



## ASSOCIATION OF BREAST SURGERY GUIDELINES

### ASSOCIATION OF BREAST SURGERY RECOMMENDATIONS FOR THE MANAGEMENT OF RADIAL SURGICAL MARGINS IN PATIENTS UNDERGOING BREAST CONSERVING SURGERY FOR DUCTAL CARCINOMA IN SITU (DCIS)

This guidance is endorsed by the following organisations:



Association of Breast Pathology



British Society of  
Breast Radiology



UK Breast Cancer Group

# Association of Breast Surgery Guidelines Recommendations for the management of radial surgical margins in patients undergoing breast conserving surgery for ductal carcinoma in situ (DCIS)

## EXECUTIVE SUMMARY

Optimal margin width following breast conserving surgery (BCS) for DCIS has been a controversial issue for many years. This has been driven by the need to ensure wide excision of the DCIS whilst minimising cosmetic disturbance to the breast. Discussions around radial margin width for DCIS necessarily differ from those related to invasive breast cancer as DCIS is recognised to have a potentially more diffuse pattern of involvement of breast tissue and there may be less use of adjuvant systemic therapies<sup>1</sup>.

Part of the complexity relating to determining optimal margin width for DCIS is that much of the published data relates to single institution observational studies with variable techniques of tissue assessment, differing definitions of clear margins and varying degrees of follow up. There has never been, and probably never will be, a randomised trial examining this issue. This has led to inconsistent guidance on optimal margins in this patient group, ranging from >1mm<sup>2</sup> to > 2mm<sup>1</sup>. Current guidance from the National Institute for Health & Care Excellence is that margins less than 2mm should lead to advice for patients to consider re-excision or mastectomy as appropriate<sup>3</sup>.

Examination of indicators of clinical outcomes following surgery for DCIS have identified decreasing margin width to be linked to increasing local recurrence and breast cancer mortality<sup>4-7</sup> but have not managed to advise on the optimum width necessary to minimise these adverse outcomes. However, more recent systematic reviews and meta-analyses have improved the clarity of available data.

This document was produced by a multi-disciplinary writing group with the aim to provide clinical teams with evidence-based recommendations for the management of radial surgical margins after BCS for DCIS. The main conclusions are that there is increasing evidence to indicate 2mm is the critical margin width following BCS for DCIS as a radial margin width less than 2mm increases risk of local recurrence. Radial margin widths greater than 2mm margin width do not provide extra clinical benefit.

## Background

In 2016, Marinovitch and colleagues reported on 7883 patients undergoing BCS for DCIS over a median follow up period of 78 months to study the influence of surgical margin width on clinical outcomes<sup>8</sup>. Median DCIS size was small (10.9mm; IQR 8.0 – 14.9mm). Most patients (71%) received whole breast radiotherapy and a minority (21%) received adjuvant endocrine therapy. The meta-analysis found that margin width of 2mm was associated with a lower risk of local recurrence (LR) compared with a narrower negative margin width of >0mm or 1mm (odds ratio [OR] = 0.51; 95% CI, 0.31–0.85). However, a more widely negative margin (>2 mm) did not further reduce the risk of LR (relative OR = 0.99; 95% CI, 0.61–1.64).

The subsequently published guidelines from the Society of Surgical Oncology/ASCO<sup>1</sup> were largely based on the Marinovitch analysis and, in relation to margin widths, concluded:

- A positive margin, defined as ink on DCIS, is associated with a significant increase in ipsilateral recurrence. This increased risk is not nullified by the use of adjuvant whole breast irradiation.
- Margins of at least 2mm are associated with a reduced risk of ipsilateral recurrence relative to narrower negative margin widths in patients receiving adjuvant whole breast irradiation.

- The practice of routinely seeking negative margin widths wider than 2 mm is not supported by the evidence.

The guidance had real world impact on the practice of breast surgeons in America<sup>9</sup>, reducing re-excision rates where margins were above 2mm and increasing re-excision rates in cases where they were <2mm.

In an observational cohort study, Mannu and colleagues evaluated the long-term risks of invasive breast cancer in the population of women diagnosed with screen-detected DCIS in England during 1988–2014 with follow-up to 2018.<sup>4</sup> For women diagnosed with unilateral DCIS during 2007–2014 who received BCS but not endocrine therapy, they noted that local recurrence rates start to rise from the second year following diagnosis and continued to do so for at least a further 20 years. With individual patient level margin measurements obtained where available, an important predictor of subsequent ipsilateral invasive breast cancer was margin width at the time of surgery for DCIS. Compared with negative margins of ≥5mm, negative margin widths of 3–4mm had a local recurrence rate ratio after adjustment of 1.32 (95% CI 0.80–2.29), while negative margin widths of 1–2mm had local recurrence rate ratio after adjustment of 1.74 (95% CI 1.15 – 2.63), and involved margins had local recurrence rate ratio after adjustment of 3.73 (95% CI 2.04–6.83).<sup>4</sup>

Kim and colleagues also examined the effect of margin width on local recurrence rates<sup>10</sup>. Their meta-analysis of 12 retrospective studies focused on patients with DCIS who had undergone mastectomy, not BCS and therefore a different cohort to those being discussed in this document. Nevertheless, their findings were strikingly similar; margin widths below 2mm resulted in 2.3 fold higher local recurrence rates compared with those seen in cases with >2mm margin width.

More recently, in an abstract of meeting proceedings, Robertson and colleagues have published outcomes in a large series of patients<sup>11</sup>. They obtained individual patient level margin measurements for 17260 patients undergoing BCS for DCIS diagnosed within the NHS Breast Screening Programme (NHS BSP) to assess the influence of margin width on clinical outcomes. Median follow up was 8.8 years. The study shows that time to recurrence was strongly influenced by margin width, with margins less than 2mm resulting in a shorter time to recurrence compared to that seen when margins were 2mm (adjusted Hazard Ratio (HR) 1.20 (95% CI 1.06 – 1.36)) for recurrence. Margin widths greater than 2mm did not improve time to recurrence. Significantly, these findings translated to reduced overall survival seen in women in whom margin width for excision of DCIS was <2mm versus those in whom it was ≥2mm (adjusted HR 1.23 (95% CI 1.06 – 1.43)). Margins >2mm did not further improve overall survival. Interestingly, this paper also revealed an effect of number of BCS procedures on local recurrence rates, with increased local recurrences seen in women having 2 (adjusted HR 1.26 (95% CI 1.10 – 1.44)) or 3 (adjusted HR 2.04 (95% CI 1.37 – 3.04)) attempts at BCS to obtain clear margins.

Complimentary to the findings of the Robertson study, a meta-analysis of the impact of margin width on the risk of local recurrence following BCS for DCIS, also published as an abstract of meetings proceedings, found that decreasing margin widths increased the relative risk of local recurrence<sup>12</sup>. The authors noted that an increasing margin width beyond 2mm offered a decreasing magnitude of risk reduction.

### Indications for Breast Conserving Surgery in DCIS

There have been no randomised trials comparing BCS to mastectomy for DCIS, and it is unlikely that there will be, as BCS is now established practice. Evidence for its oncological equivalence with mastectomy was extrapolated from the influential early trials in invasive disease, such as the NSABP-O6<sup>13</sup>. Randomised trials investigating BCS for invasive breast cancer with and without radiotherapy demonstrated that adjuvant radiotherapy reduced the risk of local recurrence<sup>14</sup>. This was confirmed by an EBCTCG meta-analysis of 4 trials, which also demonstrated that omission of radiotherapy had no significant effect on mortality (breast cancer or all-cause) at 10 years<sup>15</sup>. The UK based Sloane Project of screen detected DCIS and a recent large UK cohort study (non-screen detected DCIS) have demonstrated that BCS for DCIS (with or without radiotherapy) has a higher rate of local recurrence compared to mastectomy, but no difference in breast cancer attributable mortality<sup>16,17</sup>, therefore BCS with radiotherapy is considered a safe treatment for DCIS. Oncoplastic techniques may aid improved breast conservation rates, and some observational data suggest similar outcomes to standard BCS<sup>18</sup>.

### Non-invasive margins imaging guidance

To reduce the likelihood of close margins, accurate preoperative assessment of disease size using conventional mammogram and ultrasound is important and considered best practice. Routine use of preoperative assessment with MRI or Contrast Enhanced Mammography has been shown to be of limited value but may be helpful in mammographically occult disease, where there is a size discrepancy between clinical and radiological estimates or in cases of high grade DCIS<sup>18,19</sup>. In addition, MRI may show some utility in assessing the extent of non-calcified DCIS<sup>20</sup>. As a caveat, a recent literature review suggests that although MRI is more accurate than mammograms in DCIS size estimation, it does not seem to translate to lower re-operation or mastectomy rates following BCS<sup>21</sup>.

### Intraoperative cavity shaving for DCIS

Specimen X-ray currently remains the standard for intraoperative margin assessment in DCIS. When margins appear close or involved on specimen X-ray, the selective removal of additional tissue at the affected cavity wall is considered standard practice in many UK units. Conversely, four quadrant cavity shaving (CS) is the non-selective removal of circumferential tissue from the wide local excision cavity at the time of the initial surgery<sup>22</sup>.

A few small studies have suggested that four quadrant cavity shaving reduces reoperation rates. Chagpar and colleagues randomised control trial included only 45 patients with DCIS and the result for this cohort is not presented independently from the whole study group in which they found an overall reduction in re-excision rates from 21% to 10% (p=0.02)<sup>22</sup> in those in the 'shavings' arm. A recent retrospective study including 61 patients with DCIS, from 2 centres that practice routine 4 cavity shaving in the West of Scotland demonstrated that 18.7% of patients avoided re-excision as a result of radial CS. Conversely, in 7.1%, routine radial CS identified positive margins in the CS despite negative margins in the wide local excision<sup>23</sup>. Howard-McNatt and colleagues randomised trial inclusive of 109 women with DCIS found that cavity shaving reduced the positive margin rate by 36.2% (P < 0.001)<sup>24</sup>. Comparatively, Chen and colleagues randomised control trial of breast conserving surgery in 181 women found a trend for cavity shaves to reduce positive margins, but this did not reach statistical significance. 16.5% vs. 7.8%, P=0.073)<sup>24</sup>.

In the setting of breast conservation, a careful balance should be struck between adequate tissue resection and cosmesis. Within the published literature, the volume or thickness of breast tissue that constitutes an adequate cavity shave remains elusive. The amount of tissue removed at routine 4 quadrant CS may be sizable<sup>22</sup> and the impact on cosmesis and patient satisfaction has not been investigated.

### Treatment factors affecting local recurrence rate for DCIS

There are multiple factors affecting the risk of local recurrence including patient features, mode of presentation and numerous tumour biology factors. The subsequent treatments have been shown to affect local recurrence risk.

## Radiotherapy:

Several meta-analyses and randomised controlled trials (RCT) have evidenced the local recurrence risk reducing effects of radiotherapy; the earliest being the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17<sup>26</sup>. The Early Breast Cancer Trialist Collaborative Group's meta-analysis of 4 RCTs similarly showed an additive effect of adjuvant whole breast radiotherapy following BCS in reducing ipsilateral local recurrence with the rate being almost halved ( $P < 0.001$ ). This corresponded to a 5-year absolute risk reduction of 10.5% (standard error (SE) = 1.2%, 7.6% vs. 18.1%) and 10-year absolute risk reduction of 15.2% (SE = 1.6%, 12.9% vs. 28.1%)<sup>27</sup>. Data from the Surveillance, Epidemiology and End Result (SEER) database showed the local recurrence risk to be approximately 50% less with adjuvant radiotherapy at 10 years (adjusted HR = 0.47, 95% CI 0.42- 0.53,  $P < 0.001$ )<sup>28</sup>. The risk-reducing effects of radiotherapy on local recurrence in DCIS is irrespective of the patient's age and whether other adjuvant therapy is delivered<sup>27</sup>.

It should be noted that the need for adjuvant radiotherapy is not always predictable due to potential disparities between biopsy and surgical pathology diagnoses<sup>29,30</sup>. In addition, in some circumstances, selective avoidance of radiotherapy for low grade, small areas of DCIS<sup>31</sup> may be approved by the multi-disciplinary team.

## Endocrine therapy:

Hormone receptor status' influence on local recurrence risk for DCIS is inferred from data evaluating the effects of adjuvant endocrine therapy. The NSABP B-24 study showed that amongst 1804 women, Tamoxifen reduced the 15-year cumulative local recurrence rate from 18.3% to 16.0%. However, approximately 25% of the women randomised had involved or uncertain margins, confounding the results<sup>32</sup>. The UK/ANZ trial randomisation of 1576 women to receive Tamoxifen versus no Tamoxifen found new ipsilateral breast events at 5 years (HR = 0.71, 95% CI 0.58-0.88  $P = 0.02$ ) and 10 years (HR = 0.78, 95% CI 0.62- 0.99,  $P = 0.04$ ) to be significantly reduced amongst those receiving adjuvant Tamoxifen. When further subcategorised into concurrently receiving radiotherapy or not, however, no significant combined additive effect was found (HR= 0.93, 95% CI 0.50- 1.75,  $P = 0.8$ )<sup>33</sup>.

The NSABP B-35 randomised double blinded phase 3 clinical trial shows that the risk reducing effects of endocrine therapy on local recurrence in DCIS extends to the use of aromatase inhibitors<sup>34</sup>. However, the local recurrence risk reduction effects appears limited to women younger than 60 years (HR = 0.53, 95% 0.66-1.37,  $P = 0.78$ )<sup>34</sup>. Conversely, the IBIS-II double blinded RCT found Tamoxifen and Anastrozole to have comparable efficacy in reducing local recurrence in oestrogen receptor (ER) positive DCIS (adjusted HR = 0.83, 95% CI 0.59- 1.18,  $P = 0.31$ )<sup>35</sup>.

However, a survival benefit has not been observed for the use of endocrine therapy in women with ER positive DCIS, despite the reduction in local recurrence events of endocrine therapy. Important consideration is therefore needed regarding the selection of patients in whom antioestrogen therapy may have a particular role and also the continuation of endocrine treatment in those who experience debilitating side effects<sup>36</sup>.

## Age:

RCTs and cohort studies have shown younger age to be a positive predictor of local recurrence in DCIS<sup>27,33,37-40</sup> but the recent NRG Oncology/RTOG 9804 Trial, did not replicate these earlier findings (HR = 0.65, 95% CI 0.34-1.21,  $P = 0.17$  for women 50 years compared to those <50 years old)<sup>41</sup>.

## Managing Anterior (superficial) and Posterior (deep) Margins in BCS for DCIS

This document and the recommendations refer specifically to radial margins in BCS. The management of anterior and posterior margins in the excision of DCIS remains a difficult topic to summarize because of the lack of published data on which to develop evidence-based guidance. Good quality data on the effect of close or positive anterior or posterior margins on oncological outcomes in women undergoing BCS for DCIS cannot be found. Nevertheless, it should be recognised that the concept of removing breast tissue from skin to pectoral fascia during BCS for breast malignancies stems from guidance published in 2009 and may not be applicable for every case in current practice<sup>42</sup>.

There are a small number of single institution retrospective studies reporting outcomes of close anterior margins in women undergoing skin/nipple sparing mastectomies for DCIS. In one publication, 5 of 71 patients had positive anterior margins (defined as <0.1mm) following skin sparing mastectomy, with no recurrences at an average of 67 months follow up<sup>43</sup>. Shaffer and colleagues<sup>44</sup> reported on 161 women undergoing nipple sparing mastectomies for DCIS; of these 91 had positive or close (defined as tumour on ink or <2mm respectively) anterior or posterior margins. Only 5 patients suffered local recurrence, 2 with involved/close margins and 3 with margins with  $\geq 5$ mm clearance.

There is no robust evidence from which to produce recommendations relating to anterior and posterior margins when performing BCS for DCIS.

**RECOMMENDATIONS**

These relate to the management of ductal carcinoma in situ (DCIS), using breast conservation surgery.

- Preoperative assessment of disease size using conventional (mammogram and ultrasound) imaging is recommended.
- As accurate sizing of DCIS with mammogram and ultrasound can be challenging, preoperative assessment with MRI or Contrast Enhanced Mammography may be considered. Particularly in; mammographically occult disease, in cases where there is a size discrepancy between clinical and radiological estimates, in cases of high-grade DCIS (calcified and non-calcified) or if conventional imaging is difficult to interpret.
- For extensive lesions (e.g. widespread microcalcifications), biopsy from more than one area should be considered, targeted appropriately according to the radiological features. Further sampling (to help inform patient-clinician treatment discussion) should be directed towards areas of greater radiological concern, preferably distant from the site of the first specimen.
- BCS should be considered in all patients with DCIS, when technically feasible, and who have no contraindications to adjuvant radiotherapy.
- At pre-operative diagnosis, the area of disease should be assessed clinically and radiologically and be considered resectable with adequate margins and an acceptable cosmetic result<sup>45</sup>.
- Bracketing localisation of the area of disease may be considered to support complete surgical excision of the DCIS.
- Contraindications for BCS in women with DCIS highly likely to be offered adjuvant radiotherapy: previous breast or mantle radiotherapy, homozygous ATM mutation carriers, inability to lie flat or abduct the arm, implantable devices within radiation field (e.g. pacemaker).
- Relative contraindications for BCS in women with DCIS highly likely to be offered adjuvant radiotherapy include Li-Fraumeni syndrome, scleroderma and Systemic Lupus Erythematosus.
- Other considerations when considering BCS for DCIS include patient choice and pregnancy where treatment planning should take into account DCIS biology, stage of pregnancy and patients' wishes. Where possible, pregnant women diagnosed with DCIS should be under the care of the local multidisciplinary pregnancy associated breast cancer team.
- Intraoperative imaging (e.g. digital specimen radiography cabinet) is strongly recommended and is part of current best practice guidance for all screen-detected non-palpable lesions, which will include almost all cases of DCIS<sup>42</sup>. Specimen imaging will confirm identification and removal of the target area and give an indication of completion of excision.
- It is recommended that the optimum radial margin of clearance when surgically excising DCIS is 2mm.
- There is insufficient evidence to support or refute the routine practice of four quadrant cavity shaves, but surgeons may consider this for DCIS in view of the recognised discordancy between preoperative imaging size and true histological size. This would be undertaken following MDT discussion with the understanding that there is no current standardisation for this practice nor a consensus definition of tissue volume and what constitutes a cavity shave in the literature.
- Where BCS is performed for DCIS and does not incorporate removal of all breast tissue from skin to pectoralis fascia, this should be clearly noted on the histopathology form and the operation note so that the pathologist can thoroughly examine these aspects, and the MDT can make an informed decision regarding margin status of all six margins.

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