Ductal carcinoma in situ of the breasts: Over-diagnosis, over-treatment and a decade of lost direction

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Abstract
Ductal carcinoma in situ (DCIS) of the breast is the earliest detectable form of breast cancer. Mainstay of treatment is complete surgical removal with or without adjuvant radiotherapy. Incidence of DCIS has increased significantly over the last decade; however, increased surgical removal of DCIS has not resulted in the decreased incidence of invasive breast cancer. Whether or not we are over-treating ductal carcinoma in situ (DCIS) with complete surgical removal of the tumor has been subjected to much debate.

KEYWORDS
ductal carcinoma in situ, overdiagnosis, overtreatment

1 | INTRODUCTION

Ductal carcinoma in situ (DCIS) is the earliest detectable form of breast cancer. The incidence has increased over the last decades from 1.87 in 100 000 in the 1970s to 32.5 in 100 000 in early 2000s in the United States. This is partly due to increased public awareness on breast cancers, and partly due to the widespread use of mammogram for breast cancer screening.1,2

Over the decades with the surge in DCIS new case, surgical excision aiming for complete tumor removal remains the gold standard for treating DCIS. This is also regarded as the guideline concordant care (GCC) for DCIS. Excision is generally considered adequate for margins of more than/equal to 2 mm.3,4 This consensus was agreed and endorsed by a group of expert panel at the Biannual 15th St. Gallen International Breast Cancer Consensus Conference held in March 2017 in Vienna, Austria and remained the same in 2019. The panel endorsed recommendations and guidelines from Surgical Society of Oncology (SSO), American Society of Clinical Oncology (ASCO) and American Society for Radiation Oncology (ASTRO) that a margin of 2 mm is sufficient to avoid re-excision, although a number of members from the panel would accept narrower margins in individual cases, including "no ink on DCIS".5

2 | OVER-DIAGNOSIS AND OVER-TREATMENT

The terms "over-diagnosis" and "over-treatment" have been increasingly used in the literature to describe the situation resulted from cancer screening, in which many early cancers or even premalignant lesion are diagnosed and treated as a result of cancer screening program which do not translate into survival benefit. An independent review by the UK Department of Health in 2013 concluded that screening saves lives but also resulted in over-diagnosis.6

Unlike colonic polyp, which is also known as the precursor of colorectal cancer, where widespread introduction of screening colonoscopy and polypectomy in the older US population has already resulted in the drop of colorectal cancer incidence7; Increased detection, and then the treatment of DCIS over the last decade has not affected the incidence of breast cancers.8

In fact, several large scale studies had already demonstrated that the disease-specific survival rates were consistently greater than 95% in patients with DCIS regardless of the type of surgical treatment.9-11 Furthermore, the natural course of DCIS without curative treatment has been investigated in several retrospective series which found that not all DCIS will eventually turn invasive. Progression to invasive
breast cancer was found in 25% to 50% of cases over the span of 15 to 25 years.\textsuperscript{12,13} DCIS may have been over-diagnosed and overtreated by radical surgical treatments and radiation.

On the contrary, some other studies have demonstrated that even with standard surgical treatments for DCIS, nearly half of the recurrences were invasive.\textsuperscript{14,15} And it is these invasive recurrences that matters in treating patients with DCIS. Under-treatment will be a concern if we forgo standard surgical treatment in the management of DCIS.

3  |  CLASSIFICATION SYSTEMS OF DUCTAL CARCINOMA IN SITU

One possible way to avoid overtreatment is to stratify DCIS into high-risk and low-risk groups, in regards of the probability of invasive disease progression.

DCIS has been classified by different systems, many of which are based on the Bloom and Richardson nuclear grading.\textsuperscript{16} The Van Nuys classification is a commonly used classification system which stratifies patients into three groups.\textsuperscript{17} Van Nuys Prognostic Index (VNPI) was developed to predict the risk of local recurrence after surgery for DCIS. It is a relatively simple scoring system based on tumour size, surgical margin, nuclear grade, and presence of comedo necrosis. Studies have found that this score is relatively reproducible in real-life clinical practice.\textsuperscript{18} Some others, however, failed to demonstrate its predictability of local recurrence, in which, is the most important surrogate prognosticator in DCIS.\textsuperscript{19}

Another system for DCIS classification is The Armed Forces Institute of Pathology (AFIP) classification system which classified DCIS into grades one to three, based on the presence or absence of nuclear atypia and necrosis.\textsuperscript{20} However, up till now, there is no single classification scheme that has been universally accepted.

4  |  RISK STRATIFICATION BY GENETIC PROFILING

In the era, when genetic profiling was not as widely used as nowadays, VNPI was developed to evaluate the risk of local relapse. VNPI may help to stratify DCIS clinically into low-risk and high-risk groups, but it is still nearly impossible to predict which DCIS would be more likely to progress into invasive breast cancer. In fact, there is growing evidence that alternations in the tumor microenvironment might be the culprit for DCIS progression. Myoepithelial cells that surround the mammary ducts and lobular acini are involved in mammary gland homeostasis and prevent breast cancer progression. The “Escape” and “Release” models used in explaining the transition from in situ carcinoma to invasive carcinoma have been well-described in the literature.\textsuperscript{21,22} In the “Escape” model, the tumor cells disrupt the myoepithelial cell layer and invade into the stroma through basement membrane. While in the “Release” model, myoepithelial cells disappear and the basement membrane is disrupted allowing the invasion through the basement membrane. The questions why tumor cells “escape” and why basement membrane “releases” the tumor cells are still largely unanswered, but one important direction of investigation is definitely along the line of tumor cell genomics.

Only a few researchers have reported detailed molecular analysis of the normal cell to DCIS and DCIS to IDC transitions in breast cancer progression. The first study on microRNA deregulation in breast cancer by Iorio et al used microarrays to compare a variety of breast carcinomas (n = 76) to normal (n = 10) breast tissue,\textsuperscript{23} 17 up-regulated and 12 down-regulated microRNAs were identified in carcinomas, and specific microRNAs were identified to be differentially expressed in ER positive (11 microRNAs) and PR-positive (7 microRNAs) samples. Follow-up studies validated some of these microRNAs,\textsuperscript{24-27} and identified over 30 microRNAs differentiating tumor subtypes, and defined the cell-type-specific localization of some of these microRNAs. Schuett et al\textsuperscript{28} described a matched-pair analysis of DCIS and IDC tissues from 9 patients and identified 546 significantly differentially expressed probe sets. Wanberg et al reported a study on tumor markers in DCIS: expression of seven tumor markers was associated with tumor grade but not with invasiveness. The ability to use genetic markers to predict the risks of progression and outcomes of different DCIS subtypes is yet to be addressed, although preliminary evidence from microarray analyses in invasive cancer suggested that genetic markers may be used in this way in the future.\textsuperscript{29,30}

A nested case-control study by Kerlikowske et al studied 1162 women with DCIS treated by lumpectomy. Eight-year risk of subsequent invasive cancer was significantly higher in patients with mass-forming DCIS and those who were p16, COX-2, and Ki67 triple positive. Nuclear grade, on the contrary, is not associated with any prognostic outcome.\textsuperscript{31}

Several other studies also evaluated the prognostic implication of human epidermal growth factor 2 (HER-2) overexpression in DCIS. The recent Mustafa's study in 2017 found that HER-2 positive DCIS has significantly increased risk of upstaging to invasive breast cancer after excision.\textsuperscript{32}

5  |  CHALLENGES IN HISTOPATHOLOGICAL DIAGNOSIS

What complicate the matter further is that DCIS is now commonly regarded as a spectrum of disease; clinicians are often confronted by a broad histological spectrum of “preinvasive breast neoplasms” that ranges from atypical ductal hyperplasia (ADH), to low- and high-grade DCIS with or without microinvasion\textsuperscript{33} (Figure 1). Clinical behavior and natural history can vary significantly between the spectrum of premalignant breast neoplasms. However, there is no single reproducible pathognomonic feature that distinguishes ADH from low-grade DCIS, as both are part of the same morphologic spectrum and (Figure 1) closely related at the molecular level. One simple quantitative criterion to distinguish ADH from low-grade DCIS is by size-involvement of two separate ducts or size >2 mm have been proposed as arbitrary cutoff points for DCIS instead of ADH.\textsuperscript{34} In fact, there is always a possibility of
variability in the pathological diagnosis of DCIS—significant variability in pathological diagnosis was found in a study of 6900 slides of breast biopsies with histological diagnosis of DCIS or atypia.35

6  |  RE-EVALUATION OF THE CURRENT STANDARD OF CARE

Current standard of treatment of DCIS is surgery—lumpectomy followed by adjuvant radiotherapy (or sometimes, mastectomy). However, a recent retrospective cohort study has shown that breast cancer specific survival rates were identical among patients with low-grade DCIS regardless of the treatment received (surgery or active surveillance).36

Use of adjuvant radiotherapy for DCIS has also been re-evaluated. Meta-analysis of four randomized controlled trials on more than 3700 patients revealed that radiotherapy after lumpectomy for DCIS resulted in decreased risk of local recurrence (hazard ratio of 0.46), but not improving the survival.37 Another randomized controlled trial by Radiation Therapy Oncology Group (RTOG) echoed with similar finding that lumpectomy with adjuvant radiotherapy resulted in decreased risk of local recurrence rate to only 0.9% at median 7.2-year follow-up period, although survival data was lacking.38

Gene expression analysis (eg, Oncotype DX DCIS recurrence score) has been studied as a tool for identification of patients for whom adjuvant radiotherapy can be safely omitted after breast conserving surgery. Evidence of this is preliminary and the recurrence score was validated on patients with DCIS who participated in the Eastern Cooperative Oncology Group E5194 trial.39 Patients with a high-risk DCIS recurrence score had higher rates of local recurrence and experienced a greater absolute benefit from the addition of RT to surgery relative to those with a low-risk score.
Evidence on the use of hormonal therapy has not been strong. A systematic review of tamoxifen vs no additional treatment in DCIS patients, showed that there was no statistically significant reduction in invasive breast cancers in the Ipsilateral breast in the tamoxifen group. A large randomized controlled trial also concluded that tamoxifen reduced the risk of contralateral invasive breast cancer in DCIS patients, but no reduction in invasive breast cancer events if the ipsilateral breast was treated by surgery and/or radiotherapy.

7 | LOW-RISK LESIONS: TO TREAT OR NOT TO TREAT?

Compelling evidence on DCIS overtreatment has resulted in extensive research worldwide. Several randomized controlled trials, such as the European LORd (Low-risk DCIS) study, the American COMET study (Comparison of operative to monitoring and endocrine therapy for low-risk DCIS, NCT02926911) and the British LORIS trial (surgery vs active monitoring for low-risk ductal carcinoma in situ), are currently investigating the feasibility and non-inferiority of active surveillance with or without endocrine therapy for managing low-risk DCIS. All three trials have similar study design comparing standard surgical treatment (+/- radiotherapy and endocrine) with active surveillance only. Patients on the surveillance arm will be closely monitored with serial mammogram for 5 to 10 years. There is subtle difference in terms of inclusion and exclusion criteria between these three trials (Table 1), although the ultimate aim of all three trials are very much similar—to evaluate the best evidence on the treatment of low-risk DCIS.

8 | THE WAY FORWARD

The future direction of research for DCIS of the breasts is the feasibility to further de-escalate its treatment in selected low-risk patients. While the three randomized controlled trials (LORD, LORIS, and COMET) will provide good evidence on this important question, we are in the decade of lost direction in DCIS management.

Apart from oncologic safety that the three ongoing RCTs will probably provide us insights in due course, acceptance of de-escalating DCIS treatment from patient’s perspective is also important in the context of breast cancer treatment. Psychological burden of "living with" DCIS should be taken into account; costs of intensive clinical and radiological surveillance should also be taken into concern. Being oncologically safe for de-escalating DCIS treatment does not necessarily mean standard of care. Patient’s perspective should be taken into account in the conjoint discussion.

CONFLICT OF INTEREST

The author declares no conflict of interest.

AUTHOR CONTRIBUTIONS

MC: Conceptualization, literature review and writing and final editing.

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ETHICS STATEMENT

This article is a review article. Ethical approval is not required.

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