Surgical Management of Ductal Carcinoma in Situ (DCIS) of the Breast; a large retrospective study from a single institution

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ABSTRACT

Background: Management of breast ductal carcinoma *in situ* (DCIS) has various approaches with distinct institutional specific practice. Here, we review DCIS management in a single institution with emphasise on re-operation rates and outcome. **Methods:** DCIS cases diagnosed at the Nottingham Breast Institute between 1987 and 2017 were identified (n=1,249). Clinicopathological data was collected. Cases were histologically reviewed, and different factors associated with primary operation selection, re-excision, presence of residual tumour in the re-excision specimens, use of radiotherapy and ipsilateral recurrences were analysed. **Results:** 34% of DCIS patients were initially treated by mastectomy and were more frequently symptomatic, of high nuclear tumour grade, size >40mm, and associated with comedo necrosis and Paget's disease of the nipple. Further surgery was due to involved or narrow surgical margins. Residual tumour tissue was detected in 53% of the re-excision specimens. Re-excision rates of patients treated with breast conserving surgery (BCS) were reduced from approximately 70% to 23% and the final mastectomy rates decreased from 60% to 20%. Changes in surgical practice with acceptance of smaller excision margins and more frequent use of local radiotherapy have led to a significant decrease not only in the re-excision rate but also in the final mastectomy rate together with non-significant reduction in 5- and 10-year local recurrence rates. **Conclusion**: Although BCS is increasingly the preferred primary surgical option for DCIS management, a proportion of low-risk DCIS patients continue to undergo re-excision surgery or completion mastectomy. Despite acceptance of smaller margins, recurrence rate is decreasing.

INTRODUCTION

Breast ductal carcinoma *in situ* (DCIS) represents about 10% of all breast carcinomas [1]. Its incidence has increased dramatically in the UK since introduction of the mammographic screening programme, and currently it accounts for approximately 20-25% of mammographically screen detected breast carcinomas [2]. The breakthrough of molecular techniques shows that DCIS is a heterogeneous group of diseases. Such heterogeneity is reflected in tumour behaviour and ideally the management approach needs to be designed accordingly to decrease the risk of progression and/or recurrence [3,4]. Mastectomy was long considered the standard management for DCIS and remains so in certain situations (e.g. extensive disease, those with failed breast conservation, or where there are contraindications to radiotherapy (RT) in high-risk patients) [5,6]. It provides an effective and near total cure rate; however, for most women it is an aggressive over-treatment of a lesion with low mortality risk with potential increased psychosocial morbidity and health economic costs [3]. Breast-conserving surgery (BCS), with or without RT, is offered when DCIS can be removed with an acceptable cosmetic outcome and considered equivalent to mastectomy in terms of overall survival or breast cancer specific survival [1]. However, studies report women treated with BCS have up to 15% risk of recurrence within 10 years and half of these recurrences are invasive disease with subsequent mortality risk [7,8]. RT following BCS decreases the risk of recurrence to less than 10% at 10 years although clear guidelines for its indications in specific risk groups continue to be debated [9-13]. Over- or under-treatment of DCIS remains a problem and numerous trials have been developed to assess more personalised therapy [14,15]. Various factors affecting outcome of treated DCIS have been analysed and different risk groups can be stratified accordingly, aiding treatment decisions [16]. Age at diagnosis, clinical route of presentation, nuclear grade and lesion size, resection margin status are well recognised factors used for this purpose. The Van Nuys prognostic index (VNPI) is a popular risk assessment tool combining patient age, lesion size, nuclear grade and margin status (Supplementary table1) [17,18].

Optimal extent of free resection margins after BCS is still controversial. A UK survey in 2007 identified that approximately half of surgeons aim for a free margin of more than 2mm [19].

In 2016, the Society of Surgical Oncology, American Society for Radiation Oncology and American Society of Clinical Oncology consensus guideline on margins for BCS with whole-breast irradiation in DCIS suggest a 2mm free surgical margin [20]. Positive or close margins are the main indication for surgical re-excision or completion mastectomy after primary surgery for DCIS [21-23]. In this retrospective study, we review the different management approaches across 30 years in a single institution and the different clinicopathological factors affecting them in a large cohort of women with DCIS diagnosed at the Nottingham Breast Institute between 1987-2017.

PATIENTS AND METHODS

All pure DCIS cases diagnosed between 1987-2017 at the Nottingham Breast Institute were identified (Table 1, n=1,249). Cases associated with invasive or micro-invasive carcinoma were excluded. Patients with multiple specimens; primary excision and re-excision specimen(s), were considered as a single surgical episode and size of any DCIS identified in the re-excision specimens was added to the size of tumour in the primary excision specimen to calculate the final size. Clinicopathological data including age at diagnosis, mode of DCIS presentation (screen-detected or symptomatic), size of the lesion, nuclear grade, presence of comedo necrosis, DCIS morphological type and associated Paget's disease, was retrieved from patient records. Management options including primary operation type (BCS vs mastectomy), margins status, re-excision surgery and its type, presence of residual DCIS in the re-excised specimens and the final operation together with RT data were also collected.

Resection margin status data was further categorised based on the recent recommendations; i.e. positive margin (tumour on ink), close margin (<2mm) and negative margin (≥2mm) [20,24]. For comparison purposes; the whole cohort was further split into two groups; those diagnosed between 1987-2008 (n=803) and 2009-2017 (n=446). This was based on the guideline change with regard to margin of excision, soon after 2008, with acceptable free margin after BCS in DCIS of 5mm instead of 10mm free margin [3]. Although, the service currently follows the new guidelines published in 2016 that recommend 2mm as optimal free margin in DCIS, cases managed in 2016 and 2017, in this study, were included in the latter group to avoid bias in statistical analysis. Five and ten-year local recurrence

free interval (LRFI) was estimated (in months). Five and ten-year local recurrence is defined as any event of ipsilateral tumour recurrence (either as DCIS or invasive disease) occurred after 6 months from the first DCIS surgery and up to 60 and 120 months; respectively.

VNPI was assessed for all cases treated with BCS after the first operation (n=824) and the risk score was estimated.

Statistical analysis

Statistical analyses were performed using SPSS v21 (Chicago, IL, USA) for Windows. Chi-square test and the multivariate logistic regression model were used to correlate between different clinicopathological factors with primary operation preference, re-excision, type of re- excision, RT and presence of residual tumour tissue in the re-excised specimens. The 5 and 10-year LRFI were compared between both periods by log rank test.

This work obtained ethics approval by the North West – Greater Manchester Central Research Ethics Committee under the title; Nottingham Health Science Biobank (NHSB), reference number 15/NW/0685.

RESULTS

A total of 945/1,249 women (75%) diagnosed with DCIS were within the screening age group (50-70 years). High nuclear grade was observed in 61% of cases, while comedo type necrosis was recorded in two thirds of cases (67%). Solid DCIS was the predominant histological type, either in pure form or mixed with other morphological types and represented 58% of cases. Paget's disease was observed in 56 (9%) cases.

Regarding DCIS management; 824 (66%) cases were treated primarily with BCS, while mastectomy was performed in 424 cases (34%). The latter was the first choice in those who presented symptomatically ($p<0.0001$), diffuse DCIS lesions involving more than one breast quadrant ($p<0.0001$), DCIS size more than 40mm ($p<0.0001$), high nuclear grade ($p<0.0001$), associated comedo necrosis ($p<0.0001$), and solid DCIS ($p=0.030$) (Table 2).

After primary BCS, 317 (39%) cases showed positive margins (tumour on ink), while 88 cases (11%) showed close margins less than 2mm. Free safety margin more than 10mm was observed in 20% of cases. Over the entire study period, half of the DCIS cases treated with BCS (n=414) underwent re-excision. The re-operation was either in the form of another conservative surgery (n=232) or completion mastectomy (n=182), (Table 3).

Several factors influenced the rate of re-excision, including patients younger than 40 years old ($p=0.028$), symptomatic presentation ($p<0.0001$), lesions involving more than one breast quadrant ($p=0.003$), DCIS size more than 40mm ($p<0.0001$), presence of comedo necrosis ($p=0.009$), positive or close resection margins less than 2mm ($p<0.0001$) and high VNPI ($p<0.0001$). Moreover, presence of solid and/or micropapillary DCIS either in pure form or with other morphological types was associated with a higher rate of re-excision ($p<0.0001$). Figure 1a shows the rate of re-excision as regard to margin status. It is noteworthy that 196 (47%) of those who underwent re-excision were of low or intermediate grade. Moreover, 10% of low risk VNPI cases had a second operation. Supplementary figure 1 shows the rate of re-excision in context of margin status, tumour grade and risk groups. Table 4 and supplementary table 2 show the detailed association between re-excision and type of re-excision with the clinicopathological variables.

Completion mastectomy was more likely to be recommended for women younger than 40 years old ($p=0.018$), with symptomatic DCIS ($p<0.0001$), multiple DCIS lesions or involving more than one breast quadrant ($p=0.005$), with DCIS more than 4cm in maximum diameter ($p<0.0001$), positive or close resection margin of less than 2mm ($p<0.0001$) and high-risk DCIS according to VNPI ($p<0.0001$).

Residual tumour tissue was detected in 218/414 cases (53%) who had re-excision surgery. Presence of residual tumour tissue in the re-excised specimens was associated with DCIS presenting symptomatically ($p<0.0001$), larger tumour size more than 40mm ($p<0.0001$), DCIS with cribriform morphology ($p=0.018$), positive or close margins less than 2mm ($p=0.015$) and high risk VNPI ($p<0.0001$). Patients who underwent completion mastectomy showed a higher rate of residual tumour tissue than those who had a second re-excision operation ($p<0.0001$). Supplementary table 3 shows the different factors associated with the presence of residual tumour tissue in the re-excision or completion mastectomy specimens.

Multivariate logistic regression analysis showed that symptomatic DCIS, extent of the lesion, DCIS size, presence of comedo type necrosis and surgical margin status were the common independent factors affecting the rate of re-excision, type of re-excision and/or presence of residual tumour in the re-excised specimens. Table 5 summarise the multivariate logistic regression results.

VNPI was assessed for all cases treated with BCS after the first operation (n=824) and risk score calculated (mean score was 7.7±1.7, range 4-12). Low, moderate and high risk DCIS was observed in 195 (25%), 470 (60%) and 118 (15%) cases respectively. VNPI could not be assessed in 41 (5%) cases because one or more of the index parameters was missing.

263 out of 642 patients (41%) treated with BCS as a final surgery received post-operative adjuvant RT. Its use was associated with high risk DCIS features including tumour size more than 40mm ($p<0.0001$), higher tumour grade ($p<0.0001$), presence of comedo type necrosis ($p<0.0001$), positive or close surgical margins ($p=0.008$), and moderate and high risk DCIS (VNPI) ($p<0.0001$). Increased use of RT over the study period was observed.

Over the period of the study, the management of DCIS showed significant changes with acceptance of smaller margins, improving quality of imaging detection of DCIS and more frequent use of local RT. Figure 1 shows details of the trends of primary and final BCS, RT rate, re-excision rate and local recurrence rate. As the most significant change in the margin status was introduced in 2008, this time point was used to compare the old and recent series of DCIS in this study. After 2008, a significant reduction in the rate of mastectomy as

a first operative choice for DCIS management was observed (p=0.015), along with a marked decrease in the rate of re-excision to 37% compared to 58% prior to 2008 (p<0.0001) and an increase in the presence of residual DCIS in the re-excised specimens (p=0.04). Re-excision rate in 2017 was 23%.

Importantly, the change in surgical practice after 2008, with acceptance of narrower surgical margins, was not hazardous in terms of the ipsilateral local recurrence rate. In contrast, the 5-year recurrence rate decreased from 5.4% for DCIS managed between 1987-2008 to 2.2% for DCIS managed after 2008. The same was observed in the 10-year recurrence rate which was 8.8% in the former and dropped to 2.5% in the latter. However, these differences did not show statistical significance (p value=0.223 and 0.225, respectively).

DISCUSSION

Prior to the early 1990's, the standard treatment for DCIS was mastectomy. However, BCS with adjuvant RT show comparable outcome to mastectomy in terms of recurrence free interval and overall survival and as a result, the rate of mastectomies has declined and BCS predominates [25,26]. In the current study, documenting practice in a single institution over a 30-year period, approximately two thirds of DCIS cases were treated with BCS as a first surgical modality. Mastectomy was the preferred option for patients with symptomatic DCIS, high tumour grade, larger sized tumours (>40mm), associated comedo necrosis and those involving more than one quadrant of the breast. Over the period of the study, there was not only an increase in the rates of initial BCS but also a significant decline in the re-excision and final mastectomy rates and more importantly in the ipsilateral local recurrences rate. Although a change in the local practice occurred in 2008, in which margin width of 5mm was accepted instead of 10mm, and a recent change of practice in 2016 in which 2mm margin was adopted, the frequency of BCS, re-excision rates and local recurrence rates showed gradual change over time rather than a sudden transition at this certain time point. This may reflect the impact of several factors including the improvement of imaging quality with better assessment of DCIS size and extent, quality of surgery, and the growing use of local RT.

The current study demonstrates the radiological and pathological indications for BCS and the factors associated with the decision to perform additional therapeutic operations. The predominant factor in deciding BCS is the extent of the disease. Patient choice is also a contributing factor as evidenced by the NHS Breast Screening Programme where patient choice accounts for about 11% of mastectomies for DCIS [27]. Recently, in the UK and US, the rate of mastectomy has increased particularly in young women perceived at high risk of further breast cancer events [6,28]. In a report on 8,000 DCIS cases included in the Sloane Project and treated between 2003 and 2012 the rate of attempted BCS was 79% and successful BCS was 68% [27,29]. Achieving success at BCS for DCIS remains a challenge and it continues to be the case that a woman with DCIS is at least as likely to have a mastectomy as a woman with invasive breast cancer (IBC). It is also reported that the re-excision rates

after BCS as a treatment for DCIS is higher than re-excisions for IBC. Furthermore, invasive disease accompanying DCIS has higher re-operation rates than pure invasive disease [30,31].

The need to perform further surgery, re-excision or completion mastectomy, is governed predominantly by what is regarded as a minimum free resection margin. Positive margins is partly due to radiologic under-estimation of DCIS size which can occur in over 50% of cases [29,32]. Other studies, similar to the current findings, have shown that the diffuse DCIS growth patterns such as micropapillary and cribriform types, high nuclear grade DCIS with comedo type necrosis and high risk VNPI are factors associated with an increased rate of re-excisions [31-34].

The current study shows that half of the patients with DCIS who underwent re-excision, due to positive or close surgical margins, were of low and intermediate grade. This practice might have an impact on the pending outcome of recent trials for more conservative management of low risk DCIS [14,35]. If safe, such strategies could significantly reduce re-operation and mastectomy rates.

In this study, half of the re-excised specimens were free of residual tumour, even though some cases were reported to have tumour on ink after the primary excision. Such a finding perhaps illustrates the controversy in pathological evaluation [24]. Presence of residual DCIS was correlated to other adverse clinicopathological parameters i.e. symptomatic presentation, larger tumour size, DCIS with cribriform and micropapillary morphology. Previous studies were performed to establish a margin index based on tumour size and the closest surgical margin to show its association with presence of residual tumour tissue after re-excision, but this did not show significant association [36,37]. Another study showed that the extent of margin involvement either focal or diffuse as well as the number of involved ducts in the closest margin were the main factors associated with presence of residual DCIS in the re-excision specimens [22]. In our case series, an increased rate of residual tumour tissue in the re-excised specimens was found after 2008 perhaps reflecting a better overall strategy for further surgery.

Determining the optimal free margin for breast conservation remains a challenge particularly in pure DCIS. The Society of Surgical Oncology-American Society for Radiation Oncology has published new guidelines for the optimal margin in invasive disease and recommends no tumour on ink as a negative margin as there is no evidence that wider clear margins reduce ipsilateral recurrence [38]. In DCIS, the same group published consensus guidelines suggesting 2mm as a standard for adequate surgical margin. Systematic review and meta-analysis of 20 studies showed that negative margins minimise the risk of ipsilateral recurrence by 50% compared with positive margins defined as tumour on ink. A 2mm margin minimises the risk of recurrence compared with smaller negative margins [39-41]. However, the agreement on these recommendations is different between centres and the choice of optimal margins depends mainly on the surgeons' practice and methods of margin assessment by pathologists which was supported by the current National Institute for Health and Care Excellence (NICE) guidelines [42]. Accepting closer margins of excision is a means of reducing re-operation rates, as has been shown in invasive disease [43]. However, planning a wider macroscopic margin in higher risk cases or tailoring the scrutiny of margin assessment to the risk factors are other strategies.

The acceptable optimal margin ranged from 1mm to > 10mm. In the current study, we grouped cases according to margin status using different classification schemes. Close surgical margins less than 2mm were significantly associated with an increased rate of re-excision and presence of residual tumour tissue in the re-excised specimens which is consistent with other studies [22,44,45]. Interestingly, change in surgical practice with acceptance of narrower free margin in patients treated conservatively did not increase the recurrence rate. This indicates better risk stratification, adjuvant radiotherapy (RT) selection and individualised management for patients based on constellation of all clinicopathological factors.

All large prospective trials to evaluate the impact of adjuvant RT after DCIS BCS showed a 50% reduction in recurrence rate with adjuvant RT [10,46,47]. No specific group of patients were identified where RT could be safely avoided, hence the continued debate over RT indications after BCS. In routine practice, only about 30-50% of BCS treated patients

receive adjuvant RT [48] and the recommendation for it differs between radiotherapists as well as institutions [49]. Overall in our series, 41% of BCS treated patients were offered post-operative RT. It was a common practice in our centre before 2008 that no further treatment was suggested for patients with clear pathological margins 10 mm or more. After previous analysis of patient outcome, selective RT was introduced [50]. RT was then recommended after BCS to those with high grade DCIS, women younger than 50 years old and lesions more than 30mm, regardless of tumour grade, following a multidisciplinary team discussion [3]. Patients who undergo mastectomy will not receive postoperative RT regardless of the age, nuclear grade or lesion size.

***Conclusion**:* This study addresses the long-term experience of a single institution with DCIS management over a 30-year period. Over this time rates of successful BCS have improved but avoiding the need for second therapeutic operations remains a challenge. The dominant risk factors for failed BCS and for disease in re-excision or completion mastectomy specimens are young age (<40 years), symptomatic presentation, presence of comedo necrosis, and larger tumour size (>40mm).

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Figure 1

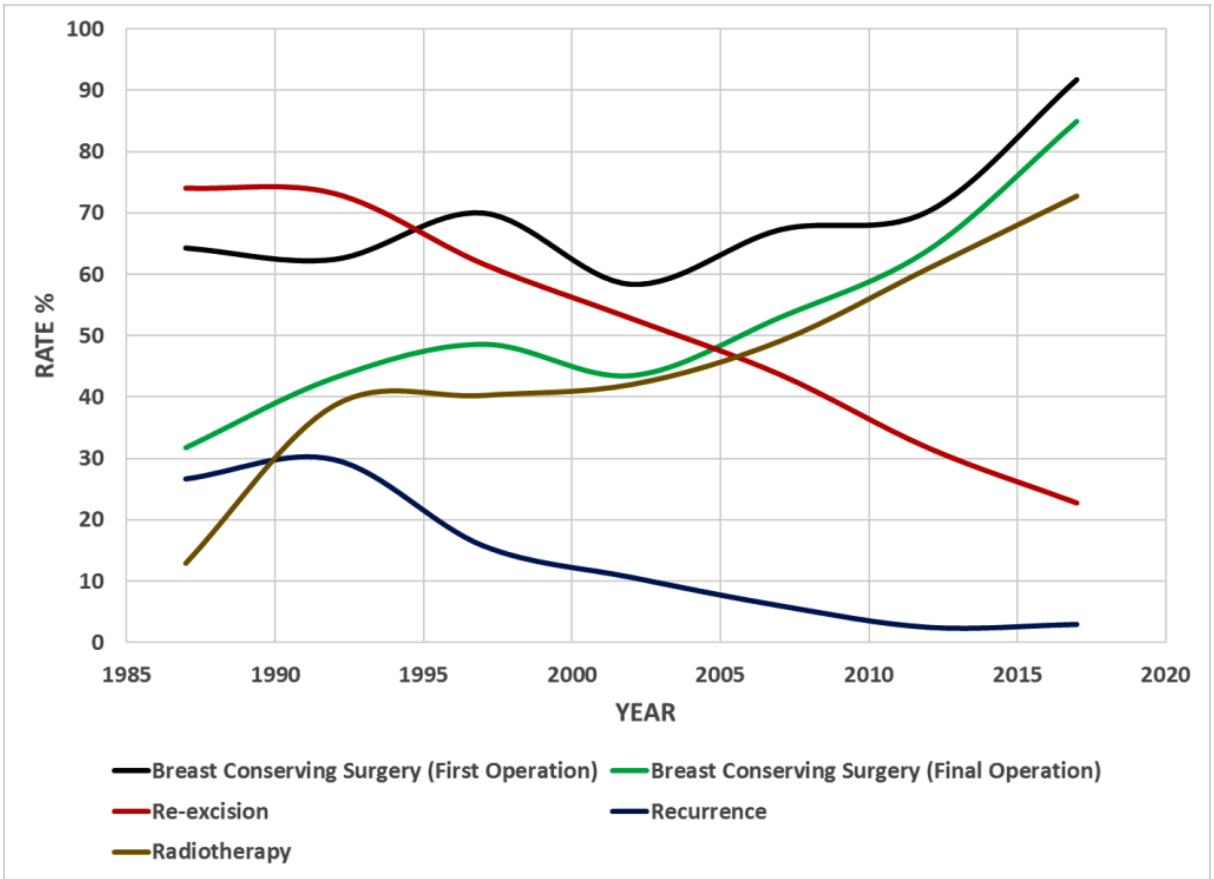

Figure 1: The annual rates, over the period between 1987-2017, of: A) Breast conserving surgery (BCS); shows the higher rates of BCS as a primary surgical choice over the years, B) Shows the comparable rates of final BCS after re-excisions. Obviously over the last 10 years the rates of BCS exceed the rates of mastectomy. C) Post-operative adjuvant radiotherapy; a significant increase of radiotherapy use post-operatively after 2000 is observed. D) Re-excision and E) Recurrence after primary BCS; A significant decrease in both is observed over the last 10 years.

Table 1: Clinicopathological parameters of the whole primary DCIS cohort stratified by time period

Parameter	Total N (%)	DCIS Diagnosed 1987-2008 (n=803) N (%)	DCIS diagnosed 2009-2017 (n=446) N (%)	X^2 P-value
Age *				
<40	32 (3)	24 (3)	8 (2)	11.9
40 to 60	688 (55)	467 (58)	221 (49)	**0.003**
>60	529 (42)	312 (39)	217 (49)	
Presentation				
Symptomatic	501 (40)	351 (44)	150 (34)	11.8
Screening	748 (60)	452 (56)	296 (66)	**0.001**
DCIS Site **				
Localised	929 (85)	590 (88)	339 (81)	11.5
Diffuse	160 (15)	79 (12)	81 (19)	**0.001**
Tumour Size *				
<16mm	457 (37)	308 (39)	149 (33)	3.6
16 to 40mm	484 (39)	304 (38)	180 (41)	0.160
>40mm	301 (24)	184 (23)	117 (26)	
Tumour Grade				
Low	156 (12)	109 (14)	47 (11)	16.8
Intermediate	333 (27)	185 (23)	148 (33)	**<0.0001**
High	760 (61)	509 (64)	251 (56)	
Comedo necrosis				
No	409 (33)	280 (35)	129 (29)	4.6
Yes	840 (67)	523 (65)	317 (71)	**0.032**
Solid DCIS				
No	529 (42)	406 (50)	123 (28)	62.3
Pure	291 (23)	164 (20)	127 (28)	**<0.0001**
Mixed with other types	429 (35)	233 (30)	196 (44)	
Cribriform DCIS				
No	649 (52)	444 (55)	205 (46)	12.1
Pure	114 (9)	75 (10)	39 (9)	**0.002**
Mixed with other types	486 (39)	284 (35)	202 (45)	
Papillary DCIS				
No	1127 (90)	729 (91)	398 (89)	0.8
Pure	42 (3)	26 (3)	16 (4)	0.663
Mixed with other types	80 (7)	48 (6)	32 (7)	
Micropapillary DCIS				
No	916 (73)	594 (74)	322 (72)	1.3
Pure	79 (7)	53 (7)	26 (6)	0.520
Mixed with other types	254 (20)	156 (19)	98 (22)	
Associated Paget's Disease				
No	559 (91)	399 (90)	160 (93)	0.7
Yes	56 (9)	43 (10)	13 (7)	0.361
Management (First Operation)				
Mastectomy	424 (34)	292 (36)	132 (30)	5.9
Breast conserving surgery (BCS)	824 (66)	510 (64)	314 (70)	**0.015**
Margin width ***				
Positive (Tumour on ink)	317 (39)	240 (47)	77 (24)	72.5
<2mm	88 (11)	36 (7)	52 (17)	**<0.0001**
≥2mm	382 (46)	202 (40)	180 (57)	
Unknown	37 (4)	32 (6)	5 (2)	
Re excision ***				
Yes	414 (50)	298 (58)	116 (37)	35.9
No	410 (50)	212 (42)	198 (63)	**<0.0001**

Type of re-excision * **				
Re excision	232 (56)	159 (53)	73 (63)	3.1
Mastectomy	182 (44)	139 (47)	43 (37)	0.078
Residual Tumour * **				
No	196 (47)	150 (50)	46 (40)	3.8
Yes	218 (53)	148 (50)	70 (60)	0.051
Management (Final Operation)				
Mastectomy	606 (49)	431 (54)	175 (39)	24.1
BCS	642 (51)	371 (46)	271 (61)	**<0.0001**
Radiotherapy ** **				
Yes	263 (41)	92 (25)	171 (63)	127.1
No	379 (59)	279 (75)	100 (37)	**<0.0001**
VNPI (after 1st operation)* **				
Low risk	195 (25)	105 (22)	90 (29)	7.1
Moderate risk	470 (60)	288 (61)	182 (59)	**0.030**
High risk	118 (15)	81 (17)	37 (12)	

DCIS: Ductal carcinoma *in situ;* N: Number; X^2: Chi square, P values in **bold** are significant

*Age and size were categorised according to Van Nuys Prognostic Index (VNPI)

** Site; Localised: DCIS is involving one quadrant, diffuse: DCIS is in more than one quadrant

*** Refers to patients treated primarily with BCS (first operation)

**** Refers to patients treated by BCS (final operation)

Table 2: Clinicopathological factors associated with the selection of type of primary surgery for DCIS management stratified by time period

Parameter	DCIS Diagnosed 1987-2008 N (%)		X^2 *p*-value	DCIS diagnosed 2009-2017 N (%)		X^2 *p*-value	Total N (%)		X^2 *p*-value
	BCS	Mastectomy		BCS	Mastectomy		BCS	Mastectomy	
Age									
<40	13 (54)	11 (46)	0.9	5 (63)	3 (37)	1.8	18 (56)	14 (44)	2.6
40 to 60	297 (64)	170 (36)	0.610	150 (68)	71 (32)	0.412	447 (65)	241 (35)	0.271
>60	200 (64)	111 (36)		159 (73)	58 (27)		359 (68)	169 (32)	
Presentation									
Symptomatic	204 (58)	146 (42)	7.6	84 (56)	66 (44)	22.5	288 (58)	212 (42)	26.4
Screening	306 (68)	146 (32)	**0.006**	230 (78)	66 (22)	**<0.0001**	536 (72)	212 (28)	**<0.0001**
Site									
Localised	365 (62)	224 (38)	51.7	250 (74)	89 (26)	10.5	615 (66)	313 (34)	48.6
Diffuse	30 (38)	49 (62)	**<0.0001**	45 (56)	36 (44)	**0.005**	75 (47)	85 (53)	**<0.0001**
Size									
<16mm	256 (83)	52 (17)	96.9	133 (89)	16 (11)	78.1	389 (85)	68 (15)	162.5
16 to 40mm	175 (58)	129 (42)	**<0.0001**	134 (74)	46 (26)	**<0.0001**	309 (64)	175 (36)	**<0.0001**
>40mm	75 (41)	109 (59)		47 (40)	70 (60)		122 (41)	179 (59)	
Grade									
Low	92 (84)	17 (16)	39.1	41 (87)	6 (13)	18.3	133 (85)	23 (15)	58.6
Intermediate	133 (72)	51 (28)	**<0.0001**	116 (78)	32 (22)	**<0.0001**	249 (75)	83 (25)	**<0.0001**
High	285 (56)	224 (44)		157 (63)	94 (37)		442 (58)	318 (42)	
Comedo necrosis									
No	215 (77)	64 (23)	33.5	109 (85)	20 (15)	17.3	324 (79)	84 (21)	48.4
Yes	295 (56)	228 (44)	**<0.0001**	205 (65)	112 (35)	**<0.0001**	500 (60)	340 (40)	**<0.0001**
Solid DCIS									
No	273 (67)	132 (33)	6.3	95 (77)	28 (23)	4.3	368 (70)	160 (30)	7.1
Pure	103 (63)	61 (37)	**0.043**	89 (70)	38 (30)	0.115	192 (66)	99 (34)	**0.030**
Mixed with other types	134 (58)	99 (42)		130 (66)	66 (34)		264 (62)	165 (38)	
Cribriform DCIS									
No	274 (62)	169 (38)	8.1	143 (70)	62 (30)	4.2	417 (64)	231 (36)	12.1
Pure	59 (79)	16 (21)	**0.017**	33 (85)	6 (15)	0.120	92 (81)	22 (19)	**0.002**
Mixed with other types	177 (62)	107 (38)		138 (68)	64 (32)		315 (65)	171 (35)	
Papillary DCIS									
No	458 (63)	271 (37)	4.7	270 (68)	128 (32)	11.7	728 (65)	399 (35)	12.6
Pure	21 (84)	4 (16)	0.095	15 (94)	1 (6)	**0.003**	36 (88)	5 (12)	**0.002**
Mixed with other types	31 (65)	17 (35)		29 (91)	3 (9)		60 (75)	20 (25)	

Micropapillary DCIS No Pure Mixed with other types	391 (66) 33 (62) 86 (55)	202 (34) 20 (38) 70 (45)	6.3 **0.043**	236 (73) 14 (54) 64 (65)	86 (27) 12 (46) 34 (35)	5.9 0.052	627 (69) 47 (60) 150 (59)	288 (31) 32 (40) 104 (41)	9.6 **0.008**
Associated Paget's No Yes	143 (36) 7 (16)	256 (64) 36 (84)	6.6 **0.010**	40 (25) 3 (23)	120 (75) 10 (77)	0.1 0.877	183 (33) 10 (18)	376 (67) 46 (82)	5.2 **0.022**

DCIS: Ductal carcinoma *in situ*; N: Number; X^2: Chi square, BCS: Breast conserving surgery, *p* values in **bold** are significant

Table 3: Detailed surgical management of the DCIS cases as a whole cohort

<table>
<tr><th colspan="5">Surgical management</th></tr>
<tr><td>Primary operation</td><td>Mastectomy
(n=424)
(34%)</td><td colspan="3">BCS
(n=824)
66%</td></tr>
<tr><td rowspan="3">Re excisions</td><td rowspan="3"></td><td colspan="2">Yes (n=414)
(50%)</td><td rowspan="3">No re-excision (n=410)
(50%)</td></tr>
<tr><td>Mastectomy</td><td>Re-excision</td></tr>
<tr><td>n=182 (44%)</td><td>n= 232 (56%)</td></tr>
<tr><td>Final operation</td><td>Mastectomy
(n=606)
(49%)</td><td colspan="2"></td><td>BCS
(n=642)
(51%)</td></tr>
</table>

BCS: Breast conserving surgery; n: number

Table 4: Clinicopathological factors associated with re excision after primary treatment with breast conserving surgery stratified by time period

Parameter	DCIS Diagnosed 1987-2008 N (%)		X^2 *p*-value	DCIS diagnosed 2009-2017 N (%)		X^2 *p*-value	Total		X^2 *p*-value
	No	Yes		No	Yes		No	Yes	
Age <40 40 to 60 >60	3 (23) 113 (38) 96 (48)	10 (77) 184 (62) 104 (52)	6.7 **0.034**	3 (60) 95 (63) 100 (63)	2 (40) 55 (37) 59 (37)	0.1 0.987	6 (33) 208 (46) 196 (55)	12 (67) 239 (54) 163 (45)	7.2 **0.028**
Presentation Symptomatic Screening	65 (32) 147 (48)	139 (68) 159 (52)	13.2 **<0.0001**	41 (49) 157 (68)	43 (51) 73 (32)	9.9 **0.002**	106 (37) 304 (57)	182 (63) 232 (43)	29.7 **<0.0001**
Site Localised Diffuse	157 (43) 13 (43)	208 (57) 17 (57)	1.6 0.459	169 (68) 21 (47)	81 (32) 24 (53)	10.9 **0.004**	326 (53) 34 (45)	289 (47) 41 (55)	11.5 **0.003**
Size <16mm 16 to 40mm >40mm	133 (52) 66 (38) 10 (13)	123 (48) 109 (62) 65 (87)	37.1 **<0.0001**	112 (84) 69 (51) 17 (36)	21 (16) 65 (49) 30 (64)	47.8 **<0.0001**	245 (63) 135 (44) 27 (22)	144 (37) 174 (56) 95 (78)	69.1 **<0.0001**
Grade Low Intermediate High	34 (37) 57 (44) 121 (42)	58 (63) 76 (56) 164 (58)	0.9 0.610	27 (66) 68 (59) 103 (66)	14 (34) 48 (41) 54 (34)	1.6 0.459	61 (46) 125 (50) 224 (51)	72 (54) 124 (50) 218 (49)	0.9 0.614
Comedo necrosis No Yes	81 (38) 131 (44)	134 (62) 164 (56)	2.3 0.128	62 (57) 136 (66)	47 (43) 69 (34)	2.7 0.098	143 (44) 267 (53)	181 (56) 233 (47)	6.7 **0.009**
Solid DCIS No Pure Mixed with other types	98 (36) 55 (53) 59 (44)	175 (64) 48 (47) 75 (56)	9.8 **0.007**	59 (62) 67 (75) 72 (55)	36 (38) 22 (25) 58 (45)	9.1 **0.011**	157 (43) 122 (64) 131 (50)	211 (57) 70 (36) 133 (50)	22.1 **<0.0001**
Cribriform DCIS No Pure Mixed with other types	108 (39) 27 (46) 77 (44)	166 (61) 32 (54) 100 (56)	1.2 0.543	97 (68) 23 (70) 78 (56)	46 (32) 10 (30) 60 (44)	4.5 0.103	205 (49) 50 (54) 155 (49)	212 (51) 42 (46) 160 (51)	0.9 0.646

Papillary DCIS No Pure Mixed with other types	188 (41) 10 (48) 14 (45)	270 (59) 11 (52) 17 (55)	0.5 0.766	168 (62) 13 (87) 17 (59)	102 (38) 2 (13) 12 (41)	3.9 0.141	356 (49) 23 (64) 31 (52)	372 (51) 13 (36) 29 (48)	3.2 0.204
Micropapillary DCIS No Pure Mixed with other types	175 (45) 6 (18) 31 (36)	216 (55) 27 (82) 55 (64)	10.1 **0.006**	160 (68) 7 (50) 31 (48)	76 (32) 7 (50) 33 (52)	9.2 **0.010**	335 (53) 13 (28) 62 (41)	292 (47) 34 (72) 88 (59)	16.8 **<0.001**
Margin width Positive (tumour on ink) <2mm ≥2mm	8 (3) 9 (25) 165 (82)	232 (97) 27 (75) 37 (18)	318.7 **<0.001**	3 (4) 18 (35) 175 (97)	74 (96) 34 (65) 5 (3)	225.1 **<0.001**	11 (3) 27 (31) 340 (89)	306 (97) 61 (69) 42 (11)	543.7 **<0.001**
VNPI (1st operation) Low risk Moderate risk High risk	73 (70) 103 (36) 5 (6)	32 (30) 185 (64) 76 (94)	108.9 **<0.001**	82 (91) 109 (60) 5 (13)	8 (9) 73 (40) 32 (87)	71.3 **<0.001**	155 (79) 212 (45) 10 (8)	40 (21) 258 (55) 108 (92)	168.9 **<0.001**

DCIS: Ductal carcinoma *in situ;* VNPI: Van Nuys Prognostic Index; N: Number; X^2: Chi square, *p* values in **bold** are significant

Table 5: Multivariate logistic regression model analysis showing the association between the various clinicopathological parameters and; a) selection of type of primary surgery for DCIS management (BCS versus mastectomy), b) re-excision after primary treatment with BCS, c) type of the re-excision surgery either another conservative operation or completion mastectomy and, d) presence of residual tumour tissue in the re excision specimens

A)

Parameter	DCIS Diagnosed 1987-2008			DCIS Diagnosed 2009-2017			Whole Cohort		
	Hazard Ratio	95%CI	p-value	Hazard Ratio	95%CI	p-value	Hazard Ratio	95%CI	p-value
Patient age	2.1	0.6-6.8	0.261	2.2	0.2-22.5	0.512	2.3	0.8-6.3	0.121
DCIS presentation	0.7	0.4-1.1	0.134	1.1	0.5-2.6	0.823	0.8	0.5-1.2	0.275
DCIS site (extent)	2.2	1.1-4.4	**0.030**	0.9	0.3-2.2	0.773	1.7	0.9-2.8	0.058
DCIS size	1.2	0.6-2.2	0.632	1.8	0.7-4.5	0.219	1.2	0.7-1.8	0.527
DCIS Nuclear grade	1.8	1.1-3.2	**0.042**	0.9	0.1-6.1	0.923	1.5	0.9-2.5	0.082
Comedo necrosis	1.7	0.9-2.9	0.075	6.4	1.8-23.1	**0.004**	2.3	1.4-3.8	**0.001**
DCIS Histological type	1.5	0.9-2.4	0.076	0.6	0.2-1.5	0.279	1.2	0.8-1.8	0.381
Presence of Paget's Disease	2.5	1.1-6.2	**0.045**	0.5	0.1-2.4	0.402	1.8	0.8-3.9	0.130

p values in **bold** are significant

*DCIS extent refers to either localised DCIS involving one quadrant or diffuse that involves more than one breast quadrant.

B)

Parameter	DCIS Diagnosed 1987-2008			DCIS Diagnosed 2009-2017			Whole Cohort		
	Hazard Ratio	95%CI	p-value	Hazard Ratio	95%CI	p-value	Hazard Ratio	95%CI	p-value
Patient age	2.2	0.1-68.3	0.661	0.5	0.2-1.3	0.155	0.9	0.1-8.6	0.974
DCIS presentation	1.2	0.5-2.9	0.646	0.2	0.1-0.9	**0.041**	1.2	0.6-2.2	0.635
DCIS site (extent)	0.1	0.01-0.2	**0.001**	1.4	0.2-6.7	0.711	0.2	0.1-0.5	**0.002**
DCIS size	1.5	0.3-8.1	0.644	2.1	0.3-13.7	0.439	2.8	1.1-6.9	**0.026**
DCIS Nuclear grade	0.4	0.1-1.2	0.114	1.7	0.2-14.7	0.649	0.6	0.2-1.5	0.280
Comedo necrosis	0.6	0.2-1.6	0.336	0.3	0.1-1.3	0.103	0.4	0.2-0.9	**0.046**
DCIS Histological type	1.2	0.5-2.8	0.605	1.6	0.5-4.9	0.409	1.4	0.8-2.4	0.282
Margin status	0.1	0.07-0.2	**<0.0001**	0.1	0.03-0.2	**<0.0001**	0.1	0.02-0.2	**<0.0001**

p values in **bold** are significant

C)

Parameter	DCIS Diagnosed 1987-2008			DCIS Diagnosed 2009-2017			Whole Cohort		
	Hazard Ratio	95%CI	p-value	Hazard Ratio	95%CI	p-value	Hazard Ratio	95%CI	p-value
Patient age	1.5	0.8-2.9	0.233	1.6	0.6-4.4	0.351	1.5	0.9-2.5	0.143
DCIS presentation	2.3	1.2-4.5	**0.014**	1.9	0.6-6.1	0.230	2.4	1.4-4.1	**0.001**
DCIS site (extent)	0.5	0.1-1.8	0.289	0.8	0.3-2.7	0.758	0.6	0.2-1.3	0.158
DCIS size	10.4	3.9-27.8	**<0.0001**	5.2	1.5-18.5	**0.010**	9.7	4.4-21.5	**0.0001**
DCIS Nuclear grade	1.1	0.4-3.0	0.929	3.1	0.8-11.9	0.084	1.3	0.5-3.2	0.590
Comedo necrosis	1.6	0.7-3.5	0.262	0.2	0.1-0.8	**0.028**	0.9	0.5-1.8	0.896
DCIS Histological type	1.3	0.7-2.4	0.491	0.8	0.3-2.6	0.748	0.9	0.5-1.6	0.856
Margin status	0.2	0.1-0.6	**0.002**	1.1	3.6-7.3	**<0.0001**	0.3	0.1-0.7	**0.005**

p values in **bold** are significant

D)

Parameter	DCIS Diagnosed 1987-2008			DCIS Diagnosed 2009-2017			Whole Cohort		
	Hazard Ratio	95%CI	p-value	Hazard Ratio	95%CI	p-value	Hazard Ratio	95%CI	p-value
Patient age	0.7	0.1-5.4	0.731	0.9	0.3-2.2	0.771	1.2	0.7-2.1	0.490
DCIS presentation	1.8	0.9-3.6	0.082	4.4	1.3-14.6	**0.017**	2.1	1.2-3.7	**0.007**
DCIS site (extent)	1.1	0.3-4.3	0.845	0.2	0.1-0.8	**0.023**	0.6	0.3-1.4	0.262
DCIS size	4.1	1.6-10.9	**0.004**	4.7	1.1-19.7	**0.034**	4.2	1.9-9.4	**0.0002**
DCIS Nuclear grade	0.7	0.2-2.2	0.596	1.2	0.3-4.1	0.794	0.7	0.4-1.4	0.297
Comedo necrosis	2.3	0.9-5.2	0.051	0.9	0.3-3.9	0.950	2.0	1.1-3.9	**0.042**
DCIS Histological type	1.3	0.7-2.6	0.359	2.1	0.7-5.6	0.162	1.8	1.1-2.9	**0.030**
Margin status	2.2	0.6-9.1	0.257	0.3	0.1-4.5	0.442	1.3	0.5-3.4	0.626
Type of re-excision*	4.8	2.4-9.5	**0.0001**	2.5	0.8-7.9	0.119	3.3	1.9-5.7	**0.0001**

p values in **bold** are significant
*Type of re-excision either another conservative surgery or completion mastectomy.