Biosensors & Bioelectronics

Mokbel, J Biosens Bioelectron 2011, S:2
http://dx.doi.org/10.4172/2155-6210.S2-001

Review Article Open Access

Management of Ductal Carcinoma *In situ*

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Abstract

Ductal carcinoma in situ (DCIS) is a heterogeneous disease characterized by noninvasive clonal proliferation of malignant epithelial cells arising from the mammary ducts and terminal ductal-lobular units. Its reported incidence is rising due to the wide adoption of screening mammography and magnetic resonance imaging (MRI). The combination of nuclear grade and presence of necrosis is currently the best predictor of biological behavior. DCIS should be managed in the context of a multidisciplinary team. Local control depends upon adequate surgical clearance with margins of at least 2mm. Sentinel lymph node biopsy (SLNB) is not routinely indicated and should be reserved for those with concurrent or recurrent invasive disease. SLNB can be considered in patients undergoing mastectomy (MX) and those with risk factors for invasion such as palpability, comedo morphology, necrosis or recurrent disease. Radiotherapy (RT) following breast conserving surgery (BCS) significantly reduces local recurrence (LR), particularly in those at high-risk. There remains a lack of level-1 evidence supporting the omission of adjuvant RT in selected low risk cases. Large, multi-centric or recurrent lesions (particularly in cases of prior RT) should be treated by MX with the opportunity for immediate reconstruction. Adjuvant Tamoxifen may reduce the risk of LR in selected cases with hormone sensitive disease.

Further research is required to determine the role of contemporary RT regimes and endocrine therapies. Biological profiling and molecular analysis represent an opportunity to improve our understanding of the tumour biology of this condition and rationalise its treatment. Reliable identification of low-risk lesions could allow treatment to be less radical or safely omitted.

Keywords: DCIS; Wide local excision; Margins; Mastectomy; Sentinel lymph node biopsy; Radiotherapy; Tamoxifen; Local recurrence; Evidence.

Introduction

Diagnosis

The introduction of national mammographic screening programmes and widespread uptake of contemporary imaging modalities, including magnetic resonance imaging (MRI) (Figure 1), have dramatically changed the clinical presentation of ductal carcinoma in-situ (DCIS). Prior to the last two decades, DCIS was diagnosed in a small proportion of patients presenting with a palpable mass, pathological nipple discharge or occasionally as an incidental biopsy finding [1,2]. In contrast, DCIS is now most frequently identified in asymptomatic women with screen-detected micro-calcifications [3]. In fact, between 1980 and 1995, Western countries appear to have experienced a four-fold 'increase' in the incidence of DCIS, particularly in women of screening age [4] and approximately one-fifth of all screen detected breast cancers are now DCIS [5]. This trend toward improved detection is likely to continue with further technological advances, including the transition from analogue to full-field digital mammography (FFDM) and the development of computer aided detection (CAD) [6]. Although, the role of MRI in the management of DCIS is yet to be fully evaluated by randomised trials, MRI is increasingly being employed to facilitate the assessment of disease extent and distribution [7,8]. A prospective observational study has also demonstrated MRI to be significantly more sensitive than mammography for the diagnosis of DCIS (92% versus 56%). In this study, mammography missed 48% of high grade DCIS, compared to only 2% for MRI. Cases missed by one modality were always detected by the other, suggesting utility as an adjunct to complement mammography [9]. Despite this, Schouten van der Velden et al. [10] reported no significant difference in local recurrence (LR) in patients with localised DCIS treated by breast conserving surgery (BCS) who underwent pre-operative MRI. Furthermore, increased imaging sensitivity has the potential to over-interpret non-malignant incidental lesions which may result in unnecessary interventions or over-treatment [10].

DCIS lesions have also been directly visualised by mammary ductoscopy. However, the potential of this technique in detection and management of DCIS requires further investigation [11]. Anatomical limitations include the observation that not all ducts are accessible from the nipple [12]. Currently, pre-operative histo-pathological diagnosis of impalpable radiologically suspicious lesions requires either stereotactic core biopsy of mammographic microcalcifications or MRI guided biopsy. Vacuum assisted core biopsy (VACB) has been shown to increase the diagnostic yield and upgrade atypical ductal hyperplasia (ADH) to DCIS in approximately 25% of cases [13]. Impalpable lesions also call for pre-operative wire localization and intra-operative specimen radiography to facilitate wide local excision [2].

Classification

The proliferation of abnormal epithelial cells referred to by DCIS has two hallmark features: firstly, it is limited by the basement membrane of the ductal system and secondly, stromal invasion is absent. DCIS behaves as a non-obligate precursor of invasive carcinoma and does not fully express the malignant phenotype [1]. The progression to invasive

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Received September 13, 2011; **Accepted** November 10, 2011; **Published** November 17, 2011

Citation: Mokbel K (2011) Management of Ductal Carcinoma *In situ*. J Biosens Bioelectron S2:001. doi: 10.4172/2155-6210.S2-001

breast cancer (IBC) is not completely understood and can not be reliably predicted. Classification systems aim to reproducibly categorize lesions and facilitate prognostication and management decisions. Conventional histo-pathological types include: comedo, solid, cribriform and micro-papillary, however, lesions often demonstrate architectural and morphological heterogeneity. Nuclear grade (Figure 2 and Figure 3) and necrosis are also important considerations [14-17].

The natural history

The elusive natural history of DCIS lesions reflects their variable malignant potential and biological diversity. Pre-invasive lesions can simply remain so, and do not invariably progress to invasive malignancy [18]. The natural history of small, non-comedo, low grade DCIS treated by biopsy alone has been evaluated in studies with long-term follow-up. After a median of thirty-one years, 39% of patients developed IBC, all of which occurred in the index quadrant and 45% of these patients died of metastatic disease [19]. The overall progression to IBC has been reported to range from 14% to 75% [20]. Hence, it would seem that patients who receive no treatment beyond a diagnostic biopsy remain at significant risk of ipsilateral IBC. Increased risk has been demonstrated in lesions of all nuclear grades; however, the onset interval seems to be longest for low grade lesions. On the other hand, a significant proportion of DCIS lesions are clinically benign and non-progressive. As diagnostic frequency continues to increase, there is an impetus to accurately identify clinically relevant lesions and rationalise management strategies, with the opportunity for treatment to be less radical or safely omitted in some cases.

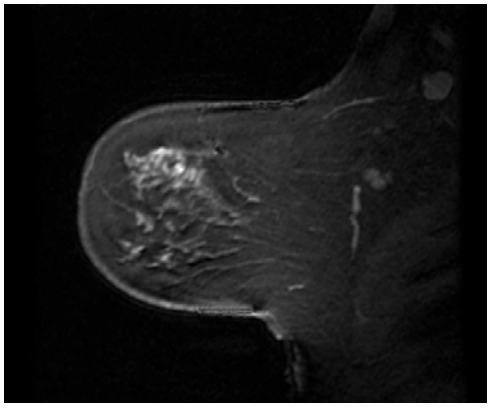

Figure 1: MRI demonstrating recurrent DCIS anterior to previous scar.

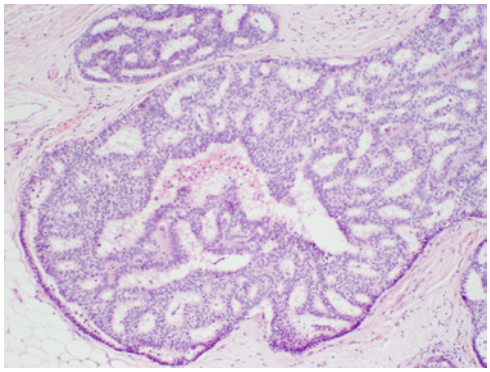

Figure 2: Low grade DCIS lesion.

Clinical features

Women with palpable DCIS and those who present symptomatically exhibit higher rates of recurrence than mammographically detected cases, 21.2% vs. 16.8% respectively, and this difference persists with the addition of adjuvant radiotherapy (RT) [21,22]. The relevance of screen detected lesions may therefore differ from their clinically detected counterparts [23]. One study has identified family history of IBC as a significant predictor of LR in women treated with BCS and RT [24]. Previous therapy with estrogens, either contraceptives or hormone replacement therapy is also reported to be a significant predictor of LR [25]. Young age (< 40 years) has also emerged as an independent risk factor for LR after BCS with or without adjuvant RT [26]. LR has been reported to range from 18-30% in this group, with the lowest rates in mammographically detected lesions [22,26-30]. Interestingly, the significance of young age as a risk factor for LR has been challenged by a recent retrospective study, which found no statistically significant difference between patients after BCS and RT, irrespective of their age. After an average follow up of 15 years, LR was identified in 10% of patients <40 years of age compared to 7% of 41-54 year olds, 11% of 55-69 year olds and 4% of those aged 70 or more. It is however noteworthy that this study involved a relatively small population size and re-excision rates were relatively high, 75% in those aged <40 [31].

Pathological features

The size of DCIS lesions has been correlated with LR. One particular study of DCIS treated by BCS alone reported 10-year LR rates of 11% and 48%, for lesions smaller and larger than 10mm respectively [32]. However these findings were not supported by the French Cancer Centre's experience which identified LR rates of 30% and 31% in the BCS group for lesions under or over 10 mm, respectively, and 11% and 13% for the same subgroups in the BCS+RT group [33]. Accurate and reliable measurement of DCIS can be challenging and several landmark studies have been criticized for their performance in this regard [22,27,34].

The surgical clearance of pathological margins has a significant impact upon LR, both in patients treated by BCS alone and in those who undergo adjuvant RT [35-38]. It is therefore somewhat surprising that consensus has yet to be reached with regard to optimal margin width [34]. The presence of DCIS at the surgical margin is associated with the identification of residual DCIS in 40-82% of re-excision specimens, and is correlated with margin width: 41% at < 1mm, 31% at 1-2 mm and 0% with ≥2 mm of clearance [39]. The French National Guidelines recommend surgical margins of ≥3mm and re-excision for margins <1mm [40]. A recent meta-analysis concluded that a margin width of ≥2mm was significantly superior to lesser margins (Odds Ratio (OR) = 0.53, 95% CI 0.26-0.96). However, there was no added value associated with clearance ≥2mm compared to >5mm (OR = 1.51, 95% CI 0.51-5.0) [41]. Despite this, total excision volume, independent of margin clearance, has also been correlated with LR. Following BCS for DCIS, the Joint Centre Experience reported LR rates at 5 years of 9% and 0% for volumes <60 cm^3 and >60 cm^3 respectively [42]. Excision volumes <60 cm^3 have been shown to increase the relative risk of LR in women under 45 years [26].

High nuclear grade is associated with a greater risk of LR and IBC (Figure 3). Studies of DCIS treated by BCS alone have reported LR rates ranging from 6% for low-grade lesions up to 31.5% for high-grade lesions [21,35,43]. The combination of nuclear grade and comedo necrosis is strongly associated with the risk of LR after BCS [44,45]. Similarly, the combination of nuclear grade and cellular polarization

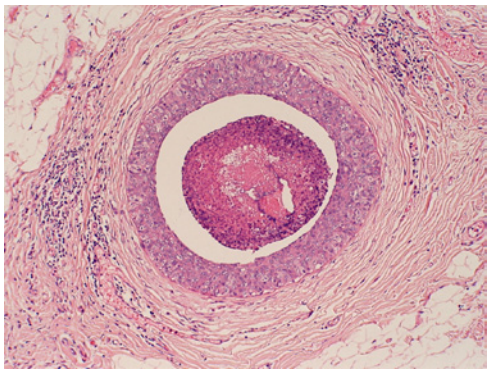

Figure 3: High grade DCIS lesion.

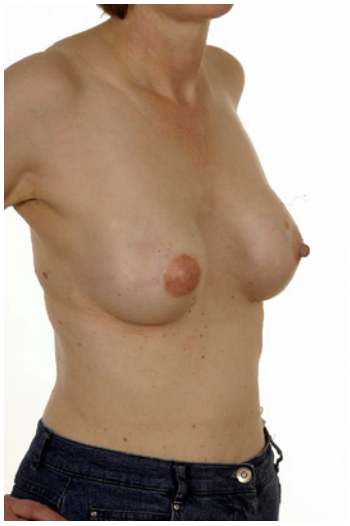

Figure 4: Aesthetic outcome of left skin-sparing mastectomy and latissimus dorsi flap reconstruction followed by nipple reconstruction and tattooing in a 48 year old woman.

has been associated with the risk of LR [46,47]. Interestingly, a recent population-based case-control study found that comedo-type DCIS shares a similar profile of hormonal and reproductive risk factors to IBC, including ≥10 years of oral contraceptive intake and an inverse association with ≥3 full-term pregnancies. These findings were in contrast to those for non-comedo lesions, providing some further support for the differential management of DCIS lesions [48]. The significance of comedo-type as a risk factor for LR has resulted in its inclusion in prognostic indices [49]. These include the Van Nuys Prognostic Index (VNPI), which is a combination of parameters (patients' age, tumour's size, surgical margin width, nuclear grade, and the presence / absence of comedo-necrosis) with predictive utility for LR after BCS (with or without adjuvant radiotherapy) and can facilitate clinical decision-making [25,50,51].

DCIS can also be associated with lobular carcinoma in-situ (LCIS). In one study, the presence of LCIS did not affect the overall 10-year LR rate, but the proportion of invasive LR was found to be 67% in lesions with LCIS compared to 43% for pure DCIS [32]. In the French Cancer Centre's series, the 7-year LR rate was similar in mixed lesions for patients treated with BCS alone, but greater in patients given adjuvant RT (23.8% and 11.7%, respectively) [52].

The hormone receptor profile of DCIS is relevant to prognosis and has clinical utility in predicting response to targeted endocrine therapy. High grade DCIS lesions which are oestrogen receptor (ER) and progesterone receptor (PR) negative are significantly associated with HER2 and p53 positivity. ER negative lesions tend to be PR negative and high grade lesions with micro-invasion tend to be HER2 positive and hormone receptor negative [53]. HER2 positivity and ER/PR negativity are individually associated with risk of recurrence [54]. HER2 over-expression represents an aggressive biological subtype of DCIS, correlating with high grade, p53 expression and hormone receptor negativity. On the other hand, hormone receptor positivity has been associated with low grade DCIS. In a recent case series, HER2 was found to be superior to lesion size or nuclear grade in predicting concurrent invasive disease. DCIS lesions over-expressing HER2 were 6 times more likely to be associated with invasive disease (OR 6.4, p=0.01) [55].

Molecular aspects

Advances in molecular analysis and high throughput technologies are likely to identify biological attributes of DCIS which can be integrated with established clinico-pathological parameters to inform management decisions. Chromosome-wide comparative genomic hybridization (CGH) has shown DCIS to be a genetically advanced lesion with alterations corresponding to adjacent invasive disease and independent pathways of genetic evolution [56]. A distinctive molecular portrait of each lesion can be obtained by gene expression profiling using complementary DNA micro-arrays, which could inform predictions about clinical behaviour and progression [57]. One such study has identified a gene expression classifier of 35 genes which differ between DCIS and IBC and a further 43 genes distinguishing well- from poorly differentiated DCIS [58]. Protein expression profiling can similarly be undertaken using matrix-assisted laser desorption / ionization (MALDI) or surface-enhanced laser desorption / ionization (SELDI). Although the relevance of each parameter may not be fully understood, combinations of features may enable the biological profiling of DCIS lesions into groups of similar natural history and prognosis. Balleine et al. [59] recently reported on a binary molecular grading scheme for DCIS, based on expression at 173 oligo-nucleotide probes, with clinical correlation. Interestingly, two conventional parameters amenable to routine evaluation, namely nuclear grade and Ki67 score, were capable of accurately assigning lesions into low or high molecular grade [59]. Proteomics analysis of DCIS and normal breast tissue has also identified differential expression patterns, distinct from previous nucleic acid-based studies [60]. Expression of Syndecan-1, E-cadherin and c-met have recently been shown to be associated with angiogenic and lymphangiogenic factors in DCIS, including endothelin A and B receptors, vascular endothelial growth factor (VEGF)-A/C and fibroblast growth factor receptor (FGFR)-1 [61]. In addition to their potential utility in prognostication, putative molecular targets may enable directed therapy in the future. The molecular profile of DCIS in BRCA1 and BRCA2 mutation carriers has recently been analysed in the context of concurrent IBC. Interestingly, these DCIS lesions demonstrated high concordance with their invasive counterparts with regard to histopathological and molecular characteristics, supporting the notion that DCIS may represent the direct pre-invasive lesion in hereditary breast cancers [62].

Treatment

The variable natural history of DCIS lesions open the intriguing possibility that intervention may not be mandatory. Furthermore,

the balance of benefit and risk has been influenced by the significant transition over the last two decades from symptomatic patients toward those with screen detected pathology. It is paradoxical that in some cases DCIS is managed with the radical intent applied to IBC. However, our inability to reliably identify non-progressive incidental lesions has understandably resulted in all patients being managed as if they harbour clinically relevant and progressive lesions. Management strategies need to consider the breast and axilla, the need for adjuvant RT and the utility of systemic adjuvant therapy. Treatment of the breast can involve BCS, with or without adjuvant RT, or mastectomy (MX). Axillary interventions, including sentinel lymph node biopsy (SLNB) and/or axillary dissection (AD), warrant particular caution in view of their low yield and potential for harm. Adjuvant systemic treatments have mainly involved endocrine manipulation with Tamoxifen. Despite these general principles, the optimal management of DCIS remains controversial [20,37].

Surgical treatment

Local clearance of DCIS remains paramount to reducing the risk of LR and IBC. MX is indicated for large tumours (>4 cm depending on breast size), multi-centric lesions, inadequate margins, recurrence after BCS (particularly with prior RT) and patient preference. MX affords excellent local control, approximately 98% at 7 years, with an overall recurrence rate of 1.5% [63]. Interestingly, in England and Wales between 1990 and 2001, the absolute number of MX for in-situ disease increased by 400%, corresponding to the introduction of national screening [64]. However, the relative rate of MX for DCIS has been decreasing over the last three decades and the procedure is now undertaken in approximately one-third of patients [65-68], supported by the 30.5% recently reported by the French Survey [69]. This study reported MX rates of 10% for lesions <10 mm compared to 72 % for >20 mm, and 11% for low grade compared to 54% for high-grade lesions. The authors justify a MX rate of 50% for patients <40 years by the lifetime risk of LR in those undergoing BCS despite adjuvant RT [69]. MX for DCIS is particularly suited to immediate breast reconstruction with an implant and/or autologous flap, as adjuvant RT and lymph node involvement are unlikely [70] (Figure 4).

Local clearance can also be achieved with BCS, which is noteworthy given the increasing incidence of smaller screen detected and incidental lesions. However, controversy remains regarding the oncological adequacy of BCS alone. Significant numbers of patients undergoing BCS alone develop LR, of which approximately half are invasive and up to one-fifth ultimately metastatic. The literature reveals an overall LR rate of approximately 28% at 7 years, 45% of which were invasive [32,35,71-74]. Concern is also raised by studies of mammographically detected DCIS with complete excision without RT, in which the 10-year LR rates were 27.8%, 22% and 19% respectively, of which approximately 35% were invasive [43,75,76]. A single-arm prospective trial of BCS without RT, including only small (mammographically ≤2.5cm), low/moderate grade DCIS with surgical margins of >1cm, was terminated at 40-months median follow-up due to the unacceptably high rate of LR, corresponding to a 5- year rate of 12.5% [77]. On the other hand, there is some evidence that acceptably low LR rates can be achieved with BCS alone, including VNPI 4-6 group (3 LRs among 176 patients with 65-month median follow-up) or with excision margins >10mm (4.6% LR rate among 197 patients) [35]. Silvestein et al reported that postoperative radiation therapy did not lower the recurrence rate among patients with DCIS that was excised with margins of 10 mm or more, however, patients in whom the margin width was less than 1 mm benefited from postoperative radiation therapy [78].

Radiation therapy

The benefit of adjuvant RT, in terms of a significantly reduced risk of LR in those undergoing BCS, has been demonstrated by several large randomized controlled trials. However, adjuvant RT should not be considered a remedy for inadequate local clearance [30,33]. Furthermore, there remains a lack of level-1 evidence supporting the omission of adjuvant RT in selected low-risk cases, which could potentially be adequately treated by complete local excision.

The National Surgical Breast and Bowel Project (NSABP B-17) trail randomized 818 patients after lumpectomy with complete excision of DCIS, to either whole breast RT or no further treatment [27]. After a median follow-up of 129-months, among 403 women treated by lumpectomy alone, 124 LRs occurred (31.7%), 67 of which were invasive (54%). Among the 410 women treated by lumpectomy and breast irradiation, 61 LRs were observed (15.7%) of which 29 were invasive (48%) (p=0.001). The absolute reduction of LR increased with time. Despite the fact that RT was associated with a 57% reduction in LR (both invasive and in-situ), no differences were observed in metastasis and overall survival.

The European Organisation for Research and Treatment of Cancer (EORTC) conducted a similar study recruiting 1010 patients [22]. With a 126-month median follow-up, local relapse-free rates were 85% in the RT group and 74% in the control group (hazard ratio: 0.53, p<0.0001). In-situ LR rates were 7% and 13%, respectively, and invasive LR rates were 8% and 13% respectively [79]. Consistent with the NSABP B-17 trial findings, the absolute reduction of LR by RT increased with time from 7% at 4 years to 11% at 10.5 years. In univariate analysis, RT showed a statistically significant benefit in all subgroups of patients, but the size of this benefit varied. The authors observed a 23.5% and 42.7% LR rate for complete and incomplete/doubtful excisions respectively in the lumpectomy alone group, versus 14.7% and 24.7% for patients receiving adjuvant RT.

The UK/ANZ DCIS trial involved 1701 patients treated by BCS, with subsequent randomisation to RT and/or Tamoxifen [80]. Thus, there were four treatment groups: BCS alone, BCS+RT, BCS+TAM and BCS+RT+TAM. 90% of the participants were 50 years or older with screen detected DCIS. After a median follow up of 53 months, the respective rates of LR were: 22%, 8%, 18% and 6%. Adjuvant RT was associated with a significant reduction (Hazard Ratio (HR) = 0.38, p<0.0001) in all ipsilateral tumour recurrence (invasive or DCIS). RT reduced the risk of DCIS by 64% (p=0.0004) and invasive cancer by 55% (p=0.01).

The Cochrane Collaboration has recently published a systematic review of four adjuvant RT trials: NSABP 2001 [27], EORTC 2006 [22], UK/ANZ DCIS 2003 [80] and the Swedish DCIS 2008 [81]. With regard to LR, they report a 51% risk reduction for DCIS (HR 0.61, 95% CI 0.39-0.95, p=0.03) or invasive cancer (HR 0.50, 95% CI 0.32-0.76, p=0.001). After a median follow-up ranging from 4.4-10.5 years, the LR rate for those receiving RT was 11.6% compared to 23.9% for BCS alone, resulting in a number needed to treat (NNT) of 9 patients to prevent one LR. Although there was no attributable increase in mortality, long term RT complications were poorly reported by the trialists [82].

Another meta-analysis of randomized trials has also concluded that adjuvant RT significantly reduces the risk of LR after BCS by approximately 60%, with most benefit to patients with high-grade lesions and positive margins. Adjuvant RT appeared to have no impact on the rate of distant metastases and survival [83]. Overall, LR rates have been reported to range from 2.7% to 18.9%, averaging 10% at 7 years, with

invasive LR accounting for approximately 60% [84]. It is noteworthy that the methodological quality of several trials has been criticised, particularly with regard to: effective mammographic-pathologic correlations, routine specimen radiography, post-operative imaging, adequate definition and classification of lesions [27], measurement of tumour size [22] or margin clearance, consistent inclusion/exclusion criteria, conventional methodology for randomisation and data analysis, adequate statistical power to determine differences in overall survival, in addition to the validity of conducting post-hoc retrospective secondary analyses. Whilst some of these issues can be resolved by meta-analysis, others are being addressed by current studies including the Eastern Cooperative Oncology Group registration trial (E5194) and the Radiation Therapy Oncology Group trial (98-04).

Population-based studies have supported trial findings. A recent study of 798 patients reported 5-year recurrence free survival of 75% following BCS alone compared to 91% with adjuvant RT [36]. Further support comes from another population-based analysis with an average follow-up of 91-months, which found LR rates of 15% and 10.7% for women treated by BCS and BCS+RT respectively. The risk of invasive LR was 49% versus 31% and the risk of breast cancer specific mortality was 2.7% versus 0.8% (p=0.02) respectively, despite patients in the RT arm tending to have worse tumor grade and larger tumor size [85].

Improved planning and delivery has been associated with high rates of local control in patients treated by BCS+RT, with 5 and 10 year recurrence rates of 5.9% and 9.8% respectively [24]. However, a study of 75 patients treated by BCS+RT, including 20 women receiving an additional 10 Gy boost to the tumour bed, identified no improvement in LR reduction after a median follow-up of 81-months [86]. The efficacy of other novel strategies including partial breast RT in the context of DCIS has yet to be evaluated [30,87]. Accelerated partial breast irradiation (APBI) aims to provide comparable local control to whole breast RT with reduced morbidity. In the largest study group of patients with DCIS (n=194) treated with the MammoSite device, the 3-year actuarial LR rate was 0% in the first 48 cases enrolled compared to 2.04% in IBC (n=352); median follow up 37.5 months [88]. Another recent study of 126 DCIS cases evaluated balloon-based brachy-therapy, with either MammoSite or Contura catheter. After a median follow-up of 40 months, the LR rate for the first 50 consecutive cases was 0.02% with a 3-year actuarial rate of 2.15% [89].

Hormonal therapy

Systemic adjuvant therapy in DCIS has concentrated on endocrine manipulation, particularly Tamoxifen. In the NSABP B-24 trial, women treated with BCS+RT, were subsequently randomized to placebo or Tamoxifen (10 mg twice a day, for 5 years) [90]. After 7-years median follow-up, the LR rates were 11.1% and 8% in the placebo and Tamoxifen groups, respectively (p=0.02). The absolute reduction was significant for invasive LR. Tamoxifen users did however incur a greater risk of endometrial cancer and thromboembolic events. No significant benefit was observed in the following groups: age >50 years, in-situ LR, complete local excision and absence of necrosis. The overall mortality was not affected [91]. A post-hoc analysis of ER status demonstrated that efficacy was limited to the 77% of cases which were ER positive [92]. The UK/ANZ DCIS trial showed that for patients not receiving RT, adjuvant Tamoxifen did not significantly reduce the incidence of ipsilateral IBC or DCIS. However, the total number of DCIS events (ipsilateral and contralateral) was significantly reduced by Tamoxifen (6% vs.10%, p=0.03). Tamoxifen had no significant effect for patients receiving adjuvant RT [80]. Therefore, the use of adjuvant Tamoxifen should be rationalised according to risk/benefit, potentially including carefully selected receptor positive women, in the absence of contra-indications. Other endocrine strategies, including aromatase inhibitors, are currently under evaluation in trials (IBIS II and NSABP B-35).

Recently, inhibition of cyclo-oxygenase 2 (COX-2), implicated in epithelial-stromal interactions and promoting the progression of DCIS, has been evaluated using non-steroidal anti-inflammatory drugs (NSAIDS). Whilst experimental studies have been encouraging [93,94], a recent prospective randomised placebo-controlled trial (ERISAC) has concluded that COX-2 inhibition does not improve the reduction in DCIS proliferation associated with aromatase inhibitor therapy. Patients randomised to Exemestane showed a 9% absolute reduction (50% relative decrease) in cell proliferation compared to placebo, however apoptosis remained unaffected. The role of aromatase inhibition in ER positive DCIS warrants further study with regard to patient oriented and clinically relevant outcomes [95].

Sentinel lymph node biopsy

Whilst the risk of lymphatic or vascular invasion in pure DCIS, by definition, should be zero [20,37], lesions can harbour concurrent foci of microscopically or frankly invasive disease. Indeed, lymph node involvement has been reported in 1-2% of patients, which may be attributable to 'missed' invasive foci within specimens containing predominantly DCIS [20]. In the last two decades, the AD rate in American studies has decreased from 34% to 15% overall and from 51.5% to 10.4% in patients undergoing MX [96]. This is consistent with findings from the recent French survey which reported overall rates of 21.3% for SLNB and 10.4% for AD (5% amongst BCS, 22.6% amongst MX) [69]. Retrospective analyses from the NSABP B-17 and B-24 trials support the notion that low yield and risk of morbidity should preclude routine axillary intervention in patients with DCIS [97,98]. The absolute indication for SLNB remains histological confirmation of concurrent or recurrent invasive disease; whereas relative indications include patients undergoing MX (due to difficulty with subsequent SLNB) and risk factors for invasion such as palpability, comedo morphology, necrosis or recurrent disease.

Local recurrence

The clinical relevance of recurrent DCIS differs considerably from primary lesions. LR may be in-situ or invasive, with potential for axillary lymph node involvement (15-20%), systemic metastasis (13-18%) and attributable mortality [74,99]. Interestingly, 75-80% of recurrences following BCS occur at the site of the original lesion or within the index quadrant. The risk of LR decreases as the extent of primary treatment increases (BCS, BCS+RT, MX). Ironically, LR can be more aggressive in those who were treated more aggressively. Whereas 40-50% of LR is invasive after BCS, LR is almost always invasive following MX. This may reflect the fact that recurrence after BCS often presents as an incidental finding of in-situ disease during surveillance mammography, whereas post-MX ipsilateral mammographic screening is obviously not undertaken and recurrence is likely to present at a more advanced stage and rely on clinical detection [85]. Invasive LR has also been found to be relatively more frequent in women treated with adjuvant RT [100]. The prognostic implications of invasive LR are significantly worse than in-situ recurrence. In particular, the overall risk of metastasis has been reported to be 0-3.6% for in-situ LR, compared to 13.2-18% after invasive LR [74,99,101]. The rate of axillary lymph node involvement with invasive LR ranges from 11-30% [74,101].

Salvage MX is frequently indicated following LR within the breast,

particularly when re-excision would be cosmetically unacceptable, or when LR is confirmed to be invasive and for those with an absolute or relative contra-indication to RT (including previous adjuvant RT). In the NSABP B-17 trial, the MX rate for LR was 48% in the BCS group and 62% in the BCS+RT group [27], consistent with similar studies reporting rates of 52.8% and 74.7% respectively [74]. Overall, salvage MX rates range from 64-84% [74,101]. BCS may still be appropriate for some women, particularly with in-situ LR, and adjuvant RT following complete local excision has been shown to reduce the risk of a second recurrence [100].

Future strategies

Minimally invasive interventions for breast cancer seek to redress the balance between benefit and risk and may therefore be of particular utility in asymptomatic patients with low risk lesions or patients deemed unfit for conventional management. Imaging-guided radio-frequency ablation therapy (RFA) has been demonstrated in pilot studies to be effective with few complications and a favourable safety profile. However, complete ablation may not be achievable in all patients and exhaustive histological specimen analysis is not possible. Furthermore, current imaging modalities are relatively imprecise at delineating the extent of DCIS and predicting/confirming complete ablation [101].

Conclusions

DCIS should be managed in the context of a multidisciplinary team and strategies tailored to both patient and tumour factors. Local control depends upon adequate surgical clearance and in order to reduce the risk of LR, surgical margins of at least 2mm should be achieved. SLNB is not routinely indicated and should be reserved for those with concurrent or recurrent invasive disease. SLNB can be considered in patients undergoing mastectomy (MX) and those with risk factors for invasion such as palpability, comedo morphology, necrosis or recurrent disease. RT following BCS significantly reduces LR, particularly in those at high-risk. There remains a lack of level-1 evidence supporting the omission of adjuvant RT in selected low-risk cases. Large, multi-centric or recurrent lesions (particularly in cases of prior RT) should be treated by MX with the opportunity for immediate reconstruction. Adjuvant Tamoxifen may reduce the risk of LR in selected cases with hormone sensitive disease. Further research is required to determine the role of contemporary RT regimes and endocrine therapies. Biological profiling and molecular analysis represent an opportunity to improve our understanding of the tumour biology of this condition and rationalise its treatment. Reliable identification of low-risk lesions could allow treatment to be less radical or safely omitted.

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This article was originally published in a special issue, **Biosensors: Diseases and diagnostics** handled by Editor(s). Dr. Alexander D. Rosenstein, UT Medical School of Houston, USA; Dr. James J. Lai, University of Washington, USA; Dr. Jaime E. Ramirez-Vick, University of Puerto Rico, Puerto Rico