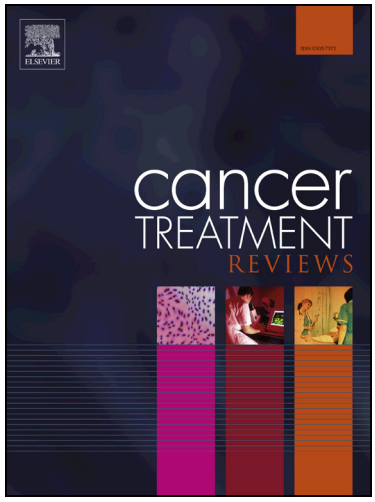
Current treatment trends and the need for better predictive tools in the management of ductal carcinoma in situ of the breast



Tumour Review

Current treatment trends and the need for better predictive tools in the management of ductal carcinoma in situ of the breast

Carlos Martínez-Pérez, Arran K. Turnbull, Gregory E. Ekatah, Laura M. Arthur, Andrew H. Sims, Jeremy S. Thomas, J. Michael Dixon

PII: S0305-7372(17)30046-4
DOI: http://dx.doi.org/10.1016/j.ctrv.2017.03.009
Reference: YCTRV 1621

To appear in: *Cancer Treatment Reviews Cancer Treatment Reviews*

Received Date: 18 January 2017
Revised Date: 21 March 2017
Accepted Date: 23 March 2017

Please cite this article as: Martínez-Pérez, C., Turnbull, A.K., Ekatah, G.E., Arthur, L.M., Sims, A.H., Thomas, J.S., Dixon, J.M., Current treatment trends and the need for better predictive tools in the management of ductal carcinoma in situ of the breast, *Cancer Treatment Reviews Cancer Treatment Reviews* (2017), doi: http://dx.doi.org/10.1016/j.ctrv.2017.03.009

Current treatment trends and the need for better predictive tools in the management of ductal carcinoma in situ of the breast

Authors:

Carlos Martínez-Pérez[a], Arran K Turnbull[a], Gregory E Ekatah[b], Laura M Arthur[a], Andrew H Sims[a], Jeremy S Thomas[c], J Michael Dixon[b]

Affiliations:

[a]Breast Cancer Now Edinburgh Research Team, Western General Hospital, University of Edinburgh

[b]Edinburgh Breast Unit, Western General Hospital, University of Edinburgh

[c]Department of Pathology, Western General Hospital, Edinburgh

Corresponding author:

Carlos Martínez-Pérez

carlos.martinez-perez@igmm.ed.ac.uk

Division of Pathology Laboratories, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XU

Title:

Current treatment trends and the need for better predictive tools in the management of ductal carcinoma in situ of the breast

Abstract *(250 words):*

Ductal carcinoma in situ (DCIS) of the breast represents a group of heterogeneous non-invasive lesions the incidence of which has risen dramatically since the advent of mammography screening. In this review we summarise current treatment trends and up-to-date results from clinical trials studying surgery and adjuvant therapy alternatives, including the recent consensus on excision margin width and its role in decision-making for post-excision radiotherapy. The main challenge in the clinical management of DCIS continues to be the tailoring of treatment to individual risk, in order to avoid the over-treatment of low-risk lesions or under-treatment of DCIS with higher risk of recurring or progressing into invasion. While studies estimate that only about 40% of DCIS would become invasive if untreated, heterogeneity and complex natural history have prevented adequate identification of these higher-risk lesions. Here we discuss attempts to develop prognostic tools for the risk stratification of DCIS lesions and their limitations. Early results of a UK-wide audit of DCIS management (the Sloane Project) have also demonstrated a lack of consistency in treatment. In this review we offer up-to-date perspectives on current treatment and prediction of DCIS, highlighting the pressing clinical need for better prognostic indices. Tools integrating both clinical and histopathological factors together with molecular biomarkers may hold potential for adequate stratification of DCIS according to risk. This could help develop standardised practices of optimal management of patients with DCIS, improving clinical outcomes while providing only the amount of therapy required for each individual patient.

Keywords *(6):* DCIS; ductal carcinoma in situ; breast cancer; risk prediction; prognostic tools; patient stratification.

1. INTRODUCTION

The term ductal carcinoma in situ (DCIS) of the breast refers to precursor, non-invasive lesions comprising malignant epithelial cells which remain confined within the basal membrane of terminal duct lobular units of the breast[1,2]. DCIS encompasses a wide spectrum of lesions heterogeneous in grade, morphology, genomic profile and clinical presentation and represents almost 90% of all precursor (stage 0) breast cancers detected[3].

Before 1980, DCIS was considered relatively rare, accounting for less than 5% of breast cancer diagnoses[4], as most non-invasive lesions are typically non-palpable and asymptomatic and were often identified only after surgical resection of a suspicious breast mass[5,6]. In the last few decades, the advent of breast cancer mammography screening has resulted in a dramatic rise in DCIS detection. In the UK, incidence has increased by 534% since the 1970s and DCIS currently accounts for 20% of all screen-detected breast cancers[7].

Despite the limited knowledge of its natural history, DCIS has long been considered a precursor of invasive breast cancer (IBC)[2,8]. In the 1980s, Page and Dupont identified a series of women with untreated DCIS in breast biopsy samples and showed they had an increased risk of developing IBC[9]. Genetic similarities also support the precursor role of DCIS[10]. While the proportion of DCIS which develop into IBC if untreated remains uncertain, studies suggest this to be around 40%[11–13].

2. CURRENT THERAPEUTIC TRENDS

2.1.Surgery

DCIS is most frequently (>90%) detected during mammographic screening as indeterminate calcifications or microcalcifications[7]. Subsequently, a core biopsy is

performed for histological assessment and grading. DCIS is categorised into low, intermediate and high grades according to cellular and nuclear morphology and presence of mitoses (see Figure 1).

In the UK, most patients (72%) diagnosed with DCIS on core biopsy undergo breast conserving surgery (BCS). Mastectomy may be performed depending on factors such as DCIS extent relative to breast size, type of DCIS, age and patient choice, as well as concern for risk of recurrence[14]. The increasing sensitivity of imaging techniques has resulted in more patients being diagnosed with extensive or multicentric disease, which presents challenges for surgical management.

Traditionally, sentinel lymph node biopsy was performed for patients undergoing mastectomy for DCIS and for those with microinvasive disease, although this approach has been contested[15]. A recent study concluded that sentinel node dissection should be reserved for patients at high risk of invasive disease, such as those with high grade or large (>4cm) lesions[16].

Surgery is followed by histopathological examination to ensure clear surgical margins, as negative margins reduce the risk of recurrence by approximately 50%[17]. If positive margins (the definition of which remains controversial) are observed, the patient should undergo re-excision.

Practical recommendation

Current consensus is that BCS with selective use of whole breast radiotherapy is the optimal treatment for the majority of women with DCIS. Sentinel node biopsy should not be performed in patients having BCS. Recent studies have shown that women over 50 years of age treated for DCIS are more likely to be alive 10 years after diagnosis than women in the

general population[18]. A recent review of DCIS patients in Edinburgh treated by BCS with selective use of radiotherapy showed no deaths from DCIS at a median of almost 8 years.

2.2.Adjuvant therapy

Surgery may be followed by adjuvant radiation or endocrine therapy. Due to the limited knowledge of the natural history of DCIS and its risk of developing into IBC, the decision-making process is not fully standardised and therapeutic strategies depend on local practice and assessment of prognostic indicators, as well as the clinician's and patient's attitude towards risks and benefits of different treatments[19–21].

Besides positive excision margins, other risk factors for recurrence after BCS are tumour grade and size; patients with higher grade and/or larger DCIS appear at higher risk of developing IBC or recurrent DCIS after lumpectomy[22,23]. A recent UK-wide survey found these are the two most common factors in decision-making for adjuvant radiotherapy (in 51.3 and 35.5% of sites surveyed, respectively[24]). Additional independent predictors of progression or recurrence are younger patient age, micropapillary architecture and the presence of comedonecrosis[23,25–28], as well as African-American race and strong family history of breast cancer or BRCA1/2 mutation[27].

2.2.1. Radiation therapy

The need for adjuvant radiation therapy (RT) in all patients remains controversial. The risk of breast cancer-specific death following surgical excision of DCIS is low (about 1-4.5% at 15 years[29]), but the 10-year risk of local recurrence is relatively high, with studies estimating around 20-44% following BCS alone[30].

The benefit from RT for patients undergoing BCS is supported by results from 4 randomised control trials: NSABP (National Surgical Adjuvant Breast and Bowel Project) B-17[31], DCIS-EORTC (European Organisation for Research and Treatment of Cancer)

10853[32], UK/ANZ (UK-Australia-New Zealand) DCIS[33,34] and SweDCIS (Swedish DCIS)[35–37]. These studies and subsequent meta-analyses of their results[38,39] show that RT following BCS for DCIS reduces overall and invasive 10-year local recurrence by 50%.

However, some studies have attracted criticism because of incomplete determination of margin status and the failure to show significant improvement in overall survival with RT[29,40]. These studies also failed to identify a patient subgroup which derived no benefit from RT, adding to the growing concern of overtreatment of precursor lesions that may present only a low risk of recurrence or development into IBC.

Recent efforts have failed to identify specific low-risk cohorts for whom RT can be safely omitted[41,42]. A retrospective study of small low-risk lesions found relatively low rates of 12-year ipsilateral recurrence, at 7.8%, for patients treated with BCS alone[43]. The more recent prospective, randomised RTOG (Radiation Therapy Oncology Group) 9804 trial did demonstrate that radiation decreased recurrence risk even in patients presenting small, low or intermediate-grade DCIS[44], although this study closed early due to limited accrual.

Other studies of low and/or intermediate-risk DCIS patients treated with BCS alone have reported a substantial, cumulative risk of local recurrence[45,46]. In particular, 12-year follow-up results from the ECOG-ACRIN (Eastern Cooperative Oncology Group, American College of Radiology Imaging Network) E5194 study reported a cumulative steady increase in ipsilateral breast recurrence, both in situ or invasive, over time with no apparent plateau[45].

Studies currently underway aim to investigate alternative treatment strategies in patients with low-risk DCIS, with patients being selected based on clinical and histopathological characteristics, with the 10-year rate of invasive local recurrence as endpoint. The phase III LORD (Low Risk DCIS) trial will compare outcomes of patients

managed by active surveillance only, treatment with BCS alone, or BCS followed by adjuvant RT[47], while the UK-based LORIS (Low Risk DCIS) trial will compare two study arms of active surveillance or BCS[48].

Margin status is an important factor in determining both the risk of recurrence and the possible benefit from RT, since studies have confirmed that margin width is a significant prognostic factor of local recurrence for patients with DCIS treated with BCS alone or followed by RT[49–51]. Consequently, a consensus on optimal margin size has been a pressing need[52,53]. A recent meta-analysis of 20 studies and an accompanying review defined new guidelines on margins for DCIS treated by BCS with adjuvant RT[17,54]. This new consensus found that minimum margin of ≥2mm followed by RT minimises the risk of local recurrence, while wider margins do not provide any significant advantage in women treated with radiation. Negative close margins (<2mm) should trigger clinical review but are not a sufficient indication for re-excision.

While these guidelines provide some scientific basis and do represent a consensus for a margin width advised to minimise recurrence, they are inconsistent with our knowledge of DCIS biology. For instance, the consensus for negative margins in IBC is no ink on tumour but in these cases the disease that is most often closest to the margin is DCIS. This raises the question of why DCIS associated with IBC should be considered differently from DCIS alone and suggests that more data are needed to refine the current consensus.

Knowledge and understanding of IBC and DCIS dictate that the same margin guidelines should be used. Meta-analysis of IBC data identified 1mm as an adequate margin[55]. However, limited available data led to 0-1 and 1-2mm margins being combined into a single category of ≤2mm in the DCIS meta-analysis. Further studies in DCIS comparing 1-2 vs 1mm margins are required for the formulation of more specific guidelines, which should

represent an understanding of the biology of DCIS rather than just being simply based on results from analysis limited by lack of margin width data.

Practical recommendation

In short, BCS should aim to excise DCIS to clear margins. Following the current guidelines, if margins are ≥2mm then surgery is complete, while if margins are <1mm then re-excision is indicated. Given the limited amount of information in patients with 1-2mm margins and based on studies of margin width in invasive and in situ cancer together with the data from our recent study we do not re-excise if margins are ≥1mm.

2.2.2. Endocrine therapy

Studies have estimated that around 60-76% of DCIS is estrogen receptor positive (ER+)[56–58] (see Figure 1). Endocrine therapy (ET) has been used to treat DCIS since the NSABP B-24 trial first randomised patients to tamoxifen in addition to treatment with BCS and RT[59]. This study found a beneficial effect of adjuvant tamoxifen, with a 37% reduction in the relative risk of ipsilateral and contralateral cancer events[29,59,60]. Further retrospective analysis revealed greater benefit in ER+ patients, with an 11% absolute reduction in breast cancer events (vs 5.2% for patients not selected according to ER)[56,60].

The UK/ANZ DCIS trial showed the beneficial effect of tamoxifen in reducing both ipsilateral DCIS recurrence (by 30%) and contralateral primary cancer (56%), although it failed to show any effect on ipsilateral invasive disease[33]. Differing findings compared to NSABP B-24 could be related to an average younger age in the US study[33]. Additionally, the UK/ANZ DCIS trial has been criticised for not establishing ER status of patients accrued, as a lower percentage of ER+ cases may have contributed to the weaker overall effect of adjuvant tamoxifen[61,62].

Chen et al[63] studied the efficacy of neoadjuvant ET in a small cohort of ER+ DCIS cases. 3-months preoperative tamoxifen (pre-menopausal patients) or letrozole (post-menopausal), induced histologic and morphologic changes and reduced proliferation. Phase 2 of this trial recently completed accrual and will assess letrozole alone as a neoadjuvant treatment.

More recently, two phase 3 randomised control trials have compared non-steroidal aromatase inhibitor anastrozole and anti-oestrogen tamoxifen as adjuvant ET in women with hormone receptor-positive DCIS[64,65]. The IBIS-II (International Breast Cancer Intervention Study-II) DCIS trial compared both treatments in 2,980 postmenopausal women which had DCIS excision with or without subsequent RT and found no significant difference in prevention of ipsilateral recurrence or primary contralateral events between both therapies[64].

The NSABP B-35 trial included 3,104 patients who had DCIS excision plus RT[65]. This trial found both agents had similar efficacy in patients over the age of 60, while recurrence was reduced with anastrozole in women younger than 60, with divergence of breast cancer-free survival curves after the first 5 years[65]. Patient-reported outcomes showed different side effects for each therapy, with anastrozole increasing musculoskeletal symptoms, while tamoxifen led to more common vasomotor problems. The under-60 cohort of patients also appeared to endure more severe side effects[66].

In short, studies have suggested a wide range of endocrine treatments are effective in the adjuvant setting for patients with ER+ DCIS. The efficacy of aromatase inhibitors as an alternative hormonal therapy to tamoxifen allows for treatment selection based on side effect profile for the over-60 cohort, while aromatase inhibitors are favoured for younger patients due to their greater efficacy if associated symptoms permit it.

Given the reported efficacy in reducing breast cancer events, 5 years of endocrine therapy is often recommended as prevention following surgery for ER+ DCIS[67]. However, given the lack of evidence for a survival benefit, the use of adjuvant ET varies locally depending on how this modest reduction of recurrence is weighed against the potential side effects[68,69]. Additionally, several studies have highlighted the issue of suboptimal adherence to ET[70–74]. Rates of non-adherence are reported to be as high as 60-70%[70,72], with patients often discontinuing treatment due to side effects, physician recommendation or lack of conviction[71,72,74,75].

Practical recommendation

Endocrine therapy does reduce the rates of recurrence and development of new breast cancer. The benefits need to be weighed against the risks of therapy. Patients should discuss benefits and risks with their surgeon and oncologist and reach a joint decision of what is best for that individual.

2.2.3. HER2-targeted therapy

Studies in DCIS have reported a variable incidence of human epidermal growth factor receptor 2 (HER2) overexpression between populations. However, a recent review of 8 clinical trials and 36 observational studies estimated that about 40% of DCIS lesions are HER2+[57], suggesting a subpopulation of DCIS could benefit from HER2-targeted therapy (see Figure 1). A meta-analysis reported that HER2+ DCIS is associated with an increased risk of recurrence[28]. Although the clinical utility of HER2 status in the management of DCIS is still unclear, it has become the focus of recent research.

An open-label phase II trial assessing the effect of 4-weeks pre-surgical treatment with the tyrosine kinase inhibitor lapatinib in 20 patients reported a significant inhibition of HER2

pathway signalling and reduced tumour size[76]. An ongoing randomised phase I/II clinical trial (NCT00555152) will study the efficacy and side effects of lapatinib in HER2+ DCIS.

Another open-label phase II study assessed the effect of 2-4 weeks pre-surgical treatment with the HER2-targeting monoclonal antibody trastuzumab in 69 patients with DCIS[77]. Although results suggested an increase in immunoresponse, they failed to show significant changes in histology, proliferation or apoptosis.

The ongoing NSABP B-43 study is the first prospective randomised phase III clinical trial to assess the effect of trastuzumab on local recurrence. A total of 1,428 patients which underwent excision of HER2+ DCIS were randomly assigned to receive radiotherapy alone or with trastuzumab, with no significant differences in toxicity observed between both arms[78].

Practical recommendation

As this trial is still underway and further studies are needed to assess the possible application of this treatment, currently HER2-directed therapy has no established role in treatment of HER2+ DCIS.

3. CHALLENGES IN THE MANAGEMENT OF DCIS: THE NEED FOR PREDICTIVE TOOLS

The last two decades have seen the improvement in our understanding of DCIS, the establishing of treatment consensus for certain categories of DCIS and the search for effective therapeutic approaches. However, due to heterogeneity and complex natural history of DCIS, we are still unable to determine which non-invasive lesions will become invasive if untreated or to predict the risk of recurrence as either DCIS or IBC following treatment[19]. These issues contribute to a lack of consensus on management[19], complicate communication with patients[79,80] and are a hurdle to optimising treatment for individual patients[81].

The ultimate goal of therapy for DCIS is to prevent development of IBC. The main challenge resides in tailoring treatment to individual risk, to avoid both over-treatment of lesions that may never develop into IBC and under-treatment of DCIS with high risk of post-excision recurrence as DCIS or IBC[81]. A review of autopsy studies revealed that 8.9% of women who died of causes other than breast cancer had undetected DCIS in their breasts[82]. Studies have found that screening with mammography in addition to clinical examination leads to a 4-fold increase in DCIS detection but fails to reduce mortality[83,84].

In order to improve clinical management of DCIS, accurate prognostic markers are needed to define low-risk DCIS cohorts for whom adjuvant therapy could be safely omitted, or high-risk cohorts which require additional systemic and/or targeted treatments to prevent recurrence. Histopathological and host factors such as DCIS grade are currently used to guide clinicians in the decision-making process, but low grade does not always necessarily mean low risk and better predictors are needed.

3.1. Predictive tools based on clinical and histopathological markers

- **Van Nuys prognostic index**

In the 1990s, Silverstein and collaborators in the University of Southern California (USC) developed the Van Nuys prognostic index (VNPI) to predict the risk of local recurrence following excision of DCIS. This clinical algorithm incorporated tumour size, margin width and pathologic classification (based on nuclear grade and presence/absence of comedonecrosis) as key risk factors for recurrence[49,85,86]. Patient age was subsequently identified as an independent predictor of local recurrence[87–89] and incorporated as a fourth factor into an amended VNPI algorithm[86] (see Table 1).

Each factor is assigned a score of 1 (better prognosis) to 3 (worse prognosis), providing an overall VNPI score which classifies DCIS lesions into different risk of recurrence groups

with associated treatment guideline: excision only (low risk: 4-6), excision plus RT (moderate risk: 7-9) or mastectomy (high risk: 10-12). These guidelines, based on which cohorts gained benefit from the addition of adjuvant RT, aimed to achieve less than a 20% local recurrence rate after 12 years for each group[86] and have been subsequently updated, considering margin width to refine treatment selection for cases in the intermediate risk group[90].

However, this index was based on a retrospective multivariate analysis of pooled data from a single institution and lacks robust independent prognostic validation; some studies supporting its efficacy[25,91], while others found no benefit from its application[92]. A study assessing validity of the VNPI in a UK population showed that it lacked discriminatory power to adequately stratify patients[50]. This study also criticised the VNPI pathologic classification and argued that the simpler DCIS nuclear grading system used across the UK and Europe (low, intermediate or high, without considering the presence/absence of comedonecrosis) allows greater reproducibility[50]. Additionally, although the USC group initially reported that patients with wide negative excision margins (>10mm) derived little added benefit from radiotherapy[93], more recent data suggests even this group gain benefit from radiation[94].

In short, the VNPI has not been shown unequivocally to be of clinical utility and this has hindered its acceptance into clinical practice. The use of this tool has also lacked support in the UK[50], with a recent survey revealing that only 15.8% of breast units across the country use it routinely and even in these sites there is a lack of consistency in the scores applied in the decision-making process[24].

- **Nomograms**

Recent years have seen the development of nomograms which integrate different clinical and histopathological factors to predict recurrence[95–99]. Van Zee and

collaborators used data from 1,681 women with DCIS to design a Memorial Sloan-Kettering Cancer Center (MSKCC) model, based on 10 markers including features such as age and tumour properties, but also the administration of adjuvant radiation or endocrine therapy[95] (see Table 1).

This nomogram estimates the 5 and 10-year risk of absolute recurrence and has been validated on external populations[100–102]. However, this nomogram has been criticised for not integrating molecular predictors such as hormone receptors or markers of proliferation and reviewers have suggested that it is likely to underestimate the heterogeneity of DCIS lesions[103].

Indeed, prognostic tools relying exclusively on clinico-histopathological markers and treatment choices for risk prediction are limited in their scope. Despite integrating markers which significantly affect recurrence, these tools fail to identify and stratify cohorts of DCIS patients with inherently different risks of recurrence due to their molecular profile. While it is well established that smaller lesions or adjuvant treatment will positively affect the chances of recurrent disease, the real clinical need is for tools that identify which lesions actually require such therapies in order to prevent over- or under-treatment.

3.2. Predictive tools based on molecular markers

- **Onco*type* DX DCIS Score**

In 2013, Solin and collaborators used a rigorous prospective-retrospective design based on archived data from 5 different studies to develop a new prognostic tool based on the 21-gene Onco*type* DX assay[104]. This led to a specific DCIS Score (DS) based on the expression level of 7 genes, including markers of proliferation and the progesterone receptor (PR), normalised to 5 reference genes (see Table 1). This continuous score (0-100) stratified

patients into groups with low (<39), intermediate (39-54) and high (≥55) risk of recurrence at 10 years[104].

Validation on a series of 327 patients with low-risk DCIS treated with BCS only, from the ECOG-AGRIN E5194 trial[105], found that DS could quantify the risk of both overall and invasive local recurrence[104]. Further validation in a similar Ontario-based population of 718 patients supported the value of DS as an independent predictor of risk of local recurrence[106]. Two recent US-based multi-institutional clinical utility studies have shown that application of DS has led to significant changes in treatment recommendations, suggesting that clinicians are considering the information provided by the test in their decision-making process[107,108].

However, several factors have prevented the adoption of this new prognostic tool on a global scale. Firstly, reviewers have criticised the fact that DS has only been validated on low-risk DCIS patients who meet the strict criteria defined by the original ECOG-ACRIN E5194 trial[109,110].

Another obstacle is the cost of this assay, which at $4175 per test is prohibitive for its application in most health services outside the US. Indeed, a recent study found no treatment strategies incorporating this test are cost-effective[111]. A recent UK-based survey studying trends in DCIS management found only 1 site out of the 76 surveyed used this test routinely[24]. Additionally, like all other Onco*type* assays, the DS test needs to be shipped to a central laboratory for processing and analysis, adding logistical constraints in countries outside the US.

Most importantly, the actual prognostic value of the different DCIS risk groups identified by this test has been questioned. The 10-year rates of local recurrence for low, intermediate and high-risk groups were validated in the two aforementioned studies as

10.6-12.7, 26.7-33.0 and 25.9-27.8%, respectively[104,112]. However, the low-risk group is still associated with an 11-13% risk of recurrence, which some clinicians consider high enough to prescribe adjuvant treatment[110]. Furthermore, this scoring system fails to adequately stratify between intermediate (27-33%) and high-risk (26-28%) patients, demonstrating the limitations of a continuous rather than a discreet prognostic score and hindering its practical application. Furthermore, this test relies exclusively on markers derived from the established DCIS knowledge base (proliferation and hormone status), failing to take advantage of novel marker discovery in its design, which could improve its predictive power.

In short, how the tool has been developed, the limited validation in low-risk groups only, the continuous nature of the scoring system and the fact that DS considers only a multigene signature without factoring in other clinical and pathological prognosticators of proven significance suggest that, even if logistical and monetary factors were not an issue, the Onco*type* DX DCIS Score is unlikely to function as a reliable, global test for the majority of patients worldwide with DCIS.

- **Hormone receptor status and molecular phenotypes as risk predictors**

A recent study by Bundred and collaborators assessed the expression level of hormone receptors (ER, PR and HER2) in 314 women with DCIS[113]. Immunohistochemistry surrogates allowed for stratification of DCIS into molecular phenotypes: Luminal A (ER/PR+,HER2-), Luminal B (ER/PR+,HER2+), HER2 type (ER-,PR-,HER2+) or triple negative (ER-,PR-,HER2-).

Comparison of recurrence rates with 10-year follow-up found that molecular phenotype was an independent predictor of both overall and invasive recurrence. Luminal A DCIS demonstrated the lowest rate of overall and invasive 10-year recurrence (7.6 and 1.3%,

respectively)[113], suggesting these lesions could be treated with BCS only. In contrast, HER2 type DCIS had the highest rate of overall and invasive 10-year recurrence (47.7 and 29.5%, respectively). This phenotype was the independent predictor with the highest risk for both overall (HR 6.46, $P < 0.001$) and invasive recurrence (HR 11.4, $P = 0.027$) when compared with Luminal A DCIS[113], encouraging the further study of HER2-targeted therapies for the management of DCIS.

While these results are supported by previous studies which linked both ER/PR-status[114] and HER2+ status[28,114,115] to increased risk of recurrence, a recent study in a cohort of 230 DCIS cases found no significant correlation between these markers and recurrence[116]. This divergence highlights the need for further work before the potential clinical utility of hormone and HER2 receptor status can be confirmed.

- **Other biological markers**

The Bundred study also identified high expression of the marker of proliferation Ki67 as an independent predictor for invasive recurrence (>14% HR 1.05, $P = 0.021$, per %)[113]. Other studies have also linked high Ki67 to an increased risk of in situ recurrence. However, the value of Ki67 as a potential predictive factor is hindered by variation and lack of consensus in its quantification across sites[117,118].

Other markers identified as independent predictors of recurrence in DCIS cases are COX-2[119–122] and cell cycle-related proteins p51[123] and p53[124,125]. However, further validation with sufficient follow-up and standardised detection methods are necessary before these markers can be of clinical use[110].

3.3. Predictive tools integrating clinical, histopathological and molecular factors

Other studies have integrated molecular biomarkers with clinical and histopathological parameters to develop risk-prediction tools with greater efficacy, accuracy, reproducibility and clinical utility than methods relying on one type of predictive marker only[126].

For instance, Altintas et al[127] refined the VNPI by replacing the nuclear grade factor for a 4-gene signature (genomic grade index, GGI, see Table 1), improving the statistical association between high scores and risk of recurrence (HR 18.14 for updated VNPI-GGI method, vs HR 7.72 for conventional VNPI). This translated into a more accurate identification of high-risk DCIS with early recurrence within 5 years[127], although further validation in a larger trial is necessary to ascertain the clinical utility of this improved index.

Other groups have investigated the correlation of the gene signature-based Onco*type* DX DCSI Score with clinical and histopathological markers[128,129]. Results have found only moderate correlation with outcome, suggesting that prognostic strategies based on different types of variables are not necessarily additive and, thus, cannot be simply combined. This supports the notion that the relationship between these different factors may be complex and their integration is challenging, though it may hold the potential to provide more accurate and reproducible prognostic tools than either clinical, histopathological or biological factors alone.

4. A UK-WIDE PROSPECTIVE AUDIT OF DCIS: THE SLOANE PROJECT

The Sloane Project is an ongoing multi-disciplinary, UK-wide prospective audit of screen-detected DCIS, LCIS and atypical hyperplasia of the breast. By correlating information on the clinical management and outcome of each case (with follow-up data on local recurrence, contralateral disease, metastases and death[130]), this audit aims to identify prognostic indicators and establish the role of margins and adjuvant therapy to improve treatment strategies for DCIS. The National Institute for Health and Care Excellence (NICE)

endorsed this audit[131] and 50% of all screen-detected DCIS diagnosed in the UK have been entered[132], with a total of 10,582 cases included as of October 2014[133].

Preliminary results revealed marked variation in the use of adjuvant RT following BCS[134], although patients were more likely to receive RT if they presented large (≥15mm), intermediate or high-grade lesions or if comedonecrosis was observed[134]. Results suggest that some clinicians apply the VNPI as a tool, despite margin width alone not being an influencing factor in the decision-making process[134].

More recent results suggest that factors such as close margins, large lesion size and microinvasion may be sufficient to consider RT following mastectomy for DCIS to reduce the risk of ipsilateral recurrence[135]. However, the risk of recurrence is small even in patients who did not receive RT, so the benefit of radiation may be limited.

Results have shown that preoperative imaging underestimates lesion size in 30% of cases[136] and, together with practice variation, this contributes to adverse surgical outcome as failed BCS or mastectomy for small lesions in approximately 15% of cases in an 8,313 patient cohort[132]. Better pre-surgical assessment of the extent and nature of DCIS by standardisation and multidisciplinary integration of radiological and histopathological data could improve the surgical management of some patients[132].

Improved sampling, ultrasonic assessment and risk stratification are also needed to reduce variation in and unnecessary surgery in patients currently undergoing axillary assessment[137]. Survey results also showed a lack of nationwide consistency in the methods and thresholds used in ER scoring[138], as well as in duration and frequency of follow-up after treatment[139].

Although the first phase of the Sloane Project has now closed, follow-up of patients enrolled continues to collect information on recurrences and survival[140]. Other ongoing

work includes a registrational study of untreated DCIS lesions (the 'Forget Me Not' project). The multidisciplinary team behind the Sloane Project also put together the LORIS trial[48] and aims for collaboration between both studies in the future.

The second phase of the project, still in the early stages, focuses on the research arm. This aims to identify biomarkers from clinical DCIS samples at diagnosis and recurrence, in an effort to find molecular classifiers predicting recurrence risk, prognosis and benefit from treatment[133,141]. Given that treatment itself has a huge influence on recurrence rates, the challenge for this project will be to identify significant biological markers against a background of hugely variable clinical management between centres. The heterogeneity in margin widths was a hurdle the consensus conference failed to overcome so it is anticipated that the Sloane Project will face similar issues.

5. CONCLUSION

In the last few decades, the introduction of breast screening programmes has led to a huge increase in DCIS diagnoses. Evidence suggests DCIS encompasses lesions that are heterogeneous in their biology and, consequently, present varying risks of recurrence following excision, or progression if untreated.

To date, clinicians lack tools to predict which lesions are most likely to progress to invasive disease or to recur following treatment. The current consensus is for the majority of patients to receive wide local excision with clear margins. Mastectomy can be performed depending on clinical and histological factors.

The administration of adjuvant therapy varies greatly across sites due to a poorly-standardised decision-making process. While adjuvant radiotherapy can reduce 10-year local recurrence by 50%, current efforts focus on identifying low-risk patients for whom RT can be safely omitted and the definition of a margin width consensus. Adjuvant tamoxifen

and aromatase inhibitors can reduce risk of subsequent cancer events in patients treated for ER+ DCIS, but the use of adjuvant ET is limited by variation in uptake and poor adherence.

The primary objective of management of DCIS is to provide treatment to patients which is relative to their risks of progression and recurrence. Tailoring of treatment to each patient's individual risk, would help to improve clinical outcomes while at the same time reducing the amount of therapy required, avoiding both under- and over-treatment.

Molecular, clinical and histopathological factors identified as independent prognosticators have been used to develop predictive tools, but shortcomings including limited validation and questionable discriminatory powers or prognostic values have prevented their widespread adoption (see Table 1). In addition, the VNPI or the MSKCC nomogram fail to incorporate molecular predictors, while the Onco*type* DX DCIS Score comes with logistic and cost limitations. Predictive molecular phenotypes and other biological markers will require further research and the definition of appropriate guidelines before they can be of use.

The clinical database created by the UK-based Sloane Project has also shed light on trends in the management of DCIS and highlighted nationwide inconsistencies, calling for the establishment of better defined standards of practice. Its research phase will face the challenge of identifying significant markers against the background of treatment variation.

There is a pressing clinical need for better and more accurate prognostic tools capable of stratifying DCIS lesions according to their different biology and associated behaviour. Future efforts need to focus on the integration of clinical and histopathological factors together with identification of new molecular biomarkers (possibly at gene expression and protein levels). The development of such tools could provide an optimal classification of patients into risk groups of clinical utility, to help provide accurate guidance on treatment

and assist in the development of standardised practices for the management of the many patients now diagnosed with DCIS.

***Funding sources**:* This work was supported by the Breast Cancer Institute (BCI).

***References**:*

[1] Broders AC. Carcinoma in situ contrasted with benign penetrating epithelium. JAMA 1932;99:1670–4. doi:10.1001/jama.1932.02740720024007.

[2] Wellings SR, Jensen HM. On the origin and progression of ductal carcinoma in the human breast. J Natl Cancer Inst 1973;50:1111–8. doi:10.1093/JNCI/50.5.1111.

[3] Cancer Resear UK. In situ breast carcinoma incidence statistics 2013. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-in-situ#ref-6 (accessed October 12, 2016).

[4] Rosner D, Bedwani RN, Vana J, Baker HW, Murphy GP. Noninvasive breast carcinoma: results of a national survey by the American College of Surgeons. Ann Surg 1980;192:139–47.

[5] Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst 2010;102:170–8. doi:10.1093/jnci/djp482.

[6] Ernster V. Mammography screening for women aged 40 through 49 - a guidelines saga and a clarion call for informed decision making. Am J Public Health 1997;87:1103–6.

[7] NHS breast screening programme. NHS cancer screening programmes. All breast cancer report. An analysis of all symptomatic and screen-detected breast cancers diagnosed in 2006. 2009.

[8] Wellings SR, Jensen HM, Marcum RG. An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. J Natl Cancer Inst 1975;55:231–73. doi:10.1093/jnci/55.2.231.

[9] Dupont WD, Page DL. Risk Factors for Breast Cancer in Women with Proliferative Breast Disease. N Engl J Med 1985;312:146–51. doi:10.1056/NEJM198501173120303.

[10] Buerger H, Otterbach F, Simon R, Schäfer K-L, Poremba C, Diallo R, et al. Different genetic pathways in the evolution of invasive breast cancer are associated with distinct morphological subtypes. J Pathol 1999;189:521–6. doi:10.1002/(SICI)1096-9896(199912)189:4<521::AID-PATH472>3.0.CO;2-B.

[11] Boughey JC, Gonzalez RJ, Bonner E, Kuerer HM. Current treatment and clinical trial developments for ductal carcinoma in situ of the breast. Oncologist 2007;12:1276–87. doi:10.1634/theoncologist.12-11-1276.

[12] Page DL, Dupont WD, Rogers LW, Jensen RA, Schuyler PA. Continued local recurrence of carcinoma 15-25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated only by biopsy. Cancer 1995;76:1197–200. doi:10.1002/1097-0142(19951001)76:7<1197::AID-CNCR2820760715>3.0.CO;2-0.

[13] Rosen PP, Braun DW, Kinne DE. The Clinical Significance of Pre-Invasive Breast Carcinoma. Cancer 1980;46:919–25. doi:10.1002/1097-0142(19800815)46:4+<919::AID-CNCR2820461311>3.0.CO;2-Z.

[14] Sue GR, Lannin DR, Au AF, Narayan D, Chagpar AB. Factors associated with decision to pursue mastectomy and breast reconstruction for treatment of ductal carcinoma in situ of the breast. Am J Surg 2013;206:682–5. doi:10.1016/j.amjsurg.2013.07.001.

[15] Julian TB, Land SR, Fourchotte V, Haile SR, Fisher ER, Mamounas EP, et al. Is Sentinel Node Biopsy Necessary in Conservatively Treated DCIS? Ann Surg Oncol 2007;14:2202–8. doi:10.1245/s10434-007-9353-4.

[16] Francis AM, Haugen CE, Grimes LM, Crow JR, Yi M, Mittendorf EA, et al. Is Sentinel Lymph Node Dissection Warranted for Patients with a Diagnosis of Ductal Carcinoma In Situ? Ann Surg Oncol 2015;22:4270–9. doi:10.1245/s10434-015-4547-7.

[17] Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, et al. Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma in Situ. Ann Surg Oncol 2016;6:287–95. doi:10.1016/j.prro.2016.06.011.

[18] Elshof L, Schaapveld M, Rutgers E, Schmidt M, Van Leeuwen F, Wesseling J. Low cause-specific mortality in women treated for ductal carcinoma in situ of the breast. Eur J Cancer 2017;72:S15. doi:10.1016/S0959-8049(17)30127-2.

[19] Morrow M, O'Sullivan MJ. The dilemma of DCIS. Breast 2007;16:59–62. doi:10.1016/j.breast.2007.07.015.

[20] Zujewski JA, Harlan LC, Morrell DM, Stevens JL. Ductal carcinoma in situ: trends in treatment over time in the US. Breast Cancer Res Treat 2011;127:251–7. doi:10.1007/s10549-010-1198-z.

[21] Allegra CJ, Aberle DR, Ganschow P, Hahn SM, Lee CN, Millon-Underwood S, et al. National institutes of health state-of-the-science conference statement: Diagnosis and management of ductal carcinoma in situ september 22-24, 2009. J. Natl. Cancer Inst., vol. 102, 2010, p. 161–9. doi:10.1093/jnci/djp485.

[22] Kerlikowske K, Molinaro A, Cha I, Ljung B-M, Ernster VL, Stewart K, et al. Characteristics associated with recurrence among women with ductal carcinoma in situ treated by lumpectomy. J Natl Cancer Inst 2003;95:1692–702. doi:10.1093/JNCI/DJG097.

[23] Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: Analysis of European Organization for Research and Treatment of Cancer Trial 10853. J Clin Oncol 2001;19:2263–71.

[24] Ashken L, Ives C, Kim B, Potter S, Rattay T, Remoundos D, et al. Variation in the management of ductal carcinoma in situ in the UK: Results of the Mammary Fold National Practice Survey. Eur J Surg Oncol 2016;42:1153–61. doi:10.1016/j.ejso.2016.05.024.

[25] Altintas S, Lambein K, Huizing MT, Braems G, Asjoe FT, Hellemans H, et al. Prognostic significance of oncogenic markers in ductal carcinoma in situ of the breast: A clinicopathologic study. Breast J 2009;15:120–32. doi:10.1111/j.1524-4741.2009.00686.x.

[26] Kong I, Narod SA, Taylor C, Paszat L, Saskin R, Nofech-Moses S, et al. Age at diagnosis predicts local recurrence in women treated with breast-conserving surgery and postoperative radiation therapy for ductal carcinoma in situ: a population-based outcomes analysis. Curr Oncol 2014;21:e96–104. doi:10.3747/co.21.1604.

[27] Collins LC, Achacoso N, Haque R, Nekhlyudov L, Fletcher SW, Quesenberry CP, et al. Risk factors for non-invasive and invasive local recurrence in patients with ductal carcinoma in situ. Breast Cancer Res Treat 2013;139:453–60. doi:10.1007/s10549-013-2539-5.

[28] Wang S-Y, Shamliyan T, Virnig BA, Kane R. Tumor characteristics as predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. Breast Cancer Res Treat 2011;127:1–14. doi:10.1007/s10549-011-1387-4.

[29] Wapnir IL, Dignam JJ, Fisher B, Mamounas EP, Anderson SJ, Julian TB, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 2011;103:478–88. doi:10.1093/jnci/djr027.

[30] Solin LJ. Is excision alone adequate treatment for low-risk ductal carcinoma-in-situ of the breast? J Clin Oncol 2006;24:1017–9. doi:10.1200/JCO.2005.04.4610.

[31] Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast and Bowel Project experience. Semin Oncol 2001;28:400–18.

[32] Bijker N, Meijnen P, Peterse JL, Bogaerts J, Van Hoorebeeck I, Julien J-P, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853 - a study by the EORTC Breast Cancer Cooperative Group an. J Clin Oncol 2006;24:3381–7. doi:10.1200/JCO.2006.06.1366.

[33] Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol 2011;12:21–9. doi:10.1016/S1470-2045(10)70266-7.

[34] Houghton J. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: Randomised controlled trial. Lancet 2003;362:95–102. doi:10.1016/S0140-6736(03)13859-7.

[35] Emdin SO, Granstrand B, Ringberg A, Sandelin K, Arnesson L-G, Nordgren H, et al. SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol (Madr) 2006;45:536–43. doi:10.1080/02841860600681569.

[36] Holmberg L, Garmo H, Granstrand B, Ringberg A, Arnesson LG, Sandelin K, et al. Absolute risk

reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. J Clin Oncol 2008;26:1247–52. doi:10.1200/JCO.2007.12.7969.

[37] Wärnberg F, Garmo H, Emdin S, Hedberg V, Adwall L, Sandelin K, et al. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS trial. J Clin Oncol 2014;32:3613–8. doi:10.1200/JCO.2014.56.2595.

[38] Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database Syst Rev 2013. doi:10.1002/14651858.CD000563.pub7.

[39] Correa C, McGale P, Taylor C, Wang Y, Clarke M, Davies C, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst - Monogr 2010:162–77. doi:10.1093/jncimonographs/lgq039.

[40] Narod SA, Iqbal J, Giannakeas V, Sopik V, Sun P. Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ. JAMA Oncol 2015;1:888–96. doi:10.1001/jamaoncol.2015.2510.

[41] Solin LJ. The impact of adding radiation treatment after breast conservation surgery for ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010;2010:187–92. doi:10.1093/jncimonographs/lgq020.

[42] Shah C, Vicini F, Khan A, Arthur D, Wazer D. Radiation Therapy and the Evolving Definition of Low Risk in Ductal Carcinoma in Situ. J Clin Oncol 2016;34:1823–4. doi:10.1200/JCO.2015.64.9202.

[43] Wehner P, Lagios MD, Silverstein MJ. DCIS treated with excision alone using the National Comprehensive Cancer Network (NCCN) guidelines. Ann Surg Oncol 2013;20:3175–9. doi:10.1245/s10434-013-3176-2.

[44] McCormick B, Winter K, Hudis C, Kuerer HM, Rakovitch E, Smith BL, et al. RTOG 9804: A prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J Clin Oncol 2015;33:709–15. doi:10.1200/JCO.2014.57.9029.

[45] Solin LJ, Gray R, Hughes LL, Wood WC, Lowen MA, Badve SS, et al. Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. J Clin Oncol 2015;33:3938–44. doi:10.1200/JCO.2015.60.8588.

[46] Wong JS, Chen Y-H, Gadd MA, Gelman R, Lester SC, Schnitt SJ, et al. Eight-year update of a prospective study of wide excision alone for small low- or intermediate-grade ductal carcinoma in situ (DCIS). Breast Cancer Res Treat 2014;143:343–50. doi:10.1007/s10549-013-2813-6.

[47] Elshof LE, Tryfonidis K, Slaets L, Van Leeuwen-Stok AE, Skinner VP, Dif N, et al. Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ – The LORD study. Eur J Cancer 2015;51:1497–510. doi:10.1016/j.ejca.2015.05.008.

[48] Francis A, Thomas J, Fallowfield L, Wallis M, Bartlett JMS, Brookes C, et al. Addressing overtreatment of screen detected DCIS; The LORIS trial. Eur J Cancer 2015;51:2296–303. doi:10.1016/j.ejca.2015.07.017.

[49] Silverstein MJ, Buchanan C. Ductal carcinoma in situ: USC/Van Nuys Prognostic Index and the impact of margin status. Breast 2003;12:457–71. doi:10.1016/S0960-9776(03)00153-X.

[50] Boland GP, Chan KC, Knox WF, Roberts SA, Bundred NJ. Value of the Van Nuys Prognostic Index in prediction of recurrence of ductal carcinomain situ after breast-conserving surgery. Br J Surg 2003;90:426–32. doi:10.1002/bjs.4051.

[51] Douglas-Jones AG, Logan J, Morgan JM, Johnson R, Williams R. Effect of margins of excision on recurrence after local excision of ductal carcinoma in situ of the breast. J Clin Pathol 2002;55:581–6. doi:10.1136/JCP.55.8.581.

[52] Van Cleef A, Altintas S, Huizing M, Papadimitriou K, Van Dam P, Tjalma W. Current view on ductal carcinoma in situ and importance of the margin thresholds: A review. Facts Views Vis Obgyn 2014;6:210–8.

[53] Morrow M, Van Zee KJ. Margins in DCIS: Does Residual Disease Provide an Answer? Ann Surg Oncol 2016;23:3423–5. doi:10.1245/s10434-016-5255-7.

[54] Marinovich ML, Azizi L, Macaskill P, Irwig L, Morrow M, Solin LJ, et al. The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-Analysis. Ann Surg Oncol 2016;23:3811–21. doi:10.1245/s10434-016-5446-2.

[55] Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014;32:1507–15. doi:10.1200/JCO.2013.53.3935.

[56] Allred DC, Anderson SJ, Paik S, Wickerham DL, Nagtegaal ID, Swain SM, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: A study based on NSABP protocol B-24. J Clin Oncol 2012;30:1268–73. doi:10.1200/JCO.2010.34.0141.

[57] Lari SA, Kuerer HM. Biological Markers in DCIS and Risk of Breast Recurrence: A Systematic Review. J Cancer 2011;2:232–61. doi:10.7150/jca.2.232.

[58] Claus EB, Chu P, Howe CL, Davison TL, Stern DF, Carter D, et al. Pathobiologic Findings in DCIS of the Breast: Morphologic Features, Angiogenesis, HER-2/neu and Hormone Receptors. Exp Mol Pathol 2001;70:303–16. doi:10.1006/exmp.2001.2366.

[59] Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 1999;353:1993–2000. doi:10.1016/S0140-6736(99)05036-9.

[60] Morrow M. Refining the use of endocrine therapy for ductal carcinoma in situ. J Clin Oncol 2012;30:1249–51. doi:10.1200/JCO.2011.40.5514.

[61] Barnes NLP, Ooi JL, Yarnold JR, Bundred NJ. Ductal carcinoma in situ of the breast. BMJ 2012;344:e797. doi:10.1136/bmj.e797.

[62] Barnes M, Freudenberg J, Thompson S, Aronow B, Pavlidis P. Experimental comparison and cross-validation of the Affymetrix and Illumina gene expression analysis platforms. Nucleic Acids Res 2005;33:5914–23.

[63] Chen Y-Y, DeVries S, Anderson J, Lessing J, Swain R, Chin K, et al. Pathologic and biologic response to preoperative endocrine therapy in patients with ER-positive ductal carcinoma in situ. BMC Cancer 2009;9:285. doi:10.1186/1471-2407-9-285.

[64] Forbes JF, Sestak I, Howell A, Bonanni B, Bundred N, Levy C, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet 2016;387:866–73. doi:10.1016/S0140-6736(15)01129-0.

[65] Margolese RG, Cecchini RS, Julian TB, Ganz PA, Costantino JP, Vallow LA, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): A randomised, double-blind, phase 3 clinical trial. Lancet 2016;387:849–56. doi:10.1016/S0140-6736(15)01168-X.

[66] Ganz PA, Cecchini RS, Julian TB, Margolese RG, Costantino JP, Vallow LA, et al. Patient-reported outcomes with anastrozole versus tamoxifen for postmenopausal patients with ductal carcinoma in situ treated with lumpectomy plus radiotherapy (NSABP B-35): A randomised, double-blind, phase 3 clinical trial. Lancet 2016;387:857–65. doi:10.1016/S0140-6736(15)01169-1.

[67] Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression. J Clin Oncol 2016;34:1689–701. doi:10.1200/JCO.2015.65.9573.

[68] Yen TWF, Kuerer HM, Ottesen RA, Rouse L, Niland JC, Edge SB, et al. Impact of randomized clinical trial results in the national comprehensive cancer network on the use of tamoxifen after breast surgery for ductal carcinoma in situ. J Clin Oncol 2007;25:3251–8. doi:10.1200/JCO.2006.10.2699.

[69] Flanagan MR, Rendi MH, Gadi VK, Calhoun KE, Gow KW, Javid SH. Adjuvant Endocrine Therapy in Patients with Ductal Carcinoma In Situ: A Population-Based Retrospective Analysis from 2005 to 2012 in the National Cancer Data Base. Ann Surg Oncol 2015;22:3264–72. doi:10.1245/s10434-015-4668-z.

[70] Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. Breast Cancer Res Treat 2012;134:459–78. doi:10.1007/s10549-012-2114-5.

[71] Livaudais JC, Hwang ES, Karliner L, Nápoles A, Stewart S, Bloom J, et al. Adjuvant hormonal therapy use among women with ductal carcinoma in situ. J Womens Health (Larchmt) 2012;21:35–42. doi:10.1089/jwh.2011.2773.

[72] Simon R, Latreille J, Matte C, Desjardins P, Bergeron E. Adherence to adjuvant endocrine therapy in estrogen receptor-positive breast cancer patients with regular follow-up. Can J Surg 2014;57:26–32. doi:10.1503/cjs.006211.

[73] Lo AC, Truong PT, Wai ES, Nichol A, Weir L, Speers C, et al. Population-based analysis of the impact and generalizability of the NSABP-B24 study on endocrine therapy for patients with ductal carcinoma in situ of the breast. Ann Oncol 2015;26:1898–903. doi:10.1093/annonc/mdv251.

[74] Yen TWF, Hunt KK, Mirza NQ, Thomas ES, Singletary SE, Babiera G V., et al. Physician recommendations regarding tamoxifen and patient utilization of tamoxifen after surgery for ductal carcinoma in situ. Cancer 2004;100:942–9. doi:10.1002/cncr.20085.

[75] Cluze C, Rey D, Huiart L, BenDiane MK, Bouhnik AD, Berenger C, et al. Adjuvant endocrine therapy with tamoxifen in young women with breast cancer: determinants of interruptions vary over time. Ann Oncol 2012;23:882–90. doi:10.1093/annonc/mdr330.

[76] Estévez LG, Suarez-Gauthier A, García E, Miró C, Calvo I, Fernández-Abad M, et al. Molecular effects of lapatinib in patients with HER2 positive ductal carcinoma in situ. Breast Cancer Res 2014;16:R76. doi:10.1186/bcr3695.

[77] Kuerer HM, Buzdar AU, Mittendorf EA, Esteva FJ, Lucci A, Vence LM, et al. Biologic and immunologic effects of preoperative trastuzumab for ductal carcinoma in situ of the breast. Cancer 2011;117:39–47. doi:10.1002/cncr.25399.

[78] Siziopikou KP, Anderson SJ, Cobleigh MA, Julian TB, Arthur DW, Zheng P, et al. Preliminary results of centralized HER2 testing in ductal carcinoma in situ (DCIS): NSABP B-43. Breast Cancer Res Treat 2013;142:415–21. doi:10.1007/s10549-013-2755-z.

[79] Smith R. More guidance is needed on how to communicate about DCIS. BMJ 2012;344:e2139.

[80] Foucar E. Carcinoma-in-situ of the breast: Have pathologists run amok? Lancet 1996;347:707–8. doi:10.1016/S0140-6736(96)90073-2.

[81] Mitchell KB, Kuerer H. Ductal Carcinoma In Situ: Treatment Update and Current Trends. Curr Oncol Rep 2015;17:48. doi:10.1007/s11912-015-0473-x.

[82] Welch HG, Black WC. Using autopsy series to estimate the disease “reservoir” for ductal carcinoma in situ of the breast: How much more breast cancer can we find? Ann Intern Med 1997;127:1023–8. doi:10.7326/0003-4819-127-11-199712010-00014.

[83] Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. J Natl Cancer Inst 2000;92:1490–9. doi:10.1093/jnci/92.18.1490.

[84] Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. BMJ 2014;348:g366. doi:10.1136/bmj.g366.

[85] Silverstein MJ, Lagios MD, Craig PH, Waisman JR, Lewinsky BS, Colburn WJ, et al. A prognostic index for ductal carcinoma in situ of the breast. Cancer 1996;77:2267–74. doi:10.1002/(sici)1097-0142(19960601)77:11<2267::aid-cncr13>3.0.co;2-v.

[86] Silverstein MJ. The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. Am J Surg 2003;186:337–43. doi:10.1016/S0002-9610(03)00265-4.

[87] Vicini FA, Kestin LL, Goldstein NS, Chen PY, Pettinga J, Frazier RC, et al. Impact of young age on outcome in patients with ductal carcinoma-in-situ treated with breast-conserving therapy. J Clin Oncol 2000;18:296–306.

[88] Goldstein NS, Vicini FA, Kestin LL, Thomas M. Differences in the pathologic features of ductal carcinoma in situ of the breast based on patient age. Cancer 2000;88:2553–60. doi:10.1002/1097-0142(20000601)88:11<2553::AID-CNCR18>3.0.CO;2-V.

[89] Sposto R, Epstein M, Silverstein M. Predicting local recurrence in patients with ductal carcinoma in situ of the breast. In: Silverstein M, Recht A, Lagios M, editors. Ductal carcinoma situ breast, Philadelphia: Williams and Wilkins; 2002, p. 255–63.

[90] Silverstein MJ, Lagios MD. Choosing treatment for patients with ductal carcinoma in situ: fine tuning the University of Southern California/Van Nuys Prognostic Index. J Natl Cancer Inst Monogr 2010;2010:193–6. doi:10.1093/jncimonographs/lgq040.

[91] Gilleard O, Goodman A, Cooper M, Davies M, Dunn J. The significance of the Van Nuys prognostic index in the management of ductal carcinoma in situ. World J Surg Oncol 2008;6:61. doi:10.1186/1477-7819-6-61.

[92] MacAusland SG, Hepel JT, Chong FK, Galper SL, Gass JS, Ruthazer R, et al. An attempt to independently verify the utility of the Van Nuys Prognostic Index for ductal carcinoma in situ. Cancer 2007;110:2648–53. doi:10.1002/cncr.23089.

[93] Macdonald HR, Silverstein MJ, Lee LA, Ye W, Sanghavi P, Holmes DR, et al. Margin width as the sole determinant of local recurrence after breast conservation in patients with ductal carcinoma in situ of the breast. Am J Surg 2006;192:420–2. doi:10.1016/j.amjsurg.2006.06.031.

[94] Van Zee KJ, Subhedar P, Olcese C, Patil S, Morrow M. Relationship Between Margin Width and Recurrence of Ductal Carcinoma In Situ: Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years. Ann Surg 2015;262:623–31. doi:10.1097/SLA.0000000000001454.

[95] Rudloff U, Jacks LM, Goldberg JI, Wynveen CA, Brogi E, Patil S, et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. J Clin Oncol 2010;28:3762–9. doi:10.1200/JCO.2009.26.8847.

[96] Werkhoven E van, Hart G, Tinteren H van, Elkhuizen P, Collette L, Poortmans P, et al. Nomogram to predict ipsilateral breast relapse based on pathology review from the EORTC 22881-10882 boost versus no boost trial. Radiother Oncol 2011;100:101–7. doi:10.1016/j.radonc.2011.07.004.

[97] Wobb JL, Chen PY, Shah C, Moran MS, Shaitelman SF, Vicini FA, et al. Nomogram for Predicting the Risk of Locoregional Recurrence in Patients Treated With Accelerated Partial-Breast Irradiation. Int J Radiat Oncol • Biol • Phys 2015;91:312–8. doi:10.1016/j.ijrobp.2014.09.029.

[98] Sanghani M, Truong PT, Raad RA, Niemierko A, Lesperance M, Olivotto IA, et al. Validation of a web-based predictive nomogram for ipsilateral breast tumor recurrence after breast conserving therapy. J Clin Oncol 2010;28:718–22. doi:10.1200/JCO.2009.22.6662.

[99] Sanghani M, Balk E, Cady B, Wazer D. Predicting the risk of local recurrence in patients with breast cancer: an approach to a new computer-based predictive tool. Am J Clin Oncol 2007;30:473–80. doi:10.1097/COC.0b013e31805c13d9.

[100] Sweldens C, Peeters S, van Limbergen E, Janssen H, Laenen A, Patil S, et al. Local relapse after breast-conserving therapy for ductal carcinoma in situ: a European single-center experience and external validation of the Memorial Sloan-Kettering Cancer Center DCIS nomogram. Cancer J 2014;20:1–7. doi:10.1097/PPO.0000000000000025.

[101] Collins LC, Achacoso N, Haque R, Nekhlyudov L, Quesenberry Jr. CP, Schnitt SJ, et al. Risk Prediction for Local Breast Cancer Recurrence Among Women with DCIS Treated in a Community Practice: A Nested, Case-Control Study. Ann Surg Oncol 2015;22:S502–8. doi:10.1245/s10434-015-4641-x.

[102] Wang F, Li H, Tan PH, Chua ET, Yeo RMC, Lim FLWT, et al. Validation of a nomogram in the prediction of local recurrence risks after conserving surgery for Asian women with ductal carcinoma in situ of the breast. Clin Oncol 2014;26:684–91. doi:10.1016/j.clon.2014.08.004.

[103] Benson JR, Wishart GC. Predictors of recurrence for ductal carcinoma in situ after breast-conserving surgery. Lancet Oncol 2013;14:e348–57. doi:10.1016/S1470-2045(13)70135-9.

[104] Solin LJ, Gray R, Baehner FL, Butler SM, Hughes LL, Yoshizawa C, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst 2013;105:701–10. doi:10.1093/jnci/djt067.

[105] Hughes LL, Wang M, Page DL, Gray R, Solin LJ, Davidson NE, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: A trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009;27:5319–24. doi:10.1200/JCO.2009.21.8560.

[106] Rakovitch E, Nofech-Mozes S, Hanna W, Baehner FL, Saskin R, Butler SM, et al. A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. Breast Cancer Res Treat 2015;152:389–98. doi:10.1007/s10549-015-3464-6.

[107] Manders J, Kuerer H, Smith B, McCluskey C, Farrar W, Frazier T, et al. The 12-gene DCIS score assay: Impact on radiation treatment (XRT) recommendations and clinical utility. Cancer Res 2016;76:Abstract P5-17-03.

[108] Alvarado M, Carter DL, Guenther JM, Hagans J, Lei RY, Leonard CE, et al. The impact of genomic testing on the recommendation for radiation therapy in patients with ductal carcinoma in situ: A prospective

clinical utility assessment of the 12-gene DCIS score™ result. J Surg Oncol 2015;111:935–40. doi:10.1002/jso.23933.

[109] Lagios MD, Silverstein MJ. Risk of recurrence of ductal carcinoma in situ by oncotype Dx technology: Some concerns. Cancer 2014;120:1085–1085. doi:10.1002/cncr.28523.

[110] Pang J-MB, Gorringe KL, Fox SB. Ductal carcinoma in situ - update on risk assessment and management. Histopathology 2016;68:96–109. doi:10.1111/his.12796.

[111] Raldow AC, Sher D, Chen AB, Recht A, Punglia RS. Cost Effectiveness of the Oncotype DX DCIS Score for Guiding Treatment of Patients With Ductal Carcinoma In Situ. J Clin Oncol 2016;34. doi:10.1200/JCO.2016.67.8532.

[112] Rakovitch E, Nofech-Mozes S, Hanna W, Baehner F, Saskin R, Butler S, et al. A large prospectively-designed study of the DCIS score: Predicting recurrence risk after local excision for ductal carcinoma in situ patients with and without irradiation. Cancer Res 2015;75:Abstr S5-04.

[113] Williams KE, Barnes NLP, Cramer A, Johnson R, Cheema K, Morris J, et al. Molecular phenotypes of DCIS predict overall and invasive recurrence. Ann Oncol 2015;26:1019–25. doi:10.1093/annonc/mdv062.

[114] Toss A, Palazzo J, Berger A, Guiles F, Sendecki JA, Simone N, et al. Clinical-pathological features and treatment modalities associated with recurrence in DCIS and micro-invasive carcinoma: Who to treat more and who to treat less. The Breast 2016;29:223–30. doi:10.1016/j.breast.2016.07.023.

[115] Holmes P, Lloyd J, Chervoneva I, Pequinot E, Cornfield DB, Schwartz GF, et al. Prognostic markers and long-term outcomes in ductal carcinoma in situ of the breast treated with excision alone. Cancer 2011;117:3650–7. doi:10.1002/cncr.25942.

[116] Poulakaki N, Makris G-M, Battista M-J, Böhm D, Petraki K, Bafaloukos D, et al. Hormonal receptor status, Ki-67 and HER2 expression: Prognostic value in the recurrence of ductal carcinoma in situ of the breast? The Breast 2016;25:57–61. doi:10.1016/j.breast.2015.10.007.

[117] Gudlaugsson E, Skaland I, Janssen EAM, Smaaland R, Shao Z, Malpica A, et al. Comparison of the effect of different techniques for measurement of Ki67 proliferation on reproducibility and prognosis prediction accuracy in breast cancer. Histopathology 2012;61:1134–44. doi:10.1111/j.1365-2559.2012.04329.x.

[118] Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 2011;103:1656–64. doi:10.1093/jnci/djr393.

[119] Barnes N, Haywood P, Flint P, Knox WF, Bundred NJ. Survivin expression in in situ and invasive breast cancer relates to COX-2 expression and DCIS recurrence. Br J Cancer 2006;94:253–8. doi:10.1038/sj.bjc.6602932.

[120] Kulkarni S, Patil DB, Diaz LK, Wiley EL, Morrow M, Khan SA, et al. COX-2 and PPARγ expression are potential markers of recurrence risk in mammary duct carcinoma in-situ. BMC Cancer 2008;8:36. doi:10.1186/1471-2407-8-36.

[121] Generali D, Buffa FM, Deb S, Cummings M, Reid LE, Taylor M, et al. COX-2 expression is predictive for early relapse and aromatase inhibitor resistance in patients with ductal carcinoma in situ of the breast, and is a target for treatment. Br J Cancer 2014;111:46–54. doi:10.1038/bjc.2014.236.

[122] Kerlikowske K, Molinaro AM, Gauthier ML, Berman HK, Waldman F, Bennington J, et al. Biomarker expression and risk of subsequent tumors after initial ductal carcinoma in situ diagnosis. J Natl Cancer Inst 2010;102:627–37. doi:10.1093/jnci/djq101.

[123] Provenzano E, Hopper J., Giles G., Marr G, Venter D., Armes J. Biological markers that predict clinical recurrence in ductal carcinoma in situ of the breast. Eur J Cancer 2003;39:622–30. doi:10.1016/S0959-8049(02)00666-4.

[124] Hieken TJ, Cheregi J, Farolan M, Kim J, Velasco JM. Predicting relapse in ductal carcinoma in situ patients: an analysis of biologic markers with long-term follow-up. Am J Surg 2007;194:504–6. doi:10.1016/j.amjsurg.2007.07.002.

[125] de Roos MA, de Bock GH, de Vries J, van der Vegt B, Wesseling J. p53 Overexpression is a Predictor of Local Recurrence After Treatment for Both in situ and Invasive Ductal Carcinoma of the Breast. J Surg Res 2007;140:109–14. doi:10.1016/j.jss.2006.10.045.

[126] Rivers AKS. Introduction, Evolution, and Application of the Van Nuys Prognostic Index in DCIS. In: Newman L, Bensenhaver J, editors. Ductal Carcinoma Situ Microinvasive/Borderline Breast Cancer, New York, NY: Springer New York; 2015, p. 155–60. doi:10.1007/978-1-4939-2035-8_16.

[127] Altintas S, Toussaint J, Durbecq V, Lambein K, Huizing MT, Larsimont D, et al. Fine tuning of the Van Nuys Prognostic Index (VNPI) 2003 by integrating the genomic grade index (GGI): New tools for ductal carcinoma in situ (DCIS). Breast J 2011;17:343–51. doi:10.1111/j.1524-4741.2011.01091.x.

[128] Badve S, Gray R, Baehner F, Solin L, Butler S, Yoshizawa C, et al. Correlation between the DCIS score and traditional clinicopathologic features in the prospectively designed E5194 clinical validation study. J Clin Oncol 2012;Supplement:Abstract 1005.

[129] Rakovitch E, Nofech-Mozes S, Hanna W, Baehner F, Saskin R, Butler S, et al. Correlation between the DCIS Score and traditional clinicopathologic features in the prospectively-designed Ontario population-based validation study. J Clin Oncol 2015;Supplement:Abstract 581.

[130] Sloane Project Steering Group. The Sloane Project n.d. www.sloaneproject.co.uk (accessed October 28, 2016).

[131] National Institute for Health and Care Excellence. NICE Clinical Guidelines CG80: Early and locally advanced breast cancer (diagnosis and treatment). 2009.

[132] Thomas J, Hanby A, Pinder SE, Ball G, Lawrence G, Maxwell A, et al. Adverse surgical outcomes in screen-detected ductal carcinoma in situ of the breast. Eur J Cancer 2014;50:1880–90. doi:10.1016/j.ejca.2014.02.023.

[133] Thomas J. Sloane Project Update. Pathol. Soc. Gt. Britain Irel. Anu. Gen. Meet., 2015.

[134] Dodwell D, Clements K, Lawrence G, Kearins O, Thomson CS, Dewar J, et al. Radiotherapy following breast-conserving surgery for screen-detected ductal carcinoma in situ: indications and utilisation in the UK. Interim findings from the Sloane Project. Br J Cancer 2007;97:725–9. doi:10.1038/sj.bjc.6603945.

[135] Clements K, Dodwell D, Lawrence G, Ball G, Francis A, Pinder S, et al. Radiotherapy after mastectomy for screen-detected ductal carcinoma in situ. Eur J Surg Oncol 2015;41:1406–10. doi:10.1016/j.ejso.2015.07.021.

[136] Thomas J, Evans A, Macartney J, Pinder SE, Hanby A, Ellis I, et al. Radiological and pathological size estimations of pure ductal carcinoma in situ of the breast, specimen handling and the influence on the success of breast conservation surgery: a review of 2564 cases from the Sloane Project. Br J Cancer 2010;102:285–93. doi:10.1038/sj.bjc.6605513.

[137] Nicholson S, Hanby A, Clements K, Kearins O, Lawrence G, Dodwell D, et al. Variations in the management of the axilla in screen-detected ductal carcinoma in situ: evidence from the UK NHS breast screening programme audit of screen detected DCIS. Eur J Surg Oncol 2015;41:86–93. doi:10.1016/j.ejso.2014.09.003.

[138] Thomas J, Hanby A, Pinder S, Ellis I, Macartney J, Clements K, et al. Implications of inconsistent measurement of ER status in non-invasive breast cancer: A study of 1,684 cases from the Sloane project. Breast J 2008;14:33–8. doi:10.1111/j.1524-4741.2007.00523.x.

[139] Maxwell AJ, Evans AJ, Carpenter R, Dobson HM, Kearins O, Clements K, et al. Follow-up for screen-detected ductal carcinoma in situ: Results of a survey of UK centres participating in the Sloane project. Eur J Surg Oncol 2009;35:1055–9. doi:10.1016/j.ejso.2009.04.002.

[140] Sloane Project Steering Group. Sloane Project Newsletter Issue 3. 2012.

[141] Sloane Project Steering Group. Sloane Project May 2014 Update. 2014.

Table1

Prognostic tool	Factors	Outcome	Limitations
Van Nuys prognostic index (VNPI)	- Lesion size (≤15mm, 16-40mm or >40mm) - Margin width (≥10mm, 1-9mm, <1mm) - Pathologic classification (grade ± comedonecrosis) - Patient age (>60, 40-60, <40)	Total score (4-12) stratifies into 3 groups with different risks of recurrence and treatment guidelines to achieve <20% local recurrence at 12 years	- Fails to incorporate molecular predictors - Lacks robust independent validation - May lack discriminatory power - Pathologic classification may have poor reproducibility
Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram	- Age at diagnosis (90-25) - Family history (no/yes) - Initial presentation (radiologic/clinical) - Radiation (yes/no) - Adjuvant ET (yes/no) - Nuclear grade (low or intermediate/high) - Necrosis (absent/present) - Margins (negative or positive/close) - Number of excisions (≤2 or ≥3) - Year of surgery (≥1999 or ≤1998)	Total score (0-500) to predict 5 and 10-year probability of absolute ipsilateral recurrence	- Fails to incorporate molecular predictors - May underestimate heterogeneity of DCIS lesions
Onco*type* DX DCIS Score (DS)	- RT-PCR expression levels of 7 cancer-related genes: 5 markers of proliferation (*Ki67*, *STK65*, *Survivin*, *CCNB1*, *MYBL2*), *PR* and *GSTM1*; normalised to 5 reference genes (*ACTB*, *GAPDH*, *RPLPO*, *GUS*, *TFRC*)	Continuous score (0-100) stratifies into 3 groups with different risks of recurrence at 10 years	- Lacks wider validation in independent cohorts - High cost - Requires shipping to central laboratory - Prognostic value has been questioned - Poor stratification of intermediate and high-risk lesions - Fails to incorporate novel molecular markers
Molecular phenotypes	- IHC surrogates for ER, PR and HER2 to classify into 4 molecular phenotypes (Luminal A, Luminal B, HER2 or triple negative)	Phenotypes are independent predictors of overall and invasive recurrence at 10 years	- Uneven results in validation
Other biological markers	- IHC measurement of COX-2, p51 or p53	Expression levels of biomarkers are independent predictors of recurrence	- Variation in methodology - Further validation with sufficient follow-up needed
Van Nuys prognostic index adjusted with genomic grade index (VNPI-GGI)	- Lesion size (≤15mm, 16-40mm or >40mm) - Margin width (≥10mm, 1-9mm, <1mm) - Patient age (>60, 40-60, <40) - GGI: RT-PCR expression levels of 4 genes linked to proliferation (*MYBL2*, *KPNA2*, *CDC2*, *CDC20*), normalised to 4 reference genes (*GUS*, *TBO*, *RPLP0*, *TFRC*)	Total VNPI-GGI score (4-12) classifies into 3 risk groups with more accurate identification of high-risk lesions with early recurrence within 5 years than VNPI score	- Need for further validation - Fails to address other limitations of the original VNPI

Table 1 Summary of the main prognostic tools for prediction of risk of recurrence following surgical excision of DCIS lesions, their methodology and main shortcomings preventing their widespread adoption to date.

Figure1

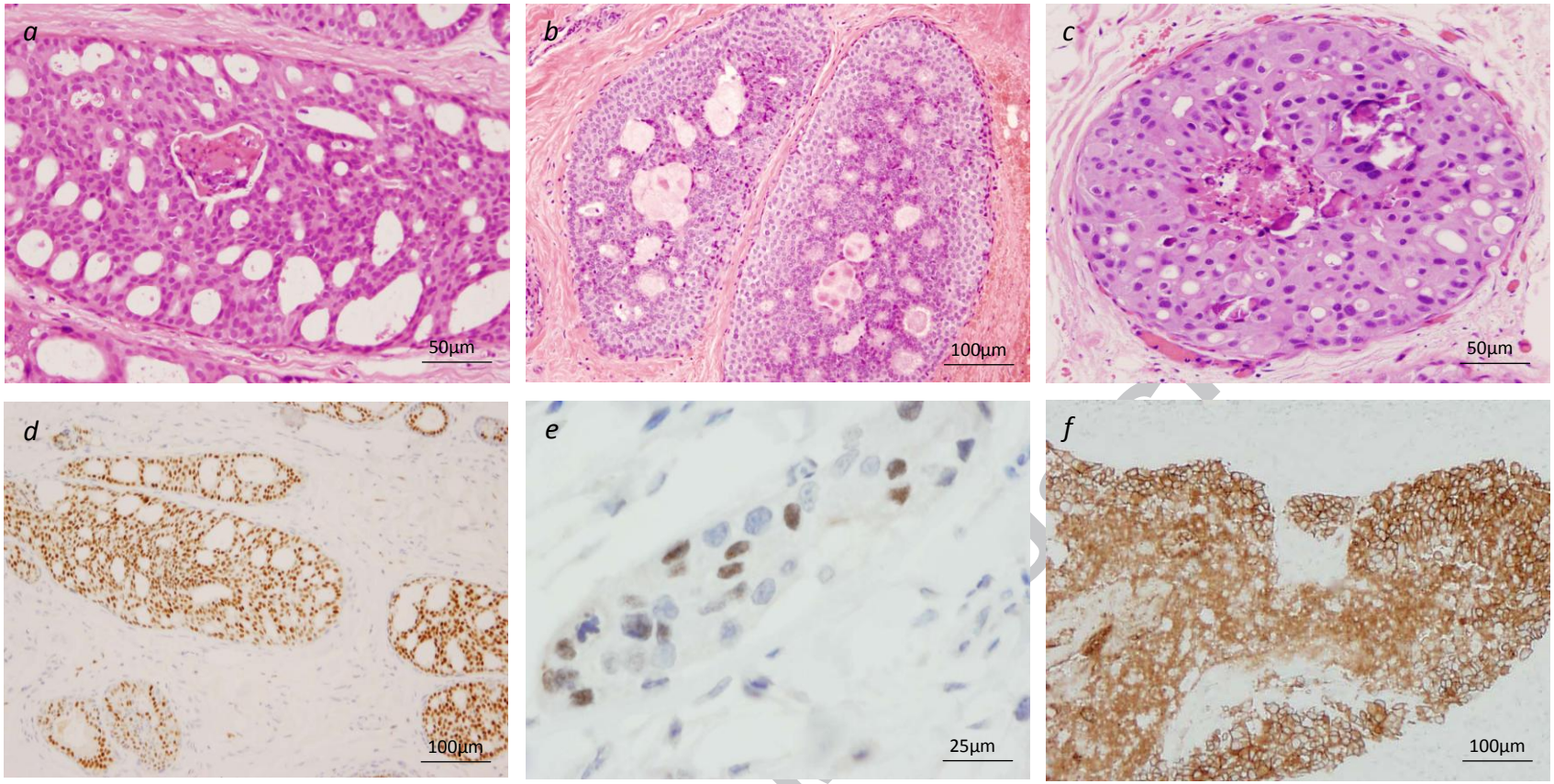


Figure 1. Histologic and immunochemistry features of ductal carcinoma in situ of the breast. This microscopy images depict some of the features typically observed upon pathologic assessment of precursor lesions. (a) Low grade DCIS: this duct is filled with small very homogeneous ductal epithelial cells typical of low grade precursor lesions. (b) Intermediate grade DCIS: a population of intermediate sized but monotonous cells fill this duct. (c) High grade DCIS: highly pleomorphic and b nucleolated cells fill this duct profile, with a small amount of central comedonecrosis. (d) Low grade ER+ DCIS: this duct presents low grade DCIS which is uniformly positive for ER. (e) High grade ER+ DCIS:

only some of the cells filling this duct profile showing high grade DCIS are staining positive for ER, suggesting that a good response to endocrine therapy is unlikely. (f) High grade HER2+ DCIS: this duct shows high grade disease, which is more commonly HER2+ than invasive carcinoma, with strong positive HER2 staining. This patient also had HER2+ invasive disease.

*Highlights (for review)

- Some DCIS lesions would never become clinically apparent if left untreated.
- Clinical management is limited by a lack consensus and inadequate risk prediction.
- Treatment needs to be tailored to the actual risk of recurrence or progression.
- No prognostic tools have been globally validated or have routine clinical utility.
- Integrating several types of predictive factors holds greater prognostic potential.

Title:

Current treatment trends and the need for better predictive tools in the management of ductal carcinoma in situ of the breast

Authors:

Carlos Martínez-Pérez[a], Arran K Turnbull[a], Gregory Ekatah[b], Laura M Arthur[a], Andrew H Sims[a], Jeremy S Thomas[c], J Michael Dixon[b]

Affiliations:

[a]Breast Cancer Now Edinburgh Research Team, Western General Hospital, University of Edinburgh

[b]Edinburgh Breast Unit, Western General Hospital, University of Edinburgh

[c]Department of Pathology, Western General Hospital, Edinburgh

Conflict of interest:

All authors of the present review article have no conflict of interest to disclose.