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Title: Adverse surgical outcomes in screen-detected ductal carcinoma in situ of the breast.

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Abstract: Background

The Sloane Project is the largest prospective audit of ductal carcinoma in situ (DCIS) worldwide, with over 12000 patients registered between 2003 and 2012, accounting for 50% of screen-detected DCIS diagnosed in the UK over the period of accrual.

Methods

Complete multidisciplinary data from 8313 patients with screen-detected DCIS were analysed for surgical outcome in relation to key radiological and pathological parameters for the cohort and also by hospital of treatment. Adverse surgical outcomes were defined as either failed breast conservation surgery (BCS) or mastectomy for small lesions (<20mm) (MFSL). Inter-hospital variation was analysed by grouping hospitals into high, medium and low frequency for these two adverse outcomes.

Results

Patients with failed BCS or MFSL together accounted for 49% of all mastectomies. Of 6633 patients embarking on BCS, 799 (12.0%) required mastectomy. MFSL accounted for 510 (21%) of 2479 mastectomy patients. Failed BCS was associated with significant radiological under-estimation of disease extent and MFSL significant radiological over-estimation of disease extent. There was considerable and significant inter-hospital variation in failed BCS (range 3-32%) and MFSL (0-60%) of a hospital's BCS/mastectomy workload respectively. Conversely, there were no differences between the key radiological and pathological parameters in high, medium and low frequency adverse-outcome hospitals.

Conclusions

This evidence suggests significant practice variation, not patient factors, is responsible for these adverse surgical outcomes in screen-detected DCIS. The Sloane Project provides an evidence base for future practice benchmarking .

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Mr Sibbering is an experienced breast surgeon currently Chair of the Association of Breast Surgeons at BASO. He has a strong interest in screening but has no connection with the Sloane Project

The Editor
European Journal of Cancer

Dear Sir

Adverse surgical outcomes in screen-detected ductal carcinoma in situ of the breast.

I should be grateful if you would consider the attached manuscript for publication in the European Journal of Cancer. This is a resubmission following appeal (previous manuscript No EJC-D-13-01702) after we had gathered additional data on hospital to hospital variation in outcomes.

We believe our study makes the following important observations on current breast screening practice and has wider implications for other multi-institution studies such as clinical trials:

1. We have quantified adverse surgical outcomes in screen-detected DCIS examining data from more than 8,000 patients – this has never been done before.
2. Having looked at a range of variables we have identified radiology/pathology size mismatch as the likely culprit at the root of these adverse outcomes.
3. There is a wide and significant variation among hospitals in the frequency of these outcomes but the case mix (as deduced by looking at the same variables again) is the same.
4. We conclude that it is likely that practice variation is at the heart of the problem and that we can learn from the best.

Our study provides an evidence base for benchmarking future practice in this area.

The study relies heavily on statistical analysis, particularly comparison of agreement between two methods of measurement (radiology and pathology) and analysis of variation among hospitals. We have used Altman Bland difference plots and one tailed Anova testing respectively for these. The inter-hospital analysis was restricted to the top quartile of hospitals submitting cases (in terms of numbers of cases registered for the Audit) however this quartile accounts for 80% of the patients in the audit. We have also explored whether the same hospitals perform similarly for a variety of measured outputs i.e. is a hospital equally bad at one area of practice as another or are hospitals good at some areas of practice and bad at others? We have tested this by comparing rates of hospital's various outputs. There was only one significant finding here – **hospitals with high overall mastectomy rates also have higher failed breast conservation rates.**

We have included an Appendix giving a fuller explanation of these methods.

We have a substantial amount of additional material that has been included in a supplementary file. The bulk of these data relate to questions that will inevitably be asked about the study – demographics and detailed comparison of key pathological variables, for example, all of which underline the fact that it is not the biology of the disease that explains the differences in outcome but how the disease is managed in different units. If the study is deemed suitable for publication and the Editors deemed it preferable to include this information in the main paper I would happily revise the manuscript accordingly.

Yours sincerely,

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Adverse surgical outcomes in screen-detected ductal carcinoma in situ of the breast

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Study concepts:	All
Study design:	All
Data acquisition:	Dr J Thomas; All
Quality control of data and algorithms:	Dr Gill Lawrence, Ms Karen Clements
Data analysis and interpretation:	Dr J Thomas, Prof S Pinder, Prof A Hanby
Statistical analysis:	Dr J Thomas, Prof Graham Ball
Manuscript preparation:	Dr J Thomas, Prof S Pinder, Prof A Hanby
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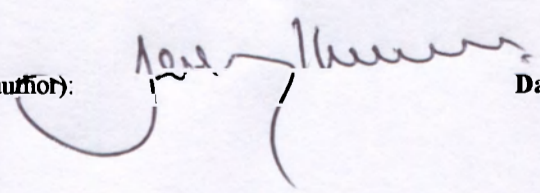
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"I confirm that all the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to the *European Journal of Cancer*".

Signed (corresponding author):



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Title: Adverse surgical outcomes in screen-detected ductal carcinoma *in situ* of the breast.

Running title: Adverse outcomes in screen-detected DCIS

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On behalf of the Sloane Project Screening Group *

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* Listed in Appendix 1

Key words: Breast Screening, DCIS, Pathology, Radiology, Outcomes, Practice variation.

Note:

These data have been submitted for presentation at the European Breast Cancer Conference, Glasgow March 2014.

ABSTRACT

Background

The Sloane Project is the largest prospective audit of ductal carcinoma in situ (DCIS) worldwide, with over 12000 patients registered between 2003 and 2012, accounting for 50% of screen-detected DCIS diagnosed in the UK over the period of accrual.

Methods

Complete multidisciplinary data from 8313 patients with screen-detected DCIS were analysed for surgical outcome in relation to key radiological and pathological parameters for the cohort and also by hospital of treatment. Adverse surgical outcomes were defined as either failed breast conservation surgery (BCS) or mastectomy for small lesions (<20mm) (MFSL). Inter-hospital variation was analysed by grouping hospitals into high, medium and low frequency for these two adverse outcomes.

Results

Patients with failed BCS or MFSL together accounted for 49% of all mastectomies. Of 6633 patients embarking on BCS, 799 (12.0%) required mastectomy. MFSL accounted for 510 (21%) of 2479 mastectomy patients. Failed BCS was associated with significant radiological under-estimation of disease extent and MFSL significant radiological over-estimation of disease extent. There was considerable and significant inter-hospital variation in failed BCS (range 3-32%) and MFSL (0-60%) of a hospital's BCS/mastectomy workload respectively. Conversely, there were no

differences between the key radiological and pathological parameters in high, medium and low frequency adverse-outcome hospitals.

Conclusions

This evidence suggests significant practice variation, not patient factors, is responsible for these adverse surgical outcomes in screen-detected DCIS. The Sloane Project provides an evidence base for future practice benchmarking .

INTRODUCTION

The recent Independent Breast Screening Review in England ^[1,2] recommended improving screening and pathology techniques in the diagnosis of breast cancer and made specific reference to the The Sloane Project, a prospective UK audit of patients with screen-detected non-invasive carcinomas and atypical hyperplasias of the breast detected by the National Health Service Breast Screening Programme (NHS BSP), named in memory of the late Professor John Sloane.^[3]

We have identified four main clinically relevant surgical outcomes in the treatment of DCIS: successful conservation, failed conservation, mastectomy for lesions <20mm and mastectomy for lesions ≥20mm and we have defined failed breast conservation surgery (BCS) and mastectomy for small lesions (MFSL) as adverse surgical outcomes. In the management of DCIS, precise imaging, primarily through mammographic assessment of microcalcifications, including nature, location and extent, combined with careful multidisciplinary discussion of each patient is critical in planning appropriate surgery. The three most important features for disease behaviour, and thus clinical management, are: lesion size, cytonuclear grade (grade) and width of tumour-free margins. Some randomised clinical trials have indicated that additional features may predict local recurrence, such as the architectural pattern of DCIS and the presence of necrosis.^[4-6]

We have previously shown that pathologists assess the extent of DCIS accurately in specimens from breast conserving surgery (BCS) but less so in mastectomies.^[7] Using this same methodology with a much larger dataset, we have now studied the

treatment of DCIS diagnosed in the UK NHS BSP, analysing radiological and pathological factors according to surgical outcome and then by hospital of treatment.

PATIENTS AND METHODS

Sources of data

Eighty two of 94 (87%) UK NHS breast screening units submitted data. Each clinical specialty (radiology, surgery, histopathology, radiotherapy) contributed specialty-specific data relating to diagnosis and treatment using specially designed proformas.

Patient population

We report on data for the entire audit period, April 2003 – March 2012, on over 8000 patients with complete datasets. All patients had screen-detected DCIS, alone or with atypical ductal hyperplasia (ADH) and/or lobular in situ neoplasia (LISN), and were aged between 46 and 83 years at diagnosis, with a median age of 60. Patients were treated in 218 hospitals.

Variables

Surgical data included the number and type of operations and nature of the final surgery. We excluded therapeutic mammoplasty and diagnostic biopsy patients from the analysis of patients with a single breast conserving surgery (BCS) procedure. When a patient had multiple operations, the final disease extent was estimated from summation of the different specimens. The main pathology and radiology data items examined are detailed in the results.

We analysed specimen weight and disease location (whether subareolar or not) and radiological calcification. Radiological disease extent was recorded in two dimensions on both the mediolateral oblique and craniocaudal views and the maximum extent used for comparison of radiological and pathological estimation of size.

For the analysis of inter-hospital variation we examined frequency of operation type for the top quartile of hospitals (by total numbers of cases submitted) and the hospital rankings by frequency of failed BCS and MFSL, to determine whether there was overlap for either adverse outcome. We further analysed our data by frequency group (high, medium and low) for the two adverse outcomes.

Data analysis and statistical methodology

All data were entered and held securely at the West Midlands Cancer Screening QA Reference Centre. This analysis was performed on a download dated 8th February 2013. Hypotheses were prospectively chosen by the authors. Data were analysed using “Analyse IT”[®] v 2.20 for Microsoft Excel [®]. Tests were deemed significant with p value <0.05. Student’s T test was used to compare groups of data where normally distributed. The chi squared test was applied to test frequency distributions across defined groups of data. Agreement between pathology and radiology size estimations was assessed using Altman Bland difference plots where the difference between the radiological and pathological size for any individual was plotted against the mean of the two values. The systematic bias in any group of paired measurements is the mean of all the differences - positive or negative. ^[8] Variance when normally distributed was measured using a one-tailed analysis of variance (Anova) test.

Homogeneity of variance was assessed using Hartley's F Max test. Pearson's correlation was used to compare hospitals' frequencies for various operations.

See Appendix 4 for further description of these statistical methods.

RESULTS

Data relating to case distribution, demographics, operation type, grade and margins are detailed in the supplementary file (supplementary-data.doc).

Patient accrual

The accrual of the 8313 patients between 2003 and 2012 in the study set (see below) is shown in **Figure 1**. There was no difference in the accrual profile of operative subgroups in comparison to the overall accrual profile over time.

Completeness of data

A four-specialty dataset is available for 8313 (66%) of the 12623 patients. Data were near-complete following data cleaning. For example, the Altman Bland analysis of the 3946 patients in the single operation BCS group had radiological and pathological size measurements for 3894 patients (98.6%). The size and/or grade were recorded for 8233 (99%) cases. The lowest levels of completeness applied to ER measurements (54%); ER is not mandated in the UK DCIS pathology minimum dataset.

Surgery, extent of disease, grade, and pathological/radiological size correlations for the different operation types

The data relating to operation type are summarised in **Table 1**.

5834 (70%) of patients, including those who underwent therapeutic mammoplasty and diagnostic biopsy (47 and 349 patients respectively), were treated by BCS whilst 2479 (26%) had mastectomy. 57 patients had successful BCS after more than two operations (range 3-5). Patients who had successful BCS at a single operation had significantly less extensive disease than those achieving successful conservation at two operations (12mm vs 17mm) (T test, $p < 0.0001$). The proportion of high grade disease and agreement between pathological and radiological size estimates was similar in both groups (Altman Bland bias of 2.95mm and -0.32mm respectively).

799 patients with failed BCS subsequently requiring mastectomy accounted for 12% of the total BCS group and were notable for having a disease extent and grade distribution similar to those undergoing primary mastectomy. In patients with failed BCS there was poor agreement between pathological and radiological size estimation, with radiology underestimating disease extent as demonstrated by a *negative* Altman Bland bias of 13.49mm. 86 (10.8%) of these patients had lesions < 20 mm (see below).

Figure 2.

There were 510 (21%) mastectomies for patients with disease histopathologically measuring < 20 mm. This could not be explained either by the location within the breast (11.3% of these were retroareolar vs 11.1% for mastectomy overall). Mastectomy weight for specimens with DCIS lesions < 20 mm was lower than for for DCIS ≥ 20 mm (median 570gm, inter-quartile range (IQR) 521.25 vs 626gm, IQR 503.08 (T test; $p = 0.017$). Notably, in this small-lesion group there was evidence of substantial overestimation of radiological size with an Altman Bland bias of

19.86mm. **Figure 3.** There was no difference in grade distribution in this subset in comparison with all mastectomies.

The Altman Bland bias was calculated for each operative subgroup for those specimens where specimen slice radiography had been carried out. There was no significant difference between those cases where slice radiography had been employed and those where it had not.

Mammographic calcification

There was no difference in frequency or pattern of mammographic calcification in the operative subgroups.

Inter-hospital variation: case numbers, operation type and reported grade

There was a wide range in the number of cases submitted by the 218 different hospitals. The median number of patients was 10 (range 1 – 387; top quartile 50-387 in 57 hospitals). These 57 hospitals accounted for 6691 of the 8313 (80%) of the patients in the study.

1. Inter-hospital variation – the top quartile (57 hospitals):

The proportions of the different operation types varied substantially between hospitals. Mastectomy rates ranged from 14-65% and for failed BCS and MFSL the ranges were 3-32% and 0–60% respectively (shown in **Table 2**). The inter-hospital

variance between failed BCS vs successful BCS operations was significant (Anova test, $p < 0.0001$). There were insufficient numbers to carry out an inter-hospital variance analysis for the mastectomy operative subgroups. There was a significant correlation between a hospital's overall mastectomy rate and its rate of failed BCS (Pearson's correlation, $r = 0.70$; $p < 0.0001$). There was no correlation (positive or negative) between a hospital's failed BCS rate and MFSL rate (Pearson's correlation, $r = 0.11$; $p = 0.41$).

2. Inter-hospital variation – the top quartile of hospitals analysed as three frequency subgroups (high, medium and low) for the two adverse outcomes:

The top quartile of 57 hospitals was compared in 3 groups of high, medium and low frequency (19 each). The differences in mean frequency for each 19-hospital subgroup both for failed BCS and MFSL (high v medium, medium v low, high v low) were all highly significant (chi squared test; $p < 0.0001$). Analysis of the principal demographic, pathological and radiological variables (including Altman Bland bias) for each of the frequency groups showed no significant differences. (**Table 3**) There was little overlap in the hospitals' frequencies of failed BCS and MFSL respectively (4/19 hospitals in the high frequency and 5/19 in the low frequency groups).

DISCUSSION

This is the largest audit of DCIS in a population-based breast screening programme and the first to quantify the magnitude and significance of the problems of under-estimation or over-estimation of disease extent in relation to operative outcome. A desire to conserve the breast, where possible, resulting in failure of conservation surgery on occasion may be inevitable. Likewise it is hard to envisage a service when mastectomy was never carried out for a small lesion, although for one of the study hospitals this was the case.

Although nearly 90% of DCIS patients treated with BCS achieved successful breast conservation, usually after a single operation, the group of patients with failed BCS comprises one third of all patients who undergo mastectomy in this study. Conversely, a sizeable subset (21%) of patients undergoing mastectomy had lesions <20mm. Although these latter patients had smaller breasts (median 570 vs 626gm) than the large-lesion mastectomy subgroup, substantial over-estimation of the disease extent appears to drive decision-making, particularly given the range of mastectomy rates. Furthermore, specimen weight and lesion location considerations cannot account for variation by hospital.

Data Quality

Central review of Sloane Project pathology has not been performed. The audit, however, represents the reality of current quality-assured NHS BSP pathology practice in the UK. The NHS BSP has strict audit protocols and outputs are closely

monitored and published annually. The very large number of patients, even in subgroup analysis, allows important messages to emerge. Our ability to band hospitals by frequency of adverse outcome also allows us to eliminate much of the “noise” of inter-hospital variability for single data items.

Variation in practice among hospitals

The wide variation in mastectomy rates and the positive correlation with failed BCS is concerning. While patient choice may be a factor, it is unlikely to explain completely the substantial differences seen between hospitals. Data from the NHS BSP indicate that patient choice accounts for just 11% of mastectomies for DCIS.^[9] The considerable variation in use of mastectomy for DCIS in different hospitals gives an opportunity to identify best practice and set criteria and measurable standards for the future. DCIS represents 20.3% of screen-detected breast cancer and addressing surgical adverse outcomes for this disease has the potential of significantly reducing screening-related morbidity. Early in the Sloane Project, the variation in practice relating to oestrogen receptor (ER) assessment and specimen handling was described.^[10, 7] The finding that the accrual profile of the different operative subgroups is the same as the overall accrual profile for the audit demonstrates that there has been no change in the various operative outcomes over time and that adverse surgical outcomes are not simply a historic problem.

Radiological under-estimation and over-estimation of disease extent

A question that must be asked in order to address this clinical issue is whether the mismatch between radiology and pathology size assessment lies predominantly with radiological or pathological interpretation.

Block-taking and pathological disease mapping is more difficult in mastectomy than in BCS specimens ⁷; this is indicated by an Altman Bland bias of 9.9mm in the primary mastectomy group. The substantial differences of Altman Bland bias in the different mastectomy (and BCS) subgroups is key to better understanding this problem. The disparity is particularly stark between the mastectomy subgroups for small and larger lesions and also failed BCS compared to the other BCS subgroups. If specimen handling methodology was an important factor in improving the agreement between the pathological and radiological assessment of disease extent then the more accurate block selection afforded by the application of specimen slice radiography should improve the Altman Bland bias. However, use of slice radiography does not appreciably improve the agreement between radiological-pathological DCIS size assessment, indicating pathological specimen-handling methodology is unlikely to account for the variation in size estimation.

The pre-operative multidisciplinary review meeting should recommend the most appropriate surgical procedure for each patient. These data indicate that in a proportion of women this decision was inappropriate, at least in retrospect. Since there were no appreciable differences in the case-mix in high, medium and low frequency hospital subgroups for these adverse outcomes it suggests that the multidisciplinary discussion could be more critical, with detailed appraisal of both the radiological analysis of calcification-morphology combined with pathological

analysis of calcification-type seen in the pre-operative core biopsy sample. Specifically, there is an opportunity to drill down on the detailed association of the calcification with the histology, for example regarding whether microcalcification is also present in adjacent benign lesions, and assessment as to how much DCIS is *not* calcified histologically. To minimise inappropriate mastectomy for small lesions the threshold for mapping the lesion extent with more than one biopsy should be considered where mastectomy is proposed based on radiological findings.

MRI is not routinely used for the pre-operative assessment of DCIS. While MRI is more accurate than mammography in high grade disease, beneficial effects on outcomes have not been demonstrated.^[11, 12] Further research is needed in this area to optimise techniques and define specific patient groups that may benefit.

Conclusion

We have identified two large groups of patients – those with failed BCS and those who underwent mastectomy for small foci of DCIS – together accounting for 15% of our 8313 patient cohort, where surgical management could be improved. There is a pressing need to improve the accuracy of assessment of DCIS extent, particularly for those women where mastectomy may otherwise be indicated. In such situations, increased utilisation of multiple biopsies to accurately determine disease extent should be considered. Similarly, detailed radiological – pathological correlation of the extent and nature of the microcalcifications should be ensured at multidisciplinary meetings. Our data provide an evidence-base for benchmarking future practice in this area, building from the best performing hospitals to raise standards.

Appendix 1

Members of the Sloane Project Steering Group

Surgery

Professor Alastair Thompson (Chair)
Mr Hugh Bishop (previous Chair) *
Mr Robert Carpenter *
Ms Adele Francis
Professor W D George *
Mr Martin Lee *
Mr Stewart Nicholson

Radiology

Dr Hilary Dobson
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Dr Anthony Maxwell
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Professor Sarah Pinder
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Molecular and Population Genetics

Professor Ian Tomlinson

Bioinformatics

Professor Graham Ball

Management

Mrs Karen Clements
Mrs Olive Kearins
Dr Gill Lawrence
Mrs Margot Wheaton

* Indicates former members of the steering group

Appendix 2

UK Breast Screening Units contributing to the Sloane Project

Avon	North Derbyshire
Barking, Havering, Redbridge & Brentwood	North East Scotland
Barnsley	North Lancs & South Cumbria
Beds and Herts	North London*
Bolton, Bury & Rochdale	North Nottinghamshire
Breast Test Wales – North	North Staffordshire
Breast Test Wales – South East	North Yorkshire
Breast Test Wales – South West	Northampton
Cambridge & Huntingdon	Nottingham
Central & East London	Oxfordshire
Chelmsford & Colchester	Pennine (Bradford)
Chester	Peterborough
City, Sandwell & Walsall	Portsmouth
Cornwall	Rotherham
Crewe	Sheffield
Doncaster	Shropshire
Dorset	Somerset
Dudley & Wolverhampton	South Birmingham
East Berkshire (Windsor)	South Derbyshire
East Cheshire & Stockport	South Devon
East Lancashire	South East London & Queen Mary's
East Scotland	South East Scotland
East Sussex, Brighton & Hove	South Essex
Gateshead	South Staffordshire
Gloucestershire	South West London (St George's)
Great Yarmouth & Waveney	South West Scotland
Greater Manchester	Southampton & Salisbury
Hereford & Worcester	Surrey (Jarvis)
Humberside	Warrington
Isle of Wight	Warwickshire, Solihull & Coventry
King's Lynn	West Berkshire
Leeds & Wakefield	West Devon & East Cornwall
Leicestershire	West Essex
Liverpool	West of London
Maidstone	West of Scotland
Medway (Gillingham, Kent)	West Suffolk
Milton Keynes	Western, Northern Ireland
Newcastle-Upon-Tyne	Wiltshire
Norfolk & Norwich	Wirral
North & Eastern Devon	Wycombe
North & Mid Hampshire	
North Cumbria	

* Unit data not included in these analyses

Appendix 3

Acknowledgements

The Project would not be possible without the dedication and hard work of a small team in the West Midlands Cancer Screening QA Reference Centre (operated by Public Health England) led by Dr Gill Lawrence, Olive Kearins and Karen Clements.

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Role of Funding Source

The various funding sources have had no influence on the conduct of this audit or its published outputs.

Appendix 3a

Author contributions

Jeremy Thomas	- Lead author; data analysis, literature search, writing
Andrew Hanby	- Co author, audit design, data interpretation, literature review, editing
Sarah Pinder	- Co author, audit design, data interpretation, literature review, editing
Graham Ball	- Review of statistical methods, manuscript review
Gill Lawrence	- Audit design, data supervision and review, quality assurance, manuscript review
Karen Clements	- Data management and supervision, manuscript review
Anthony Maxwell	- Audit design, radiology advice, manuscript editing and review
Matthew Wallis	- Audit design, radiology advice, manuscript review
Andrew Evans	- Audit design, radiology advice, manuscript review
Hilary Dobson	- Audit design, radiology advice, manuscript review
Alastair Thompson	- Project lead, audit design, manuscript review and editing

Appendix 3b

Conflicts of interest

No conflicts of interest have been declared by the authors

Appendix 4

Statistical Methods

The study has three separate elements:

1. Comparison of agreement between pathological and radiological measurement of DCIS extent in different operative subgroups
2. Analysis of variation of various parameters in different hospitals
3. Assessment of hospitals' different operation rates.

1. Comparison of agreement between pathological and radiological measurement of DCIS extent in different operative subgroups.

Agreement between pathology and radiology size estimations was assessed using Altman Bland difference plots (also known as a Tukey mean-difference plot), where the difference between the radiological and pathological size for any individual is plotted against the mean of the two values. The systematic bias in any group of paired measurements is the mean of all the differences - positive or negative.

We have compared two completely unrelated measurement techniques for assessing the extent of DCIS in our patients. Radiological and pathological measurements of DCIS extent are made independently – the former at the time of initial diagnosis on the basis of the extent of a radiological abnormality (normally calcification.) and the latter from the extent of disease as measured on histological tissue sections (glass slides) from the excised tissue. The Altman Bland analysis is particularly relevant to our study population as it allows an estimate of systematic bias in any particular subgroup and the identification of outliers. It is widely used as a method in the analysis of agreement between clinical measurements.

2. Analysis of variation of various parameters in different hospitals

We have restricted this analysis to the top quartile of the hospitals in the audit in terms of numbers of patients entered. This is because our median value (10) is very low and our distribution has a long tail. The top quartile has a range from 387 to 50 patients and within that quartile the distribution of patients is nearly normal. We have attached sample charts of our key data groups in a supplementary Excel file to illustrate this.

We should also state that the only meaningful analysis of variance is between one subgroup and the parent group (excluding that subgroup) because one subgroups will inevitably also vary in counter-step with another. For example, if a hospital does x conservation operations then, crudely, there will be two possible outcomes: successful or unsuccessful conservation, y or $x-y$. It is meaningful to compare the variance of one or other of those outcomes with the variance in the parent group among different hospitals. But if one subgroup is significantly different then so will be the other.

We have used a one tailed Anova test to compare the variance of a particular measurable among hospitals:

b) One-tailed ANOVA test

For the pair of data we examined (BCS parent group minus unsuccessful BCS cases v unsuccessful BCS cases) we confirmed homogeneity of variances using Hartleys F max test giving an F max value of 1.07. This is below the critical value (N=122, 2 groups, 1.15) at the 0.05 level of significance. There were significant differences in the variance of the two BCS subgroups (p=0.0001). We have supplied the descriptive analysis for the data underpinning tests including the residual plots.

The assumptions of ANOVA were met as follows:-

Independence of sample groups was achieved through the selection of groups. All cases were members of only one analysis group.

The data fits well with a normal distribution. Normality was assessed by examination of the residual plots from the variance model. This indicated that the probability of a non normal distribution was <0.0001 for successful and failed BCS.

It was not possible to carry out ANOVA analysis of the by-hospital mastectomy subgroups because the case numbers were too small.

3. Assessment of hospitals' different operation rates.

We have used Pearson's Test to quantify the relationship between a hospital's overall mastectomy rate and its rate of failed BCS and included the output for that analysis.

We have subdivided the top quartile (57 hospitals) into three frequency groups each of 19 hospitals for failed BCS and MFSL respectively. It should be noted that there was little overlap in the frequency subgroupings for the two adverse outcomes and therefore the numbers of patients in each subgroup for each outcome are inevitably different. A chi squared test was used to test significance between the frequencies for each subgroup in an outcome group. Each frequency subgroup comprised over 1800 patients.

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Legends

Tables

Table 1: Disease extent (pathological), radiological/pathological size agreement, DCIS grade, ER positivity and use of slice radiography relating to operation type.

Table 2: Distribution of different operation types by submitting hospital (top quartile). The percentages referred to in the ranges refer to breast conservation and mastectomy totals respectively, e.g mastectomy for lesions <20mm accounted for 3-60% of all mastectomies in the different hospitals.

Table 3: Data analysis for high, middle and low frequency hospitals as ranked for failed BCS and mastectomy for small tumours respectively.

Figures

Figure 1. Accrual profile for patients registered in the audit between 2003 and 2012.

Figure 2. Altman Bland plot for mastectomy patients following failed breast conservation surgery.

Figure 3. Altman Bland plot for mastectomy patients with lesions < 20mm.

Table 1

	BCS 1 Op	BCS 2 Ops	BCS followed by Mastectomy	Primary Mastectomy	Mastectomy
Number ^a	3946	1435	799	1680	
Median pathology size (mm)	12	17	40	35	
95% CI (mm)	12-12	16-18	36-40	32-37	
Inter Quartile Range (mm)	13.0	15.00	30.00	30.00	
Altman Bland Bias (mm) ^b	2.95 (2.90)	-0.32 (0.01)	-13.49 (-11.43)	9.9 (9.82)	-2
% High grade DCIS	58.5	59.3	70.2	77.5	
% ER Positive	83.2	79.9	72.8	69.1	
Slice radiography (%)	21.0	20.3	21.5	15.1	

BCS 1 Op – Successful breast conserving surgery by one surgical operation; BCS 2 Ops - Successful breast conserving surgery by two surgical operations; Primary mastectomy

^a excludes therapeutic mammoplasty - 47 patients; diagnostic biopsy - 349 patients; successful BCS after more than two operations - 57 patients

^b data in brackets refer to specimens with slice radiography

Table 1: Disease extent (pathological), radiological/pathological size agreement, DCIS grade, ER positivity and use of slice radiography relating to operation type.

Table 2

	BCS 1 Op	BCS 2 Ops	BCS followed by Mastectomy	Primary Mastectomy	Mast tumor
Number of Hospitals	57	57	57	57	
Range of Cases per Hospital	14-201	4-72	2-38	3-89	
Percentage of all (BCS or mastectomy) (median)	65	22	12	63	
Range (% of all BCS or Mastectomy)	37-85	9-32	3-32	33-96	4
95% CI	60-68	19-25	11-13	32-37	
Inter Quartile Range	14	12	7	23	
Mean (% of all BCS or Mastectomy)	64.4	22.5	12.4	62.5	
Standard Deviation	10.1	7.9	5.9	15.1	

BCS 1 Op – Successful breast conserving surgery by one surgical operation; BCS 2 Ops - Successful breast conserving surgery by two surgical operations; Primary mastectomy

Table 2: Distribution of different operation types by submitting hospital (top quartile). The percentages referred to in the ranges refer to breast conservation and mastectomy totals respectively, e.g mastectomy for lesions <20mm accounted for 3-60% of all mastectomies in the different hospitals.

Table 3

	Ranked for Frequency of Failed BCS			
	Frequency Group	High	Medium	Low
No. of Hospitals		19	19	19
Total Patients (BCS and Mastectomy)		1856	2539	229
No. of patients with failed BCS/MFSL		272	237	123
Total no. of BCS Cases/Mastectomies		1220	1764	176
Mean Frequency of failed BCS/MFSL (%)		22.3	13.4	7.0
Frequency Range (%)		13.2 - 31.6	10.0 - 13.1	2.6 -
Median Age of Patient		59	60	60
Median Spec Weight (gms)		42.1	40	35
Central Lesion (%) (all cases in group)		6.6	6.4	6.4
Central lesion (%) Mx <20mm		-	-	-
Central lesion (%) Mx ≥20mm		-	-	-
Median Pathology Size (mm) - all cases		17	16.15	16
Median Maximum Radiology Size - all cases		18	19	18
High Grade DCIS (%)		62.9	59.6	64.
ER positive (%)		82	69	80
Comedo Necrosis (%)		62.1	68.5	70.
Solid Pattern (%)		58	56	64
Cribriform Pattern (%)		29	33	26
Micropapillary Pattern (%)		8	5	5
Altman Bland Bias (mm):				
Successful BCS 1 Operation		2.75	2.73	3.0
Successful BCS 2 Operations		-1.24	1.09	-0.9
Failed BCS		-10.64	-15.42	-13.
Primary Mastectomy		6.6	8.47	11.
Mastectomy lesion ≥20mm		-6.65	-3.99	2.1
Mastectomy lesion <20mm (MFSL)		17.44	20.14	23.

BCS 1 Op – Successful breast conserving surgery by one surgical operation; BCS 2 Ops - Successful breast conserving surgery by two surgical operations; Primary mastectomy

Table 3: Data analysis for high, middle and low frequency hospitals as ranked for failed BCS and mastectomy for small tumours respectively.

Figure 1

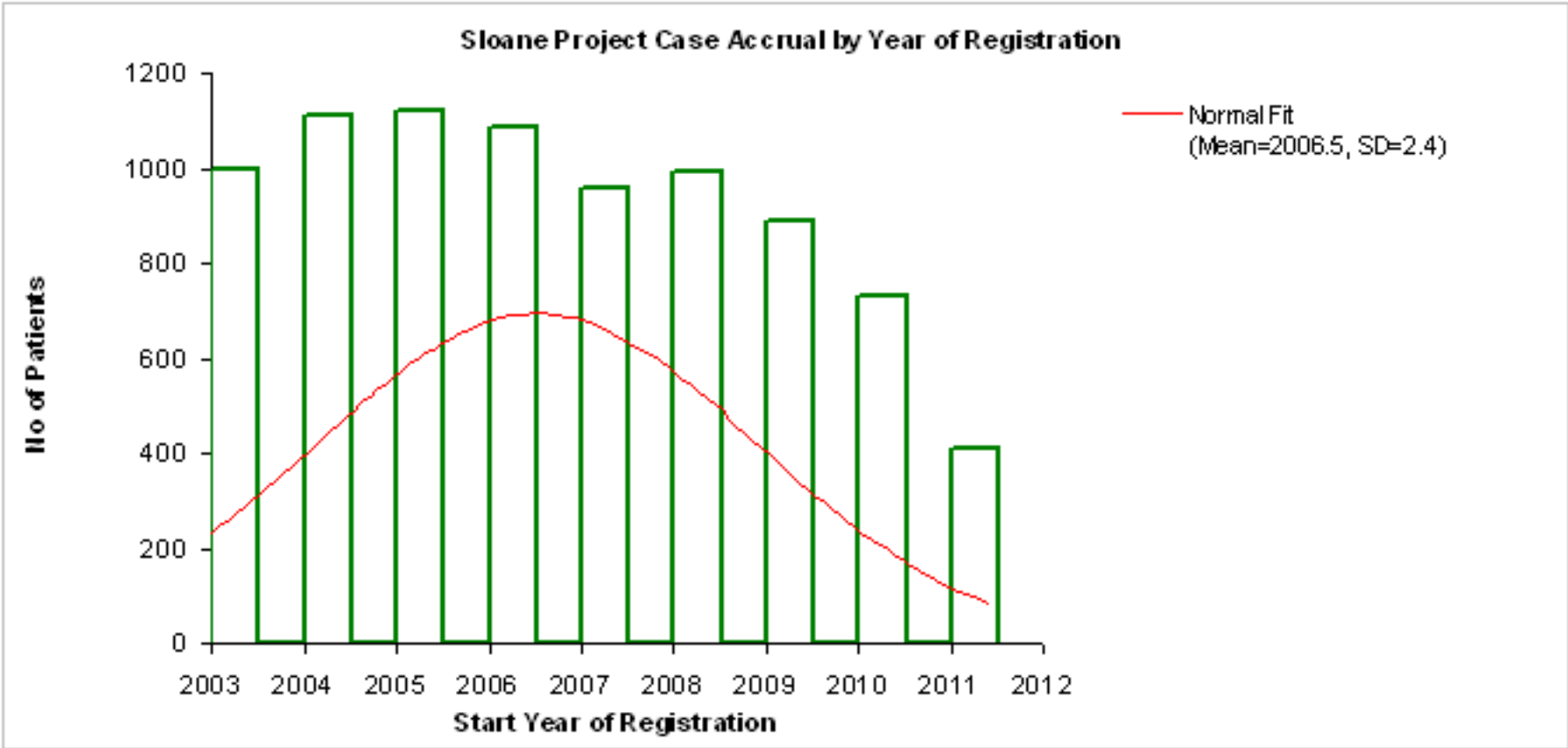


Figure 2

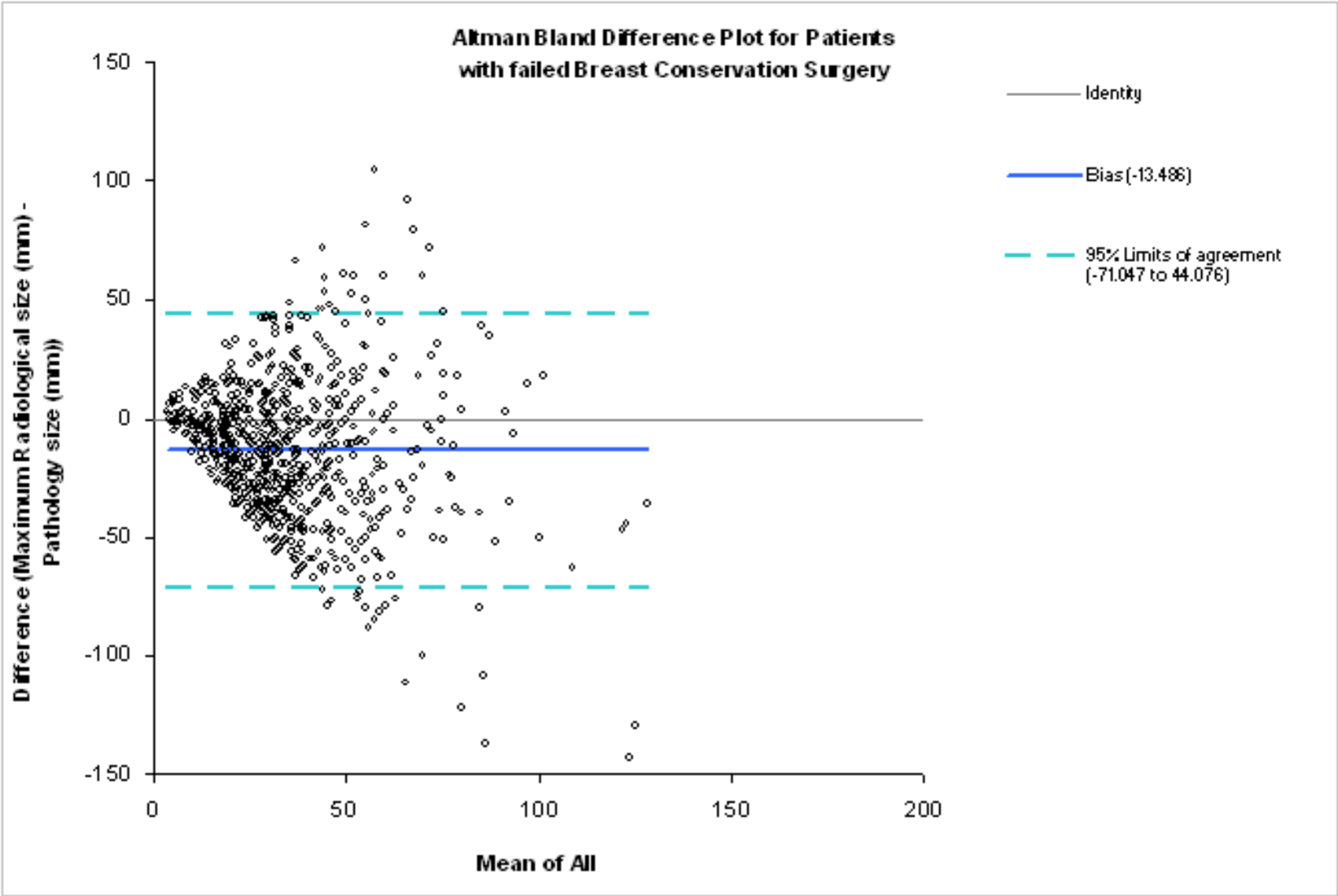
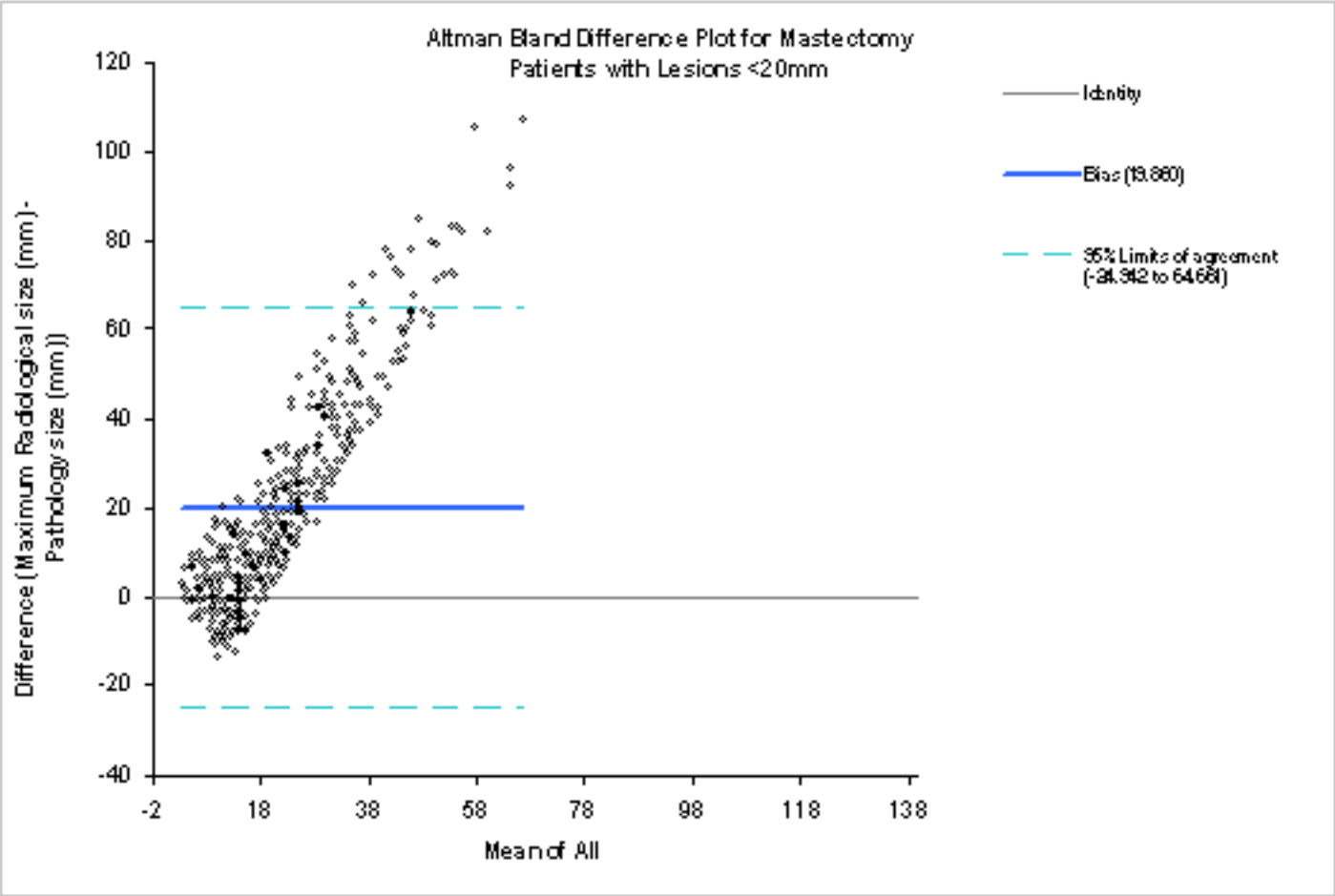


Figure 3



Conflicts of Interest

Adverse surgical outcomes in screen-detected ductal carcinoma *in situ* of the breast.

The authors listed below have declared no conflicts of interest relating to this study.

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SUPPLEMENTARY RESULTS

Case distribution:

7537/8313 (84.4%) cases were of pure DCIS; 776 (8.7%) DCIS combined with atypical ductal hyperplasia (ADH) and/or lobular in situ neoplasia (LISN); The distribution of cases by operation type (mastectomy or BCS) is shown in **Supplementary Table 1**.

Demographics, operation type and tumour grade

218 (2.6%) of patients were under 50 years of age; 5866 (70.7%) were 50-64 years; 1827 (22.0%) were 65-70 years; and 381 were (4.6%) aged over 70 years and 21 patients (0.25%) of unknown age. There was no difference in the frequency of operation types between the different age groups.

The overall grade distribution (8313 cases) was: high grade 62.0%, intermediate grade 28.5% and low grade 9.2%, with 0.2% of cases ungraded. Although the under 50 years age group (a group not screened routinely in the UK NHS BSP) showed less high grade disease (55%) in comparison to the 50-64 years age group (63%) this difference was not significant (Chi squared test; $p=0.25$).

Margins

Of the patients who had only one operation for BCS 351 (9%) and 137 (3%) had a final radial margin of <2mm and <1mm respectively. The median minimum final radial margin was 5mm (IQR 6mm).

Morphological pattern/architecture: frequency, extent, grade and comedo necrosis

The architectural pattern was recorded in over 7846 cases. A single growth pattern of DCIS was reported in 4532 (57%) of cases and two patterns in 2800 cases (36%). The most commonly reported descriptions were solid or cribriform and these accounted for 88% of single-pattern disease. The distribution of architectural pattern vs grade, comedo necrosis and disease extent in addition to ER status and Altman Bland bias is shown in **Supplementary Table 2**. The analysis has been restricted to the 4532 cases where a single pattern of DCIS was reported.

Cribriform disease was significantly larger than either solid or micropapillary DCIS (T test, $p < 0.0001$). No difference was seen between the size of solid and micropapillary DCIS (T test, $p = 0.19$). Only 310 cases showed a pure micropapillary pattern.

There were substantial differences in the percentages of the two more common patterns of DCIS (solid and cribriform), grade, comedo necrosis and ER positivity among the top quartile of treatment hospitals. There was no correlation between grade, comedo necrosis or histological pattern and a hospital's operative profile.

Extent of DCIS: Grade and ER status

There was a significant difference in the grade distribution between smaller lesions $\leq 15\text{mm}$ and larger lesions (T test; $p < 0.0001$); there was 50% more high grade disease in more extensive lesions. However, there was no significant difference in the grade distribution between 15-40mm and $>40\text{mm}$ DCIS.

4579 (55%) of cases had recorded ER status and 78.8% of these ($n=3581$) cases were ER positive. ER negative disease was significantly more extensive than ER positive disease in the high grade subgroup only (median 23.0mm vs 20.0mm; IQRs 22.0 vs 23.0) (T test, $p < 0.0001$).

SUPPLEMENTARY DISCUSSION

Pathological variables

A pure architectural pattern of DCIS was recorded in over half of our patients. Three main points emerge: solid pattern DCIS is very commonly high grade and associated with comedo necrosis, while cribriform DCIS is more commonly a smaller lesion and more frequently low grade. Notably, and in contrast to a previous report, we have no evidence that micropapillary DCIS is a particularly extensive or multicentric lesion. ^[1]

Invasive breast cancer is graded by assessing three variables and consistency of grading is considered acceptable with published kappa values for overall consistency (j value) for grade 1 and grade 3 of 0.45 and 0.63, respectively. ^[2, 3] Consistency of

grading and classifying DCIS where a single feature (cytonuclear morphology) is used is poor in comparison (Schuh et al.).^[4] Although comedo necrosis has been shown to be of prognostic significance^[5] this feature is not routinely combined with the single-feature cytonuclear grade to improve discrimination in UK practice and although assessment of the pattern of DCIS has been shown to add value to this exercise, mixed patterns are seen frequently and therefore is difficult to apply in practice.^[6] A major goal of the Sloane Project is to improve prognostic assessment of DCIS and reviewing prognostic algorithms such as the Van Nuys Prognostic Index^[7] will be possible as more complete recurrence data become available. Data on margin width will be of considerable interest at that time too.

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Supplementary Legends

Supplementary Table 1: Disease types in mastectomies and breast conservation cases.

Supplementary Table 2: Frequency of pathological variables by architectural pattern of DCIS

Supplementary Table 1

	ALL	%	Mastectomy ^a	%	BCS ^b	%
Pure DCIS	7537	90.7	2282	92.1	5255	90.1
DCIS + ADH	323	3.9	16	0.6	307	5.3
DCIS + LISN	304	3.7	84	3.4	220	3.8
DCIS + ADH + LISN	149	1.8	97	3.9	52	0.9
Total	8313	100	2479	100	5834	100

^a Includes 799 failed
BCS Patients

^b Excludes 799 failed
BCS Patients

Supplementary Table 1: Disease types in mastectomies and breast conservation cases.

Supplementary Table 2

	No	Frequency (%)	Size (median - mm)/ 95%CI	Grade (No /(%)				Comedo Necrosis No (%)	ER Pos No (%)	Altman Bland Bias
				Low	Intermediate	High	Ungraded			
Solid	2573	57	16 / (16-17)	62 (2)	454 (18)	1985 (77)	71 (3)	2040/2487 (82)	963/1396 (68)	3.68
Cribriform	1398	31	10.5 / (10.0-11.0)	294 (22)	562 (42)	488 (36)	54 (4)	692/1304 (53)	678/775 (87)	4.99
Micropapillary	310	7	17 / (15-20)	68 (22)	74 (24)	125 (40)	43 (14)	169/281 (60)	118/145 (81)	4.96
Others	251	6								
Total	4532									

Supplementary Table 2: Frequency of pathological variables by architectural pattern of DCIS