INTRODUCTION

Breast ductal carcinoma in situ (DCIS) represents about 10% of all breast carcinomas. Its incidence has increased dramatically in the UK since introduction of the mammographic screening program, and currently it accounts for approximately 20%-25% of mammographically screen-detected breast carcinomas. The breakthrough of molecular techniques shows that DCIS is a heterogeneous group of diseases. Such heterogeneity is reflected in tumor behavior and ideally the management approach needs to be designed accordingly to decrease...
the risk of progression and/or recurrence.\textsuperscript{3,4} Mastectomy was long considered the standard management for DCIS and remains so in certain situations (eg, extensive disease, those with failed breast conservation, or where there are contraindications to radiotherapy [RT] in high-risk patients).\textsuperscript{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.\textsuperscript{5} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9-13} Over- or under-treatment of DCIS remains a problem and numerous trials have been developed to assess more personalized therapy.\textsuperscript{14,15} Various factors affecting outcome of treated DCIS have been analyzed and different risk groups can be stratified accordingly, aiding treatment decisions.\textsuperscript{16} Age at diagnosis, clinical route of presentation, nuclear grade, and lesion size, resection margin status are well-recognized 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 (Table S1).\textsuperscript{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 2 mm.\textsuperscript{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 2 mm free surgical margin.\textsuperscript{20} Positive or close margins are the main indication for surgical re-excision or completion mastectomy after primary surgery for DCIS.\textsuperscript{21-22} 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 and 2017.

2 | PATIENTS AND METHODS

All pure DCIS cases diagnosed between 1987 and 2017 at the Nottingham Breast Institute were identified (Table 1; n = 1249). 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 tumor 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 were further categorized based on the recent recommendations; that is, positive margin (tumor on ink), close margin (<2 mm), and negative margin (≥2 mm).\textsuperscript{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 5 mm instead of 10 mm free margin.\textsuperscript{3} Although the service currently follows the new guidelines published in 2016 that recommend 2 mm 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 tumor recurrence (either as DCIS or invasive disease) occurred after 6 months from the first DCIS surgery and up to 60 and 120 months; respectively.

Van Nuys prognostic index was assessed for all cases treated with BCS after the first operation (n = 824), and the risk score was estimated.

2.1 | Statistical analysis

Statistical analyses were performed using SPSS v21 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 tumor 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.

3 | RESULTS

A total of 945/1249 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

\textsuperscript{10} Clinical 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 2 mm free surgical margin.\textsuperscript{20} Positive or close margins are the main indication for surgical re-excision or completion mastectomy after primary surgery for DCIS.\textsuperscript{21-22} 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 and 2017.

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| Parameter                     | Total N (%) | DCIS diagnosed 1987-2008 (n = 803) N (%) | DCIS diagnosed 2009-2017 (n = 446) N (%) | $\chi^2$ | P-value |
|------------------------------|-------------|----------------------------------------|------------------------------------------|---------|---------|
| **Age**<sup>a</sup>         |             |                                        |                                          |         |         |
| <40                          | 32 (3)      | 24 (3)                                 | 8 (2)                                    | 11.9    |         |
| 40-60                        | 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**<sup>b</sup>    |             |                                        |                                          |         |         |
| Localized                    | 929 (85)    | 590 (88)                               | 339 (81)                                 | 11.5    |         |
| Diffuse                      | 160 (15)    | 79 (12)                                | 81 (19)                                  | 0.001   |         |
| **Tumor size**<sup>a</sup>   |             |                                        |                                          |         |         |
| <16 mm                       | 457 (37)    | 308 (39)                               | 149 (33)                                 | 3.6     |         |
| 16-40 mm                     | 484 (39)    | 304 (38)                               | 180 (41)                                 | 0.160   |         |
| >40 mm                       | 301 (24)    | 184 (23)                               | 117 (26)                                 |         |         |
| **Tumor 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)                                 | 0.015   |         |
| **Margin width**<sup>c</sup> |             |                                        |                                          |         |         |
| Positive (tumor on ink)       | 317 (39)    | 240 (47)                               | 77 (24)                                  | 72.5    |         |
(Continues)
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 40 mm ($P < 0.0001$), 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 (tumor on ink), while 88 cases (11%) showed close margins less than 2 mm. Free safety margin more than 10 mm 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 40 mm ($P < 0.0001$), presence of comedo necrosis ($P = 0.009$), positive or close resection margins less than 2 mm ($P < 0.0001$) 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. Figure S1 shows the rate of re-excision in context of margin status, tumor grade, and risk groups. Table 4 and Table S2 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 4 cm in maximum diameter ($P < 0.0001$), positive or close resection margin of less than 2 mm ($P < 0.0001$) and high-risk DCIS according to VNPI ($P < 0.0001$).

Residual tumor tissue was detected in 218/414 cases (53%) who had re-excision surgery. Presence of residual tumor tissue in the re-excised specimens was associated with DCIS presenting symptomatically ($P < 0.0001$), larger tumor size more than 40 mm ($P < 0.0001$),

### Table 1 (Continued)

| Parameter                  | Total N (%) | DCIS diagnosed 1987-2008 (n = 803) N (%) | DCIS diagnosed 2009-2017 (n = 446) N (%) | $\chi^2$ | P-value |
|----------------------------|-------------|-----------------------------------------|-----------------------------------------|---------|---------|
| Re-excision                |             |                                         |                                         |         |         |
| Yes                        | 414 (50)    | 298 (58)                                | 116 (37)                                | 35.9    |         |
| No                         | 410 (50)    | 212 (42)                                | 198 (63)                                |         |         |
| Type of re-excision        |             |                                         |                                         |         |         |
| Re-excision                | 232 (56)    | 159 (53)                                | 73 (63)                                 | 3.1     |         |
| Mastectomy                 | 182 (44)    | 139 (47)                                | 43 (37)                                 | 0.078   |         |
| Residual tumor             |             |                                         |                                         |         |         |
| 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)                                |         |         |
| Radiotherapy               |             |                                         |                                         |         |         |
| Yes                        | 263 (41)    | 92 (25)                                 | 171 (63)                                | 127.1   |         |
| No                         | 379 (59)    | 279 (75)                                | 100 (37)                                |         |         |
| 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)                                 |         |         |

Note: P values in bold are significant.
Abbreviations: DCIS: Ductal carcinoma in situ; N: Number; $\chi^2$: Chi-square.

*Age and size were categorized according to Van Nuys prognostic index (VNPI).
*Site: Localized: 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 (%) | DCIS diagnosed 2009-2017 N (%) | Total N (%) | \( \chi^2 \) | P-value |
|--------------------|---------------------------------|---------------------------------|-------------|----------|---------|
|                    | BCS (No.) | Mastectomy (No.) | BCS (No.) | Mastectomy (No.) | BCS (No.) | Mastectomy (No.) | BCS (No.) | Mastectomy (No.) | BCS (No.) | Mastectomy (No.) |
| Age                |          |                  |          |                  |          |                  |          |                  |          |                  |
| <40                | 13 (54)  | 11 (46)          | 5 (63)   | 3 (37)           | 18 (56)  | 14 (44)          | 2.6      |                  |          |                  |
| 40-60              | 297 (64) | 170 (36)         | 150 (68) | 71 (32)          | 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)         | 84 (56)  | 66 (44)          | 288 (58) | 212 (42)         | 26.4     |                  |          |                  |
| Screening          | 306 (68) | 146 (32)         | 230 (78) | 66 (22)          | 536 (72) | 212 (28)         | <0.0001  |                  |          |                  |
| Site               |          |                  |          |                  |          |                  |          |                  |          |                  |
| Localized          | 365 (62) | 224 (38)         | 250 (74) | 89 (26)          | 615 (66) | 313 (34)         | 48.6     |                  |          |                  |
| Diffuse            | 30 (38)  | 49 (62)          | 45 (56)  | 36 (44)          | 75 (47)  | 85 (53)          | <0.0001  |                  |          |                  |
| Size               |          |                  |          |                  |          |                  |          |                  |          |                  |
| <16 mm             | 256 (83) | 52 (17)          | 133 (89) | 16 (11)          | 389 (85) | 68 (15)          | 162.5    |                  |          |                  |
| 16-40 mm           | 175 (58) | 129 (42)         | 134 (74) | 46 (26)          | 309 (64) | 175 (36)         | <0.0001  |                  |          |                  |
| >40 mm             | 75 (41)  | 109 (59)         | 47 (40)  | 70 (60)          | 122 (41) | 179 (59)         |          |                  |          |                  |
| Grade              |          |                  |          |                  |          |                  |          |                  |          |                  |
| Low                | 92 (84)  | 17 (16)          | 41 (87)  | 6 (13)           | 133 (85) | 23 (15)          | 58.6     |                  |          |                  |
| Intermediate       | 133 (72) | 51 (28)          | 116 (78) | 32 (22)          | 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)          | 109 (85) | 20 (15)          | 324 (79) | 84 (21)          | 48.4     |                  |          |                  |
| Yes                | 295 (56) | 228 (44)         | 205 (65) | 112 (35)         | 500 (60) | 340 (40)         | <0.0001  |                  |          |                  |
| Solid DCIS         |          |                  |          |                  |          |                  |          |                  |          |                  |
| No                 | 273 (67) | 132 (33)         | 95 (77)  | 28 (23)          | 368 (70) | 160 (30)         | 7.1      |                  |          |                  |
| Pure               | 103 (63) | 61 (37)          | 89 (70)  | 38 (30)          | 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)         | 143 (70) | 62 (30)          | 417 (64) | 231 (36)         | 12.1     |                  |          |                  |
| Pure               | 59 (79)  | 16 (21)          | 33 (85)  | 6 (15)           | 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)         | 270 (68) | 128 (32)         | 728 (65) | 399 (35)         | 12.6     |                  |          |                  |
| Pure               | 21 (84)  | 4 (16)           | 15 (94)  | 1 (6)            | 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                 | 391 (66) | 202 (34)         | 236 (73) | 86 (27)          | 627 (69) | 288 (31)         | 9.6      |                  |          |                  |
| Pure               | 33 (62)  | 20 (38)          | 14 (54)  | 12 (46)          | 47 (60)  | 32 (40)          | 0.008    |                  |          |                  |
| Mixed with other types | 86 (55)  | 70 (45)          | 64 (65)  | 34 (35)          | 150 (59) | 104 (41)         |          |                  |          |                  |
| Associated Paget's |          |                  |          |                  |          |                  |          |                  |          |                  |
| No                 | 143 (36) | 256 (64)         | 40 (25)  | 120 (75)         | 183 (33) | 376 (67)         | 5.2      |                  |          |                  |
| Yes                | 7 (16)   | 36 (84)          | 3 (23)   | 10 (77)          | 10 (18)  | 46 (82)          | 0.022    |                  |          |                  |

Note: P values in bold are significant.
Abbreviations: BCS: Breast-conserving surgery; DCIS: Ductal carcinoma in situ; N: Number; \( \chi^2 \): Chi-square.
DCIS with cribriform morphology \( (P = 0.018) \), positive or close margins less than 2 mm \( (P = 0.015) \) and high-risk VNPI \( (P < 0.0001) \). Patients who underwent completion mastectomy showed a higher rate of residual tumor tissue than those who had a second re-excision operation \( (P < 0.0001) \). Table S3 shows the different factors associated with the presence of residual tumor 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 tumor in the re-excised specimens. Table 5 summarizes the multivariate logistic regression results.

Van Nuys prognostic index 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. Van Nuys prognostic index could not be assessed in 41 (5%) cases because one or more of the index parameters was missing.

A total of 263 out of 642 patients (41%) treated with BCS as a final surgery received postoperative adjuvant RT. Its use was associated with high-risk DCIS features including tumor size more than 40 mm \( (P < 0.0001) \), higher tumor 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 and 2008.
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 (%) | $\chi^2$ | P-value | DCIS diagnosed 2009-2017 N (%) | $\chi^2$ | P-value | Total | $\chi^2$ | P-value |
|-------------------------------|---------------------------------|----------|---------|---------------------------------|----------|---------|-------|----------|---------|
| **Age**                       |                                 |          |         |                                 |          |         |       |          |         |
| <40                           | 3 (23)                          | 6.7      | 0.034   | 113 (38)                        | 95 (63)  | 0.987   | 0.028 | 208 (46) | 239 (54) |
| 40-60                         | 184 (62)                        |          |         | 102 (63)                        | 59 (37)  |         |       | 196 (55) | 163 (45) |
| >60                           | 104 (52)                        |          |         |                                 |          |         |       |          |         |
| **Presentation**              |                                 |          |         |                                 |          |         |       |          |         |
| Symptomatic                   | 139 (68)                        | 13.2     | 0.034   | 41 (49)                         | 43 (51)  | 9.9     | 0.001 | 106 (37) | 182 (63) |
| Screening                     | 159 (52)                        |          |         | 157 (68)                        | 73 (32)  |         |       | 304 (57) | 232 (43) |
| **Site**                      |                                 |          |         |                                 |          |         |       |          |         |
| Localized                     | 208 (57)                        | 1.6      | 0.205   | 169 (68)                        | 81 (32)  | 10.9    |        | 326 (53) | 289 (47) |
| Diffuse                       | 17 (57)                         | 0.459    | 0.044   | 21 (47)                         | 24 (53)  |         |       | 34 (45)  | 41 (55)  |
| **Size**                      |                                 |          |         |                                 |          |         |       |          |         |
| <16 mm                        | 123 (48)                        | 37.1     | <0.001  | 112 (84)                        | 21 (16)  | 47.8    |        | 245 (63) | 144 (37) |
| 16-40 mm                      | 109 (62)                        |          | <0.001  | 69 (51)                         | 65 (49)  |         |       | 135 (44) | 174 (56) |
| >40 mm                        | 65 (87)                         |          | <0.001  | 17 (36)                         | 30 (64)  |         |       | 27 (22)  | 95 (78)  |
| **Grade**                     |                                 |          |         |                                 |          |         |       |          |         |
| Low                           | 58 (63)                         | 0.9      | 0.013   | 27 (66)                         | 14 (34)  | 1.6     |        | 61 (46)  | 72 (54)  |
| Intermediate                  | 76 (56)                         | 0.610    | 0.001   | 68 (59)                         | 48 (41)  |         |       | 125 (50) | 124 (50) |
| High                          | 164 (58)                        | 0.128    | 0.005   | 136 (55)                        | 48 (45)  |         |       | 224 (51) | 218 (49) |
| **Comedo necrosis**           |                                 |          |         |                                 |          |         |       |          |         |
| No                            | 134 (62)                        | 2.3      | 0.019   | 62 (57)                         | 47 (43)  | 2.7     |        | 143 (44) | 181 (56) |
| Yes                           | 164 (56)                        | 0.128    | 0.610   | 136 (55)                        | 48 (45)  |         |       | 224 (51) | 218 (49) |
| **Solid DCIS**                |                                 |          |         |                                 |          |         |       |          |         |
| No                            | 175 (64)                        | 9.8      | 0.007   | 59 (62)                         | 36 (38)  | 9.1     |        | 157 (43) | 211 (57) |
| Pure                          | 48 (47)                         |          | <0.001  | 67 (75)                         | 22 (25)  |         |       | 122 (64) | 70 (36)  |
| Mixed with other types        | 75 (56)                         | 0.128    | 0.610   | 72 (55)                         | 58 (45)  |         |       | 131 (50) | 133 (50) |
| **Cribriform DCIS**           |                                 |          |         |                                 |          |         |       |          |         |
| No                            | 166 (61)                        | 1.2      | 0.007   | 97 (68)                         | 46 (32)  | 4.5     |        | 205 (49) | 212 (51) |
| Pure                          | 32 (54)                         | 0.543    | 0.013   | 23 (70)                         | 10 (30)  |         |       | 53 (54)  | 42 (46)  |
| Mixed with other types        | 100 (56)                        | 0.128    | 0.610   | 78 (56)                         | 60 (44)  |         |       | 155 (49) | 160 (51) |
| **Papillary DCIS**            |                                 |          |         |                                 |          |         |       |          |         |
| No                            | 270 (59)                        | 0.5      | 0.131   | 168 (62)                        | 102 (38) | 3.9     |        | 356 (49) | 372 (51) |
| Pure                          | 11 (52)                         | 0.766    | 0.001   | 13 (87)                         | 2 (13)   |         |       | 23 (64)  | 13 (36)  |
| Mixed with other types        | 17 (55)                         | 0.128    | 0.610   | 17 (59)                         | 12 (41)  |         |       | 31 (52)  | 29 (48)  |
| **Micropapillary DCIS**       |                                 |          |         |                                 |          |         |       |          |         |
| No                            | 216 (55)                        | 10.1     | 0.006   | 160 (68)                        | 76 (32)  | 9.2     |        | 335 (53) | 292 (47) |
| Pure                          | 27 (82)                         |          | <0.001  | 7 (50)                          | 7 (50)   |         |       | 13 (28)  | 34 (72)  |
| Mixed with other types        | 55 (64)                         |          | <0.001  | 31 (48)                        | 33 (52)  |         |       | 62 (41)  | 88 (59)  |
| **Margin width**              |                                 |          |         |                                 |          |         |       |          |         |
| Positive (tumor on ink)       | 232 (97)                        | 318.7    | 3.4     | 74 (96)                         | 225.1    |         |       | 11 (3)   | 306 (97) |
| <2 mm                         | 27 (75)                         |          | <0.001  | 18 (35)                        | 34 (65)  |         |       | 27 (31)  | 61 (69)  |
| ≥2 mm                         | 175 (97)                        | 5 (3)    | 0.010   | 7 (50)                          | 7 (50)   |         |       | 340 (89) | 42 (11)  |
| **VNPI (1st operation)**      |                                 |          |         |                                 |          |         |       |          |         |
| Low risk                      | 32 (30)                         | 108.9    | 0.131   | 82 (91)                         | 8 (9)    | 71.3    |        | 155 (79) | 40 (21)  |
| Moderate risk                 | 185 (64)                        |          | <0.001  | 109 (60)                        | 73 (40)  |         |       | 212 (45) | 258 (55) |
| High risk                     | 76 (94)                         |          | <0.001  | 5 (13)                          | 32 (87)  |         |       | 10 (8)   | 108 (92) |

Note: P values in bold are significant.
Abbreviations: DCIS: Ductal carcinoma in situ; N: Number; VNPI: Van Nuys prognostic index; $\chi^2$: Chi-square.
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 tumor tissue in the re-excision specimens

| 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 |
| (a) | | | | | | | | | |
| 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 |
| (b) | | | | | | | | | |
| 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** |
| (c) | | | | | | | | | |
| 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** |
| (d) | | | | | | | | | |
| 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-excisionb | 4.8 | 2.4-9.5 | **0.0001** | 2.5 | 0.8-7.9 | 0.119 | 3.3 | 1.9-5.7 | **0.0001** |

Note: P values in bold are significant

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

bType of re-excision either another conservative surgery or completion mastectomy.
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).

4 | DISCUSSION

Prior to the early 1990s, 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.\textsuperscript{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 tumor grade, larger sized tumors (>40 mm), 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 5 mm was accepted instead of 10 mm, and a recent change of practice in 2016 in which 2 mm 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.\textsuperscript{27} Recently, in the UK and United States, the rate of mastectomy has increased particularly in young women perceived at high risk of further breast cancer events.\textsuperscript{6,28} In a report on 8000 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%.\textsuperscript{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.\textsuperscript{20,31}

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 are partly due to radiologic under-estimation of DCIS size which can occur in over 50% of cases.\textsuperscript{39,42} 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.\textsuperscript{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.\textsuperscript{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 tumor, even though some cases were reported to have tumor on ink after the primary excision. Such a finding perhaps illustrates the controversy in pathological evaluation.\textsuperscript{24} Presence of residual DCIS was correlated to other adverse clinicopathological parameters that is symptomatic presentation, larger tumor size, DCIS with cribriform and micropapillary morphology. Previous studies were performed to establish a margin index based on tumor size and the closest surgical margin to show its association with presence of residual tumor tissue after re-excision, but this did not show significant association.\textsuperscript{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.\textsuperscript{22} In our case series, an increased rate of residual tumor 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 tumor on ink as a negative margin as there is no evidence that wider clear margins reduce ipsilateral recurrence.\textsuperscript{38} In DCIS, the same group published consensus guidelines suggesting 2 mm as a standard for adequate surgical margin. Systematic review and meta-analysis of 20 studies showed that negative margins minimize the risk of ipsilateral recurrence by 50% compared with positive margins defined as tumor on ink. A 2 mm margin minimizes the risk of recurrence compared with smaller negative margins.\textsuperscript{39-41} However, the agreement on these recommendations is different between centers 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.\textsuperscript{42} Accepting closer margins of excision is a means of reducing re-operation rates, as has been shown in invasive disease.\textsuperscript{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 1 mm to >10 mm. In the current study, we grouped cases according to margin status using different classification schemes. Close surgical margins less than 2 mm were significantly associated with an increased rate of re-excision and presence of residual tumor tissue in the re-excision specimens which is consistent with other studies.\textsuperscript{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 individualized 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 postoperative RT. It was a common practice in our center 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 30 mm, regardless of tumor 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.

5 | 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 tumor size (>40 mm).

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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