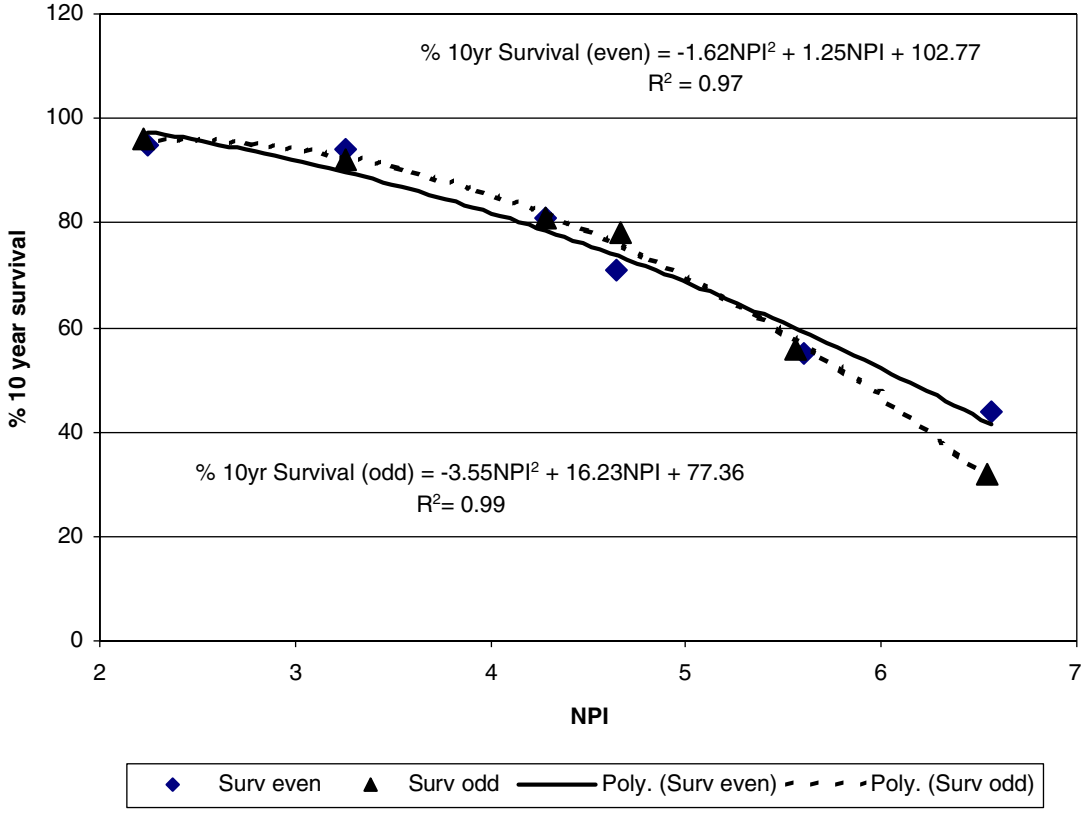


Fig. 4 – Internal validation. Fitted polynomial curves for 'odds' and 'evens' in data set, applied to median NPI's of each NPI group against % 10 year survival for each division.

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

	10 year % survival		1980–1986 versus 1990–1999			
	1980–1986	1990–1999	Wilcoxon Gehan	*p*	PRR	% ARR
	95% CL					
EPG	88 ± 6	96 ± 2	4.990	0.025	0.67	8
GPG	72 ± 8	93 ± 2	48.974	<0.001	0.75	21
MPGI	61 ± 6	81 ± 4	34.747	<0.001	0.51	20
MPG II	42 ± 6	74 ± 4	59.898	<0.001	0.55	32
PPG	15 ± 8	55 ± 8	47.836	<0.001	0.48	41
VPG	12 ± 10	38 ± 12	12.377	<0.001	0.29	26
All	55 ±	80 ± 2	186.029	<0.001	0.56	25

PRR is simply calculated as number of deaths: $\frac{E-O}{E} \times 100$. 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

	n	Obs BCS survival	– Expec extra dead	=Exp % survival	Observed % survival (all causes)
EPG	320	96	−6	90	88
GPG	475	93	−6	87	86
MPG I	634	81	−5	76	78
MPG II	489	74	−5	69	69
PPG	233	55	−3	52	53
VPG	86	38	−2	36	32

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[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,[21] stages I and II cases diagnosed in Addenbrooke's Hospital, Cambridge in 1947–1950 had a 10 year survival of

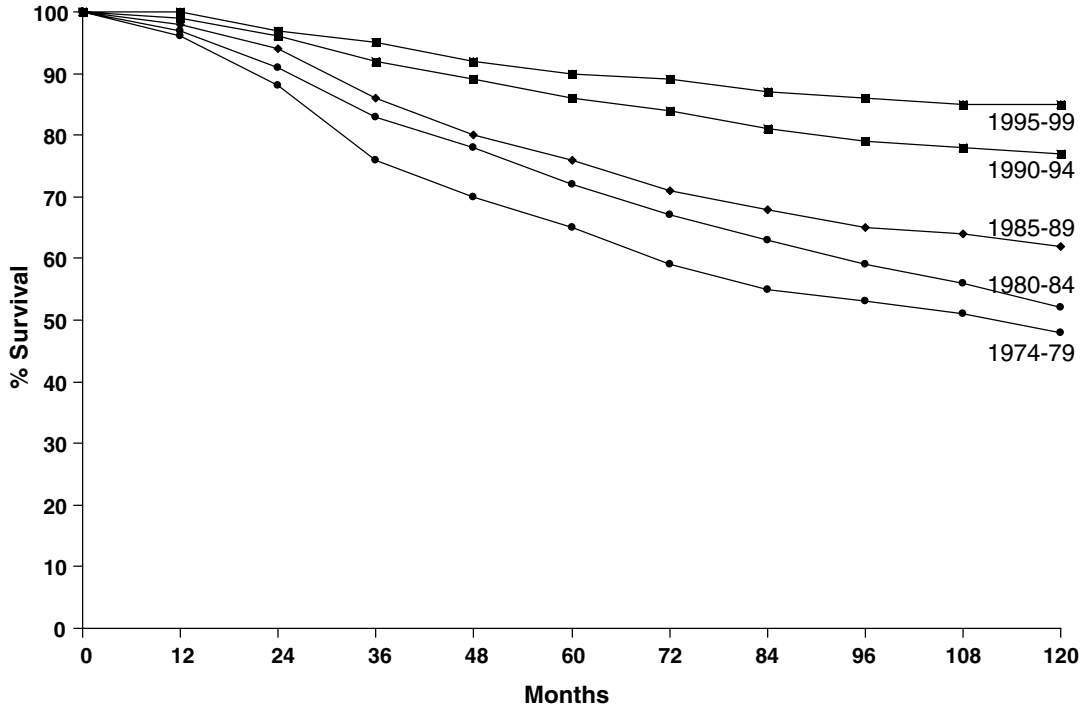


Fig. 5 – Overall (breast cancer specific) survival in 5 year cohorts between 1974 and 1999: improvements in survival are seen in all successive cohorts together.

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[22]; selection criteria for breast conserving surgery were less strict with clear margins not a requirement, resulting in a high rate of uncontrolled local recurrence.[23] 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[24,25] 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.[15] 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.[8] The stratification provided by the NPI has allowed audit of the performance of units in screening[10] 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.

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