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ONCOPOOL – A European database for 16,944 cases of breast cancer

R.W. Blamey [a,*], B. Hornmark-Stenstam [a,b], G. Ball [c], M. Blichert-Toft [a], L. Cataliotti [a], A. Fourquet [a], J. Gee [d], K. Holli [a], R. Jakesz [a], M. Kerin [a], R. Mansel [a], R. Nicholson [a,d], T. Pienkowski [a], S. Pinder [e], M. Sundquist [a], M. van de Vijver [a], I. Ellis [e]

On behalf of ONCOPOOL Consortium at Breast Institute, Nottingham City Hospital, NG5 1PB, UK

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ABSTRACT

ONCOPOOL is a retrospectively compiled database of primary operable invasive breast cancers treated in the 1990s in 10 European breast cancer Units. Sixteen thousand and nine hundred and forty four cases were entered, with tumours less than 5 cm diameter in women aged 70 or less (mean age 55).

Data: Data were date of birth, mode of diagnosis, pathology (size, lymph node status, grade, type, lympho-vascular invasion and hormone receptor) and therapies and outcome measures: first local, regional or distant recurrences, contralateral primary, date and cause of death.

Tumour characteristics: Mean diameter 1.8 cm, 66% lymph node negative, 24% 1–3 lymph nodes involved and 10% had 4 or more involved. Grade 1, 29%; Grade 2, 41%; and Grade 3, 30%. Polynomial relationships were established between grade, stage and size.

Seventy-five percent were oestrogen receptor (ER) positive. ER closely related to grade.

Outcomes: Overall Survival was 89% at 5 years from diagnosis, 80% 10 years and 73% 15 years; Breast Cancer-Specific survivals were 91%, 84% and 79%.

Survival strongly related to the Nottingham Prognostic Index (NPI).

Cases detected at screening had 84% 10-year survival, those presenting symptomatically 76%.

ER positive cases treated with adjuvant hormone therapy had a reduction in risk of death of 13% over those not receiving adjuvant therapy ($p = 0.000$). ER negative cases treated with chemotherapy showed a risk reduction of 23% over those not receiving chemotherapy ($p = 0.000$).

* Corresponding author: Tel.: +44 (0)115 9625707; fax: +44 (0)115 9627765.
E-mail address: rogerblamey@btinternet.com (R.W. Blamey).

[a] Co-applicant for grant support.
[b] Clinical QA.
[c] Data analyst.
[d] Endocrine QA.
[e] Pathology QA.

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1. Introduction

ONCOPOOL (Pooling of European Data to Harmonise Translational Research in Breast Cancer) is a dataset compiled in a European Commission Framework 5 Project in the Quality of Life and Living Resources Programme. Cases of operable breast cancer from 12 European breast cancer Units in 10 European states, diagnosed in the 1990s were entered retrospectively, with the collection of data on the primary tumours being carried out between 2000 and 2003 and longer term follow-up data being collected since that date.

The SEER (surveillance, epidemiology and end results programme) database[1,2] with 851 citations has long been regarded as providing the best overall picture of the features of breast cancer at primary presentation and of the survival of primary breast cancer. Since SEER was published survival has improved enormously in breast cancer[3]; SEER is also entirely North American based. It is appropriate to have an up-to-date, standard setting, large European database available in the breast cancer literature.

In ONCOPOOL cases of operable primary breast cancer in women aged 70 or less and diagnosed consecutively in each Unit in periods defined by the Unit within 1990–1999 were entered retrospectively. Units mainly treated the population local to them so that few cases came from tertiary referral. All cases received their whole treatment for primary breast cancer under the care of their Unit. Data entry and follow-up were carried out by the Units, resulting in very good data capture at entry; these factors ensured that the dataset reflected the tumour features and behaviour in the whole population. Quality assurance has been applied to clinical, pathology and endocrine data.

A large range of tumour variables and outcomes has been inspected, including data on the method of detection, the treatment given, pathology and extra tumour factors to those standard for prognosis, such as HER2-neu, lympho-vascular invasion and outcome data on recurrences and the types of recurrence. Prognosis has been inspected by use of an index integrating prognostic factors, the well-recognised and validated Nottingham Prognostic Index (NPI).[4–7]

2. Materials and methods

ONCOPOOL is a European Database for Primary Breast Cancers built as a European Community Framework 5 Project.

2.1. Clinical Units and personnel

Of the two Units originally involved in designing the project, one withdrew before entering any cases because both surgeon and clinical oncologist (B.H.-S.) moved from the Unit shortly before entry began. Twelve specialist breast cancer Units pooled the data. The Units invited fell into two groups: those in provincial cities, diagnosing and treating almost all the breast cancers arising in their areas (Nottingham, Cardiff, Florence, Kalmar, Gothenburg and Tampere) and those in large capital cities (Amsterdam, Copenhagen, Dublin, Paris, Vienna and Warsaw), each being one of the number of hospitals treating breast disease within those cities. Units are not elsewhere named in this publication but are numbered 1–12. All received symptomatically referred women, some also received cancers detected at breast cancer screening in their area. Only one Unit received a significant number of tertiary referrals. Medical and non-medical staff of the Units in all disciplines had special experience in and specialised in Breast Cancer.

The Project Coordinator and the Central Data Managers (consecutively M.M. and A.O.), were housed at the Coordinating Unit (Nottingham City Hospital) in which the Central Database was installed. Each Unit had a local coordinator who was a clinician (all except one were surgeons), a nominated breast specialist pathologist, a data manager and several had an associate clinician working on the project.

Data managers were appointed at each Unit and the data were directly entered by the Units and anonymised prior to transfer to the Project Data Centre.

Pathology QA was carried out by the two project pathologists (S.P. and I.E.) at Nottingham City Hospital. Endocrine QA was carried out by the Tenovus Laboratory (J.G. and R.N.), Cardiff University. Data QA was by the Central Data Manager (M.M. and then A.O.) and by the QA clinician (B.H.-S. a clinical oncologist). Analysis of data was carried out by G.B. and the Project coordinator (R.B.).

The clinician acting as Unit coordinator, one other clinician with major involvement, the lead pathologist and the data manager on each Unit are appended, together with the project data analyst and those responsible for QA.

2.2. Cases entered

The cases entered were women with primary operable invasive breast cancers, less or equal to 4.9 cm in maximum diameter on clinical examination or imaging or microscopy, age at diagnosis 70 years or less, treated consecutively in any one centre by first line operative therapy in a continuous period between 1990 and 1999 (Table 1). Women over 70 years of age at primary diagnosis were not entered because treatment was not always operative, because axillary status was not established in all, because adjuvant systemic therapies were frequently not applied and to avoid the confounding factor of high mortality from causes other than breast cancer. Tumours of 5 cm or more on clinical or pathological measurement were not entered, again because treatment for those was frequently not that usual for primary cancer but more appropriate to locally advanced breast cancer e.g. primary radio- or medical therapy and continuing hormonal therapies. Women receiving primary medical (neoadjuvant) therapies were not entered because such treatments alter the prognostic features without necessarily altering the prognosis (i.e. lower tumour size and mitotic count and may render involved nodes negative). Any cases entered but later found not to have met the entry criteria were withdrawn from the clinical database.

The case numbers entered by each Unit and the periods within which these were diagnosed are shown in Table 1.

Eight Units each entered over 1200 cases diagnosed over a 10-year period and two each entered 600 cases. Units 10 and 12 contributed only 358 and 311 cases. The protocol stipulated consecutive cases over a 10-year period undergoing primary surgery and as Unit 10 is a large Unit, it is clear that they

Table 1 – Numbers of cases, period of entry and mean age by Unit and for all cases. Units 10 and 12 were excluded from all follow-up analyses (see text).

Unit Number	Cases per Unit	Entry date range	Mean age
1	2231	1/1/90–23/12/99	54
2	1301	8/1/90–23/12/99	53
3	562	1/1/90–29/12/99	56
4	2391	5/1/90–20/12/99	56
5	1282	26/1/93–28/12/99	56
6	603	3/1/90–22/12/99	55
7	1538	1/12/90–28/12/99	56
8	1488	3/1/90–30/12/99	53
9	4136	2/1/90–15/12/99	54
10	376	3/5/90–9/12/00	n/a
11	1412	22/1/90–28/12/99	54
12	311	26/1/90–28/2/01	n/a
All cases	17,631		
Excluding Units 10 and 12	16,944	1/1/90–30/12/99	55 (53–56)

did not enter consecutive cases which introduced a possible selection bias. Unit 12 entered only 311, nearly all in the first 4 years of the period and the coordinator moved from Unit 12, which jeopardised the receipt of follow-up information so that only 35% were available for analysis at 5 years; therefore all cases entered by Units 10 and 12 were withdrawn from analysis.

2.3. *Data*

The database was built and held at the Data Centre. The principal design was to allow overall and inter-Unit comparisons of tumour characteristics, prognostic factors, recurrence and survival and effects of intervention. Mandatory data were tumour and patient characteristics: date of birth; method of diagnosis (screening or symptomatic); pathology – size (maximum diameter on microscopy), lymph node stage (by axillary sampling or clearance), histological grade and type, oestrogen receptor status; therapies – operation (mastectomy or breast conservation), completeness of excision at breast conserving surgery, adjuvant radiotherapy, adjuvant systemic therapy given and whether endocrine or chemotherapy, axillary surgery (sample or clearance); outcomes (with dates) – local, regional and distant recurrence, contralateral primary, date last known alive, date of death and cause of death.

Tumour size in all but one Unit was measured as the maximum diameter (cm) on microscopy of the tumour as a continuous variable; Unit 9 entered size in three ranges (0.3–1.49, 1.5–2.49 and >2.5 cm).

In all cases axillary lymph node status was established by sampling or at clearance. In Unit 1 an internal mammary node for medial half tumours and an apical node (adjacent to the first rib) were sampled in the earlier part of the entry period.

The lymph node (LN) staging applied was to regard LN negative disease as stage 1, 1–3 nodes positive as stage 2 and >3 nodes positive (or) axillary and internal mammary chains involved (or) axillary apical node involvement (adjacent to 1st rib) as stage 3; a micro-metastasis in a lymph node (single and less than 1 mm extent) was scored 2 but was noted to be a micro-metastasis.

Grade was assessed by the method of Elston–Ellis (E–E)[8] in all Units: Tubule formation, Pleomorphism and Mitoses are each scored 1–3. Scores of 3–5 were designated as Grade 1, 6 and 7 as Grade 2 and 8 and 9 as Grade 3.

The above factors determined by post-operative histological examination of the primary tumour were combined to give the Nottingham Prognostic Index (NPI) score for each patient. The NPI is calculated[4,5] from grade (1–3) + lymph node stage (1–3) + (0.2 × the size in cm). Cases missing any factor necessary for calculating the NPI (e.g. all the cases from Unit 9 because of the lack of exact measurements of tumour diameter) were excluded from all analyses by NPI.

Percentage positivity rates for oestrogen receptor (ER) and progesterone receptor (PgR) as recorded by the Units were tabulated. These were determined by different assays and the scores for positivity levels were: for ligand-binding assay (LB) – $\geqslant$10 fmol/mg; for enzyme immunoassay – $\geqslant$20 fmol/mg; for immunohistochemical assay (ICC) – $\geqslant$2 IRS (or) H-score (as percent of cells staining × intensity 1–3) $\geqslant$20 (or) $\geqslant$10% cells staining positive.

Extra data could be entered voluntarily by any Unit e.g. family history, presence or absence of lympho-vascular invasion (LVI), BRCA1 and mutation status, HER2-neu status, basal phenotype, MIB1, progesterone receptor, CA 15.3 and any other tumour factor particularly studied by the Unit; width of margin after breast conserving surgery; number of nodes sampled and number positive; details of radiotherapy – to which areas given, dose, fractions and boost.

All data were transferred to the Central Database at Nottingham City Hospital anonymised prior to transfer (with identifications preserved at the contributing Units).

2.4. *Definitions of operations, radiotherapy, systemic therapies, recurrences and cause of death*

Operative therapy was recorded mandatorily as mastectomy or wide local excision: whether reconstruction was carried out was not recorded; whether histology confirmed complete excision at breast conserving surgery was recorded as assessed by the local pathologist as clear or not.

Post-operative radiotherapy was mandatorily recorded as to intact breast or to mastectomy flaps and/or to axillary nodes.

Local recurrence (LR) was defined as breast cancer (invasive or *in situ*) in the treated breast parenchyma or overlying skin following breast conserving surgery or in the mastectomy flaps, prior to any diagnosis of distant metastasis. No attempt has yet been made to establish whether a second tumour in the conserved breast was a new primary or a recurrence.

Regional recurrence (RR) was defined as metastatic tumour presenting subsequent to the primary treatment of the tumour, in the ipsilateral axillary, supraclavicular and/or internal mammary nodes, prior to any diagnosis of distant metastases.

Cause of death was defined as with/from breast cancer or without known active breast cancer. For a 'with/from' definition the original intention was that there must have been a prior diagnosis of distant metastases (or) post mortem evidence of distant metastases (or) uncontrolled local or regional recurrence present at death. Even if distant metastases were in complete response at death, the death was recorded as 'with/from breast cancer'. Deaths after previous local or regional recurrence without residual evidence of cancer after surgery or radiotherapy (or) in complete response to systemic therapies were defined as 'other causes', i.e. without known active breast cancer. In the absence of such evidence inclusion of 'breast cancer' as the notified cause of death was accepted.

Neither the methods of diagnosis nor characteristics nor treatments nor responses of local, regional or distant recurrences were recorded.

2.5. *Analyses*

The analyses carried out and reported in this paper are age at diagnosis; the standard prognostic factors (size, stage and grade) and oestrogen receptor (ER), their distribution in each Unit and overall; cross correlations between tumour factors; the influences they and other factors had on survival, both separately and combined into the Nottingham Prognostic Index (NPI); survival in different prognostic groups by NPI; Overall Survival (OS – all causes of death) and Breast Cancer-Specific (BCS); derivation of polynomial curves allowing reading of prognosis for an individual down to 0.1 values of NPI; the effect of screening and of adjuvant therapies on survival.

2.6. *Statistics*

Summaries for each Unit were produced based upon the composition breakdown and by presenting mean values.

Percentage compositions of LN stages were determined for different size bands of 5 mm ranges. The relationship between tumour size and LN stage was explored by correlating the two parameters. Polynomial formulae were derived for the relationship.

Survival analysis was conducted for each Unit and for all cases in ONCOPOOL, from Kaplan–Meier (K–M) analysis using SPSS 17. Since cause of death was poorly recorded in most Units (see data QA) the main analysis has been of OS (from all causes of death). Breast Cancer-Specific (BCS) survival has been compared against OS corrected by adding the numbers of expected deaths from all causes by use of the population survival figures for women aged 55, issued by the Office of National Statistics (UK).

OS and BCS survival were determined for each Nottingham Prognostic Index group.

Polynomial curves for OS and BCS survivals, relating 10-year survivals within nine ranges of NPI rising at 0.5 intervals, to NPI values were plotted and compared by cross prediction of survival percentages from the polynomial formulae. This allowed reading of survival for individuals down to 0.1 differences in NPI.

2.7. *Quality assurance (QA)*

2.7.1. *Clinical data QA*

On receipt the Central Data Manager inspected the data for cases not obeying the entry criteria, which were then withdrawn. At analysis cases without any follow-up information since operation were also withdrawn.

Units are being visited by the QA Clinician (B.H.-S.) who inspects notes in predetermined cases and checks others randomly for the data entered and discusses the collection of follow-up data and the accuracy of recording of cause of death.

The clinical follow-up by individual Units was examined. All cases at the time of analysis were more than 9 years since entry.

2.7.2. *Pathology QA*

Pathology QA was carried out by the two responsible pathologists (S.P. and I.E.) inspecting slides submitted from each Unit and by consideration of the concordance of results in all Units.

The slides were requested from each Unit to be sent for review to the ONCOPOOL QA pathologists (I.E. and S.P.). Ten were requested for each grade and extra slides for the difficult Types. On receipt the histological grade components and overall grade were re-assessed and compared with the submitted date. Histological tumour type was also re-assessed. The results were compared with those given by the contributing pathologists from each Unit Other comments (such as on tissue preparation and preservation) were noted.

2.7.3. *Endocrine Receptor QA*

Endocrine Receptor status/level was inspected by the responsible QA Unit, which also monitored methodological information and made recommendations regarding cut-points applied, in order to allow global evaluation of receptor data for the ONCOPOOL series (Tenovus Laboratories, J.G. and R.N.).

Only three Units had ER values of the primary tumour recorded in all cases. Since all three used different scoring methods this enabled them to be compared using the cumulative frequencies of ER values in each Unit.

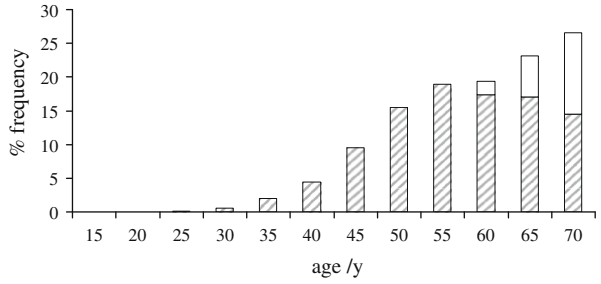


Fig. 1 – Frequency histogram of age at presentation within the ONCOPOOL population. Hatched areas show percentages of the ONCOPOOL cancers presenting in 5-year intervals. The clear areas show the corrections to the frequency of presentation expected, allowing for the decline in total population at risk due to natural mortality rates.

3. Results

3.1. *Patient ages*

The mean ages at patient entry are shown for each Unit and overall in Table 1. Mean age for all cases was 55, with the range of means for the Units being 53–56 years.

Fig. 1 shows the percentage frequency of all cases entered into ONCOPOOL by patient age at diagnosis. With very few cases in women in their early twenties (only two were below 20), numbers of cancers diagnosed rose sharply (approaching an exponential), to 50 years of age after which numbers fell at an increasing rate; when correction is applied for the fall in size of the at risk population due to natural mortality the rise in incidence appears to continue in 60–70-year-old women but at a lower rate than in 35–55-year-olds.

3.2. *Tumour diameter*

Unit 9 was excluded from this analysis because size was not entered as a continuous variable (see Section 2). In the remaining 9 Units maximum invasive tumour dimension was recorded in 12,342 out of 12,808 cases (96%). The mean of all cases was 1.8 cm, with the range of means of the results for each Unit being 1.7–2.0 cm. Numbers in tumour size categories are shown in Table 2; 70% of tumours were 2 cm or less in dimension.

Table 2 – Number diagnosed within each tumour size category (cases for Unit 9 have been excluded because size was not entered as a continuous variable).

Size category (CM)	Total cases	% in category
⩾1.0	2937	24
1.01–2.0	5790	46
2.01–3.0	2633	21
3.01–4.0	809	6
4.01–4.9	173	1
Total	12,342	100

Whether tumours were detected at breast cancer screening (i.e. at an attendance) or from symptomatic presentation (i.e. screening playing no part) was recorded in 7768 cases. The mean size of tumours detected at screening was 1.7 cm and of those detected from symptomatic presentation was 2.0 cm. Eighty-two percent of screen detected cancers were 2 cm or less in diameter compared with 64% of symptomatic tumours and twice as many screen detected (37%) as symptomatic cancers were less than 1.1 cm in size.

3.3. *Lymph node status*

Table 3 shows the number of cases retrieved to study LN status. Returns were over 90% in all Units and averaged 97% overall.

The average numbers of nodes removed by each Unit was 12. Only Unit 1 (with an average of 5 removed) came close to the aim of '4 node sampling'.[9] Units 1, 3 and 8 removed less than 10 nodes on average and were defined as 'Partial Clearance Units'. The six Units which removed averages of between 12 and 21 nodes are here defined as 'full clearance Units'.

The lymph node staging applied is described in Section 2. Lymph Node Staging of all cases (Table 3) was Stage 1 66% (range for Unit averages 60–71), Stage 2 24% (21–28) and Stage 3 10% (7–15). The averages for each stage analysed by Unit show good agreement all being within ±4 of the percentage distribution by LN stage for the whole population; statistical analyses show significant agreement for Stages 1 and 2 and highly significant agreement for Stage 3.

In the full clearance Units 4% less LN negative cases (67% versus 63%) were found and a few more cases with 4 or more nodes involved, than in the partial clearance Units; thus even without sentinel node guidance (not carried out by any Unit in ONCOPOOL in the 1990s) 4-node sampling appears as efficient in the detection of node positivity as full clearance.

In cases detected at breast cancer screening 78% were lymph node negative versus 60% in cases which presented symptomatically.

3.4. *Relationship between LN stage and size*

In Fig. 2 polynomial curves show tumour size against LN positivity: 13% were LN positive at 5 mm; at 2 cm 42% of cases were LN positive and LN positivity reached 50% at 2.3 cm; 4 or more nodes positive was 11% at 2 cm but rose rapidly to a maximum of 38% at 4.4 cm. The formulae for the curves are shown in Fig. 2.

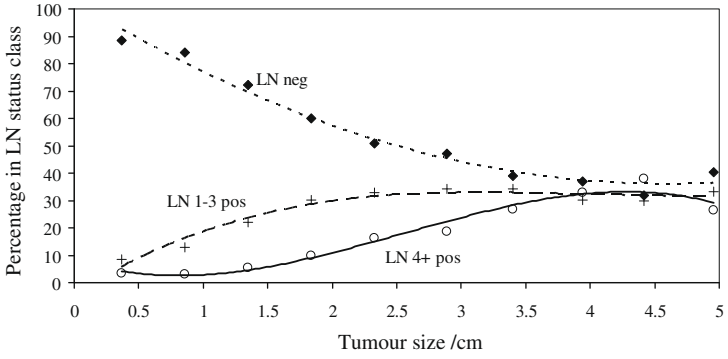
3.5. *Grade*

Grading data were returned in 91% of cases overall (Table 4) and in 100% in four Units.

There appears to be poor agreement between Units in grading, as shown by the ranges of the percentage distributions of Grade by Unit, particularly for Grades 1 and 3 (Table 4). Of all cases 29% of cancers were Grade 1, 41% Grade 2 and 30% Grade 3. However this means that 80% of cases in

Table 3 – LN status, composition and number of nodes sampled, by centre and for total population.

Unit number	% returned of total for Unit	% distribution			Average number of nodes sampled
		LN –ve	1–3 +ve	>3 +ve	
Total population (all cases)	97 (16,502)	66	24	10	12
Range of Unit averages		60–71	21–28	7–15	Range by Unit averages (5–21)



LN	Formulae	r^2
1 (neg)	% LN neg = 3.15 .Size^2 – 29.04 .Size + 102.96	0.98
2 (1-3 pos)	% LN1 – 3 pos = 0.66 .Size^3 – 7.88 .Size^2 + 30.17 .Size – 4.22	0.95
3 (4+ pos)	% LN4 + pos = -1.48 . Size^3 + 11.26 .Size^2 – 15.41 .Size + 8.44	0.96

Fig. 2 – Polynomial relationships between tumour size and LN stage. ♦, LN negative, +, 1–3 lymph nodes positive and ○, 4 or more lymph nodes positive. Formulae and correlation coefficients for polynomial relationships are shown.

Table 4 – Grade composition for total population with ranges by centre.

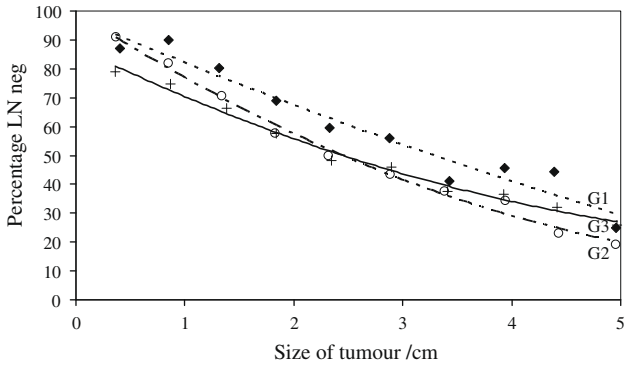
Unit number	Returned %	% distribution of grades		
		Grade 1	Grade 2	Grade 3
Total population (all Units)	91 (15,402)	29	41	30
Range by Unit	64–100	(15–43)	(27–56)	(17–53)

Table 5 – Distribution of Grade by age.

Age	Grade 1		Grade 2		Grade 3		Total
	n	(%)	*n*	(%)	*n*	(%)	
30	4	(4)	28	(28)	68	(68)	100
40	152	(13)	413	(36)	567	(50)	1132
50	1193	(24)	2004	(40)	1844	(37)	5041
60	2900	(28)	4159	(40)	3255	(32)	10,314
70	4292	(29)	6133	(41)	4464	(30)	14,889

any one Unit were scored the same as the mean scoring for all Units (a figure also found in Pathology QA).

One thousand and four hundred and fifty cancers were typed as lobular of which 38% were not graded; one Unit did not grade any lobular. Since lobular invasive cancer is most often graded as 2, the ungraded lobulars had their grade entered as 2 for a further analysis (not shown); this raised the percentage of all cases with grading returned to 94% but since only 11% of cancers were lobular and only one third were ungraded, even with the addition the distribution of tumour grades remained much the same (Grade 1 28%, Grade 2 43% and Grade 3 29%).



Grade	Formulae	r² for formula
1	% LN neg = 0.48.Size^2 - 16.1.Size + 97.7	0.95
2	% LN neg = 1.7.Size^2 – 24.4.Size + 99.7	0.99
3	% LN neg = 1.3.Size^2 – 18.3.Size + 87.5	0.99

Fig. 3 – Relationship between lymph node negativity and size broken down by grade. ♦, Grade 1, ○, Grade 2 and +, Grade 3. (Unit 9 was excluded because size was not entered as continuous variable). Formulae and correlation coefficients for polynomial relationships between LN negativity and tumour size (cm) for each grade are shown.

3.6. *Relationship between size and LN status and influence of grade*

Fig. 3 shows a strong inverse correlation between the time-dependent factors of lymph node negativity and tumour size. Specifically, there is for each grade an increase in size of 10 times over an increase in LN positivity of 4.5 times. Grade, a pathobiological factor not changing with time – grade. ER and molecular portraits in microarray[10] remain the same in primary tumour and metastases – did not influence this relationship but increased the chance of LN positivity from Grade 1 to Grade 2 at all sizes by up to 10%.

3.7. *Relationship between grade and age at diagnosis (Table 5)*

Grade 3 tumours were predominantly in young women, forming 68% of tumours in women aged 30 or less against only 4% grade 1 in this age group. The distribution of grade appears to stabilise around age 50 at the overall cumulative distribution of 29% Grade 1, 41% Grade 2 and 30% Grade 3 cancers.

3.8. *Tumour type*

Type was entered in 12,746 cases, with categorisation into one of the 15 types. Commonest were invasive ductal/NST (no special type) (72%) and invasive lobular (11%), 4% were tubular, 6% metaplastic and 1% mixed. All other types were seen in less than 1% of cases.

Given the rarity of all except ductal NST and lobular and the poor agreement on these between Units (see results of Pathology QA), the effect on outcomes has not been analysed for all histological types. However, lobulars are usually Grade 2[11] and tubular cancers[12] fare better than even their grading of one suggests and these views have been tested in this large dataset (see Outcomes).

3.9. *Endocrine receptors*

For the return for oestrogen receptor status (ER) and for progesterone receptor (PgR), measured on the primary tumour, nine of the 10 Units submitted a total of 13,108 ER results and five Units added PgR data.

The mean positivity in all cases for ER was 77% and for PgR was 60%. The ranges for positivity reported by Units were 73–83% for ER and 50–69% for PgR; for ER there was fairly good agreement in the range, with only three Units differing from the mean by more than 5%.

The cumulative frequencies for ER scores in three Units each using different scoring methods for immunochemical staining are shown in Fig. 4. Only three Units (1, 7 and 8) entered 100% of raw ER values. The maximum score for Unit 1 using immunocytochemistry (ICC) was an *H*-score (percentage of cells staining × intensity of 1–3) of 300, for Unit 7 (using% of cells staining) was 100 and for Unit 8 using ICC a 'Histoscore' of 500. In Fig. 4 to make these comparable, the individual scores have been weighted down for Units 1 and 8 to maximums of 100 to equalise the ranges across the Units.

The percentages of primary tumours with ER of zero were 27, 8 and 21, respectively, in the three Units; in addition to these were cases with low scores considered ER negative according to the pre-study definitions. The low percentage at zero and the high percentage at 100% for Unit 7 were to be expected from the method using percent of cells staining without modification by a measure of intensity of staining.

3.10. *Relationship between oestrogen receptor and grade*

Table 6 shows a clear relationship between ER and Grade, with 91% Grade 1 being ER positive against only 55% of Grade 3 ($\chi^2 = 120.08$, $p = 0.000$).

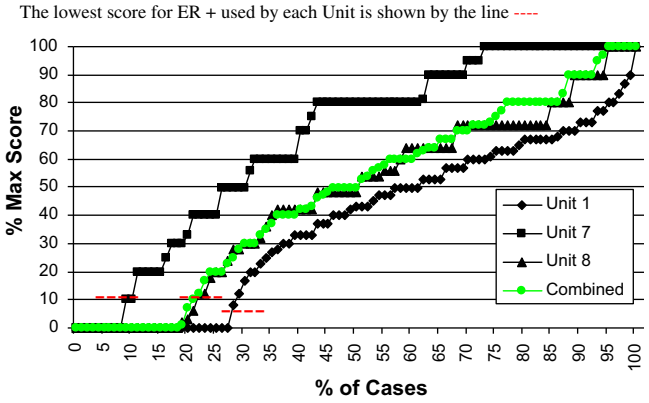


Fig. 4 – Cumulative % positioning frequency for ER score levels (Units 1, 7 and 8).

Table 6 – Relationship between ER status and Grade.

Grade	Total *n*	ER Pos		ER Neg	
		n	%	*n*	%
1	3207	2918	91	289	9
2	4580	3918	86	662	14
3	3455	1895	55	1560	45
Total	11,242	8731	78	2511	22

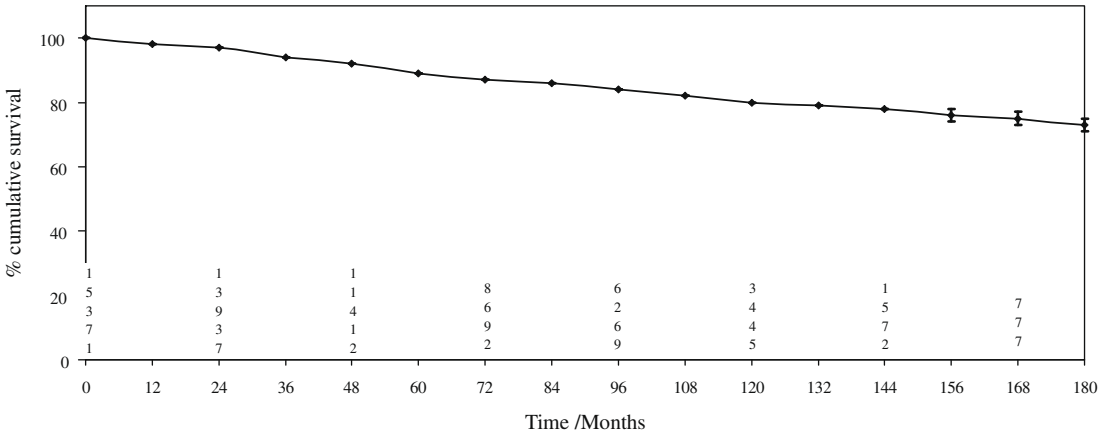


Fig. 5 – Overall Survival (OS) in all cases. (Kaplan–Meier showing 95% confidence intervals). Numbers for analysis entering each interval are shown; the curve beyond 160 months is largely based on extrapolation.

Table 7 – Percentage Overall Survival (OS) and Breast Cancer-Specific (BCS) survival for all cases (Kaplan–Meier). Overall 15-year survival is from Units 1, 3 and 8 only. The range of survival in each Unit is shown. The highest survivals at 5 and 10 years are from Unit 9 which is a large Radiotherapy Unit receiving a high number of Tertiary referrals.

Unit	*n*	5-year	10-year	15-year
Overall	15,371	89 ± 00	80 ± 00	73 ± 1
(range by Unit)		(82–95)	(63–87)	(64–76)
BCS	15,371	91 ± 00	84 ± 00	
(range by Unit)		(86–95)	(77–90)	

3.11. *Survival*

3.11.1. *From all causes of death*

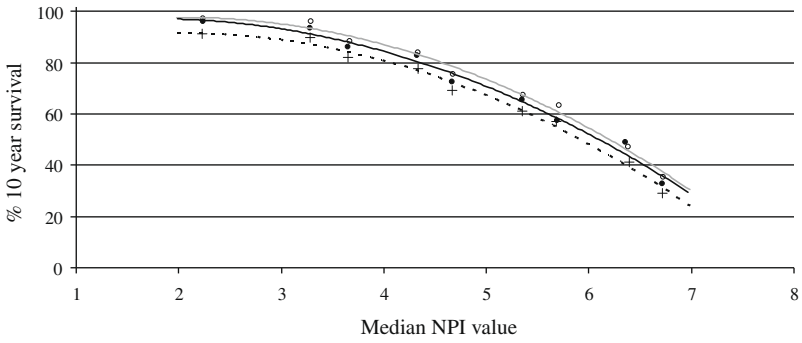
Fig. 5 and Table 7 show the Overall Survival (OS – from all causes of death) for all cases entered to ONCOPOOL. Survival at 5 years was 89%, at 10 years 80% and at 15 years 73%.

Analysed by Unit at 5 years, only one Unit was more than 2% above the mean of 89% and only two Units were more than 3% below; at 10 years all others lay within ±4%. Only 3 Units had sufficiently good follow-up to show 15-year survivals. Unit 9 reported the highest survivals; this Unit is a large radiation centre in a capital city and receives a number of tertiary referrals; this gave tumours of better prognosis, as demonstrated by the highest percentage of any Unit of LN negative tumours.

3.11.2. *Breast Cancer-Specific (BCS) survival*

The results for Breast Cancer-Specific survival (BCS) from all Units are shown in Table 7 and are compared with the overall survival. The means for BCS of 91% at 5 years and 84% at 10 years are 2–4% higher than OS.

To the 10-year survivals by OS were added the percentage of natural deaths expected (taken from the UK Office of National Statistics) in the survivors at 5, 10 and 15 years for women aged 55; this then gives comparison with the BCS survivals at these times. The OS for all cases adjusted in this way are 92% at 5 years and at 10 years 84%; these compare well with the recorded BCS survivals (Table 7) in the preceding paragraph. The comparisons between OS, BCS and OS adjusted to give BCS are also shown in Fig. 6.



The Polynomial functions for these are given below.

Polynomial functions and regression coefficients for the Polynomial relationships

Data source	Polynomial Functions	r^2
O/S All Cases	% 10 year survival = -2.468.NPI^2 + 8.515.NPI + 89.881	0.99
BCS All Cases	% 10 year survival = -2.721.NPI^2 + 10.908.NPI + 80.729	0.99

Fig. 6 – Relationship between individual NPI value and% 10-year survival. (+) represents all causes survival (OS), fitted with the - - - - - line. (●) represents breast cancer-specific survival BCS fitted with the ▬ line. (○) represents overall survival with the addition of the expected number of deaths from causes other than breast cancer fitted with the — line.

Table 8 – Overall Survival by size (maximum diameter), LN Stage (see text) and Grade (Elston–Ellis). The overall comparisons for each are highly significant and all pairwise comparisons between adjacent Size, LN Stage and Grade are also highly significant.

Size (cm)	*n*	Overall Survival (%) 10 years
<1	2716	88 ± 1
1.1–2	7989	83 ± 1
2.1–3	3269	73 ± 1
3.1–4	695	63 ± 2
4.1–4.9	262	53 ± 4
Wilcoxon (Gehan) 465	df 4	*p* .000
Lymph node stage		
1	9996	86 ± 00
2	3594	77 ± 1
3	1481	49 ± 2
Wilcoxon (Gehan) 921	df 2	*p* .000
Grade		
1	4108	91 ± 1
2	5774	82 ± 1
3	4158	68 ± 1
Wilcoxon (Gehan) 686	df 2	*p* .000

3.11.3. Traditional prognostic factors and survival

The Time-Dependent Factors, Tumour size and Lymph Node Stage and the Biological factor of Grade all showed highly significant relations to survival (Table 8).

Since tumour type showed poor agreement between Units (see Pathology QA) and since survival of much the commonest type (Ductal NST) is strongly dependent on grade, survival according to type has not been considered for all cases.

Lobular and Tubular Cancers were among those types with fair agreement in the QA examination. Lobular cancer has been held to have similar survival as Ductal NST Grade 2[11] and this is confirmed in ONCOPOOL with a Breast Cancer-Specific survival in Lobular/Grade 2 Cancers

Table 9 – 10-year Overall and Breast Cancer-Specific (BCS) survivals for all cases with NPI available (therefore Unit 9 was excluded). Analyses by NPI and for all Cases (Kaplan–Meier). To calculate the expected BCS Survival from OS (5th column) the expected number of natural deaths (UK office of population statistics) of 6% is added to the OS figures.

NPI group	*n* (%)	Overall Survival % 10 yr ± SE	BCS Survival % 10y (BCS)	Expec. BCS Survival (%) calc. from OS
EPG	1802 (16)	92 ± 1	96 ± 1	97
GPG	2362 (21)	89 ± 1	93 ± 1	94
M1	2497 (23)	81 ± 1	84 ± 1	86
M2	1738 (16)	71 ± 1	72 ± 1	75
PPG	865 (8)	54 ± 2	57 ± 2	57
VPG	318 (3)	36 ± 4	40 ± 3	38
All cases	11,017	80 ± 0	84 ± 0	85

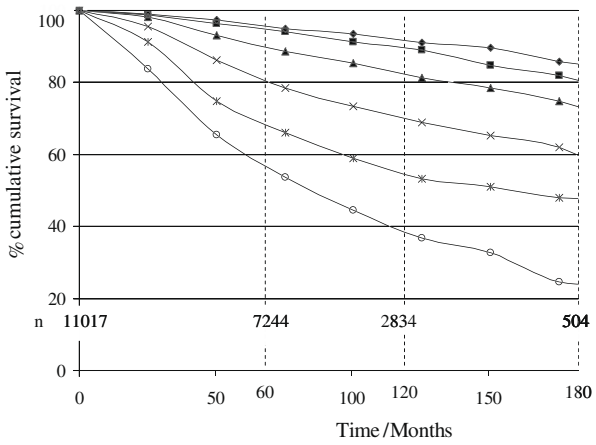


Fig. 7 – Overall Survival (Kaplan–Meier) by NPI for all cases from all Units except Unit 9 ♦, EPG; ■, GPG; ▲, M1; X, M2, *, PPG and ○, VPG. Numbers for follow-up date of end of 5-year periods are shown below for all cases.

($n = 454$) of 81 ± 1% at 10 years against the survival of Ductal NST/Grade 2 cancers ($n = 2881$) of 80 ± 1%. Tubular Cancers have been reported to have a survival comparable to DCIS[12]; their 10-year survival in ONCOPOOL was 98%, the same as that often quoted for DCIS, confirming their excellent survival.

3.11.4. *Nottingham Prognostic Index (NPI) and survival*

An integrated prognostic index, well validated 13 and widely used in the UK and recognised across Europe, is the Nottingham Prognostic Index[4–7,13] which has over 1000 citations.

The NPI combines tumour size, lymph node stage and histological grade. Calculation of the NPI is (0.2 × size in cm) + LN stage 1–3 + Grade (1–3). The range of NPI for tumours up to 5 cm (tumours of 5 cm and above were not included in ONCOPOOL) is 2.04–6.99. The NPI score for each patient places them in one of six prognostic groups (EPG – excellent ⩽2.4, GPG – good 2.41–3.4, M1PG – moderate 1 3.41–4.1, M2PG – moderate 2 4.11–5.4, PPG – poor 5.41–6.4, VPG – very poor 6.41–6.9).

The NPI was not calculable for Unit 9 because size was not recorded as a continuous variable.

Percentage survivals (OS and BCS) by NPI for all cases in the ONCOPOOL dataset and the percentages of cases placed into each NPI group are shown in Table 9 and OS by NPI is shown in Fig. 7. A rank order of survival in NPI groups is seen and there are significant differences in survival between all adjacent NPI groups excepting the best two. Again the correction applied to OS allowing for non-breast cancerous deaths shows a good agreement with BCS survival, for all cases and within each NPI group (see Tables 10 and 11).

Fig. 6 shows the polynomial curves for the relationship of individual values of NPI with percentage 10-year survivals. The curves for both OS and BCS give r^2 of 0.99 with an average 3% difference in deaths, with larger the difference, the worse the prognosis. The curve for OS modified by addition of deaths expected from non-breast cancerous causes shows a very good fit against the BCS survival. Comparison of the three curves for the opposing data points is apparent from the figure.

3.12. *Effects of interventions*

3.12.1. *Effect of screening*

Method of detection was recorded in 7139 cases but only Units 1, 5, 6 and 11 recorded this data in all cases; two Units did not enter any data.

The 10-year OS for cases detected at screening ($n = 2470$) was 84% and for the 4669 cases which presented symptomatically 76%.

3.13. *Effects of adjuvant systemic therapies*

3.13.1. *Effects of hormone therapy*

Only ER positive cases have been examined making the assumption that endocrine therapy has no effect on ER negative cases. Cases receiving chemotherapy have been excluded in order to eliminate the hormonal effect of ovarian ablation.

The effects of adjuvant systemic therapies have been examined using Cox multivariate regression, entering receipt of therapy against non-receipt and NPI as a continuous variable.

Adjuvant hormone therapy (including all regimes) was given as a single adjuvant therapy to 4505 women with ER

Table 10 – Overall Survival in ER positive cases with NPI available analysed by Cox multivariable regression according to the receipt of adjuvant endocrine therapy only (n = 4505) versus no adjuvant therapy (n = 2962) and NPI as a continuous variable.

Factor	β	HR	p
Endocrine versus no adjuvant therapy	–0.14	0.87	0.047
NPI	0.64	1.9	0.000

Table 11 – Overall survival in ER negative cases with NPI available analysed by Cox multivariable regression according to receipt of adjuvant Chemotherapy only (n = 1311) versus no Chemotherapy (n = 1225) and NPI as a continuous variable.

Factor	β	HR	p
Chemotherapy versus no CT	–0.26	0.77	0.006
NPI	0.62	1.86	0.000

positive tumours. This was compared with 2962 women with ER positive tumours receiving no adjuvant therapy.

Cox regression gave β values for receipt of therapy (entered 0 or 1) of minus 0.14 (p = 0.047) and for NPI (entered between 2.2 and 6.9) of 0.64 (p = .000).

Hazard ratios were for receipt of endocrine therapy 0.87 and 1.72 for NPI across the range. Relative risk reduction from hormone therapy was therefore 13%.

There was little difference in survival with hormone therapy in all ER positive cases from that in women with high ER (>70% of maximum score for the method used) with 10-year overall survivals of 79%.

3.13.2. Effects of adjuvant chemotherapy

3.13.2.1. ER negative cases. The effect of chemotherapy (CT) was examined only in ER negative cases in order to avoid the confounding influence of hormone therapy.

Adjuvant chemotherapy (±hormone therapy) was given to 1225 women with ER negative tumours who were compared with 1311 women with ER negative tumours, not receiving chemotherapy but to some of whom hormone therapy was applied.

Cox regression gave a β value for receipt of chemotherapy of minus 0.26 (p = 0.006) and for NPI of 0.618 (p = 0.000). Hazard ratio for receipt of CT was 0.77 and for NPI 1.86, giving a relative risk reduction for chemotherapy of 23%.

3.14. *Quality assurance (QA)*

3.14.1. Clinical data QA

3.14.1.1. Follow-up. Survival curves (Kaplan–Meier) were constructed for each Unit with analysis of the six NPI groups. Only Units 1, 7, 8 and 11 showed smooth curves with even censoring rates. The causes of the fluctuation in Kaplan–Meier curves from the remaining Units were low numbers or poor follow-up data.

At 5 years (with all cases at least 5 years from entry), 74% of the 15,371 had information on whether alive or dead at the end of the period; two Units had information on 100% and one on 95% and all but two Units had information in over 60%. At 10 years only 35% of those entered were assessable for analysis; one Unit had 100%, 5 were above 70%. At 15 years only three Units had assessable data on the 4983 women who had reached that time of follow-up (i.e. entered before January 1993); combined information at 15 years from these three Units was of 27% (830 deaths and 504 entering the next interval).

To consider whether the fall off in follow-up affected the survival figures at 5 and 10 years were analysed for the Units 1, 3 and 8, which had the best follow-up: known outcomes, respectively, in 100%, 100% and 95% at 5 years and 74%, 86% and 86% at 10 years. The combined Overall Survivals for these three Units were 89% at 5 years, 80% at 10 years and 73% at 15 years, exactly the same as that found from the data from all Units (Table 7).

Cause of death was generally recorded satisfactorily (over 70%): in 100% of deaths in only one, in over 92% in a further five Units. In two Units 16% did not have a cause of death and in another two over 40% did not.

3.14.1.2. Effect on survival of calendar years of diagnosis. Considering whether cases diagnosed in the early years of the entry period fared different from those in the later years, 10-year OS for women diagnosed in 1990–1993 was 79% and for those diagnosed in 1997–1999, 81%.

3.14.2. Pathology QA

Information on re-assessment of pathological features are for reporting on QA only and have not been taken into account in the above analyses.

3.14.2.1. Grade. Three Units did not submit tumour material; in the seven remaining Units grade as categorised by the Unit pathologists was agreed on review by the two pathologists in 168 out of 208 slides submitted (81%).

The QA pathologists disagreed with the local Grade in 20% of all cases reviewed. Overall for Grade 1 there was agreement on only 45 of 66 cases (66%), for Grade 2 60 of 73 (82%) were agreed and for Grade 3 63 of 72 (86%) were confirmed as correctly classified. Changes were mostly of one grade: in the 28 cases altered from Grade 1 only one was re-assessed as 3 and in tumours altered from Grade 3 only one of 9 was changed to Grade 1.

3.14.2.2. Type. Tumour type was re-assessed and disagreement with the original record was noted in 45 out of the 135 cases submitted for QA (33%). Performance from Unit to Unit varied widely in all four Units which submitted slides for typing. Case Type was judged in variance with the opinions of the QA pathologists in over 20% of cases and in one Unit there was disagreement in 51%. There was, however, fair agreement (80%) for four of the commonest categories: ductal NST, lobular, tubular and mixed, against only 46% agreement for the totalled less common categories.

4. Discussion

This ONCOPOOL analysis provides information from a large dataset on Invasive Breast Cancers diagnosed in 10 European Specialist Breast Units in the 1990s. Details of the pathological make-up of tumours, of prognostic factors and of the inter-relation of these factors are recorded. Five- and 10-year survivals are given and the effects of interventions examined.

ONCOPOOL resembles SEER in the accrual of tumour pathology, inter-relation of pathological factors, recording of treatments and relation of all these factors to outcomes but differs from SEER in other ways. SEER is entirely USA based and draws from cancer registries in five states and four large metropolitan areas. In the original publications,[1,2] there was a very large amount of incomplete data so that of 117,000 cases originally inspected, only 28,000 were presented.[2] This is very likely to have given rise to selection biases. Predominately only 5-year follow-up was presented, which is now regarded as giving an incomplete picture of long-term events. However a recent publication from SEER[14] reports on 302,000 cases treated in the years 1998–2001.

ONCOPOOL has several advantages in these aspects: data on tumour characteristics, treatment and outcomes came direct from the treating Units. Whether death was breast cancer specific or from other causes was generally well recorded. A number of factors in addition to the standard prognostic factors have been entered and data on factors assessed (notably grade) and outcomes were much more complete than in the SEER publication. Quality assurance has also been applied to clinical, pathological and endocrine data.

In the 1990s population screening was widely introduced; the reports of the EBCTCG[15,16] led to much commoner use of adjuvant systemic therapies; the introduction of specialist Breast Cancer Units with multidisciplinary working between specialists in breast cancer to standardise protocols ensured patients receiving the best agreed therapies. Survival has consequently improved hugely in breast cancer.[3] To re-examine the factors and outcomes recorded in SEER, in a European dataset compiled two decades later, is now timely.

In ONCOPOOL the characteristics of breast cancers and the pathological characteristics of breast cancers following first line surgery for primary breast cancer are largely consistent from Unit to Unit.

There was good consistency in the measurement of size and LN status. Mean tumour size at diagnosis was 1.8 cm and 70% of tumours measured 2 cm or less. Sixty-six percent of cases were LN negative on clearance or sampling. The inter-relation of these time-dependent factors is shown in polynomial functions; relation of LN status to size is consistent supporting the quality of the data. The cases detected at screening were on average smaller than those referred with symptoms, and 78% were LN negative.

The consistency of the distribution of grades in the Units appeared poor, with wide differences in the percentages placed in Grades 1 and 3; the QA pathologists (S.P. and I.E.) attribute this partly to poor fixation of the specimens. Whilst one anticipates a distribution of 2:3:5: for Grade 1:Grade 2:Grade 3: tumours in the symptomatic setting,[8] some Units had an unlikely frequency distributions. It is well recognised that poor fixation influences in particular the assessment of the mitotic count component of grade, and an apparent reduction in the number of Grade 3 cancers is then seen with an excess of tumours graded as 2. Even though the percentages for each grade given by the Units differ considerably it is likely from interpretation of the ONCOPOOL figures and from the Pathology QA results that over 80% of cases would receive the same grade from the majority of Unit pathologists and that it is the differences in specimen handling rather than discordance between pathologists' interpretations which is likely to be the more significant contribution to this variation.

The Nottingham grading system[8] gives 3–9 possible total points (1–3 for each of tubule formation, pleomorphism and mitotic frequency) being summed to give only three grades: G1 3–5 points, G2 6–7 and G3 8–9. This means that a small disagreement of one point between pathologists, such as a one point difference in assigning a score for pleomorphism, can result in a difference of one whole grade and this in turn would change the NPI group in which the patient lay. A re-analysis of grade in the Nottingham dataset, using the point scores of the Elston–Ellis classification but dividing into six grades, is currently being carried out in Nottingham and will be tested on the ONCOPOOL dataset and reported. This will make differences at the margins between grades less important because changes could only move grade by 1 of 6 rather than 1 of 3, with therefore half the effect on NPI.

Grade as a biological factor was not as strongly related to LN stage and size as these time-dependent factors are to each other. Thus as grade increases LN status in relation to size increases by only a relatively small amount. Polynomial relationships are given for the combinations of these three prognostic factors.

Tumours presenting in young women were largely Grade 3 and few Grade 1. A likely explanation is that inception in a single cell may occur at the same time in Grade 3 and Grade 1 tumours but Grade 3's reach the size at which they present much more quickly. Taken with other observations this gives a method for calculating rates of growth for different grades and will be the subject of a further ONCOPOOL presentation.

Tumour typing showed poor consistency between Units but the similar survival in lobular cancers to that in ductal NST Grade 2 was confirmed, as was the excellent survival (akin to DCIS) of tubular cancers.

Hormone receptor data showed good consistency in percentage ER positivity between Units. Most Units rely on oestrogen receptor only; the mean ER positivity for all cases was 75%.

The cumulative frequencies of ER levels are shown to be of use for comparisons between different ER assays. A definition of ER high positivity would appear to be the level at which the percentage of the maximum score for each Unit is reached by 70% of their cases, e.g. for *H*-score and histoscore around 60%

of maximum score and for percent cells positive 100%. Also with few cases between zero and the percent scores for the threshold of positivity used by each Unit, a better definition of negativity might be zero.

The highly significant relation between ER and grade[17] is confirmed.

As expected survival related strongly to the traditional prognostic factors of grade, stage and size and these were combined in the well-recognised Nottingham Prognostic Index.

The NPI was originally described in 1979[4] compiled from a Cox multivariate analysis in which only three factors remained significant – size, lymph node status and grade and the NPI incorporated these three only. The survival figures according to NPI have subsequently been validated in several series.[13,18] Survival, however, has increased greatly since the NPI was designed and a publication[6] updating the survival figures according to NPI was published from Nottingham in 2007. An accompanying editorial in the European Journal of Cancer[19] states 'with such high survival discrimination it would be justified to consider the NPI as a benchmark model for breast cancer prognosis'. The NPI is further validated in ONCOPOOL by comparison with the most recently published figures from Nottingham[6] and in addition a method for estimating the prognosis of the individual with breast cancer, using a polynomial curve fitted to NPI scores was published from Nottingham[7]; the formula for that curve is very well validated in the ONCOPOOL dataset after the exclusion of Nottingham cases entered into ONCOPOOL (not shown in this paper).

OS for all cases was at 5, 10 and (largely from extrapolation) 15 years 89%, 80% and 73% and BCS was 91%, 84% and 79%. Analysed in NPI groups overall 10-year survivals were in rank order ranging down from 92% in the Excellent Prognostic Group to 35% in the Very Poor Prognostic Group.

There was no evidence that cases diagnosed in the last 3 years of the entry period had better survival than cases in the first 3 years.

The effects on survival of interventions are shown. In all these more detailed analysis would be required to eliminate confounding variables. For the analysis of the effect of detection in breast cancer screening it must be noted that this is not a study of invitation to population screening against no invitation but a comparison of cases detected at a screening examination (population or opportunistic or on request) against cancers presenting symptomatically. In the analyses of therapeutic effects these are not figures from a randomised trial and are also very short of the power required to detect even a 20% effect remembering that the overall survival is close to 80% giving few events.

Eighty-three percent of screen detected cases were $\leqslant$2 cm and 37% $\leqslant$1 cm; these are close to figures shown by Joensuu et al.[20] of 82% and 38%; 78% of screen detected cases were LN negative in both series. Screen detected cases had 10-year survivals of 84% against symptomatically presenting cases of 76%. However this does not include the effects of detection in screening of ductal carcinoma *in situ*, many of which are prevented from progressing to invasive cancers nor of the high number of Grade 1 carcinomas detected particularly in the prevalent screen and reducing at later screens.

The effect of hormone therapy was examined only for ER positive tumours and cases that received chemotherapy in addition were not analysed.

A highly significant effect of hormone therapy for ER positive tumours was shown, although with a 13% reduction in risk of death by 10 years was less than expected.[15]

For the effects of chemotherapy in order to eliminate the hormonal effects of chemotherapeutic ovarian ablation only ER negative tumours were examined.

Examination of the effect of chemotherapy was complicated by a considerable majority of cases that received chemotherapy lying in the worst NPI groups, with poor predicted outcomes, whilst the majority of those who did not receive chemotherapy lay in the best NPI groups. Analysis by Cox regression entering only receipt or non-receipt of chemotherapy and NPI as a continuous variable corrected for these differences and showed a highly significant survival advantage to chemotherapy, with a risk reduction of death of 23% at 10 years, much as would be anticipated from the EBCTCG overviews.[16]

This publication from ONCOPOOL has examined invasive operable breast cancers, presenting in women of 70 years or less; the important pathological and prognostic factors, their characteristic state at presentation, their relationships to survival; survivals (OS and BCS) at 5, 10 and 15 years after primary treatment; the effects of interventions on survival and the relationship of individual NPI to survival across all Units. The combined results give the most detailed picture so far advanced of the pathology and survival of these cancers across Western Europe.

Further publications from ONCOPOOL are planned, including 20-year and even longer term survivals; other outcome measures – the operative and radiotherapeutic treatments used to breast and lymph nodes and their effects on local and regional recurrences and the effects of these on survival; new ipsilateral primary and contralateral breast cancers; influence of extra prognostic factors such as lympho-vascular invasion and HER2 status; further analyses of the effects of systemic interventions; a potential new scoring system for grade; comparisons with the up-to-date SEER data for cases entered in the same period to ONCOPOOL; comparison of NPI and adjuvant in the prediction of survival in ONCOPOOL

Contributors

The submission was from Nottingham City Hospital and was supported by EUSOMA (European Society of Breast Cancer Specialists). The project was designed and the protocol and proposal were written by R.W.B. (Project coordinator and Grant Holder) and by B.H.-S, and they and the local coordinators of all the partner Units (including the Tenovus Centre) were co-applicants for grant support.

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Unit	Coordinator (additional clinician)		Data Managers
ONCOPOOL			
Project Coordinator and grant holder	R.W. Blamey		Central Database M. Mitchell (original) A. Oates (current)
Clinical units	Local coordinators and additional clinicians	Local pathologists	Local Data Managers
Amsterdam	M. van de Vijver (E.J. Rutgers)	M. van de Vijver	T. Van der Velde
Cardiff	R. Mansel	A. Douglas-Jones	S. Roberts
Copenhagen	M. Blichert-Toft (original) N. Kroman (current)	F. Rank	Maj-Britt Jensen
Dublin	M. Kerin	M. Kennedy	B. O'Loughlin
Florence	L. Cataliotti	S. Bianchi	R. Segantini
Kalmar	M. Sundquist	S. Thorstenson	A.-S. Junga
Nottingham	R.W. Blamey	I. Ellis S. Pinder	M. Mitchell (original) A. Oates (current)
Paris	A. Fourquet (Y. Kirova)	B. Sigal	C. Gauthier
Gothenburg	M. Sundquist (original) R. Sandstrom (current)	A. Kovacs	A. Markstrom
Tampere	K. Holli	T. Kuukasjarvi	K. Rouhento
Vienna	R. Jakesz	A. Karnolinski	M. Mittboeck
Warsaw	T. Pienkowski (E. Towpik)	W. Olszewski	
Quality assurance			
Clinical QA	B. Hornmark-Stenstam		
Pathology QA	I. Ellis and S. Pinder		
Endocrine QA	R. Nicholson and J. Gee		
Data analysis	G. Ball		
Project Manager	C. Skentelbery		

Contact details			
Unit	Address (coordinator or data manager)	Tel.: (for use)	e-mail
ONCOPOOL			
Central Database and Nottingham Unit and Pathology QA	Breast Institute Nottingham City Hospital Nottingham NG5 1PB, UK	office: +44 (0)115 9627934	allan.oates@nuh.nhs.uk
Amsterdam	The Netherlands Cancer Institute Plesmanlaan 121 Amsterdam 1066 Netherlands	+31 205664100	mvijver@nki.nl
Cardiff	Univ Dept of Surgery University of Wales College of Medicine Cardiff CF14 4XN, UK	+44 (0)292 0742749	Manselre@cf.ac.uk
Copenhagen	Surgical Department, Breast Unit Rigshospitalet 3104 Blegdamsuej 9 2100Copenhagen Denmark	+45 35452117	d252743@dadlnet.dk
Dublin	Breast Unit Mater Misericordiae Hospital Dublin 7 Ireland		boloughlin@mater.ie
	Prof M Kerin Dept of Surgery University College Hospital Galway	+353 91 524390	grace.clarke@nuigalway.ie

(*continued on next page*)

Florence	Azienda Ospedaliero-Universitaria Careggi Viale Morgagnie 85 Florence 50134 Italy	+30 055411608	luigi.cataliotti@unifi.it
Kalmar	County Hospital 39185, Kalmar, Sweden	+46 737334768	mariesu@ltkalmar.se
Paris	Dept of Radiation Oncology Institut Curie 26 Rue D'Ulm 75005 Paris France	+331 44324631	alain.fourquet@curie.net
Gothenburg	Breast Unit Department of Surgery Sahlgrenska University Hospital 41345 Gothenburg	+46313420000	rolf.sandstrom@vgregion.se
Vienna	Dept of Gen Surgery General Hospital Waehringer Guertel 18-20 Vienna A-1090 Austria	+431 404006916	raimund.jakesz@meduniwien.ac.at
Tampere	Dept of Oncology Univ Hospital of Tampere PO Box 2000 Teiskontie 35 33521 Tampere Finland	+358 3 2473 029	kaija.holli@uta.fi
Warsaw	Maria Sklodowska Curie Memorial Cancer Centre Warsaw, Poland	+48 225462000	Tadeusz.Pienkowski@gmail.com
Data Analysis	Dept of Bioinformatics Nottingham Trent University NG1 4BU, UK	+44 (0)115 8488308	graham.balls@ntu.ac.uk
Clinical QA	Landstinget Sormland, Nykoping, Sweden	+ 46 709224244	britta.h-stenstam@dll.se
Endocrine QA	(J. Gee and R. Nicholson) Tenovus Centre for Cancer Research Welsh School of Pharmacy Cardiff University King Edward VII Avenue Cardiff CF10 3NB, UK	+44 (0)2920 875226	gee@cardiff.ac.uk
Pathology QA	Department of Histopathology Nottingham City Hospital NG5 1PB, UK	+44 (0)115 9627875	Ian.Ellis@nottingham.ac.uk
	Dept of Academic Oncology Guy's Hospital London SE1 9RT, UK	+44 (0)2071884260	sarah.pinder@kcl.ac.uk

Conflict of interest statement

None declared.

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