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Overview

The Management of Ductal Carcinoma *in Situ*: Current Controversies and Future Directions

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Abstract

The incidence of ductal carcinoma *in situ* (DCIS) has increased in recent decades, primarily due to the widespread implementation of breast cancer screening. Traditionally, the management of DCIS has mirrored that of invasive breast cancer, with a focus on adequate surgical excision, breast-conserving surgery, adjuvant radiotherapy and endocrine therapy. However, an increasing understanding of the biology of this spectrum of conditions many mean that some cases may be managed more conservatively, reserving aggressive therapies for those patients at high risk of progression to invasive disease, ultimately aiming for a personalised approach based on individual risk factors. This overview highlights the key evidence behind current practice and discusses the rationale for current and future clinical trials in DCIS.

Key words: Breast cancer; DCIS; ductal carcinoma *in situ*

Statement of Search Strategies Used and Sources of Information

This overview is based on a detailed review of international peer-reviewed literature. A search of PubMed, ClinicalTrials.gov and the Cochrane Library was carried out for published articles containing the following key words in the title: 'DCIS', 'ductal carcinoma *in situ*' OR 'ductal carcinoma *in situ* of the breast'. A manual search of the Proceedings of the American Society of Clinical Oncology (ASCO) annual meeting was also carried out and epidemiological information was obtained from www.cancerresearchuk.org. The reference lists from previous extensive review articles were also reviewed to obtain pertinent articles.

Introduction

Previously a rare condition, the worldwide incidence of ductal carcinoma *in situ* (DCIS) of the breast has increased markedly since the introduction of population screening. In the UK, 4563 cases were diagnosed in 2009 [1]. Patients with DCIS have an increased future risk of invasive cancer [2] and therefore its management has traditionally been similar to those approaches used to manage early invasive breast cancer.

However, an increasing understanding of the natural history of 'clinically occult' DCIS, with outcomes from several surgical series, has led adaptations of this approach. By identifying factors that predict risk of future invasive disease, clinicians may potentially manage some cases more conservatively, enabling patients to avoid the potential long-term consequences of adjuvant therapy, whereas patients at higher risk may benefit from more intensive adjuvant therapy. However, these strategies are the focus of present and future clinical trials and cannot currently be considered the standard of care.

This review summarises existing evidence supporting current treatment strategies for DCIS. We discuss the limitations of these data and the ways in which current and future clinical research seeks to develop more patient-specific treatment plans.

The Impact of Screening

Population screening has led to marked reductions in breast cancer morbidity and mortality, and as a result

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'clinically occult DCIS' has become a common diagnosis [3]. No prior knowledge of the natural history of this condition therefore existed before screening; accurately quantifying risk was impossible immediately after its introduction on a mass scale. The focus of DCIS management has been on minimising the risk of recurrence and progression to invasive breast cancer, using local therapy (surgery and radiotherapy) and endocrine therapy. In many aspects, knowledge of effective strategies for the management of invasive breast cancer, as well as data from pre-screening DCIS series, defined DCIS management in the immediate post-screening era.

The Importance of Surgical Margins, Risk of Invasive Component and Lymph Node Sampling

A retrospective analysis of 469 patients with DCIS treated in California from 1972 to 1987 [4] showed that tumours excised with a margin width 1 cm or greater in every dimension had an estimated probability of recurrence of 4% (±2%) at 8 years, and that in this group postoperative radiotherapy did not seem to add benefit ($n = 133$). Similarly, there was no significant benefit found with radiotherapy for patients with margins 1–10 mm, whereas a benefit did exist for those with margins less than 1 mm, suggesting that radiotherapy may be compensating for suboptimal surgery and showing the importance of obtaining clear surgical margins. At 12 years of follow-up [5], a small benefit for the addition of radiotherapy had emerged for tumours with excision margins of 10 mm or greater. However, it is noted that this benefit is small, and the number needed to treat to prevent one recurrence (invasive *or* non-invasive) was 10. In addition, many of these patients will have presented with clinically detectable relatively large tumours. However, these data do strongly support the practice of wide excision.

Several series have shown that an invasive component may be detected in biopsy-proven DCIS after excision [6–9]. A recently published series of 506 patients [10] showed that this occurred in 42.7% of cases of DCIS diagnosed on core biopsy. Risk factors for the presence of invasion include a palpable mass, ultrasonic lesion >20 mm, mammographically detected masses (as opposed to microcalcification) and high grade. Furthermore, 20% of patients undergoing sentinel node biopsies at surgery ($n = 406$) were found to have lymph node positivity, although all the associated primary tumours contained an invasive component. Tumour size was significantly associated with lymph node positivity.

These data suggest that there may be a role for sentinel node biopsy at the time of wide excision in patients with extensive high-grade disease, preventing the need for a separate operation in cases where invasive disease is detected. However, the incidence of lymph node positivity in patients with pure DCIS after wide excision is low, and so this approach is not universally advocated.

According to the Surveillance, Epidemiology and End Results (SEER) database [11], between 2000 and 2008 15% of US women undergoing lumpectomy for DCIS underwent sentinel node biopsy or axillary node sampling. The American Society of Clinical Oncology recommends lymph node assessment in patients with DCIS measuring >5 cm, although this is rarely the case, as most tumours are detected at an earlier stage [12]. Further prospective studies are required to determine the true value of lymph node assessment in DCIS.

Adjuvant Radiotherapy

The development of breast-conserving surgery (BCS) for early invasive breast cancer in the 1980s led to the adoption of this strategy for DCIS. The rate of local recurrence is inevitably higher with BCS than with mastectomy, and a proportion of recurrences will be invasive — these cases of invasive disease can largely be prevented with adjuvant radiotherapy, a logical adjunct to BCS. Conversely, however, radiotherapy itself can have long-term consequences, including an increased risk of vascular death, pulmonary fibrosis and second malignancies in the treated volume [13]. Specific studies therefore aimed to evaluate its value in DCIS.

In a US National Surgical Adjuvant Breast and Bowel Project (NSABP) trial, NSABP-B17 [14] (see Table 1), patients with DCIS were randomised to receive lumpectomy + radiotherapy (LRT) or lumpectomy with no further treatment (LO). The primary end point was event-free survival (defined by the presence of no new ipsilateral or contralateral breast cancers, regional or distant metastases, or other cancers and by no deaths from causes other than cancer). At 5 years, event-free survival was 84.4% in the LRT group compared with 73.8% in the LO group ($P = 0.001$). This was specifically due to a reduced number of ipsilateral breast recurrences. Notably, half of these ipsilateral recurrences were non-invasive; overall the rate of invasive disease recurrence was 8% (32/391), compared with 2% (8/399) in the LRT group.

Following this, BCS and adjuvant radiotherapy became a standard alternative to mastectomy in patients with DCIS. However, a number of questions surrounding the role of radiotherapy remained: the NSABP-B17 investigators did not stratify patients by tumour grade; patients with low-grade disease have the lowest rates of recurrence after treatment for DCIS — it may be safer to omit radiotherapy altogether in these patients, given the risks of long-term consequences from radiotherapy itself.

Other criticisms of NSABP-B17 included a lack of central laboratory review of diagnostic specimens [19] and the short initial follow-up period.

With longer follow-up [15], the LRT group had a cumulative invasive ipsilateral breast tumour recurrence incidence of 8.9% compared with 15.9% in the LO group at 15 years. This was supported by combining these results with those from the NSABP-B24 trial [20], where the 15 year invasive ipsilateral breast tumour recurrence rate was 10% in the group receiving LRT without tamoxifen.

Long-term results from a similar large UK and Australasian trial [16] (Table 1) were published in 2011. In total, 1701 patients were recruited into a 2 × 2 factorial randomised trial of adjuvant radiotherapy, adjuvant tamoxifen, both or neither

Table 1
Results of Published Randomised Controlled Trials Evaluating Adjuvant Radiotherapy for ductal carcinoma *in situ* (DCIS)

Reference	Randomisation	Non-invasive recurrence	*P*-value	Invasive recurrence	*P*-value	Comments
Fisher *et al.* (NSABP-B17) [14]	Lumpectomy + radiotherapy ($n = 401$) versus lumpectomy with no further treatment ($n = 393$)	10.4% versus 7.5% ipsilateral DCIS recurrence at 5 years in favour of lumpectomy + radiotherapy	<0.055	10.5% versus 2.9% ipsilateral invasive recurrence at 5 years in favour of lumpectomy + radiotherapy	<0.001	Event-free survival 84.4% versus 73.8% at 5 years ($P = 0.001$) 15 year results combined with NSABP-B24 group (see below)
Wapnir *et al.* [15] (NSABP-B17 and B24 long-term follow-up)	NSABP-B17 as above; NSABP-B24 lumpectomy + radiotherapy + placebo ($n = 900$) versus lumpectomy + radiotherapy + tamoxifen ($n = 899$) 15 years of follow-up	Ipsilateral DCIS recurrence rates at 15 years: NSABP-B17 lumpectomy only 15.4%, NSABP-B17 lumpectomy + radiotherapy 9.0%, NSABP-B24 lumpectomy + radiotherapy + placebo 7.6% NSABP-B24 lumpectomy + radiotherapy + tamoxifen 6.7% Hazard ratio 0.53, favours radiotherapy (NSABP-B17)	<0.001	Ipsilateral invasive recurrence rates at 15 years: NSABP-B17 lumpectomy only 19.6%, NSABP-B17 lumpectomy + radiotherapy 10.7%, NSABP-B24 lumpectomy + radiotherapy + placebo 9.0% NSABP-B24 lumpectomy + radiotherapy + tamoxifen 6.6% Hazard ratio 0.48, favours radiotherapy (NSABP-B17)	<0.001	Combined results of NSABP-B17 and B24 trials. No evaluation of oestrogen receptor or Her-2 status made.
Houghton *et al.* (UK-ANZ) [16]	2 × 2 factorial design: lumpectomy ± radiotherapy, tamoxifen or both ($n = 1030$ in radiotherapy randomisation)	9.7% versus 3.8% ipsilateral DCIS recurrence (median follow-up 12.7 years) in favour of radiotherapy	<0.0001	9.1% versus 3.3% ipsilateral invasive recurrence (median follow-up 12.7 years)	<0.0001	
Emdin *et al.* (SweDCIS) [17]	Wide local excision + radiotherapy versus wide local excision and no radiotherapy ($n = 1067$, 1:1, 1046 analysed)	13.3 % (69/520) versus 4.4% (23/526) ipsilateral DCIS recurrence (median follow-up 5.2 years)	<0.0001 for all ipsilateral recurrences	9.2% (48/520) versus 4.0% (21/526) (median follow-up 5.2 years)	<0.0001 for all ipsilateral recurrences	
Bijker *et al.* (EORTC) [18]	Radiotherapy versus no radiotherapy (1:1) after complete local excision of lesion ($n = 1010$)	Risk of ipsilateral DCIS recurrence reduced by 48% at 10.5 years' median follow-up	0.0011	Ipsilateral invasive recurrence reduced by 42% at 10.5 years' median follow-up	0.0065	Margin width not specified. Combined (DCIS + invasive) local recurrence-free rates 74% and 85% for local excision alone and local excision + radiotherapy, respectively

after BCS for DCIS. The primary end point in the radiotherapy arm was the incidence of invasive ipsilateral new breast events. With a median follow-up of 12.7 years, it was observed that radiotherapy ($n = 1031$ randomised to radiotherapy or not) reduced the risk of ipsilateral invasive disease from 9.1% to 3.3% (hazard ratio 0.32, $P < 0.0001$), with a reduction in all ipsilateral breast events from 19.4% to 7.1%. These effects were independent of tamoxifen administration.

A 2009 systematic review [21] included these two trials, with the addition of a Swedish study ($n = 1067$) [17] (Table 1) and a European Organization for Research and Treatment of Cancer (EORTC) trial ($n = 1010$) [18] (Table 1), both of which used a similar 1:1 randomised design. Using pooled results from the four trials, the authors concluded that the addition of radiotherapy results in a hazard ratio of 0.49 (95% confidence interval 0.41–0.58, $P < 0.00001$) for all ipsilateral breast events. In addition, all four individual trial results were consistent with this finding. Specific data for invasive cancer recurrence were not reported in a consistent way in all trials and so a pooled analysis was not possible for this end point.

Subgroup analyses within the individual trials have identified several factors that confer a higher risk of recurrence, including age 40 years or under, intermediate or poorly differentiated DCIS, a cribriform or solid growth pattern and comedo necrosis. However, in the EORTC study [18], where these analyses were carried out, a benefit from radiotherapy was still observed in all subgroups.

Patient Selection for Radiotherapy: How Do We Know Who is Really 'Low Risk'?

Whereas BCS followed by radiotherapy has become the standard of care in DCIS, retrospective series have suggested that in some circumstances it may be preferable to omit adjuvant radiotherapy for patients with small tumours and wide surgical margins who are at lower risk for recurrence.

Historical recurrence data have led to various predictive tools to aid patient selection for adjuvant treatment, the Van Nuys Prognostic Index (VNPI) being the most widely recognised. Originally based on a retrospective series of 330 patients, this incorporates known risk factors for recurrence and invasion (grade, tumour size and surgical margin width) (Table 2) [23].

Within the original cohort, those with VNPI 3 or 4 were considered 'low risk' and were found to have an 8 year actuarial recurrence-free survival rate of 97% ($n = 101$), compared with 77% for patients scoring 5, 6 or 7 ($n = 209$) and 20% for patients scoring 8 or 9 ($n = 23$). Following this, there was enthusiasm for the use of the VNPI as a risk stratification tool, and some clinicians advocated the omission of adjuvant radiotherapy in the low-risk group [22]. However, despite further series and the incorporation of age to create the modified VNPI [22] (Table 2), this tool has not been prospectively validated, and the results of the large prospective trials discussed above have shown a benefit for adjuvant radiotherapy across all subgroups. Therefore, many currently consider that there is insufficient objective evidence to advocate the omission of radiotherapy even in low-risk patients. Further factors continue to be added; for example a study published in 2011 showed improved prognostic value when the genomic grade index was incorporated into the VNPI, especially for predicting early relapse [24].

Prospective studies directed at assessing the safety of BCS alone for low-risk patients have been difficult to design and to recruit to. A single-arm observational study in patients with predominantly grade 1 or 2 DCIS, ≤2.5 cm in size and surgical margin width ≥1 cm [25] failed to identify a subgroup of patients who may be safely treated with wide local excision alone. In fact, the study closed early after 158 of a planned 200 patients had been recruited, due to the number of local recurrences meeting predefined stopping criteria.

A larger Eastern Cooperative Oncology Group (ECOG) study [26] set out to evaluate ipsilateral breast event rates and survival outcomes in patients with small DCIS tumours treated with BCS alone, while simultaneously assessing pathological reporting of DCIS grade, identifying factors to predict recurrence, and recording approaches to treatment of subsequent relapsed disease. Two groups of patients were recruited: (a) patients with low- or intermediate-grade DCIS measuring 2.5 cm or smaller; and (b) patients with high-grade DCIS 1 cm or smaller. All patients were required to have had BCS with margins 3 mm or greater. Patients with residual microcalcifications on postoperative mammography were ineligible. In total, 565 eligible patients were assessed in the low-/intermediate-grade group; 105 patients were assessed in the high-grade group.

Table 2
Modified Van Nuys Prognostic Index with author's recommendations

Score	1	2	3
Size (mm)	≤15	16–40	≥41
Margin width (mm)	≥10	1–9	<1
Pathology	Non high grade without necrosis (nuclear grades 1 or 2)	Non high grade with necrosis (nuclear grades 1 or 2)	High grade with or without necrosis (nuclear grade 3)
Age (years)	>60	40–60	<40
Score		Recommendation	
4–6		Excision alone	
7–9		Excision + radiation	
10–12		Mastectomy	

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For patients with low- or intermediate-grade DCIS ($n = 558$ patients analysed), at a median follow-up of 6.2 years there had been 49 ipsilateral breast events, of which 53% were invasive. The 5 year ipsilateral breast event rate was 6.1% (95% confidence interval 4.1–8.2%) and at 7 years this was 10.5% (7.5–13.6%). Ten year data are awaited. Twenty-one of these 49 patients with ipsilateral breast events were treated with further BCS at the time of relapse; 24 patients underwent mastectomy and four patients received systemic therapy only after biopsy. Three patients developed ipsilateral nodal disease and one patient both nodal and distant metastases. Five year disease-free survival was 85.6% (82.6–88.6%). Although 41 patients had died at the time of reporting, there were no breast cancer deaths in this group.

Accrual into the high-grade DCIS group was slow and so a decision was made to stop recruitment early; data were available for 103 patients at the time of reporting. In this group the 5 year ipsilateral breast event rate was higher at 15.3% (8.2–22.5%) and was 18.0% at 5 years. Thirty-five per cent of the 17 ipsilateral breast events observed were invasive.

The authors concluded that for patients with low- to intermediate-grade disease, the ipsilateral breast event rate of 6% at 5 years was probably acceptable to patients and physicians, whereas the 15% rate in the high-grade group would not be. It was noted, however, that the incidence of ipsilateral breast events continued to increase at 5 years, and so it could not be stated whether BCS only would be acceptable in the longer term.

A randomised trial of radiotherapy versus no radiotherapy after BCS in selected patients with low- or intermediate-grade DCIS (using the same selection criteria as the above ECOG trial) (RTOG 98-04) [27] was closed due to poor accrual and so the definitive answer to the question of omission of radiotherapy in this group remains elusive.

Biomarkers and other Prognostic/ Predictive Factors

The use of prognostic and predictive markers is well established in invasive breast cancer. One of the earliest such markers to be studied was the oestrogen receptor and measurement of tumour oestrogen receptor expression can reliably guide adjuvant therapy with tamoxifen and aromatase inhibitors, although it remains a weak prognostic marker [28]. It is commonly expressed by DCIS cells [28–32], is more frequently expressed by well-differentiated DCIS than poorly differentiated disease, and is associated with a lower risk of local disease recurrence [32]. However, the real relevance of these observations is difficult to gauge, as various methods of retrospective analysis have been used, and surgery and adjuvant therapy are not consistent across all cohorts. The role of adjuvant endocrine therapy in DCIS is discussed below.

Similarly, other markers known to have prognostic and predictive value in the management of invasive breast cancers have been evaluated in DCIS, including the progesterone receptor and androgen receptor [33], proliferation markers such as Ki-67 [20], cell cycle regulation and apoptotic markers [34], proteins involved in angiogenesis [35], Her-2/*neu* [20] and other related receptors, proteins of the extracellular matrix and cyclooxygenase-2 [36]. As with the oestrogen receptor, although some associations can be made between the markers and outcomes in DCIS, published studies are small and retrospective, so drawing clinically meaningful conclusions is difficult; current prospective studies will be the key to identifying those markers that may be used to guide therapy.

Interestingly, the distribution of many markers seems to differ between pure DCIS and tumours with invasive components. Her-2/*neu*, which traditionally predicts a more aggressive disease course in invasive breast cancer, is expressed in a greater proportion of DCIS tumours than in invasive cancers [37]; however, there is still controversy as to whether this increased expression predicts for recurrence or invasion independently of other factors in DCIS [20]. However, because of the high rate of overexpression, studies are ongoing to evaluate the role of traztuzumab and other anti-Her-2 therapies in the DCIS population.

Adjuvant Endocrine Therapy

The NSABP-B24 trial, a phase III randomised trial of tamoxifen versus placebo after BCS and radiotherapy for DCIS in 1708 women [38] showed a significant reduction in breast cancer events (including invasive and non-invasive disease) at 5 years in patients who had received tamoxifen (8.2% versus 13.2%, $P = 0.0009$). There was a non-significant trend towards an increased incidence of invasive disease in the placebo group. However, patients were not selected on the basis of oestrogen receptor positivity – with further follow-up in oestrogen receptor-positive patients a larger benefit was seen (hazard ratio for all breast cancer events 0.49 at 10 years, $P < 0.001$), but no survival benefit has been observed and it is noted that only a very small reduction in the risk of invasive breast cancers was observed even when oestrogen receptor status was taken into account.

The UK/ANZ DCIS study [16] assessed the role of adjuvant tamoxifen alongside the radiotherapy assessment. A reduction in risk of new ipsilateral DCIS, but not ipsilateral invasive disease, was observed in the tamoxifen group. However, there was a reduction in risk of all new contralateral breast events in the tamoxifen group. Overall, a reduction in all breast events was observed in the group receiving tamoxifen with no radiotherapy, but not in the group receiving tamoxifen and radiotherapy. However, the authors noted that a relatively small number of patients were included in this particular analysis and that patients were not selected to receive tamoxifen on the basis of oestrogen receptor positivity.

Current Research

Radiotherapy

Current radiotherapy research in DCIS focuses on patients with 'non low-risk' disease, where the benefits of radiotherapy

after BCS are more obviously apparent from the results of existing trials. Previous research in invasive breast cancer has led to shorter dose-fractionation schedules for adjuvant therapy, which have been shown to have no adverse effect on late toxicity, and possibly improved tumour control; studies designed to evaluate similar end points in DCIS are ongoing. The International BIG 3-07 trial [38] (Figure 1) seeks to assess a shorter fractionation schedule, as well as evaluating the benefit of a tumour bed boost in the reduction of local recurrence after BCS for DCIS in this group.

Low-risk Ductal Carcinoma in Situ

Low-grade DCIS has been the subject of much discussion in recent years, and, as discussed above, clinical and biological research data suggest that this diagnosis may not predict the high risk of invasive breast cancer seen in other patients with DCIS, so the value of any treatment, including excision, in this group is being questioned. A proposed study in patients with low-risk (low- or intermediate-grade) DCIS aims to evaluate standard treatment (surgery ± radiotherapy and follow-up as per local practice) with a programme of active monitoring including annual mammography and clinical surveillance for 5 years and follow-up for 10 years. Close follow-up is clearly imperative if this approach is to be explored, and although this is an important exploration of a new approach, it remains to be seen whether recruitment into such a study will be feasible.

Endocrine Therapy

Following the benefits seen in the NSABP-B24 trial in patients with oestrogen receptor-positive DCIS, a large-scale trial is currently recruiting to assess whether larger benefits may be seen using an aromatase inhibitor in the adjuvant setting, as observed in invasive disease [39]. IBIS-II DCIS is a double-blind randomised phase III trial of tamoxifen versus anastrozole for 5 years after BCS for DCIS. The trial has closed to recruitment in early 2012 and data are awaited.

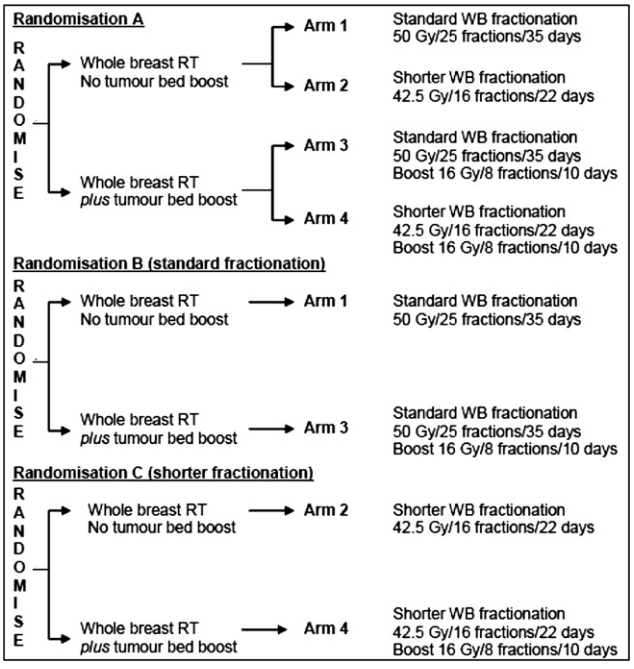

Fig 1. BIG 3-07 trial schema [38]. Patients are first randomised to boost versus no boost (A) and then to standard versus hypofractionated radiotherapy (B, C).

Other Targeted Therapy

The development of the Her-2 receptor-targeted monoclonal antibody trastuzumab has dramatically altered the outlook for patients with invasive Her-2/*neu*-positive breast cancer when given after surgery in early disease. In DCIS, Her-2 positivity may be associated with an increased risk of invasive recurrence [40,41] and ongoing studies are evaluating the use of trastuzumab in the neoadjuvant and adjuvant settings. For example, a current NSABP trial [42] seeks to establish DCIS and invasive cancer recurrence rates in a randomised trial of standard whole breast irradiation versus whole breast irradiation plus trastuzumab given in weeks 1 and 4 concomitantly.

Summary

Clinically occult DCIS has become a common diagnosis since the introduction of screening and a consensus approach to its management is yet to be reached. Research to date has not always provided clear answers, possibly because DCIS represents a spectrum of disease, and large trials have not always included sufficient stratification. Some evidence supports a more conservative approach in patients with biologically less aggressive DCIS, as it is possible that some patients are currently overtreated. Conversely, patients with a high risk of recurrence may benefit from higher doses of adjuvant radiotherapy, using a tumour bed boost. Current and future clinical research directions are designed to address these longstanding questions surrounding adjuvant therapy in the era of mass screening, but are also becoming more disease and patient specific, as a greater understanding of the natural history of breast cancer and DCIS evolves. The future will probably hold a more personalised approach after carefully conducted prospective research.

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