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Risk factors for the development of invasive cancer in unresected ductal carcinoma in situ

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ABSTRACT

Background: The natural history of ductal carcinoma in situ (DCIS) remains uncertain. The risk factors for the development of invasive cancer in unresected DCIS are unclear.
Methods: Women diagnosed with DCIS on needle biopsy after 1997 who did not undergo surgical resection for ≥1 year after diagnosis were identified by breast centres and the cancer registry and outcomes were reviewed.
Results: Eighty-nine women with DCIS diagnosed 1998–2010 were identified. The median age at diagnosis was 75 (range 44–94) years with median follow-up (diagnosis to death, invasive disease or last review) of 59 (12–180) months. Twenty-nine women (33%) developed invasive breast cancer after a median interval of 45 (12–144) months. 14/29 (48%) with high grade, 10/31 (32%) with intermediate grade and 3/17 (18%) with low grade DCIS developed invasive cancer after median intervals of 38, 60 and 51 months. The cumulative incidence of invasion was significantly higher in high grade DCIS than other grades ($p = .0016$, log-rank test). Invasion was more frequent in lesions with calcification as the predominant feature (23/50 v. 5/25; $p = .042$) and in younger women ($p = .0002$). Endocrine therapy was associated with a lower rate of invasive breast cancer ($p = .048$).
Conclusions: High cytonuclear grade, mammographic microcalcification, young age and lack of endocrine therapy were risk factors for DCIS progression to invasive cancer. Surgical excision of high grade DCIS remains the treatment of choice. Given the uncertain long-term natural history of non-high grade DCIS, the option of active surveillance of women with this condition should be offered within a clinical trial.

Introduction

Ductal carcinoma in situ (DCIS) is diagnosed predominantly through mammographic screening programmes and now comprises 20% or more of new breast cancers [1]. Concern has been expressed regarding possible overtreatment [2], given the excellent long term survival of women with DCIS [3,4]. Some have suggested that "nothing is better than something" [5] and proposed long-term

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surveillance for estrogen receptor (ER) positive DCIS [6,7]. Randomised trials comparing the outcomes of active surveillance (AS) with conventional surgery and adjuvant treatment have opened in the UK (the LORIS trial) [8], the US (the COMET trial) [9] and Europe (the LORD trial) [10]. Endocrine therapy in the AS arms is optional in COMET, optional but not encouraged in LORIS and not allowed in LORD.

While there is an historic literature describing the natural history of DCIS in small, predominantly pre-screening series of symptomatic disease [11], there is also a growing understanding that DCIS is a heterogeneous condition. It has been reported as a common incidental finding at autopsy with a median 8.9% prevalence in a review of seven studies of women who died of unrelated causes [12]. These series, conducted over 30 years ago, used variable diagnostic criteria, compounded by the difficulty of diagnosing DCIS in tissue that is likely to have been poorly preserved. The current prevalence of undiagnosed DCIS therefore remains uncertain.

Whatever the true prevalence, surgery, radiotherapy and endocrine therapy remain the mainstays of guideline-concordant care. However, some 2.0–2.3% of patients diagnosed with DCIS in the USA choose AS for management of their disease [4,13]. Without treatment, it has been estimated that only 20–30% of DCIS will progress to invasive cancer [11,14].

Furthermore, it is not known whether long-term disease outcome is adversely impacted by awaiting progression to invasive disease.

Given this background, we sought to identify women in the recent breast screening era who had not received surgical resection for histologically diagnosed DCIS and to consider risk factors and long-term outcomes for such women as a comparator for active surveillance trials.

Material and methods

The West Midlands Cancer Intelligence Unit (WMCIU, now incorporated into the National Cancer Registration and Analysis Service, part of Public Health England) and the Scottish Cancer Registry identified 2505 possible eligible patients from cancer registrations of women diagnosed in England and Scotland between 1 January 1996 and 31 December 2009

These women had a needle biopsy diagnosis of DCIS but no record of subsequent surgery. Details were sent to Lead Clinicians in each hospital following completion of a confidentiality agreement. In addition, National Health Service (NHS) Breast Units and NHS Breast Screening Programme (NHSBSP) centres in the United Kingdom were invited to submit details of known patients with DCIS diagnosed from 1 January 2010 onwards who had not undergone surgical excision for at least one year following confirmed histological diagnosis on needle biopsy. Additionally, some women diagnosed between 2003 and 2012 were identified via the NHSBSP prospective cohort study of screen-detected non-invasive neoplasias, the Sloane Project (www.sloaneproject.org.uk).

A comprehensive registration form was completed for each case by the submitting centre, including details of the imaging and clinical findings, mode of biopsy, histopathology, reasons (where known) for not performing surgery and relevant drug treatment and/or radiotherapy. A follow-up form was completed for each subsequent episode, which included one or more of clinical assessment, mammogram and ultrasound (continuing drug treatment was not formally recorded). A third form was completed for any further needle biopsy or surgery. Forms were returned to the WMCIU/Public Health England where the data were entered onto a database. Missing data on tumour characteristics together with date and cause of death were obtained from the National Cancer Registration and Analysis Service. Data were exported to an Excel spreadsheet for analysis. Registration opened in 2012 and closed in December 2016.

Statistical methods

Univariate analysis only was performed due to the relatively small size of the dataset. Comparisons of categorical data were made using Fisher's Exact test. Continuous variables were assessed by the Mann-Whitney *U* test. Cumulative incidence curves were compared using Kaplan-Meier analysis and the log rank test. Analysis was conducted using Stata version 14 (StataCorp LLC, College Station, Texas, USA).

Results

Data from 89 eligible women identified from 31 breast units were returned. In all cases the initial DCIS diagnoses were made between 1998 and 2010 (no eligible cases diagnosed after 2010 were submitted despite specific requests for such cases). The median patient age at diagnosis was 75 years (range 44–94 years). The DCIS was screen-detected in 39 women (44%) with a median age of 65 years; the remaining 50 were diagnosed through other routes (symptomatic clinics and incidental findings) and had a median age of 82 years. The median duration of follow-up (diagnosis to death, invasive disease or last review) was 59 months (range 12–180 months).

The symptoms of the 50 women who were diagnosed other than through screening are poorly documented. Three each presented with a lump, a nipple discharge and nipple changes. Clinical examination was recorded as normal in 7, benign in 3, indeterminate in 9, suspicious in 8 and malignant in 8; clinical findings were not recorded in 15. It is likely that a number of DCIS lesions were incidentally detected on mammography performed for investigation of unrelated symptoms.

Thirty-five women (39%) were recorded as being unfit for surgery (without details of the comorbidities), 37 (42%) declined surgery, four (4%) were both unfit and declined surgery, other (unspecified) reasons were stated for eight (9%) and the reasons were unknown for five (6%) patients.

Mammographic features

The predominant mammographic features were known for 75 of the 89 women. Fifty (67%) were microcalcification, granular microcalcification being the most common. Nine of the 25 women with other predominant features (mass or deformity) had microcalcification as a secondary feature. The median mammographic lesion size for women in whom both size and grade were known was 34 mm (range 8–88) for high grade DCIS (n = 23), 32 mm (5–126) for intermediate grade DCIS (n = 23) and 15 mm (4–64) for low grade DCIS (n = 11).

Needle biopsy

In 63 women, the initial DCIS diagnosis was made with 14-gauge (G) core needle biopsy (CNB). Only ten women were known to have been diagnosed with vacuum-assisted biopsy (VAB) (one each of 14G and 11G, five 10G and unknown gauge in three). In sixteen women, the biopsy technique was classed as either 'other' or unknown but were not open biopsies (12 were image-guided and one freehand; the remaining three were in women unfit for surgery). Of the 72 women where the mode of guidance was known, 37 biopsies were performed under stereotaxis, 28 ultrasound and seven

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