

Breast ductal carcinoma in situ in an unscreened population: presentation, diagnosis and management at a single tertiary centre

M Mutebi¹, H Simonds², L Cairncross¹, E Panieri¹

¹*Surgical Oncology and Endocrine Unit, Division of General Surgery*

²*Division of Radiation Oncology. University of Cape Town Faculty of Health Sciences and Groote Schuur Hospital*

Corresponding author: Miriam Mutebi (mcmutebi@yahoo.com)

Background: To determine the clinical presentation of patients presenting with isolated ductal carcinoma in situ at a single tertiary center in the Cape Town, South Africa. To review the diagnostic techniques most commonly used and the primary surgery performed for these patients.

Methods: We performed a retrospective folder review of patients diagnosed with DCIS over a period from Jan 2005 to Dec 2012, at the Combined Breast Cancer Clinic at Groote Schuur Hospital. Patients with a histological diagnosis of DCIS were identified from a prospectively collected patient database and the South African National Health Laboratory System (NHLS) histological reports and operative records.

Results: 42 patients with isolated DCIS were identified. This represents 1.1% (42/3636) of all breast malignancies managed in this period. The average age of presentation was 58 years. Most patients presented with a breast lump (23/42). The diagnosis was made on core biopsy in 14 patients while 8 patients required excision of the palpable lump to make the diagnosis. 23 patients underwent a primary mastectomy, 6 patients had a wide local excision (WLE) and 6 patients had radio-guided occult lesion localization (ROLL) with therapeutic intent.

Conclusion: Though rare, the management of DCIS in this setting highlights the challenges of diagnosing and managing early breast malignancies in LMICs.

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Introduction

Isolated in situ carcinomas of the breast constitute 25–30% of all screen detected tumors in countries that practise routine screening.¹ Of the in situ tumors, at least 80% are ductal carcinomas in situ (DCIS).² In the United States, DCIS accounts for at least 25% of all newly diagnosed breast cancers.^{2,3}

DCIS represents a continuum of conditions with different clinical presentations and histological behavior. In centers where formal mammographic screening programs exist, the presentation of DCIS is usually a radiological finding.⁴ Clinical presentations are typically with a palpable lump or thickening, nipple discharge or Paget's disease of the nipple. Histologically, DCIS is classified by its architectural pattern,

the tumor grade and the presence or absence of comedo necrosis.^{1,2} The Van Nuys Prognostic Index (VNPI) is a simple score for predicting the risk of local recurrence (LR) in patients who have had local excision of DCIS.⁵

In Low to Middle Income Countries (LMICs), breast cancer is characterized by a later stage of presentation.⁶ Mammography services are frequently lacking⁷ and in this clinical setting, mammography is primarily used in the diagnostic evaluation of a patient presenting with a breast lump or done as 'opportunistic' screening* in breast or surgical clinics. This may result in a different pattern of presentation for ductal carcinoma in situ.

South Africa is defined as a middle income country with a diverse socio-economic spectrum.⁸ Previous South African series conducted in the private health sector, where some

*Opportunistic screening refers to mammography that may be done as a result of the patient's age or family history on presentation to a health facility. This may frequently be the first time that the patient has a clinical breast examination, a discussion on breast awareness and risk factors with the clinician and a mammogram subsequently performed

breast cancer screening is practised, demonstrated an isolated DCIS rate of 11.5%, in a review of 165 patients undergoing breast conservation surgery.⁹ Similar findings were reflected by Edge and colleagues who demonstrated an overall DCIS rate of 13% of all breast cancers seen in a series of 730 breast cancer patients.¹⁰

There is, however, limited data on the incidence, presentation and management of isolated DCIS in the public health sector in South Africa, which caters predominantly to a low socio economic group of patients. This cohort may be reflective of other populations seen in Sub-Saharan Africa (SSA), where mammography is done to supplement clinical findings and not as part of a screening program.

Aims and objectives

The primary aim of the study was to determine the clinical presentation of patients diagnosed with isolated ductal carcinoma in situ at a single tertiary center in Cape Town. Secondary objectives were to review the diagnostic techniques most commonly used, the primary surgery performed for these patients and their adjuvant treatment.

Materials and methods

We performed a retrospective folder review of patients diagnosed with DCIS over a period from January 2005 to December 2012, at the Combined Breast Cancer Clinic at Groote Schuur Hospital, a large, public tertiary teaching hospital, in Cape Town, South Africa.

Patients with a histological diagnosis of DCIS were identified from the prospectively collected Combined Breast Cancer Clinic database, a computerized diagnostic search of the South African National Health Laboratory System (NHLS) histological records, as well as a search of the Surgical Oncology and Endocrine Unit operative notes, as this is the unit responsible for all procedures for patients with breast carcinoma and DCIS at Groote Schuur Hospital.

Patients with an accompanying diagnosis of invasive carcinoma were excluded from the study group, as were those with incomplete records.

Data was obtained from the folders on patient demographics and the diagnosis and treatment of their DCIS. Ethical approval was obtained from our institutional review board for the study. Descriptive statistics were used to categorize the results.

Results

A total of 3768 patients with breast malignancy were diagnosed in the study period. Of these, 132 had incomplete clinical records or absent histology reports. Thus, 3636 patient records were reviewed. Of these 500 had a diagnosis of DCIS in the presence of invasive carcinoma and only 42 (1.1% of all cancers patients) had isolated DCIS.

There were 41 female patients and 1 male. The average age at presentation was 58 years (range 26-77 years).

Key findings

Clinical Presentation and Diagnosis

Most patients presented with overt symptoms and clinical signs (34/42, 81%). The commonest presentation was with a breast lump (23/42). 6 patients presented with nipple ulceration (Paget's disease) and 5 with a spontaneous nipple discharge. DCIS was identified on mammography done as opportunistic screening, in 8 patients.

The initial diagnosis was made on core biopsy in 14 patients while 8 patients required excision of the palpable lump to make the diagnosis after an initial non-diagnostic core biopsy. The 6 patients who presented with nipple ulceration had a punch biopsy performed which confirmed the clinical suspicion of Paget's disease of the nipple. In these patients, subsequent surgery confirmed the presence of isolated DCIS. Four of the 5 patients who presented with a nipple discharge underwent a diagnostic micro-ductectomy and 1 had a stereotactic biopsy. Seven other patients underwent a stereotactic biopsy and 2 patients, a diagnostic radio-labelled occult localization of lesion (ROLL). The radiolabeled occult localization of a lesion is a technique employed through the use of the nuclear medicine facilities where a macro-colloid (radiolabeled albumin) is injected into the lesion and a gamma probe subsequently used intraoperatively to localize the lesion. This method can be used to diagnose lesions (diagnostic roll) or to a therapeutic end for lesions diagnosed on previous biopsy.¹¹

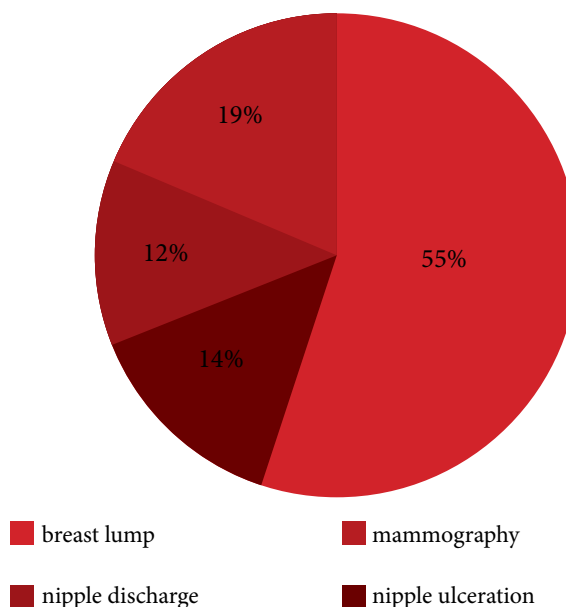


Figure 1. Presentation of DCIS in non- screened population

Radiology

Mammographic records were traceable in 31 cases. Sixteen patients (52%) were noted to have isolated microcalcifications. The average size of the microcalcifications was 2 cm (the range was from 1 cm to 8 cm) with pleomorphic arrangements.

6 patients had a mass and microcalcifications and 3 patients presented with a spiculated mass only. 6 patients had a normal mammogram.

None of the 31 patients who had mammography had a breast ultrasound. Though sonographic services were available, the primary imaging modality of the unit during the time of study was mammography. Due to the limited human resources and equipment, the use of breast ultrasound was restricted.

Ultrasound guided biopsies of breast lesions and ultrasound guided FNACs were only performed in selected patients. Patients with palpable breast findings underwent clinically guided biopsies.

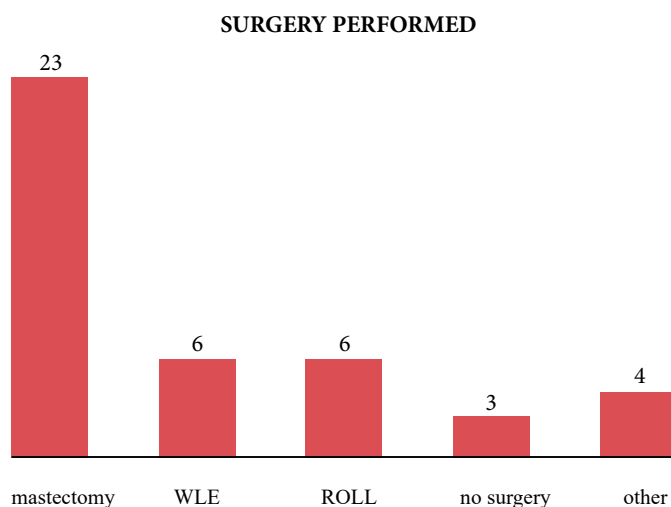
Patients with impalpable microcalcifications had a stereotactic biopsy performed in keeping with international guidelines.

Surgical management: Breast and Axilla

Breast

Twenty-three patients underwent a primary mastectomy. Twelve patients had breast conserving surgery. Of these, six patients had a wide local excision (WLE) and six patients required localization with a ROLL, for an impalpable lesion. The ROLL performed in two of these patients was both diagnostic and therapeutic. In total, 7 patients did not undergo surgical treatment: 3 were deemed poor surgical candidates and were placed on hormonal treatment only and 4 others declined surgery. Of the 12 patients who had initial breast conservation therapy (either ROLL or WLE), 10 required further surgery for close or involved margins. Eight of these underwent a mastectomy and 2 had re-excision of margins. Of the 23 patients who underwent a primary mastectomy, two underwent an immediate reconstruction and 2 underwent a delayed reconstruction.

Figure 2. Primary Breast surgeries performed



Axillary Surgery

In the group of patients who underwent primary mastectomy, 9 underwent an axillary lymph node dissection and 9 had a

sentinel lymph node biopsy. The rest had a simple mastectomy. None of the patients who underwent breast conserving surgery had an axillary procedure. All the lymph nodes obtained from the different procedures were clear of metastatic disease on final histology.

Histological findings

Seventeen of the 42 patients had high grade DCIS. A Van Nuys score was determined for 10 out of the 12 BCT patients and came to a median score of 8/12. Two patients did not have sufficient information to complete the Van Nuys score. 31 patients had assessment of ER/PR status and of those, 16 were hormone receptor positive. Only 6 patients in our series, had their HER-2 status documented.

Adjuvant Therapy

Seventeen patients did not receive any adjuvant treatment. Twelve patients received adjuvant endocrine therapy, 11 with tamoxifen and one with an aromatase inhibitor. Six patients who underwent breast conserving surgery received adjuvant radiotherapy. Eleven patients had no follow-up and no documented adjuvant strategies. Two patients subsequently died due to non-cancer related causes.

Discussion

Globally the incidence of clinically occult DCIS has risen in the screening era.¹² Before screening mammography was implemented, the incidence ranged between 2–5%.¹³ The results of this series are in keeping with these reports.

The commonest clinical presentation for DCIS in our series was the finding of a self-identified breast lump. In our setting trained radiology personnel and mammographic equipment are a scarce resource, and mammography is performed primarily as an adjunct to clinical evaluation. In our series, only 8 patients were diagnosed with DCIS following mammography prior to the development of clear clinical signs. In these patients, the clinical indications for mammography were a family history of breast cancer⁵ and long term HRT use.¹

Two patients above 50 were diagnosed with DCIS, on mammography imaging for other complaints (new onset mastalgia). Though these numbers are too small to draw any robust conclusions, the findings could perhaps underscore the need for comprehensive history taking and the judicious use of mammographic screening in selected cohorts.

The diagnosis was most frequently made with a clinically guided core biopsy. It is interesting to note the high failure rate of this, and as many as 8 of the 23 patients required surgical excision for diagnosis. This probably reflects the fact that the palpable lump caused by DCIS is frequently ill defined, and vague in extent, and may be more correctly defined as a ‘thickening’, making accurate sampling without imaging guidance more problematic. There is clearly a need to strengthen the diagnostic capacity through training physicians in the use of ultrasound guided imaging to improve diagnostic accuracy and to minimize the need for repeat biopsies. This model has been successful in the setting of trauma and

anesthesia and would decrease the demands on the limited radiology personnel available.

Our diagnostic yield could also be improved by strengthening the capacity in imaging. There is a role for task shifting^{14,15} and training clinical personnel to develop skills in both imaging and core biopsy would help to improve the diagnostic yield of these tests.

ROLLs and stereotactic biopsies were occasionally used to make a diagnosis but these procedures require access to nuclear medicine and radiology expertise that is lacking in most regional centers in South Africa.⁷

A large number of our patients underwent mastectomy. The reasons for this are multifaceted and not easily recorded in a retrospective study. It has been observed that a large number of our patients frequently present with more extensive DCIS at diagnosis, than is seen in developed countries that have screening programs. These reports are largely anecdotal and more prospective studies are required to support these observations. However more extensive, diffuse disease would make patients intrinsically unsuitable for breast conservation surgery.

Furthermore, access to radiotherapy is limited, and close clinical and radiological follow up are unpredictable in our resource constrained circumstances. Many differences exist in what resources are available in many tertiary or regional referral centers. Mastectomy may remain the option of choice in this environment, as its event-free survival compares favorably with that of the combination of breast conservation surgery and radiation therapy.^{16,17,18}

Twelve patients underwent initial breast conservation surgery but as many as 10 required repeat surgery due to involved or close margins. This is a disappointingly high number. Two patients had an initial diagnostic and therapeutic ROLL and had a subsequent mastectomy for involved margins. The remaining 4 patients who underwent ROLL after a stereotactic proven biopsy also required mastectomy due to involved margins. Two of the 6 patients who had wide local excisions (WLE) also underwent subsequent mastectomy and 2 had a successful re-excision of margins.

The high re-operative rate of the ROLLs (6 out of 6) is interesting. In our opinion, it reflects the fact that this technique is primarily a diagnostic procedure, and accurate intraoperative evaluation of margins of resection in cases done with therapeutic intent is problematic.

The decision to offer mastectomy as opposed to margin re-excision is mostly reflective of system constraints. The patients were offered a mastectomy at a peripheral hospital after initial excisions. This helped to avoid the delays in management caused by prolonged waiting times at the single specialized center that offered breast conservation surgery in the region.

Diagnostic and sampling concerns often arise with a diagnosis of DCIS on core biopsy. Studies show that up to 10–33% of specimens diagnosed by core biopsy may have an associated invasive component on the final surgical

specimen.^{19,20} Diffuse disease on mammography, alongside a diagnosis of high grade DCIS, would serve as an indication for a sentinel lymph node biopsy in most centers. This is due to concerns about missing a possible invasive component.²⁰

As the yield of lymph node metastases tends to be low (about 1–2%) several attempts have been made to define predictors for invasive disease.²¹ Dillon and colleagues suggest a combination of radiological features (tumor greater than 5 cm, features of a mass on mammography, etc.) alongside pathological features such as high grade lesions.²⁰

There is no consensus on the criteria for surgery, and the decision to perform axillary surgery is frequently made on a case by case basis. A recent review by Osaka and colleagues demonstrates that certain histological factors may predict the presence of invasive disease, but may fail to translate to lymph node positivity.²² However, their findings of low sentinel node involvement (using the one-step nucleic acid amplification – OSNA assay technique in this case) further reinforces the argument for less aggressive axillary surgery.

The high axillary clearance rate in our patients is reflective of diagnostic concerns over concurrent invasive disease and the previously limited availability of sentinel lymph node biopsy facilities. However, the current body of evidence suggests that this rate of axillary clearance is inappropriate, particularly in view of the potential associated morbidity. Patients from the latter years of the series were more likely to be offered sentinel lymph node biopsies reflecting a shift of practice to this as standard of care.

Adjuvant therapy

Traditionally mastectomies were carried out for control of the DCIS and subsequent studies showed similar outcomes with breast conservation surgery and radiotherapy.¹³ The majority of our patients underwent mastectomy and required no further therapy. Several studies have shown the benefit of adding radiotherapy in preventing long term recurrence of DCIS.^{23,24,25} There has however been no difference in the overall survival, as DCIS generally carries a favorable prognosis.

Of the 6 patients who had a definitive breast conservation therapy, 4 underwent radiotherapy. Their Van Nuys scores ranged between 7–9. Our practice incorporates the Van Nuys score to predict the risk of local recurrence and need for additional surgery. Though the utility of Van Nuys has not been validated in prospective series,^{10,26,27,28} it is used in several centers to help predict a sub-group of patients in whom radiotherapy may be avoided.²⁸ This question remains particularly pertinent in low resource settings with limited radiation facilities. More studies are currently ongoing to define these subsets of patients.

No current consensus exists on adjuvant endocrine therapy in DCIS.²⁹ Staley, in his 2012 metanalysis using pooled data from both NSABP 17 and NSABP 24 trials, showed that there was no demonstrable benefit in overall survival with tamoxifen. While tamoxifen may have reduced the ipsilateral

and contralateral recurrence of DCIS, there was only a trend to reduction of invasive recurrences. The main critique of these studies is the lack of randomization and assignment of hormone receptor status.

Twelve of the 16 ER/PR positive patients were commenced on tamoxifen or an aromatase inhibitor. It was used as monotherapy in patients who were deemed poor surgical or radiotherapy candidates. These patients had several cardiac and pulmonary comorbid conditions. The HER-2 status was only documented in 6 of our patients. However, the use of trastuzumab remains experimental in this context and ongoing studies are being done to review the utility in this set-up.³⁰

Limitations

Due to the retrospective nature of the study and our paper record system, data was missing in a number of patients. While presentation and initial management was consistently documented, many patients were lost to follow up and therefore it was not possible to report the incidence of local recurrence rates or survival data in this study. Creation of cancer registries with clear follow-up and electronic records may help in the prospective follow-up of patients.

Conclusions

Isolated DCIS is rare in our clinical context and the clinical presentation differs markedly from countries which practise mammographic screening. Though our numbers are small, the series highlights the challenges of diagnosing and managing early breast malignancies in LMICs.

Practical strategies like increasing human capacity in cancer diagnostics, developing health worker training in core biopsy techniques and in the use of supportive adjuncts like stereotactic guided biopsies could help to mitigate these challenges. Interventions aimed at improving comprehensive diagnostic services, to ensure the early diagnosis of breast cancer and pre-malignant conditions in these settings are essential.

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