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Current Treatment of DCIS

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ABSTRACT

Abstract: Ductal carcinoma *in-situ* DCIS is a heterogeneous entity in breast neoplasm with unpredictable biological behavior. This poses challenge in the management of DCIS. Various trials on DCIS have shown good outcome with integral treatment of adequate surgery, radiotherapy and hormonal therapy. Identification of subgroup of DCIS for radiotherapy and hormonal therapy could improve recurrence rate, contralateral tumours incidence and perhaps overall survival. Various risk score calculations could help to direct radiotherapy and hormonal treatment verses surgery alone and to avoid over treatment. Oncotype DX assay could be a new way of risk calculation to direct types of DCIS treatment. The recent increased use of MRI could increase the detection of DCIS and a more accurate extent of disease estimation. This article is a summary of major literatures and major trials result for DCIS.

KEYWORDS

Early Breast Cancer; DCIS; Breast Cancer Diagnosis and Treatment

1. Introduction

The introduction of national mammographic screening programmes and the increasing use of digital mammography and magnetic resonance imaging (MRI) have dramatically changed the clinical presentation of ductal carcinoma *in-situ* (DCIS). Prior to this, DCIS made up a small proportion of all breast cancers and was only diagnosed in patients presenting with a palpable mass, pathological nipple discharge or occasionally found as an incidental biopsy finding. In contrast, DCIS is now most frequently identified in asymptomatic women as screen-detected micro-calcifications [1]. High spatial resolution MRI seems to be more sensitive than mammography in the detection of high and intermediate grade DCIS [2].

DCIS is a heterogeneous pathological entity at a molecular level with a variable and unpredictable biological behavior. Although it is considered to be the precursor of the most invasive breast cancers, however not all DCIS will progress to this stage. The overall progression to invasive breast cancer has been reported to range from 14% to 75% [1]. Therefore the challenge in the modern management of DCIS is to avoid over-treatment.

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2. Discussion

Screen-detected DCIS accounts for approximately 25% of newly diagnosed breast cancers and seems to be associated with lower rates of local recurrence after treatment compared with symptomatic disease [3,4] and therefore a proportion of these cases may be less clinically relevant [5,6].

Integral to the successful management of DCIS, is surgical excision of the disease with clear margins [7] (this may involve breast conservation surgery BCS or mastectomy with or without reconstructive techniques). MRI seems to be a more accurate imaging modality than digital mammography to assess the extent of DCIS [2] and hence could help in better case selection for BCS. MRI may over-estimate the extent of disease and therefore tissue sampling of MRI detected abnormalities should be considered in order to avoid overtreatment. Breast radiotherapy (RT) and hormonal treatments are also given as adjuvant therapies where appropriate but can these be safely omitted in certain cases?

Treated DCIS has an excellent overall prognosis and therefore differences in survival have been difficult to demonstrate even in large trials. Differences in local recurrence (LR) rates have been used as a surrogate marker for survival. RT was shown to reduce LR in early invasive breast-cancer in 1995 [8] and to be indirectly associated with improved survival in 2005, in that one death was prevented for every four local-recurrences avoided [9]. A direct improvement in overall survival (OS) in early breast-cancer attributable to RT of around one sixth has since been demonstrated [10].

An analysis of long term data on patients treated for DCIS from the NSABP B-17 and NSABP B-24 trials [11] showed that at 15 years, the RT treated patients had significantly fewer local recurrences and that this effect increased over time. Of those that did recur 54% were invasive, and for these patients overall survival was lower (HR of death = 1.75, 95% CI = 1.45 to 2.96, P < 0.001).

A recent update from the EORTC 10853 randomized trial showed that RT reduced the risk of any LR by 48% (hazard ratio [HR], 0.52; 95% CI, 0.40 to 0.68; P < 0.001). At 15 years, almost one in three non-irradiated women developed a LR after local excision for DCIS and RT reduced this risk by a factor of 2 [12].

The UK/ANZ DCIS trial assessed the effect of adjuvant treatment with tamoxifen and radiotherapy after BCS for DCIS. After a median follow-up of 12.7 years [13], a significant reduction in LR and contra-lateral tumors in the tamoxifen treated patients was seen (HR 0.70, CI 0.51-0.86, p = 0.03 for reducing ipsilateral DCIS recurrence; HR 0.44, CI 0.25-0.77, p = 0.005 for contralateral tumour; HR 0.71, 95% CI 0.58-0.88, p = 0.002 for reducing incidence in all new breast events). A recent metaanalysis of the UK/ANZ DCIS and B-24 trials showed that the addition of tamoxifen to surgery and RT for DCIS reduced the risk of local invasive and contra lateral *in situ* relapses, but did not improve the overall survival. The benefit was independent of age [14]. Trials are ongoing to determine if aromatase inhibitors are superior to tamoxifen in the adjuvant setting after BCS for estrogen receptor (ER) positive DCIS (NSABP B-35 and IBIS II).

In a population-based cohort study involving 1676 patients with an average follow up of 7.1 years, Sprague et al reported that the 5-year DFS was similar among women treated with ipsilateral mastectomy compared to women treated with BCS and RT, though women receiving BCS without radiation experienced poorer disease free survival DFS. Women treated with tamoxifen in addition to BCS and RT had a similar risk of a second breast event, although the hazard ratio (HR) suggested a potential benefit however the difference was not statistically significant (0.70, 95% CI 0.41 - 1.19) [15].

It is clear that there is a significant potential benefit overall for patients with DCIS from adjuvant treatments, but given the very good overall prognosis of this condition, patients with a low risk of LR are likely to be those in which adjuvant treatments could be omitted. Tumour size and grade, age, the presence or absence of necrosis and the "comedo" sub-type have been found to be statistically associated with the risk of LR in an independent pathological review of cases from the UKCCCR/ANZ DCIS trial [16]. Margin width was the most significant factor associated with local-recurrence in a large meta-analysis [7]. These factors in isolation are insufficient to safely omit adjuvant treatments or to validate less extensive surgery but in combination may be useful. For example a 70 year old woman with a small low grade DCIS can be treated with adequate local excision alone (margin width > 2 mm), whereas a 45 year old woman with a high grade DCIS will benefit from adjuvant RT (and tamoxifen if the DCIS is ER positive) after BCS.

The Van Nuys index (VNI) which is derived from the patients' age, tumor size, surgical margin width, nuclear grade, and the presence/absence of comedo necrosis is used to determine the risk of LR after BCS for DCIS and guide therapeutic decision-making. [17] Recent advances in genomic profiling have led to the development of molecular signatures that have a prognostic utility. The Oncotype-DX-DCISTM is a genomic signature that has been introduced to guide RT decisions in DCIS by generating a score which predicts the risk of LR [18]. This score was validated using data from the ECOG 5194 study which included patients treated with BCS alone [19].

3. Conclusion

Further research is required to determine the role of new RT regimes, such as accelerated partial breast irradiation and endocrine therapies. Biological profiling and molecular analysis represent an opportunity to improve our understanding of the tumor biology of this condition and rationalize its treatment. Reliable identification of low-risk lesions could allow treatment to be less radical or safely omitted.

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