The Breast 35 (2017) 151–156

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Current trials to reduce surgical intervention in ductal carcinoma *in situ* of the breast: Critical review

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ARTICLE INFO

Article history:
Received 15 June 2017
Accepted 13 July 2017

Keywords:
Breast
Duct carcinoma *in situ*
DCIS
Management

ABSTRACT

The high proportion of ductal carcinoma *in situ* (DCIS) presented in mammographic screening and the relatively low risk of progression to invasive disease have raised questions related to overtreatment. Following a review of current DCIS management protocols a more conservative approach has been suggested. Clinical trials have been introduced to evaluate the option of avoiding surgical intervention in a proportion of patients with DCIS defined as "low-risk" using certain clinicopathological criteria. These trials can potentially provide evidence-based models of active surveillance (with or without endocrine therapy) as a future management approach. Despite the undisputable fact of our need to address the obvious overtreatment of screen-detected DCIS, some important questions need to be considered regarding these trials including the eligibility criteria and definition of risk, the proportion of patient eligible for inclusion, and the length of time required for proper analysis of the trials' outcome in view of the long-term natural history of DCIS progression particularly the low-risk group. These factors can potentially affect the practicality and future impact of such trials. This review provides critical analysis of current DCIS management trials and highlights critical issues related to their practicality and the expected outcome.

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1. Introduction

Ductal carcinoma *in situ* (DCIS) refers to proliferation of malignant epithelial cells within the ducto-lobular system of the breast surrounded by a layer of myoepithelial cells and intact basement membrane [1]. The incidence of DCIS has significantly increased from less than 5% of breast cancer (BC) up to 20% of screen detected cancers following the introduction of mammographic screening [2,3]. DCIS *per se* does not result in cancer-related mortality, however it is widely accepted that a significant proportion of DCIS lesions will progress to invasive cancer which is a potentially fatal disease. Despite limitation of the numbers and study cohort bias, available data indicates that between 14 and 53% of DCIS will progress to invasive carcinoma if left untreated within period of 10

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http://dx.doi.org/10.1016/j.breast.2017.07.012
0960-9776/

years or more [4,5]. Despite this, almost all DCIS diagnosed in routine practice are treated by ablative surgery, with or without radiotherapy, due to lack of accurate prediction of its potential progression to an invasive lesion. The latter is the result of a combination of factors including: i) the complexity of the progression process with multiple molecular and biological variables, in addition to, interplay between malignant cells and surrounding microenvironment, ii) *in vitro* models are not optimal for assessment of DCIS progression and, iii) almost all DCIS are treated surgically and therefore recurrence can be as a result of a new primary, underestimation of the extent of the original DCIS lesion or progression of residual initially undetected DCIS foci.

Recently, the value of population-based mammographic screening has been questioned in view of the balance between harm and benefits [6]. One important question raised is the overtreatment of screen detected lesions; some of which are unlikely to kill the patients during their expected lifetime, which are mainly DCIS lesions, especially in the non-high risk groups [7,8]. This view was supported by the high prevalence of DCIS (7–39%) found in autopsy studies of patients who died of causes other than BC and at age-group similar to that of population-based screening [9] providing evidence that a proportion of DCIS go undetected and does not cause significant symptoms or mortality. Other authors have questioned the legality of treating all DCIS patients with current standard methods to avoid an approximately 1% annual risk of progression to invasive disease [10]. Only half of DCIS recurrences, which are currently estimated at approximately 10–15% of all treated cases, are invasive [11,12]. A large proportion of patients with DCIS will never develop invasive disease or die of BC even if left untreated. Moreover, the significant improvement in cancer molecular prognostic stratification in recent years has increased the possibility of utilising a personalised therapy approach [13,14]; avoiding over-treatment and hence, preserving the quality of life and saving health service costs without compromising the outcomes presently achieved and limiting aggressive interventions to the high risk groups.

The current standard treatment of all DCIS lesions is complete surgical excision with or without postoperative radiotherapy [15,16]. Although breast conserving surgery (BCS) is widely used, there remains a high rate of surgical re-excisions or conversion to mastectomy and a proportion of patients are treated with mastectomy from the start. To reduce surgical intervention in screen-detected DCIS, it has been suggested that patients with DCIS unlikely to progress to invasive disease can be subjected to active surveillance only [11,17–20]. Subsequently multiple clinical trials (Table 1) aimed at assessing the safety of active surveillance as an alternative to surgical intervention in the so called "low-risk" DCIS group have been introduced including i) the LOw-RISk DCIS (LORIS) trial, ii) the LOw Risk Dcis (LORD) trial, iii) Comparison of Operative to Monitoring and Endocrine Therapy (COMET) trial, and lastly the proposed trial; Low And intermediate RIsK ductal carcinoma IN situ study (LARRIKIN) trial. Although these trials are a way forward and the drive behind them is understandable, certain important questions should be considered to better comment on the practicality and expected outcome of these trials. These questions include: 1) have the inclusion criteria in these trials defined the low-risk group of DCIS patients precisely? 2) What is the percentage of DCIS patients who meet these criteria and to what extent will this approach be practical and rational? and, 3) What is the expected outcome that can be used as a measure of success in view of the long-term natural history of DCIS progression particularly in the low-risk group? This review addresses these trials and highlights the definition of low-risk, their practical significance and expected outcome.

2. DCIS and risk of progression

Accurate risk stratification and precise definition of risk in DCIS remains a challenge not only because of the complexity and multifactorial nature of the disease but also due to the lack of definition of risk when BC mortality is considered as the outcome measure in the setting of mammographic screening. DCIS regardless of its grade, extent or even its recurrence as an *in situ* disease does not have potential to cause BC mortality. Even lesions which recur as/or progress to invasive disease do not have equal risk of mortality. Some invasive cancers develop after long interval time, and are indolent; therefore are unlikely to cause mortality in a population subjected to regular screening tests. Taken together, when defining risk in DCIS, the expected outcome should be considered in the development of a stratification system and in guiding management decisions.

Although there is an increasing trend to define the risk using molecular profiling which can add value to current risk stratification or may be used solely in the future, these remain to be refined and validated [14,21]. The current risk stratification systems still rely on the more established clinicopathological parameters (Table 2). However, no single factor is sufficient on its own to define DCIS risk and a combination of multiple factors is used to stratify patients akin to invasive disease stratification. For instance patients aged more than 45 years old, with a small size DCIS (less than 15 mm) that lacks comedo necrosis can be considered low-risk whereas patients with high grade lesions are considered high risk [22–24]. In addition, despite the fact that high grade DCIS is considered high-risk, only about half of them will recur or progress to invasive disease if left untreated; although there have been very few studies [4,5].

3. Critical view to the current management trials

To identify patients eligible for recruitment in the DCIS active surveillance clinical trials, the established clinicopathological risk factors have been utilised, despite the known limitations, as the only available parameters. Nuclear grade has been used as the main criterion for definition of low-risk DCIS in all trials. However; low grade DCIS comprises approximately 20% of cases [9,10] and this percent is much reduced when other inclusion criteria are considered; limiting the applicability of these trials to routine practice. In addition, cytonuclear grading of DCIS, which is the most commonly used grading method, is known to be subjective and with low concordance rates even amongst expert pathologists [25–29]. Trials based on the current simple nuclear grading system will be influenced by its inherent subjectivity. This view is supported by the very low number of patients recruited in the LORIS trial where only 100 patients have been recruited in the trial over 2-year period which has been reduced to 55 patients following central histopathology review prior to randomisation [30]. Other complex grading systems comparable to invasive cancer grading have been promoted [31] but are less reproducible and agreed.

However, there remains scope for an improved and reproducible DCIS morphological grading system perhaps including cytonuclear grade combined with simple biomarkers such as Estrogen Receptor (ER), HER2 and growth pattern.

Additionally, despite the strict inclusion criteria used to define low-risk DCIS in these trials, they cannot exclude the possibility of progression to invasive disease. Approximately 30% of low grade DCIS will progress to invasive disease within a period of 20 years if left untreated [32–34]. If we assume that the 30% chance of progression of low grade DCIS will be markedly reduced by the other selection criteria of the trials such as absence of necrosis (Table 1), these findings should alert us to intervals of interpretation of the