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Ductal Carcinoma *in Situ* Treatment Requires a Multidisciplinary Approach

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ABSTRACT

Correct diagnosis and treatment are crucial for DCIS because it is a direct precursor of potentially lethal invasive breast cancer (IBC). As a result of mammographic screening, the incidence of DCIS rose from 1.87% per 100,000 women from 1973-1975 to 32.5% per 100,000 in 2005. The incidence of DCIS is strongly associated with advanced age, an older age at the time of the first birth or nulliparity, family history of a first-degree relative with BC, BRCA1 and BRCA2 mutation carriers, history of biopsy, late age at menopause, and elevated body mass index, the use of HRT over 5 years. With the use of screening mammography, eight population-based trials showed an increase in DCIS incidence reaching 20% with significant reductions in breast cancer mortality. MRI is also used in combination with the mammography for the diagnosis of DCIS. Three grades of DCIS are ultimately recognized: grade 1/low grade, grade 2/intermediate grade, and grade 3/high grade. Several options are available for the management of DCIS, including breast-conserving surgery, with or without postoperative radiotherapy, and with the clear margin being the most important factor for reducing risk of local recurrence. A 2 mm margin is superior to <2 mm, but there was no significant difference in relapse rate in those with margins of 2 or 5 mm when combined with radiotherapy. The use of mastectomy for treatment of DCIS has declined steadily. Sentinel lymph node biopsy (SLNB) should be performed on patients undergoing mastectomy for DCIS, and a case-by-case decision should be made to perform SLNB in patients who have a high risk DCIS or large tumours. Prospective and retrospective studies have demonstrated excellent long-term results after BCS and radiotherapy, as opposed to BCS alone that has shown a higher rate of local recurrence. Tamoxifen also reduces ipsilateral and contralateral breast cancer events in women with DCIS and is the only systemic therapy approved by Food Drug Administration for this disease. Aromatase inhibitors and other targeted therapies are currently being evaluated in ongoing studies.

Keywords: Ductal Carcinoma *in Situ*; Epidemiology; Molecular Profile; Surgery; Radiotherapy; Tamoxifen

1. Introduction

The human breast comprises thousands of lobules, interconnected by small ducts, which join to form larger ducts that carry milk to the nipple. Ductal Carcinoma *in Situ* (DCIS) describes lesions characterised by the proliferation of abnormal epithelial cells but without evidence of invasion through the basement membrane into the surrounding stroma. Since DCIS represents local disease without regional involvement, it is not considered life-threatening. Nonetheless, correct diagnosis and treatment are essential since DCIS is a direct precursor of potentially lethal invasive breast cancer (IBC). During the latter half of the 20th century, as a result of early diagnosis by screening mammography and results of several randomized controlled trials (RCTs) of therapies for DCIS there was a change in perception of the nature and treatment of DCIS [1-10].

2. Epidemiology

As a result of screening mammography, the incidence of DCIS rose from 1.87/100,000 women in 1973-1975 to 32.5/100,000 in 2005. This increase occurred in all age groups. There was a fivefold increase between 1983 and 2003 among women aged ≥50 years and older, which started to decline in 2003, possibly because of the reduced use of hormone replacement therapy. In women

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<50 years there was an almost threefold increase which continues to rise [11-13]. The "epidemic" of DCIS has not been uniform across histological types: comedo DCIS remained constant or decreased whereas non-comedo DCIS is diagnosed more frequently across all age groups [12].

There is a strong association with advanced age, peaking at 65 - 69 years and declining slowly by the age of 79. DCIS is extremely uncommon before the age of 35 - 39 [14,15]. There is a similar incidence among white, African American and Asian/Pacific Islanders [16,17]. As for IBC, risk factors for DCIS include older age at first birth, nulliparity, family history of a first-degree relative with BC, BRCA1 and BRCA2 mutation carriers, history of biopsy, late age at menopause, and elevated body mass index [18-24]. Furthermore, increased mammographic breast density, is also associated with an increased risk of DCIS; women with density >45 cm^2 have greater odds for developing DCIS than those with density less than 15 cm^2. No association has been found between current or past use of the oral contraceptive pill and DCIS [20,22,23, 26-28]. In contrast, a large prospective cohort study in the UK found a 56% increased risk of DCIS among current users of HRT compared to never users [29]. Other studies reported that DCIS risk was associated with the duration of HRT use; those presently using it for <5 years have a significantly reduced risk of DCIS than the never users, whereas those currently on HRT for >5 years had a greater risk than the never users [30,31]. The Women's Health Initiative randomized trial found no increased risk of DCIS associated with HRT [32].

In a cohort study with 486 cases of DCIS, Kabat *et al.* reported no increased risk of DCIS in postmenopausal smokers [33]. Lactation, early menarche and increased alcohol consumption were not associated with an increased risk of DCIS. Exercise for >4 hours may diminish the risk for DCIS [34]. This was confirmed in a second study of 1925 DCIS survivors in whom the risk of a second breast diagnosis was reduced by increasing physical activity and reducing alcohol consumption [35].

3. Diagnosis

3.1. Mammography and DCIS

In the pre-mammography era, DCIS was only 1% - 2% of breast cancers, presenting as a large palpable lesion with mastectomy was the standard therapy [36]. Subsequently 8 population-based trials showed an increase in DCIS incidence reaching 20% with significant reductions in breast cancer mortality [37-44]. The sensitivity of mammography in the detection of DCIS is 86%, with 80% - 85% of DCIS detected by mammography and the remaining 15% clinically detected as a lump [14,45]. DCIS usually appears as calcifications which can take on a range of shapes, including amorphous, coarse, fine pleomorphic, and fine linear calcifications. They can also and these can be linked with disease biology; fine-linear/ linear-branching calcifications are being investigated as a factor of poorer prognosis [46]. Mammographic detection of non-palpable and smaller DCIS lesions allowed breast-conserving surgery (BCS) also to be considered as a treatment option.

3.2. MRI and DCIS

The use of MRI for DCIS has prompted recommendations as to its use. There are two main indications: determination of extent of disease as mammography may underestimate the size due to non-calcified lesions, and detection of DCIS in high-risk women who may have mammographically occult lesions [47]. Contrast-enhanced 3D T1-weighted images are used to evaluate DCIS which usually appears as non-mass-like enhancement, with clumped internal enhancement in a segmental, linear or regional distribution [48-52].

The sensitivity of MRI compared to mammography has been investigated in several studies and been found to be higher in the detection of DCIS [53,54]. Screening trials also confirmed the higher sensitivity of MRI, especially for high-grade lesions [55,56] but others did not concur, possibly dependent upon the experience of the radiologist [57-59].

Unfortunately, there are some limitations as to the use of MRI. Whereas a mammogram can underestimate extent an MRI can overestimate significantly. Recent studies report 40% false negative results for DCIS [52,53, 60-63]. The proportion of BRCA-positive DCIS detected on MRI is only 10%, probably because BRCA-positive cancers may be more aggressive and also, as suggested by Warner *et al.*, due to the learning curve of the radiologist [64,65]. Furthermore, the benefit of obtaining free surgical margins with the use of MRI has yet to be established [66-69]. Solin *et al.* in a study of 136 DCIS found no improvement in re-excision or local recurrence rates among patients undergoing pre-operative MRI [69]. Similarly, Pilewskie *et al.* in a study of 352 DCIS patients, 217 of whom underwent MRI, reported that the type of initial operation and number of re-operations were similar for the 2 groups and MRI was not superior to mammography for determination of DCIS extent preoperatively [70].

4. Pathology

Historically, DCIS has been classified according to the predominant architectural microscopic pattern of the proliferation. This classification includes comedo, cribriform, micropapillary, solid, and papillary subtypes. In the pre-mammography era, the comedo DCIS was the most com-

mon type, usually comprising large, irregularly shaped, rapidly dividing cells growing as a palpable mass with a necrotic centre. Other types were rarely found before the diagnostic mammogram was established, as they are seldom palpable or symptomatic and the cells are smaller, of more normal appearance and less necrotic than comedo DCIS. However, a system of categorization based on the growth pattern alone is problematic as 62% of DCIS lesions tend to have a mixture of architectural patterns [71]. Hence, newer systems of taxonomy are based on nuclear grade and evolved to reflect differentiation and growth. Three grades are ultimately recognized: grade 1/low grade, grade 2/intermediate grade, and grade 3/high grade [72,73]. (**Table 1**) Grading of DCIS can be helpful in estimating the risk of local recurrence and is also relatively reproducible. A core biopsy showing high-grade DCIS represents a 48% risk of the presence of a radiologically occult invasive focus; in order to avoid a second surgical procedure, the patient could benefit from sentinel lymph node biopsy combined with a wide local excision of DCIS [74].

Following a full pathological review of 72% of the 1694 cases entered into the UKCCCR/ANZ DCIS trial, Pinder *et al.* [75] proposed a new pathological classification for DCIS with substantially better prognostic discrimination for ipsilateral recurrence than the classical categorization based on cytonuclear grading alone. They identified a group of patients with a particularly poor outcome: women who had DCIS not only of high nuclear grade, but also of pure (>50%) solid architecture with extensive necrosis (>50% of ducts) displayed a significantly worse outcome than those with a high cytonuclear grade alone. The new mode of classification (**Table 2**) can help to identify women of low risk that would gain no benefit from any further adjuvant therapy, and those at high risk who would require maximal local therapy. More large series are needed to validate these findings [76].

Table 1. DCIS histological grades [145].

Grade	Cells morphology	Nuclei	Mitoses
High-grade DCIS	Large, pleomorphic cells	Nuclei more than 2.5 red blood cells in diameter. Nucleoli often multiple prominent	frequent
Intermediate-grade DCIS	This is diagnosed when the lesion cannot be assigned to the high or low nuclear Grade. Nuclei show moderate pleomorphism, less than that seen in the high-grade cell disease but lack the monotony and regularity of size and spacing of the low-grade form		
Low-grade DCIS	Spaced small, regular cells	Round monotonous nuclei, typically 1.5 - 2 red blood cells in diameter. Nucleoli are typically not prominent	Mitoses are sparse and chromatin is usually finely dispersed

Table 2. Pinder *et al.* proposed system of classification for DCIS [76].

Three group system	Risk for ipsilateral recurrence for dcis and ibc
GROUP 1: of low- and intermediate-cytonuclear-grade disease	6.1%
GROUP 2:high-nuclear-grade DCIS of non-solid architecture or with <50% ducts bearing necrosis	10.9%
GROUP 3: high-nuclear-grade DCIS with extensive confluent comedo-type necrosis (>50% ducts) and with solid architecture	18.2%

5. Molecular Biology

Many studies have compared the gene expression, genetic and epigenetic profiles of DCIS and invasive breast carcinomas in order to identify diagnostic markers that differentiate between *in situ* and invasive tumours, and predictive markers that correlate with the risk of invasive progression [77]. *In situ* and invasive carcinomas of the same histological subtype share the same genetic and epigenetic alterations, unlike luminal A, luminal B, HER2+ and basal-like molecular profiles that are completely different. Mutations in numerous oncogenes and suppressors, including TP53, PTEN, PIK3CA, ErbB2, and MYC, have been analyzed in IDC and DCIS by several comparative studies. Differences in the frequency of these changes have been found according to the tumour subtype but not histological stage; HER2 and basal-like subtypes displayed TP53 mutation more frequently than the luminal type, whereas loss of PTEN and amplification of ErbB2 was more specific for HER2 subtypes [78]. In a study of 236 DCIS patients treated with breast-conserving surgery, Knudsen *et al.* [79] examined the association of two major tumour suppressor genes—retinoblastoma (RB) and phosphatase and tensin homolog (PTEN)—and the risk for ipsilateral breast event (IBE) or progression to invasive breast cancer (IBC). Loss of RB immunoreactivity in DCIS was strongly associated with the risk of IBE occurrence and IBC recurrence. PTEN loss occurred frequently in DCIS but was not associated with recurrence or progression. However, patients with DCIS lesions that were both RB and PTEN-deficient were at further risk of IBEs which indicates that RB and PTEN together can be used as a prognostic marker and also as aggressive target treatment [79]. Pandey *et al.* [80] exam-

ined the expression of key lipogenic genes, including ACLY, ACC1 and FAS, in 111 clinical samples of DCIS and found that these genes were significantly up-regulated in all grades of DCIS compared to normal breast tissue. They have also shown that in animals, the inhibition of lipogenic gene expression in cancer stem-like cells (CSCs) with resveratrol suppressed their ability to generate DCIS [80].

Comparative genomic hybridization (CGH)-based analysis of DCIS and invasive carcinoma performed by Buerger *et al.* revealed that losses of 16q were seen almost exclusively in low- and intermediate-grade DCIS, whereas a higher frequency of 1q gain and 11q loss was observed in intermediate-grade DCIS [81]. However, high-grade DCIS demonstrated complex genomic alterations characterized by loss of 8p, 11q, 13q, and 14q, gains of 1q, 5p, 8q, and 17q, and by high-level amplifications of 17q 12 and 11q 13 [81]. Moreover, an analysis of CGH data generated from synchronous and metachronous IDC and DCIS lesions revealed a near-identical pattern of genetic change, supporting a direct precursor relationship between DCIS and IDC [81-83].

Gautherier *et al.* reported that high expression of COX-2 and Ki67 in DCIS correlated with higher risk of local recurrence of *in situ* or invasive carcinoma [84]. Additionally, Lu *et al.* demonstrated a functional cooperation between ErbB2 and 14-3-3ζ that may increase the risk of invasive progression by promoting the epithelial to mesenchymal transition [85].

Micro RNAs might be used as novel biomarkers for the diagnosis of early breast cancer as they increase with tumour progression [86,87]. The analysis of the expression of miR-21, a microRNA and its targets (PTEN, PDCD4 and TMI) in a normal breast and in DCIS and IDC showed a gradual increase in miR-21 expression during tumorigenesis [86]. Another independent study by Sempere *et al.* also found higher miR-21 expression with tumour progression along with increased miR-45 in DCIS compared with atypical hyperplasia [87].

The increase of tumour invasiveness by the loss of CD34 expression from the CD34 fibrocytes of normal mammary stroma and the acquisition of α-smooth muscle actin (SMA) expression was examined by Catteau *et al.* [88] who found them to be more frequent in high-grade *in situ* lesions than in intermediate and low-grade lesions ($p < 0.001$); the loss of CD34 was even higher in the presence of necrosis. The SMA expression was not associated with necrosis [88].

The association of DCIS with triple negative invasive breast cancer (TNBC) was examined by Aye *et al.* after evaluating 241 invasive TNBC, of which 62.6% *in situ* lesions were of high nuclear grade and 68% revealed basal-like expression of both *in-situ* and invasive components of the same case. These data support the thesis that triple negative carcinoma *in situ* is the precursor of the corresponding invasive counterpart and that the basal-like phenotype in the majority of cases harbours basal-like *in situ* to basal-like invasive BC.

The limitation of all the above-mentioned studies is the small population of patients. In contrast to the significant progress made in the molecular-based classification of invasive breast cancer, the management of DCIS is based on histopathological findings due to the small number of DCIS samples from large cohorts of uniformly treated patients with long-term clinical follow-up. Recently, Solin *et al.* reported a series of 327 patients with DCIS treated by surgical excision without radiation within the Eastern Cooperative Oncology Group (ECOG) E5194 study. [89] associated with the risk of developing an ipsilateral breast event. They identified low, intermediate, and high groups, with 10-year risks of developing IBC being 4%, 12%, and 19%, respectively. Using this approach it may be possible to use gene expression to determine need for additional surgical or systemic therapy.

6. Treatment

Several options for the management of DCIS include breast-conserving surgery (BCS), with or without post-operative radiotherapy, and mastectomy. Achieving a clear margin is the most important determinant of the treatment as it constitutes a major risk factor for local recurrence.

6.1. Breast Conserving Surgery

Several randomized clinical trials in Europe and North America have evaluated BCS with or without radiotherapy for patients with DCIS (**Table 3**). Lumpectomy alone, without radiotherapy, resulted in consistently higher rates of local recurrence, (8% - 34% vs. 0% - 17%) respectively. The most common risk factors for local recurrence involved margins, young age and high-grade tumours with comedo necrosis. There was a notable variation among studies in terms of the optimal width of a negative margin. In a meta-analysis [90] of BCS for DCIS studies (1970-2010), negative margins as opposed to positive margins, with or without radiotherapy, were associated with a reduced risk of IBR (ipsilateral breast recurrence). Compared with a negative margin >2 mm, a negative margin of at least 10 mm was associated with a lower risk of IBR. Wang *et al.* concluded that the surgeon must try to achieve margins as wide as possible but of course such an approach will lead to poor cosmetic outcomes for many patients. Another meta-analysis by Dunne *et al*. examined margin width and risk of IBR in patients with pure DCIS treated by wide excision and radiotherapy. A negative margin was associated with a significant reduction in IBR (OR 0.36, 95 & CI 0.27 -

Table 3. Randomised trials of radiotherapy in DCIS.

Study	Purpose	Follow-Up (Months)	arms	No pt	No LR/%	OS%	Risk factors for LR
NSABP B-06 [102]	Evaluation the safety of BSC for IBC inked margin tumor free	83	1) lump 2) lump + XRT 3) Mastectomy	21 27 28	9/42.8 2/7.4 0/0	96 96 96	1) No XRT after lumpectomy 2) comedo necrosis 3) positive margins
EORTC 10853 [128,146]	Evaluation BCS with vs without breast XRT; mammographically detected DCIS ≤5 cm; no margin width specification	65	1) lump 2) lump + XRT	426 437	83/19.5 54/12.4	97 97	1) No XRT after lumpectomy 2) comedo necrosis/solid/ cribriform patterns 3) positive margins 4) age ≤ 40 5) symptomatic DCIS
NSABP B-17 [123,124]	Evaluation BCS with vs. without breast XRT; DCIS detected by mammogram or physical examination; inked margin tumor free	90	1) lump 2) lump + XRT	403 411	104/25.8 47/11.4	97 96	1) Lack of XRT 2) calcifications on mammogram
NSABP B-24 [137]	Evaluation the added benefit of tamoxifen as adjuvant therapy for DCIS patients treated with lumpectomy and breast XRT; DCIS detected by mammogram or physical examination; inked margin tumor free	74	1) lump + XRT 2) lump + XRT + tamoxifen	902 902	87/9.6 63/7.0	97 97	1) Lack of tamoxifen 2) age <50 3) involved margins 4) comedonecrosis 5) symptomatic DCIS
UK/ANZ[130]	Evaluation of the effectiveness of adjuvant TAM and/or XRT after BCS for DCIS inked margin tumor free	53	1) lump 2) lump + TAM 3) lump + XRT 4) lump + XRT + tamoxifen	544 567 267 316	119/22 101/18 22/8 21/6	NR NR NR NR	1) lack of XRT

Pt: patients, LR: local recurrence, OS: overall survival, BCS breast conserving surgery lump: lumpectomy,XRT radiotherapy, IBC:invasive breast cancer, DCIS: ductal carcinoma *in situ*, TAM tamoxifen, NR = not reported; NSABP = National Surgical Adjuvant Breast and Bowel Project; Symptomatic DCIS = palpable mass, nipple discharge UK/ANZ = DCIS trialists in the United Kingdom, Australia, and New Zealand.

0.47). A 2 mm margin was superior to <2 mm, but there was no significant difference in relapse rate in those with margins of 2 or 5 mm when combined with radiotherapy [91]. Silverstein *et al.* examined 496 specimens of DCIS and concluded that there was no benefit to be gained from adjuvant radiotherapy in patients that had margin widths of 1 - 10 mm or >10 mm, whereas the rate of local recurrence was lower among patients with margin <1 mm after adjuvant radiotherapy [9].

Owing to the expense, inconvenience and potential adverse effects of radiotherapy, its routine use for low grade DCIS after lumpectomy has been questioned. Hence, in 2008, the National Comprehensive Cancer Network included excision alone as an acceptable treatment choice for DCIS, but without defining which group of patents is eligible for such treatment. Some groups have developed grading systems with the most popular being Van Nuys Prognostic index (VNPI), developed by Silverstein *et al.* in 1995 [92]. VNPI is an algorithm that quantifies five measurable prognostic/risk factors for local recurrence [93] (**Table 4**). Initially, this index only used nuclear grade and necrosis as predictor factors; in 1996, size and margin were added, and age was later to be included in 2002. If excision alone is to achieve a local recurrence rate of less than 20%, the patients concerned must have a score of 4, 5, or 6; margins >3 mm are required in patients with a score of 7.

Once the choice of BCS is made, the patient must be made aware of the possibility that for an extended period she will undergo diagnostic mammograms and invasive procedures in the conserved breast. In a study by Nekhlyudov *et al.* of 2948 women with DCIS treated with BCS, 907 (30.8%) were submitted to 1422 diagnostic mammograms, and 1813 (61.5%) underwent 2305 ipsilateral invasive procedures [94]. The estimated 10-year cumulative risk of having at least one diagnostic mammogram after initial DCIS excision and one invasive procedure was 41% and 66% respectively [94].

6.2. Mastectomy

The use of mastectomy for treatment of DCIS has declined steadily. Ernster *et al.* evaluated the treatment of DCIS using Surveillance Epidemiology and End Results data from 1973 to1992 and found that the number of patients treated with mastectomy fell from 71% in 1983 to 44% in 1992 [11]. Mastectomy usually advised for the following indications: extensive and/or multifocal DCIS involving 4 - 5 cm for disease or more than one quadrant,

Table 4. Van nuys prognostic index [93].

Score	1	2	3
Size	≤15 mm	16 - 40	>40
Margin	≥10 mm	1 - 9	<1
Class	Grade 1/2 without necrosis	Grade 1/2 with necrosis	Grade 3
Age	>60	40 - 60	<40

Score 4, 5, 6 or 7 with ≥3 mm: eliglible for excision alone Score 7 with <3 mm margin, 8 with ≥3 mm and 9 with ≥5 mm: excision plus radiotherapy Score 9 with margin <5 mm, 10, 11, 12: mastectomy.

inability to obtain tumour-free margins by lumpectomy and/or re-excision(s), patients in whom breast irradiation is potentially contraindicated or who lack access to irradiation, suboptimal tumour to breast size ratio, where a margin-negative lumpectomy will yield an unacceptable cosmetic result (as defined by the patient), and sometimes the patient's strong preference for mastectomy. There are various surgical approaches to mastectomy for DCIS: simple mastectomy (excision of the breast tissue and overlying skin), skin-sparing mastectomy (removal of the breast with preservation of the skin envelope) and nipple-preserving mastectomy techniques. The risk for local recurrence in these three approaches is very low, provided a complete excision of the breast tissue is performed [36,95,96]. The low recurrence reported for the nipple-sparing mastectomy may be due to the fact that DCIS rarely involves the nipple-areola complex as opposed to invasive ductal carcinoma and invasive lobular carcinoma [97], and the exclusion of patients with centrally located disease, extensive DCIS or radiographic abnormalities in proximity to the nipple-areolar complex.

Clinical trials and population-based studies with long-term follow up report excellent clinical outcomes following mastectomy for DCIS with a 1% - 2% rate of local recurrence (LR) [98,99]. The majority of LRs are detected on palpation [36]. In a series of 80 DCIS patients who had undergone mastectomy, Rashtian *et al.* [100] reported six (7.5%) with LR at median follow-up of 61 months. This was associated with high grade and margins of less than 1mm. In another small review, 10 chest wall recurrences were associated with young age and multifocality [101]. Women with isolated locoregional recurrence after mastectomy displayed long-term disease-free survival after surgical excision combined with chest wall radiotherapy [101].

To date, no prospective randomized trial has directly compared mastectomy and lumpectomy. In the NSABP B-06 trial [102] (**Table 3**), 78 DCIS were incidentally included; the overall survival between mastectomy/BCS/BCS + radiation was similar. Local recurrence was higher for BSC alone (43%) but decreased after the addition of radiotherapy (7%). Although the LR risk is low, there is a difference in the long-term outcome in terms of progression to invasive cancer, with a two-fold higher mortality rate.

Immediate breast reconstruction is often offered after mastectomy to DCIS patients as these patients rarely undergo radiotherapy post mastectomy. In a study of 238 patients treated with radical mastectomy for DCIS, 57.1% had immediate breast reconstruction and 42.9% no reconstruction [103]. The main reason for a patient not having reconstruction was simply because it was not offered by the surgeon [103].

6.3. Sentinel Lymph Node Biopsy (SLN) and Management of the Axilla in Ductal Carcinoma *in Situ*

DCIS does not cause invasion and metastasis. Axillary lymph node dissection (ALND) is no longer indicated for DCIS patients. Silverstein *et al.* [104] reported a study of 100 patients treated with mastectomy (n49) or BCS (n51) and ALND, all of whom had negative lymph nodes. In a review of the NSABP B-17 and NSABP B-24 trial, the risk of axillary lymph node recurrence was less than 1% [105]. Similarly, a low axillary recurrence was reported by the City of Cancer Center after a long-term follow-up of DCIS patients treated with lumpectomy and whole breast irradiation [106].

Theoretically, sentinel lymph node biopsy (SLN) does not appear to be indicated in patients with pure DCIS. However, about 15% of patients who are preoperatively diagnosed with DCIS on core-needle biopsy were upstaged postoperatively to microinvasive (extension of the cancer cells beyond the basement membrane into adjacent tissues with focus no more than 1 mm in greatest dimension) or invasive disease in the final pathology report, thereby eliminating the benefit of a one-stage procedure [107-110]. The question that arises is which patients with an initial diagnosis of DCIS present a high possibility of having invasive or microinvasive disease and should consequently undergo axillary evaluation with SLN?

Multiple investigators have stressed the need for SLN in patients with high-risk DCIS in order to rule out invasive disease and also as not to operate on patients twice [111-113]. Among the independent predictor factors that increase the probability of DCIS being upstaged to microinvasive or invasive disease are: patients aged 55 years or under, mammographic abnormality greater than 4 cm, high grade of DCIS or comedo necrosis on histological evaluation, and the presence of a palpable tumour [114-116].

Conversely, other investigators fail to see any benefit in subjecting the patients to SLN which can cause troublesome morbidities (lymphoedema, pain, nerve injury, paraesthesia, numbness, decreased limb use, and shoulder dysfunction) unless invasive disease is confirmed

with core biopsy or final histology [117-119]. As shown in studies of patients with DCIS or microinvasion by both Murphy *et al.* [119] and Lara *et al.* [120], a positive SLN was not associated with a high risk of local or distant recurrence.

Performing SLN at mastectomy has also been evaluated [111,112,114,121]. Those same indications that favour mastectomy in these patients can also be considered as risk factors for invasive or microinvasive disease and that SLN is less efficacious after mastectomy [122] lend credence to SLNB being a reasonable procedure to carry out before or during mastectomy. In conclusion, SLNB should be performed on patients undergoing mastectomy for DCIS, and a case-by-case decision should be made to perform SLNB in patients who have a high risk DCIS or large tumours.

6.4. Role of Radiotherapy in the Management of DCIS

As most women with DCIS are interested in breast conserving treatment, a major decision for these women is whether or not to add radiotherapy. As mentioned above, four prospective randomized clinical trials measured the value of adding radiation after BCS for DCIS (**Table 3**) [123-130]. A meta-analysis of these trials yielded a total of 3729 women were randomized either to receive radiation after BCS or not. The 10-year rate for ipsilateral LR (IBLR) (invasive carcinoma plus DCIS) decreased by 15% with the addition of radiotherapy. Additionally, the 10-year rate of invasive and DCIS local failure was reduced 9% and 8% respectively. There were no differences in the 10-year overall survival rate (8.2% vs. 8.4% respectively), mortality without recurrence (5.7% vs. 5.4% respectively) or cardiac mortality (most important when evaluating a patient with left-sided DCIS for radiation treatment) [131]. Another meta-analysis of these randomized trials by EBCTCG demonstrated that only a very large randomized clinical trial or meta-analysis would have sufficient statistical power to determine whether any survival benefit was to be gained from the addition of radiotherapy [132].

In a study by Solin *et al*. [133], 1003 women with unilateral, mammographically detected DCIS were treated with lumpectomy followed by radiotherapy. The median follow-up was 8.5 years, and the mean patient age was 5 years. The 15-year overall survival rate was 89%, the 15-year cause-specific survival rate was 98%, and the 15-year distant metastases-free survival was 97% with most patients having died of causes unrelated to the breast cancer. The 15-year rate of LR (DCIS or IBC) was 19%. Patient age ≥50 years at the time of treatment and negative margins were both independently associated with a decreased risk of local failure, with LR in these two groups being ≤8% [133].

Rakovitch *et al.* [134] analysed 3762 DCIS patients treated with BCS, 1895 of whom also received radiotherapy. At 10-year median follow-up, the actuarial rate of LR in women receiving radiotherapy was 13% as compared with 20% in those not submitted to irradiation. It was estimated that 22% of LR could have been avoided had radiotherapy been added.

The ECOG E5194 study had 2 arms: 1) low- or intermediate-grade DCIS 2.5 cm in size or less (565 pt), and 2) high-grade DCIS 1cm or less (105 pt). A minimum 3 mm negative margin was required and no radiotherapy was given. At median 6.7-year follow-up, the 5-year rate and 7-year rate of LR for HG DCIS stood at 15% and 18% respectively compared with 6% and 11% at 6.2-year follow-up for low and intermediate grade DCIS. These data suggest that patients with HG DCIS are not suitable for BCS alone [135]. These results are consistent with another study by Balleine *et al.* with 134 patients [136].

Prospective and retrospective studies have demonstrated excellent long-term results after BCS and radiotherapy, as opposed to BCS alone that has shown a higher rate of local recurrence. Following a multivariate analysis, age was found to be a significant variable associated with LR in HG DCIS [135]. Margin width is also an important variable, with the minimum negative margin being 10 mm [9] for BCS alone, as compared to a 2 mm minimum margin that is recommended if BCS is combined with radiotherapy [91]. Additional markers are needed to identify a low-risk group in whom radiation can be safely given.

6.5. The Role of Systemic Therapy in Ductal Carcinoma *in Situ*

6.5.1. Tamoxifen

Two randomized phase III trials have been conducted to assess the efficacy of Tamoxifen after BCS, with or without radiotherapy, to reduce recurrence (**Table 3**). In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial [125,137], 1804 women with DCIS were randomly given Tamoxifen or placebo for five years. Those eligible had also received radiotherapy. At 12-year follow-up, Tamoxifen had reduced the risk of all breast cancer LR by 31% (ipsilateral invasive breast cancer by 31%, contralateral breast cancer events by 43%). Similar benefits applied to women under 50 years of age or older. Overall survival did not differ between the Tamoxifen and the placebo group. ER status was not analyzed initially, but in a retrospective analysis evaluating ER status in 732 cases, 76% proved to be ER-positive. The risk of recurrence for invasive breast cancer was reduced by 40% in ER-positive women compared to the placebo group.

In the United Kingdom/Australia/New Zealand (UK/

ANZ) trial [130] (**Table 3**), at 52-month median follow-up 1701 patients showed a statistically significant reduction of 32% in ipsilateral and contralateral non-invasive cancers in the Tamoxifen vs. non-Tamoxifen groups. In the group receiving radiotherapy, the addition of Tamoxifen made no statistically significant difference to invasive or non-invasive breast cancers. As concerns the side effects, Tamoxifen was well-tolerated; serious and adverse events (thrombo-embolic disease and endometrial cancer) are rare and age-related [138].

Given the low rate of recurrence, few DCIS patients become candidates for Tamoxifen after mastectomy. Further studies with an adequate selection of patients will help to identify those who could really benefit from receiving Tamoxifen.

6.5.2. Aromatase Inhibitors

NSABP B-35 trial and International Breast cancer Intervention Study-II (IBIS-II) are currently evaluating the role of Anastrozole as adjuvant therapy for patients with DCIS. In the NSABP B-35 trial, post menopausal women with ER-positive and/or progesterone receptor-positive DCIS treated with lumpectomy and radiotherapy are randomized to receive Anastrozole or placebo and Tamoxifen or placebo for a period of five years. The IBIS-II trial is also evaluating Anastrozole and Tamoxifen, but not always combined with radiotherapy. Aromatase inhibitors are also being investigated in a neoadjuvant setting in a pilot study of Tamoxifen or Letrozole in 40 women with ER (+) DCIS. The response to the endocrine therapy that commences 3 months prior to surgery is evaluated with mammograms, MRI and tissue biomarkers [139,140]. Bundred and colleagues randomized 90 postmenopausal women with ER-positive DCIS to receive Exemestane or placebo in a preoperative, 14-day, window-of-opportunity trial. The response and impact on KI-67 was evaluated, and Exemestane was shown to have reduced Ki67 by 9% ($p < 0.001$) [141].

6.5.3. Other Targeted Therapy

A number of other molecular targets are under investigation with regard to DCIS (**Table 5**). Pure DCIS is more likely to express HER2/neu than invasive breast cancer [142]. Farnie *et al.* cultured two DCIS cell lines, MCF10 DCIS.com (ErbB2-normal) and SUM225 (ErbB2-overexpressing), and seven human primary DCIS samples in the presence, absence or combination of the Notch inhibitor, DAPT and ErbB1/2 inhibitors, Lapatinib or Gefitinib. Combined DAPT/Lapatinib treatment emerged as more effective at reducing acini size in both DCIS cell lines than monotherapy, regardless of ErbB2 status. Targeted therapies combining Notch and ErbB1/2 inhibitors should be investigated regardless of ErbB2 receptor status [143]. Cycloxygenase (COX-2) expression is also common in invasive carcinomas and DCIS [144].

7. Conclusion

DCIS is not life-threatening since it represents local disease with no regional involvement. However, being an immediate precursor of potentially lethal invasive breast cancers, its diagnosis and treatment command a multidisciplinary approach. With the use of mammography and MRI, the extent of DCIS can be assessed and it can guide the surgeon to decide whether BCS or mastectomy is indicated for complete removal of the disease. The type of surgery and the pathology report detailing the grade, size, width of clear margin, and also the age of the patient will help the oncologist decide on the appropriate adjuvant treatment for the patient. Radiotherapy has been found to significantly reduce the risk of LR after BCS, especially

Table 5. Targeted therapies for DCIS.

Study	Regimen	N patients	Setting	Arms	Comments
NSABP B-43 phase III trial [147]	Trastuzumab	open	adjuvant	All patients will receive 6 weeks of whole-breast irradiation A) with 2 cycles of trastuzumab B) without trastuzumab	ongoing
Kuerer *et al.* phase II trial [148]	Trastuzumab	69	neoadjuvant	Single dose of Trastuzumab is given 2 weeks before the operation	No significant, clinically overt, histologic, antiproliferative, or apoptotic changes
NCT00570453 [149]	Lapatinib	open	Neoadjuvant	Neoadjuvant lapatanib in 3 different doses (750 mg, 1000 mg, 1500 mg) compared with placebo for HER2new positive or EGFR (+)	ongoing

if the clear margin is 2 mm or less. Tamoxifen also reduces ipsilateral and contralateral breast cancer events in women with DCIS and is the only systemic therapy approved by Food Drug Administration for this disease. Aromatase inhibitors and other targeted therapies are currently being evaluated in ongoing studies.

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