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Ductal carcinoma in situ of the breast - Long term results from a twenty-year cohort

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ABSTRACT

Introduction: Long-term survival is excellent in ductal Carcinoma in situ (DCIS); whether or not we are over-treating DCIS has been a major public concern. This study aims at reviewing the long-term survival outcome of DCIS and identifying adverse prognosticators for DCIS.

Patients and methods: Patients treated for DCIS between 1st January 1997 and 31st December 2016 were identified from a prospectively maintained database. Multivariate analysis was performed to evaluate the adverse factors for surgical margin involvement and local recurrence

Results: 3042 female patients were treated for breast cancer over the 20-year study period, of which 203 (6.7%) had DCIS in final pathology. The median age of diagnosis was 53 year-old (Range 30–85). 57 (28.1%) were detected by screening mammogram, 101 had breast mass on presentation.

132 (65%) patients received mastectomy and the remaining received breast conserving surgery (BCS); Sentinel lymph node biopsy was performed in 86 (42.4%) patients. 19 (9.4%) patients had positive resection margin, 18 were re-operated for clear resection margin. Multivariate analysis found that high grade DCIS is the only independent risk factors for margin involvement (HR 2.55, 95% CI 1.02–6.42).

After median follow-up of 106 months (6–223 months), the overall survival was 97%. 4 (2%) patients developed local recurrence. Multivariate analysis found that positive surgical margin is the only independent factor of local recurrence (HR 9.58, 95% CI 1.43–64.18).

Conclusion: High grade DCIS is associated with increased risk of surgical margin involvement which is in turn an independent factor of local recurrence.

Background

Ductal carcinoma in situ (DCIS) is a precursor of invasive breast cancer; it is the earliest detectable form in the spectrum of breast cancer. By definition, the malignant cells in DCIS are confined within the basement membrane of the breast ductal system [1]. Due to the increased availability of screening mammograms, incidence of DCIS has increased since mid-80s [2]. However, this has also resulted in over-diagnosis and overtreatment [3]. Natural history of DCIS, a pre-malignant form of invasive breast cancer [4], is still poorly understood [5]. Long-term survival studies have found that mortality of DCIS in 28 years could be as low as 5% [6]. The mainstay of treatment of DCIS is surgery, with or without radiotherapy and /or tamoxifen. While mastectomy and breast conserving surgery (BCS) for DCIS have never been compared in a randomized trial, an early meta-analysis of clinic-based observational studies of DCIS suggested that local recurrence rates were substantially lower among women treated with mastectomy [7].

With increased detection of DCIS after widespread use of screening mammogram in the recent few years in many Western countries, there is an on-going debate questioning if we are over-treating these pre-malignant lesions with unnecessary operations. Some researchers pioneered watchful-waiting strategy for DCIS based on the fact that not all DCIS will progress into invasive cancer [8]. However, DCIS is a heterogeneous group of disease with significantly different tumor behavior between different subtypes; it is therefore important to identify the high risk subtype of DCIS before we can safely manage it with watchful waiting policy.

Van Nuys Prognostic Index (VPNI) was a model developed to estimate the risk of local relapse or recurrence [9]. In addition to the three original parameters used, including the size of DCIS, margin and histological grade, patient's age was added in the revised version of VPNI. VPNI may help to classify DCIS into low risk and high risk groups using those clinical parameters; however it is still nearly impossible to predict which DCIS is more likely to progress into invasive breast cancer.

The pathophysiology of DCIS is better understood now. Instead of being a single disease entity, DCIS is now considered a heterogeneous

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group of disease, ranging from low grade to high grade DCIS, with or without microinvasion. Microinvasive DCIS (T1mic) is defined by The American Joint Committee on Cancer (AJCC 7th edition) as invasive component of no more than 1mm in size [10]. To date, there are only a few studies performed on T1mic using the AJCC definition; after 36–107 months of follow-up, the local recurrence rate was reported to be 0–9.3% and the distant recurrence rate was reported to be 0–2.1% [11–14]. Due to heterogeneity of disease behaviour across the spectrum of DCIS, treatments should be tailor-made.

Unlike many Western countries, population-based breast cancer screening is not available in many Asian countries including Hong Kong. DCIS was reported to be more frequently detected in the higher social class due to self-initiated breast cancer screening. More than half of these patients were successfully managed with breast conserving surgery [15]. However in public settings like in our centre, the situation is very different, our mastectomy rate could be as high as 70% even in early breast cancers [16]. Many patients present late with symptoms or even with breast mass. In fact, DCIS accounts for only a small proportion of breast cancers treated in public hospitals.

The purpose of this study is to evaluate the long-term outcomes of DCIS treated in our center and to identify the factors associated with adverse prognostic outcomes in DCIS.

Patients and methods

Clinical, radiology, pathology and survival data of all breast cancer patients treated in Queen Mary Hospital, a tertiary breast center in Hong Kong, were entered into a prospectively maintained database with informed consent. Institutional board review approval was sought for patient data collection. All patients with final histopathology of DCIS after resection were included in the analysis. Patients with co-existing invasive breast cancers and residual DCIS after neoadjuvant chemotherapy were excluded. In addition, patients with DCIS diagnosed by core needle biopsy (CNB) but refused operation were also excluded from the study due to the possibility of misdiagnosis of IDC as DCIS by CNB without surgical excision. Finally, microinvasive breast cancer (T1mic) were excluded from our analysis due to its heterogeneous characteristics and natural history.

In our center, all newly diagnosed breast cancer patients will undergo triple assessment, with pre-operative histological diagnosis made by CNB. Metastatic work-up will be offered to patients with biopsy-proven invasive cancers only. All patients will be managed through multidisciplinary approach by breast surgeons, oncologists, pathologists and radiologists. In patients with pre-operative diagnosis of DCIS, patient will be offered the surgical options of mastectomy or BCS. Surgical decision is made based on tumor size, patient cup size and patient preference. Sentinel lymph node biopsy (SLNB) will be offered to patients who opt for mastectomy due to the possibility of incidental invasive cancer detected after mastectomy, in which SLNB will no longer be feasible.

Histopathologic examinations of all mastectomy or BCS specimens are performed in our histopathology laboratory (accredited by American College of Pathologists, CAP Accreditation Number 71755-25). Microscopic examination of H&E stained slide sections will be performed. The formalin-fixed paraffin embedded sections are assessed by Immunohistochemistry (IHC) technique, using Novocastra Estrogen receptor (ER) (clone:6F11), Dako Progestrogen receptor (PR) (clone: PgR636) with the Bond polymer refine detection system. (Please note that IHC examination was not routinely performed on early specimens in this cohort).

Continuous and categorical variables were analysed using student's t-test and chi-square or Fisher's exact test where appropriate respectively. Prognosticators of DCIS were analysed with multivariate analysis. A statistical significance level of 0.05 was used.

Results

From 1st January 1997 to 31st December 2016, 203 patients were identified from the database for being treated for DCIS, which accounts for 6.7% of all breast cancers (N = 3042) treated during the same period of time. Median age at diagnosis was 53 (Range 30–85). All patients were female. Number of DCIS diagnosed has increased significantly from 33 patients in the first decade (1997–2006) to 170 patients in the second decade of the study period (2007–2016).

All patients received standardized management under our departmental protocol, in which triple assessment with mammogram and/or breast ultrasound followed by core needle biopsy were performed in all breast cancer patients. All cases were managed by multidisiplinary approach. Surgical options and subsequent treatment plans were tailored accordingly.

57 (28.1%) DCIS were incidental, detected by screening mammogram; while 101 (49.8%) presented with breast mass; the others had nipple discharge, mastalgia or nipple retraction as initial presentation. 22 (10.8%) had multifocal or multicentric DCIS. 121 (59.6%) patients had microcalcifications only on mammogram, others had abnormal mass shadow or architectural distortion on mammogram. 132 patients (65%) underwent mastectomy and the others received BCS. Reasons for mastectomy include large tumor mass on presentation, small breast volume and patient's wish. None of the mastectomy patients underwent adjuvant locoregional radiotherapy (LRRT), whereas 64 (90.1%) patients who had undergone BCS received adjuvant LRRT. 86 patients who received mastectomy had decided to undergo SLNB, which was negative for metastasis in all patients. Summary of patient demographic and clinical details were summarized in Table 1.

Concerning the grade of DCIS, 48 (23.6%) were low grade, 51 (25.1%) were intermediate grade and 84 (41.3%) were high grade. 20 patients from early period of study did not have reported grade. 122 (60.1%) patients in the current series were hormonal receptor positive (Defined as Allred score > =3), 76 (62.3%) of them received tamoxifen

Table 1
Patient characteristics.

Characteristic	Number (%)
Tumor size	
< 2 cm	125 (61.6%)
> =2 cm	50 (24.6%)
Unknown	28 (13.8%)
Multifocality	
Yes	181 (89.2%)
No	22 (10.8%)
Presenting symptom	
Asymptomatic (Screen-detected)	57 (28.1%)
Symptomatic (Mass, nipple discharge, etc)	146 (71.9%)
Mass-forming lesion	
Yes	101 (49.8%)
No	102 (50.2%)
Paget's disease of the nipples	
Yes	16 (7.9%)
No	187 (92.1%)
Tumor grade	
Low grade	48 (23.6%)
Intermediate grade	51 (25.1%)
High grade	84 (41.4%)
Not reported	20 (9.9%)
Hormonal receptor status	
Estrogen receptor negative	43 (21.2%)
Estrogen receptor positive	122 (60.1%)
Not reported	38 (18.7%)
Operative type (Breast)	
Mastectomy	132 (65.0%)
Breast conserving surgery	71 (35.0%)
Sentinel lymph node biopsy	
Yes	86 (73.5%)
No	117 (26.5%)