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Justifies the use of RadioTx in HG DCIS (HR1.5) to prevent recurrence, especially if young

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Original Research

Management and 5-year outcomes in 9938 women with screen-detected ductal carcinoma in situ: the UK Sloane Project

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GOOD:
10k patients with DCIS
Prospective audit
Standardised pathology and radiology 78 of the 95 UK units participated
Good rate of complete data sets

So one of the largest datasets of DCIS
Authors acknowledge limitations
Justified need for LORIS/LORD

LIMITATIONS:
AUDIT and so prospective and standardised high quality cohort BUT still will be confounders.
Also only 5yrs - they do update this though
Doesn't show margins data in main nor supplementary but states association.

MAIN FINDINGS:
RadioTx reduced ipsilateral risk of INVASIVE recurrence significantly 3.8% to 1.9% HR 0.51 i.e. halves. BUT not of DCIS recurrence.
Endocrine for any breast event by HR 0.56 on multivariate.
High Grade (HR 1.5)
and Comedo necrosis (HR 1.3) carry significantly higher rates of recurrence.
Margin <2mm associated with recurrence.
BUT TAKE-HOME is that that overall survival is excellent - breast cancer mortality of just 0.5%. While RadioTx and Endocrine both reduce recurrence they do not confer OS benefit.

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KEYWORDS
Ductal carcinoma in situ;
Radiotherapy;
Margins;
Recurrence

Abstract ***Background:*** Management of screen-detected ductal carcinoma in situ (DCIS) remains controversial.
Methods: A prospective cohort of patients with DCIS diagnosed through the UK National Health Service Breast Screening Programme (1st April 2003 to 31st March 2012) was linked to national databases and case note review to analyse patterns of care, recurrence and mortality.
Results: Screen-detected DCIS in 9938 women, with mean age of 60 years (range 46–87), was treated by mastectomy (2931) or breast conserving surgery (BCS) (7007; 70%). At 64 months median follow-up, 697 (6.8%) had further DCIS or invasive breast cancer after BCS (7.8%) or mastectomy (4.5%) ($p < 0.001$). Breast radiotherapy (RT) after BCS (4363/7007; 62.3%) was associated with a 3.1% absolute reduction in ipsilateral recurrent DCIS or invasive breast cancer (no RT: 7.2% versus RT: 4.1% [$p < 0.001$]) and a 1.9% absolute reduction for ipsilateral invasive breast recurrence (no RT: 3.8% versus RT: 1.9% [$p < 0.001$]), independent of the excision margin width or size of DCIS. Women without RT after BCS had more ipsilateral breast recurrences ($p < 0.001$) when the radial excision margin was <2 mm. Adjuvant endocrine therapy (1208/9938; 12%) was associated with a reduction in any ipsilateral recurrence, whether RT was received (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.41–0.80) or not (HR 0.68; 95% CI 0.51–0.91) after BCS. Women who developed invasive breast recurrence had a worse survival than those with recurrent DCIS ($p < 0.001$). Among 321 (3.2%) who died, only 46 deaths were attributed to invasive breast cancer.
Conclusion: Recurrent DCIS or invasive cancer is uncommon after screen-detected DCIS. Both RT and endocrine therapy were associated with a reduction in further events but not with breast cancer mortality within 5 years of diagnosis. Further research to identify biomarkers of recurrence risk, particularly as invasive disease, is indicated.

1. Introduction

Although described more than 80 years ago [1] ductal carcinoma in situ (DCIS) became a common management problem after the introduction of breast screening and now comprises 20–25% of screen-detected breast cancer. Similar to invasive breast cancer, DCIS is heterogeneous in terms of underlying biology, presentation and outcome [2]. The clinical behaviour of DCIS is unpredictable, challenging clinical decision-making. Recently, concern regarding the overtreatment of DCIS [2] has been fuelled by large retrospective American series demonstrating excellent (>95%) long-term survival 10–20 years after diagnosis although others have suggested that detection and treatment of screen-detected DCIS may prevent subsequent invasive disease [3–5].

Standard treatment for DCIS includes mastectomy or breast-conserving surgery (BCS), with or without radiotherapy (RT) and/or endocrine therapy to decrease ipsilateral recurrence and/or contralateral breast carcinoma [6–8]. It remains unclear which patients benefit from these adjuvant therapies. Prospective data are lacking, and the clinical significance of early detection and treatment for DCIS remains unclear. Here, we report the first analysis of recurrence and mortality from a prospective cohort study of DCIS detected through a contemporary national screening programme. Using diagnostic imaging, surgery, histopathology and adjuvant therapy data provided by the local breast screening unit where diagnosis was reached, along with longitudinal follow-up of patients through case note review and linkage to national databases, we describe the features and outcomes after diagnosis of screen-detected DCIS.

2. Methods

The United Kingdom National Health Service (NHS) Breast Screening Programme (NHSBSP) invites women aged 50–70 years to attend breast screening every 3 years (Supplementary Figure and text p2). The Sloane Project was established in memory of Professor John Sloane, a breast pathologist, to audit the features, patterns of care and outcomes for women with non-invasive neoplasia detected within the NHSBSP. Data capture was via radiology, pathology, surgery and radiotherapy (RT) paper proformas collected at screening unit level, sent to Public Health England, then each patient's data entered on a secure database held on an SQL server that generated an individual patient and tumour identifier. The data reported here are for women in the dataset who had DCIS identified. For the 34 women with bilateral DCIS, the higher grade and/or larger lesion was considered the index.

Data included demographic, diagnostic, treatment and vital status. Adherence to NHSBSP guidelines and participation in the relevant quality assurance

K sample test is non-prarmetric. Curve with culmulative risk of the event over time then vectors = shape of curve and compare those vectors - are they significantly different?

Standardised pathology/radiology reporting

programmes were mandatory. Participating units were required to follow a pathology protocol containing definitions for DCIS, microinvasion, cytonuclear grade, comedo necrosis and assessment of excision margins and to handle and report specimens to NHSBSP pathology standards [9]. Radiology guidelines mandated that participating radiologists should complete detailed radiology proformas [10] and participate in the NHSBSP PERFORMS external quality assurance scheme [11].

Very acceptable level of missing data

Missing (unknown) data were rare for key comparisons including the use of radiotherapy (0.5%), grade of DCIS (0.1%), lesion size (0.4%) or cause of death (0.1%). Events were identified by matching women by NHS number and date of birth to information provided by breast screening units and to routinely collected UK data sets including Hospital Episode Statistics, Cancer Waiting Times, the English Cancer Analysis System/ National Cancer Registration and Analysis Service, the English National Radiotherapy Dataset and the Information Services Division, Scotland. The census date was the date of death or 31st December 2012. Validation of data was undertaken by cross-checking with original screening unit source documents for those patients with recurrence and more generally, for the overall dataset, against the Association of Breast Surgery national audits 2006–2012.

Ethics Committee approval was not required for this prospective cohort study originally conducted under the NHS Cancer Screening Programme's application to the Patient Information Advisory Group. More recently, access to patient data was approved to quality assure national cancer screening programmes under the Health and Social Care Act 2006 (Section 251) via the Confidentiality Advisory Group.

2.1. Classification of recurrence and mortality

Given the difficulties in distinguishing local recurrence from a new primary lesion in the same breast, the following terminology was used (see Supplementary Figure and text p 2–3). A 'breast event' was defined as (any of) ipsilateral breast recurrence (or new primary) after BCS; ipsilateral recurrence (includes post-mastectomy/chest wall recurrence); regional or distant recurrence or contralateral re/occurrence. (See Supplementary Figure and text, [p3–4] for definitions of mortality).

2.2. Statistical analyses

Logistic linear regression analysis was used to test the relationship between a binary variable and continuous or ordered categorical dependent variables. The importance of factors was determined by likelihood ratio tests that compared the full model and a reduced model with one factor removed at a time. A factor with a lower p-value from the likelihood ratio test was deemed to be more important than the one with a higher p-value.

For disease recurrence, cumulative incidence plots were produced, taking account of the competing risks between recurrence and death. K-sample tests were performed to compare the groups in the cumulative incidence plots. For overall and breast cancer–specific survival, Kaplan–Meier survival plots were produced; log-rank tests were used to test the difference between survival curves. All time to event analyses were performed using the Cox semi-parametric proportional hazard regression. Tied times were adjusted using the Breslow's method. The proportional hazard assumption was assessed by Schoenfeld residuals test. For most analyses, the proportional hazard assumption is valid. Analyses were performed in R. Considering the high number of variables and groups within the variables, probability values lower than one in a hundred (0.01) were used to assign statistical significance.

3. Results

3.1. Patterns of care

From 12,788 patients (12,838 non-invasive lesions) diagnosed from 1st April 2003 to 31st March 2012, complete data were available for 9938 women (age range 46–87, mean age 60) diagnosed with DCIS (with or without lobular carcinoma in situ and/or atypical ductal hyperplasia) (Fig. 1). Seventy-eight breast screening units in England and Scotland contributed data (82% of the 95 units). Median follow-up was 64 months (range 6–116 months). Over the same decade in the UK, 30,187 women were diagnosed with non-invasive and microinvasive breast cancers through the NHSBSP; thus, the data analysed represent 77% (9938/12,838) of non-invasive lesions within this prospective cohort and 33% (9938/30,187) of women with a final diagnosis of in situ breast carcinoma diagnosed through the NHSBSP.

Good external validity for the method

3.2. Surgical treatment

BCS was the definitive surgery in 7007 (70%) women and was used more often with increasing age up to 59 years and thereafter appeared constant. Mastectomy was the definitive surgery for 2931 (30%) women. The use of mastectomy was associated with DCIS of high or intermediate rather than low grade ($p < 0.001$) and with larger lesion size ($p < 0.001$). The use of BCS versus mastectomy was unchanged over time.

3.3. Radiotherapy

For 7007 women who had BCS, 62% also had RT; the use of RT increased over time ($p < 0.001$). Women aged 70 years or older were less likely to have RT than women aged 50–70 years ($p = 0.006$). The use of RT

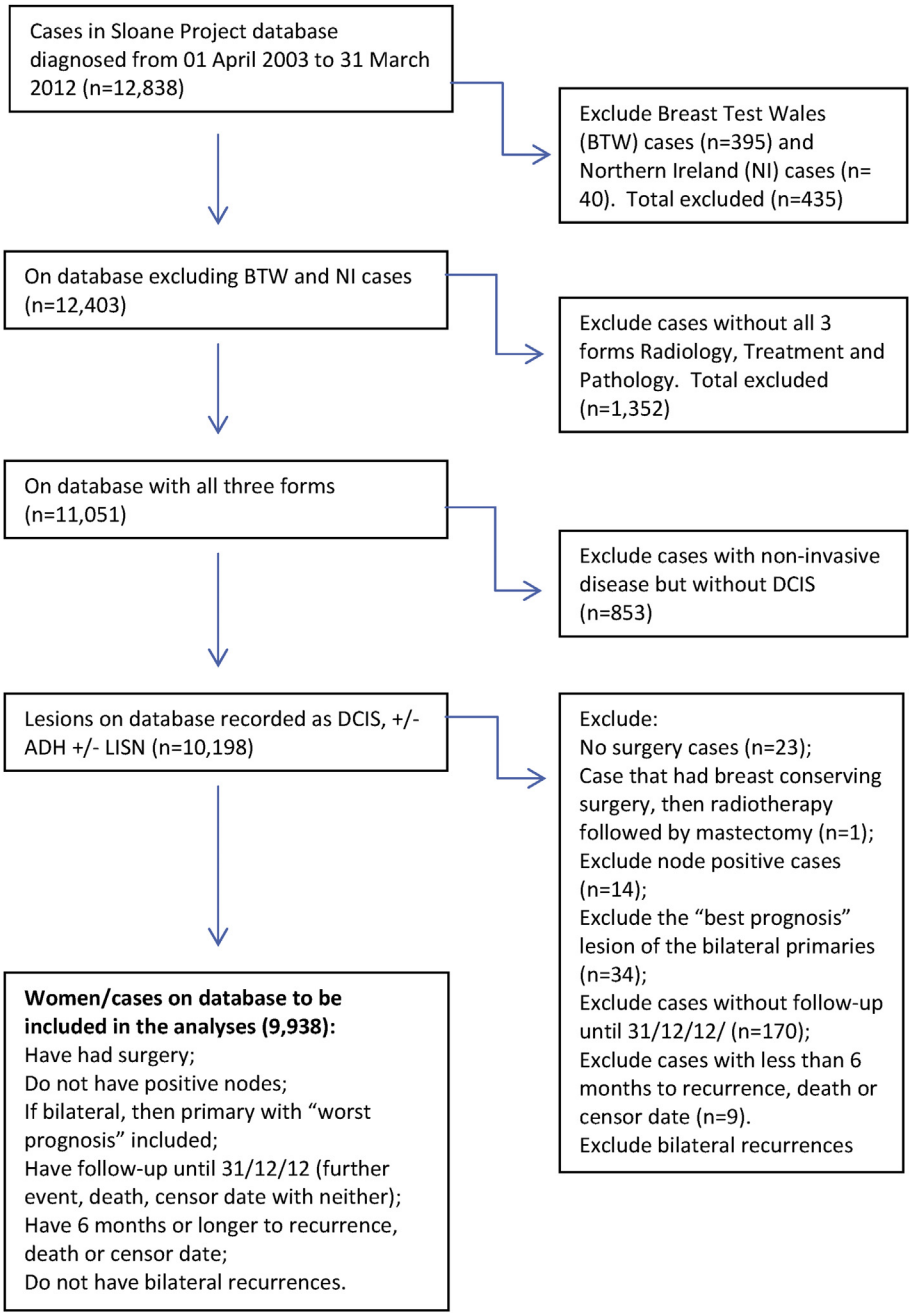


Fig. 1. 9938 UK patients with screen-detected DCIS (2003–2012). LISN, lobular in situ neoplasia; ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ.

after BCS increased with the grade of DCIS ($p < 0.001$), DCIS size ($p < 0.001$), the presence of microinvasion ($p < 0.001$) and comedo necrosis ($p < 0.001$), but not with margin width (Table 1), confirmed by multivariable analysis (result not shown). RT was performed after mastectomy in 33 (1%) women, as previously reported [12].

3.4. Endocrine therapy

Endocrine therapy was prescribed to more women after BCS (14%) than mastectomy (8%) ($p < 0.001$). The use of endocrine therapy was not related to age and it was prescribed less frequently over time ($p < 0.001$). There was no relationship between the receipt of endocrine therapy and RT after BCS.

3.5. Outcomes

At a median follow-up of 64 months, 6.8% of women (679/9938) had a breast (DCIS or invasive) event: 451 (4.5%) were ipsilateral breast, regional or distant recurrences and 228 (2.3%) represented a re/occurrence in the contralateral breast/nodes. Ipsilateral breast

Table 1
Radiotherapy (RT) use and pathological features after breast conserving surgery (BCS).

Pathological feature	No RT (% all cases)	RT (% all cases)	All cases (% with each feature type)
Total number of cases	5497 (55.3)	4396 (44.2)	9938 (100.0)
Number of BCS cases	2616 (37.3)	4363 (62.3)	7007 (70.5)
Number of Mx cases	2881 (98.3)	33 (1.1)	2931 (29.5)
Cytonuclear grade			
High	770 (19.2)	3240 (80.6)	4020 (57.4)
Intermediate	1223 (54.9)	993 (44.6)	2227 (31.8)
Low	616 (82.1)	127 (16.9)	750 (10.7)
Unknown	7 (70.0)	3 (30.0)	10 (0.1)
Tumour size (mm)			
<10	1403 (58.0)	1002 (41.44)	2418 (34.5)
10–<20	808 (33.2)	1619 (66.5)	2434 (34.7)
20–<30	247 (19.4)	1022 (80.2)	1274 (18.2)
30–<40	85 (16.7)	423 (82.9)	510 (7.3)
40–<50	33 (15.8)	176 (84.2)	209 (3.0)
50+	26 (19.0)	110 (80.3)	137 (2.0)
Unknown	14 (56.0)	11 (44.0)	25 (0.4)
Microinvasion			
Yes	70 (19.0)	298 (81.0)	368 (5.3)
No	2519 (38.4)	4020 (61.2)	6566 (93.7)
Unknown	27 (37.0)	45 (61.6)	73 (1.0)
Comedo necrosis			
Yes	1006 (24.3)	3116 (75.3)	4137 (59.0)
No	1431 (59.2)	975 (40.4)	2416 (34.5)
Unknown	179 (39.4)	272 (59.9)	454 (6.5)
Radial margin (mm)			
0	72 (34.6)	132 (63.5)	208 (3.0)
>0 to <1	72 (35.5)	129 (63.6)	203 (2.9)
1–<2	183 (35.0)	337 (64.4)	523 (7.5)
2–<5	480 (34.5)	907 (65.2)	1391 (19.9)
5–<10	642 (35.2)	1176 (64.5)	1823 (26.0)
10+	1055 (41.4)	1486 (58.3)	2547 (36.4)
Unknown	112 (35.9)	196 (62.8)	312 (4.5)

Mx, Mastectomy.

recurrence after BCS was 5.3% (368/7007); ipsilateral chest wall recurrence after mastectomy was 0.8% (24/2931). The risk of a further breast event did not differ by the year of screening.

3.6. Recurrence after BCS

After BCS, there was a greater risk of ipsilateral breast recurrence for those who did not have RT than those who had RT ($p < 0.001$, hazard ratio [HR] = 0.59; 95% confidence interval [CI] 0.53–0.67) (no RT: 7.2% versus RT: 4.1%) (Fig. 2). There was a significantly lower risk of invasive ipsilateral breast recurrence (no RT: 3.8% versus RT: 1.9%) ($p < 0.001$, HR = 0.51; 95% CI 0.43–0.60) but not ipsilateral DCIS recurrence (no RT: 3.3% versus RT: 2.2%) ($p = 0.05$, HR = 0.69; 95% CI = 0.58–0.82.) in women who received RT.

After BCS, the risk of developing ipsilateral breast recurrence was greater in patients with a negative or close DCIS margin (0 to <2 mm: 7.4% versus ≥2 mm: 4.8%; $p < 0.001$, HR = 0.67; 95% CI 0.57–0.78) ($p < 0.001$) whether patients received RT ($p = 0.011$, HR = 0.75; 95% CI 0.60–0.94) or not ($p < 0.001$, HR = 0.59; 95% CI 0.47–0.73).

RT and endocrine therapy were independently associated with a decreased risk of ipsilateral breast recurrence (RT: $p < 0.001$, HR = 0.59; 95% CI 0.52–0.66; endocrine therapy: $p = 0.003$, HR = 0.7; 95% CI 0.55–0.89; interaction: $p = 0.20$).

3.7. Multivariable analyses for recurrence

By multivariable analyses, after BCS, the use of RT (HR 0.38; 95% CI 0.33–0.45) and endocrine therapy (HR 0.63; 95% CI 0.50–0.78) were each independently associated with a significantly reduced risk of breast events and ipsilateral breast recurrence (RT: HR 0.40; 95% CI 0.34–0.48) (endocrine therapy: HR 0.56; 95% CI 0.44–0.72).

After adjusting for all other factors, the presence of high grade of DCIS and comedo necrosis were significantly associated with a higher risk of breast events (excluding contralateral occurrence) (high grade of DCIS: HR 1.50; 95% CI 1.14–1.98; comedo necrosis: HR 1.31; 95% CI 1.09–1.57) and of ipsilateral breast recurrence (high grade of DCIS: HR 1.40; 95% CI 1.05–1.87; comedo necrosis: HR 1.30; 95% CI 1.07–1.57).

3.8. Contralateral disease

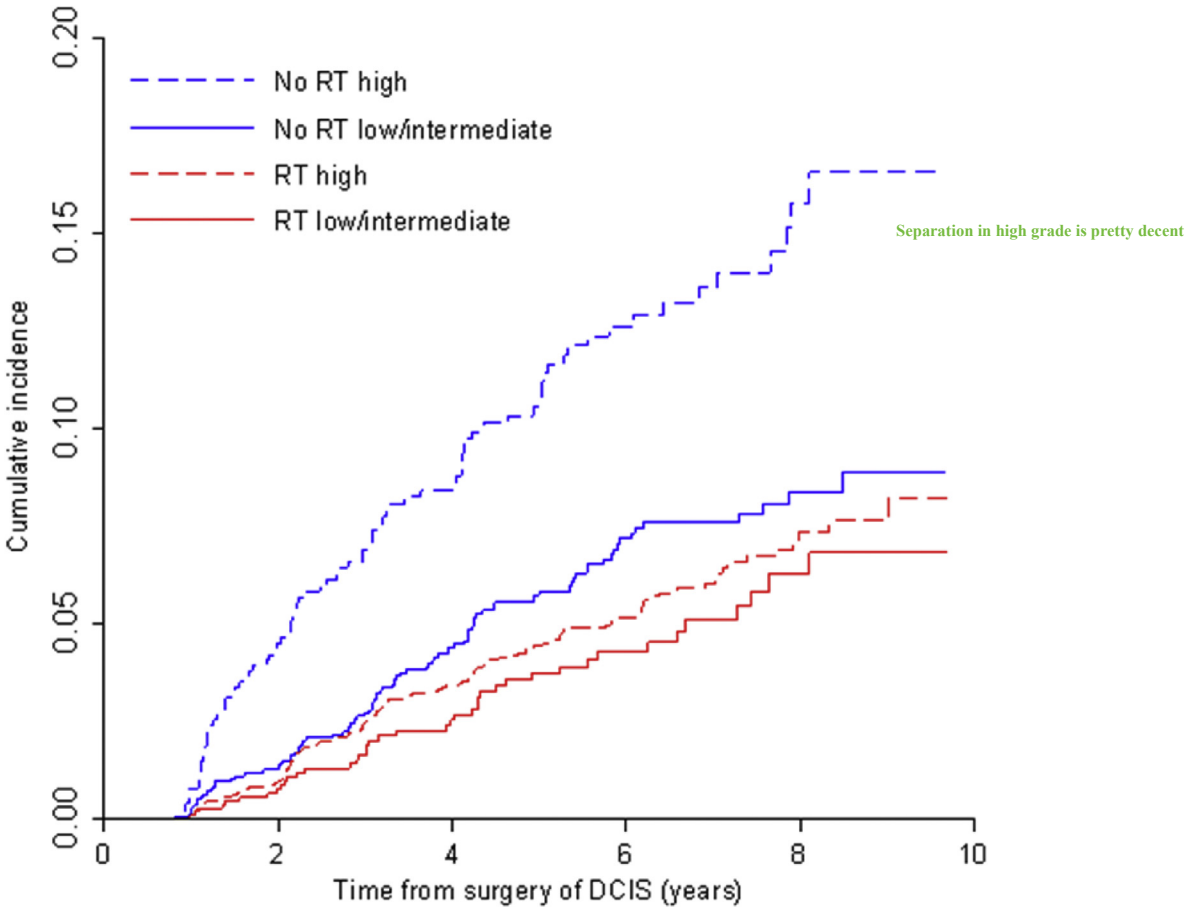
Contralateral breast cancer was seen in 218 women (2.2%) more commonly after mastectomy (81/2931; 2.8%) than after BCS (137/7007; 1.9%) ($p < 0.001$).

3.9. Survival

Among the 9938 women, there were 321 deaths (3.2%), 46 attributed to breast cancer. There was no difference in overall (or breast cancer related) mortality comparing BCS (3.1% [218/7007]) with mastectomy (3.5% [103/2931]).

Women treated with RT after BCS had a lower all-cause mortality (RT: 2.5% versus no RT: 4.2%; $p < 0.001$), even when corrected for age ($p < 0.001$, HR = 0.65; 95% CI 0.49–0.85), but not a lower breast cancer mortality ($p = 0.41$, HR = 0.73; 95% CI 0.34–1.56) The use of endocrine therapy was not associated with overall or breast cancer–specific mortality.

Women who developed an invasive breast cancer recurrence had a significantly worse overall survival (log-rank p-value <0.001) and breast cancer–specific survival (log-rank p-value<0.001) from the time of the further event compared with those who developed recurrent DCIS (Fig. 3) (Supplementary Fig. 1).



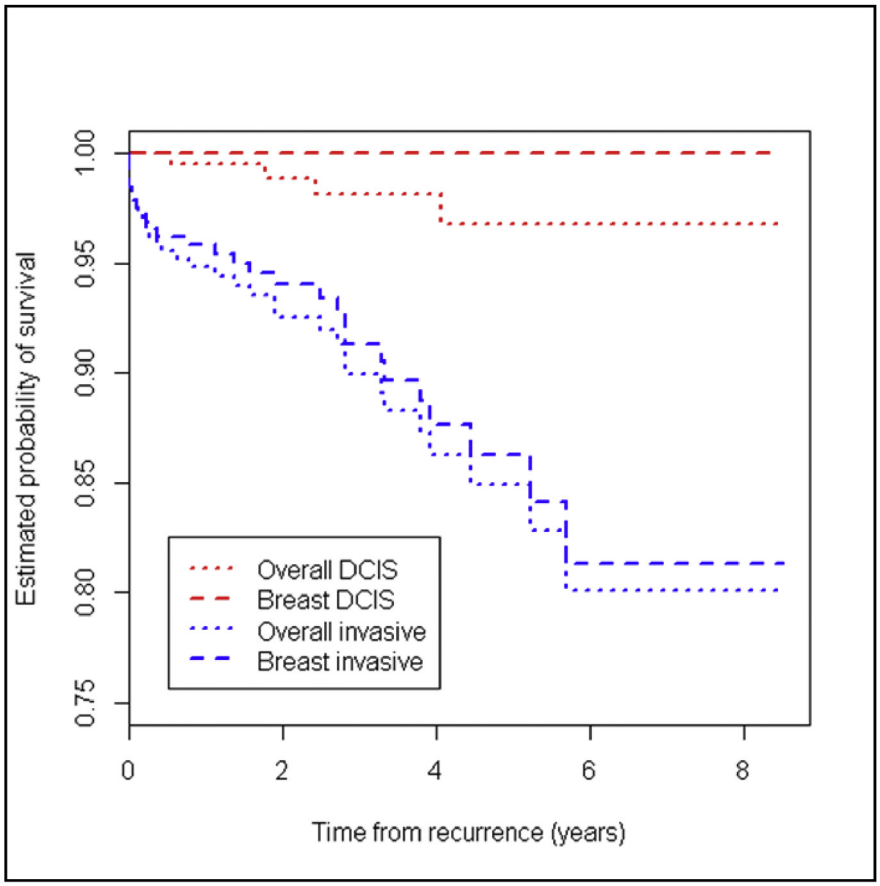
	Time from surgery of DCIS				
	0	2	4	6	8
Number at risk					
RT low/int	1120	969	688	441	180
RT high	3240	2763	1898	1098	420
No RT low/int	1839	1587	1138	684	275
No RT high	770	665	492	308	119
Cumulative censoring					
RT low/int	0	133	380	602	850
RT high	0	424	1172	1904	2553
No RT low/int	0	199	569	965	1356
No RT high	0	54	185	336	508

Fig. 2. Radiotherapy (RT), DCIS grade and ipsilateral breast events. DCIS, ducal carcinoma in situ.

4. Discussion

This study of 9938 women with DCIS detected through the UK NHSBSP confirms that recurrent DCIS or invasive cancer remain a concern after modern management of screen-detected DCIS. Both RT and endocrine therapy were associated with a reduction in further events but not with breast cancer mortality within 5 years of diagnosis. The present prospective cohort study contrasts with recent but retrospective studies of US [3,4] and European data [13]. Unlike those series, we report prospectively collected data from the setting of an established national breast screening programme, with built-in quality assurance of imaging, surgery, pathology and RT [11,14]. An additional major strength, in contrast to other studies including the randomised clinical trials, is the prospective collection of margin status, an area of significant international controversy. In addition, available data include the use of endocrine therapy with linkage to outcomes [3,4].

Take home is that either way survival is very good.



	Time from recurrence				
	0	2	4	6	8
Number at risk					
Overall DCIS	226	149	73	27	3
Overall Invasive	322	179	78	23	2
Breast DCIS	226	149	73	27	3
Breast Invasive	322	179	78	23	2
Cumulative censoring					
Overall DCIS	0	75	150	195	219
Overall Invasive	0	122	215	267	288
Breast DCIS	0	77	153	199	223
Breast Invasive	0	126	219	271	292

Fig. 3. Survival from the date of recurrence. DCIS, ductal carcinoma in situ.

Conversely, one limitation of the present study, in keeping with the recently published retrospective series [3–5,13], is its observational nature with the consequent difficulty in accounting for all possible confounders. Follow-up is also relatively short in the context of the long natural history of DCIS.

Breast conservation was the definitive surgery for 70.5% of women, more frequently used with increasing age. This may reflect perceptions about the risk of within-breast recurrence in younger patients. Although it is likely that RT after BCS was used in patients perceived (based on pathological and patient-related factors) to be at higher risk of recurrence, RT use was, surprisingly, not associated with close or involved circumferential resection margins. Conversely, mastectomy was, not unexpectedly, associated with features of more aggressive DCIS.

RT after BCS was associated with a significant reduction in all ipsilateral breast further events (DCIS or

invasive) at a median follow-up of 64 months. The association of RT with reduced recurrence risk is consistent with the effects seen in the overview of the prospective randomised trials [15]. Significantly, however, in the present study, the reduction of breast recurrence associated with RT was independent of the margin of excision. Differing minimum margin widths for DCIS have been proposed [16,17]. One recent series has suggested that a 1-mm margin may be sufficient, with or without RT [18]. Others have suggested that those with margin widths <1 mm may benefit from postoperative radiation therapy, whereas those with >10 mm margins receive no benefit [19]. However, specifically for women who did not receive RT in this series, there was an association between a DCIS margin of <2 mm and ipsilateral breast recurrence. This provides direct evidence in support of more recent reviews, meta-analysis and consensus guidelines [20,21] as well as recent studies [22].

Association but not significant and not shown

The higher all-cause mortality in patients not receiving RT after BCS is likely to reflect comorbidities not captured in the present study. Nevertheless, patients not receiving RT had a higher (7.2%) breast recurrence rate, confirming that patient selection for RT could be improved [23].

Endocrine therapy was associated with a non-significant reduction in ipsilateral breast recurrence independent of RT, although the greatest effect was seen for the reduction of invasive further events in the absence of RT. In a contemporary analysis of the US retrospective National Cancer Database (70% of the US population), 36.5% of women (most commonly between 50 and 59 years of age) received adjuvant endocrine therapy for DCIS [24] compared with 12.2% in this UK-based study, and no one in a cohort in the Netherlands [13], reflecting the inconsistent interpretation of evidence from trials examining the impact of endocrine therapy for DCIS on local recurrence, the associated toxicities and issues of adherence to adjuvant tamoxifen treatment.

Significantly, neither the use of RT and endocrine therapy nor the type of surgery appeared to influence breast cancer mortality, although women who developed invasive ipsilateral breast cancer had a poorer survival than those who had DCIS recurrence. Indeed, breast cancer mortality (0.46%) was a fifth of other-cause mortality, in keeping with several retrospective studies [3,4,13].

The increasing incidence of DCIS, likely to be sustained with the enhanced visualisation that digital mammography provides, now deployed in the UK NHSBSP, emphasises the potential for overtreatment of women diagnosed through breast screening [1,25]. Because digital mammography was not deployed during the time of data collection for this study, the impact of digital mammography and any influences on the data reported here remain uncertain. However, the present study findings do re-emphasise the issue of potential overtreatment of DCIS and the need to improve the selection of adjuvant therapy. This requires a greater understanding of the underlying biology of DCIS on reliable predictive and prognostic assessment, particularly to select women at risk of invasive breast cancer recurrence. Predictive models of ipsilateral breast recurrence after DCIS and a more recent prognostic score for DCIS for RT benefit require prospective validation if they are to be widely adopted [26–30]. Meanwhile, a major international initiative between the UK, Netherlands and the US, the PRECISION (PREvent ductal Carcinoma In Situ Invasive Overtreatment Now) study funded by Cancer Research UK and the Dutch Cancer Society, seeks to define underlying molecular mechanisms in DCIS related to the risk of progression and, together with diagnostic and clinical elements, construct risk models for the future management of patients (http://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/grand-challenge-award/funded-teams-wesseling) [30]. Emulating studies in prostate, thyroid and renal neoplasia, active surveillance, rather than initial surgery, for carefully selected patients with low-risk DCIS has been advocated and may avoid the potential sequelae of breast surgery. Indeed, prospective randomised trials of active surveillance versus conventional surgical care, e.g. the LOw RISk DCIS (LORIS) trial in the UK, COMET in the USA and LORD in mainland Europe [31–33] seek to identify a cohort of patients with sufficiently low risk to obviate the need for surgical excision.

5. Conclusions

This large prospective cohort study allows us to examine, in contemporary practice, the effects of present-day treatments and the patient and pathological features that have previously been described in retrospective studies and randomised clinical trials. The reduction in recurrence rates seen with the use of RT and endocrine therapy has not, to date, yielded a survival benefit to patients, although other-cause mortality is five times greater than that attributable to breast cancer. Ipsilateral breast recurrence risk is, however, higher in patients treated by BCS without RT, particularly if the radial excision margin is narrow (<2 mm). Women with recurrence as invasive disease have poorer survival than those with recurrent DCIS, and further research targeting clinical, biological and imaging biomarkers of risk of invasive recurrence after a diagnosis of screen-detected DCIS is indicated to improve personalisation of therapy and outcomes.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.06.027.

Appendix

UK Breast Screening Units contributing to the Sloane Project:

Avon	North Derbyshire
Barking, Havering, Redbridge & Brentwood	North East Scotland
Barnsley	North Lancashire & South Cumbria
Bedfordshire & Hertfordshire	North London
Bolton, Bury & Rochdale	North Nottinghamshire
Breast Test Wales – North[a]	North Staffordshire
Breast Test Wales – South East[a]	North Yorkshire
Breast Test Wales – South West[a]	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[a]
Newcastle-Upon-Tyne	Wiltshire
Norfolk & Norwich	Wirral
North & Eastern Devon	Wycombe
North & Mid Hampshire	
North Cumbria	

[a] Unit data not included in these analyses.

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