Profile of Digital Mammography Findings in Patients with Histopathologically Proven Ductal Carcinoma in Situ (DCIS): A Retrospective Study

Ankit Prabhakar*, Dawood Iqbal Wani, Shivani Sharma, Sajjad Ahmad Dar, Shaafiya Ashraf

Abstract
Breast carcinoma is a heterogeneous group of tumors with a wide spectrum of clinical presentations, lesion characterization and diagnostic evaluation. Ductal carcinoma in situ accounts for 15%-20% of breast carcinomas detected in screened populations. Ductal carcinoma in situ has a variable appearance on mammography. The use of mammography has become a very helpful tool for the early detection of larger number of patients with ductal carcinoma in situ and, thus, offering timely surgery and the need for the appropriate radiation treatment to patients. This study was undertaken as a hospital-based retrospective study to evaluate the varied spectrum of mammographic findings in 57 women with histopathological diagnosis of ductal carcinoma in situ. The spectrum of mammographic findings of ductal carcinoma in situ was found to vary widely. A thorough and vigilant inspection of a mammogram is necessary for all the patients to avoid the possibility of missing early diagnosis of this entity, since the findings are very subtle. Most cases show microcalcifications on mammograms and their early detection can help in early diagnosis, thereby offering conservative surgical approach to a patient. Microcalcifications can be present isolated or in association with a mass. These are mostly clustered in distribution followed by regional, segmental and ductal pattern of distribution. The morphology of microcalcifications is mostly amorphous, followed by pleomorphic and fine heterogenous types. Hence, the mammogram must be interpreted with strict vigilance and proper attention to all aspects for early and correct diagnosis of ductal carcinoma in situ to help in proper guidance of its treatment.

Keywords
ductal carcinoma in situ; mammogram; mass; microcalcification.

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Problem statement and analysis of the latest research
Breast carcinoma is a heterogeneous group of tumors with a wide spectrum of clinical presentations, lesion morphology, growth pattern, histological types and response to treatment [1]. It is one of the most common cancers in females worldwide, the leading cause of cancer death in women in less developed countries and the second cause of death in more developed countries. One of its variants is ductal carcinoma in situ (DCIS), which accounts for 15%-20% of breast carcinomas detected in screened populations [2]. It is a non-invasive entity exhibiting malignant proliferation of ductal epithelium. There is no invasion of the basement membrane with the tumor confined within the mammary ducts [3]. Mammography is one of the initial investigations for breast imaging. The use
of mammography has become a very helpful tool for the detection of larger number of patients with DCIS. This aids in early diagnosis and offers limited surgical approach to their disease. The size of a breast tumor determines the future course of surgery and the need for the appropriate radiation treatment. This study was undertaken to evaluate the varied spectrum of mammographic findings in women with histopathological diagnosis of DCIS.

The objective of the research was to evaluate the varied spectrum of mammographic findings in patients with histopathological diagnosis of DCIS.

1. Materials and Methods

1.1 Study Design
This study was a hospital-based retrospective study conducted in the Post Graduate Department of Radiodiagnosis and Imaging, Government Medical College, Srinagar, Jammu and Kashmir, India.

1.2 Study Sample
Study group consisted of patients with histopathological diagnosis of DCIS, who underwent mammography and were referred from various departments of Government Medical College, Srinagar during the study period. They were called as Cases. There were no Controls. Cases were included both from OPD and IPD. A final set of 57 cases was enrolled in our study.

1.3 Inclusion Criteria
Only women with pure DCIS without any other malignancy found on histologic frozen or paraffin sections were included in the final study population. All age groups were included.

1.4 Exclusion Criteria
Patients were excluded if they were pregnant or presented with other histological types of breast cancer.

1.5 Duration of Study
It was conducted over a period of approximately 20 months from December 2017 to August 2019.

1.6 Methodology
An adequate detailed history was elicited from all patients, followed by clinical examination and relevant laboratory investigations of every patient prior to imaging procedure. A brief account of the procedure was explained to the patients. Informed and written consent was taken from all patients prior to the procedure. Ethical clearance was elicited from the Institutional Ethical Committee of Government Medical College Srinagar.

1.7 Imaging Technique and Protocol
Imaging acquisition: For mammograms, standard craniocaudal view and mediolateral oblique were obtained with proper compression using the Selenia Dimensions Hologic machine. Additional views or spot compression were obtained when necessary. Technical scan parameters were as follows:

- Target/Filter: W/Rh or Ag
- Detector: amorphous selenium
- Pixel pitch: 70 \( \mu m \)
- Acquisition time: < 4s
- Dose radiation: 1.2 mGray
- Coronary artery disease (CAD): present

Image interpretation: Mammograms were retrieved from the local picture archiving and communication (PACS) system and analyzed. The images were interpreted by two dedicated radiologists. In addition, all images were reviewed and interpreted by a third radiologist, who was blinded.

The original mammogram, according to which the decision for biopsy was made, was usually not available for review. Mammograms available were of variable quality, often obtained at other hospitals, clinics, and offices from which the patient was referred for biopsy. The films were analyzed retrospectively for the presence of mass, calcification, or both as the indication for biopsy. The maximum diameter of the mammographic anomaly region was recorded. Different patterns of multicentricity included more than one cluster of microcalcifications, more than one mass, or parallel linear, irregular intraductal calcifications.

Tumor extent and additional findings were defined as follows:

Multifocality: an additional malignant lesion in
the same quadrant, separated from the index tumor by benign tissue.

- **Multicentricity:** an additional malignant lesion in a different quadrant than the index cancer.
- **Contralateral disease:** an additional malignant lesion found in contralateral breast.
- **Multiplicity:** two or more of these features: multifocality, multicentricity and contralateral disease.
- **Clustered calcification:** > 5 calcification in a cubic centimeter of tissue.
- **Ductal calcification:** fine linear branching within a duct.
- **Segmental calcification:** within a single duct network of a lobe.
- **Regional calcification:** occupying a quadrant or more.
- **Amorphous microcalcification:** round or flake-shaped deposits too small to characterize.
- **Pleomorphic microcalcification:** irregular, vary in size and shape.

### 1.8 Histological analysis
All slices of DCIS were reviewed by a dedicated pathologist to correctly determine integrity of basement membrane and invasion.

### 1.9 Statistical analysis
Data were analyzed using IBM SPSS statistics version 23.0 software (SPSS Inc., Chicago, IL, USA). Categorical variables were summarized in terms of frequencies and percentages.

### 2. Results
The present study evaluated patients with DCIS found by mammography over a period of 20 months. Adequate records were available for review in 57 patients. A total number of 60 lesions including three patients who had six lesions of synchronous bilateral DCIS were studied. The patients’ age ranged from 37 to 82 years (mean, 55.5 years) (Fig. 1).

There were 24 clinically asymptomatic women including 3 patients with a strong positive family history, who also were under observation. There was a history of prior or concurrent breast cancer in eighteen patients. Among them, seven patients had previously undergone mastectomy, six patients had contralateral synchronous invasive ductal carcinoma, and five patients had a previous history of ipsilateral cancer treated with lumpectomy and postoperative radiotherapy. A palpable mass was seen in four patients. Three patients had enlarged nipples, nipple retraction and nipple discharge as signs of presentation. Presentation cause was unknown in 2 patients (Table 1).

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Clinical Feature</th>
<th>Frequency (n)</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Asymptomatic</td>
<td>24</td>
</tr>
<tr>
<td>2.</td>
<td>History of prior/concurrent breast cancer</td>
<td>18</td>
</tr>
<tr>
<td>3.</td>
<td>Palpable mass</td>
<td>4</td>
</tr>
<tr>
<td>4.</td>
<td>Enlarged nipple</td>
<td>3</td>
</tr>
<tr>
<td>5.</td>
<td>Nipple retraction</td>
<td>3</td>
</tr>
<tr>
<td>6.</td>
<td>Nipple discharge</td>
<td>3</td>
</tr>
<tr>
<td>7.</td>
<td>Unknown presentation</td>
<td>2</td>
</tr>
</tbody>
</table>

In our study, 31 tumors were present on the right side of the breast and 29 tumors were present on the left side of the breast (Fig. 2).

In quadrant wise distribution, fifty-five percent of tumors (33 out of 60 lesions) were located in the upper outer quadrant of the breast; 13.3% (8 out of 60) of tumors were seen in the lower outer quadrant of the breast; 8.3% (5 out of 60) of tumors were found in the upper inner quadrant of the breast; 10%
Profile of Digital Mammography Findings in Patients with Histopathologically Proven Ductal Carcinoma in Situ (DCIS): A Retrospective Study — 4/11

(6 of 60) of tumors were detected in the lower inner quadrant of the breast. In about 13.4% (8 of 60 lesions) of cases, there was an extension beyond a single quadrant of the breast (Fig. 3).

Out of 57 women, screening mammograms revealed suspicious finding in 42 cases (Table 2). A large portion of the patients included in this study had more than one breast malignancy. A second ipsilateral or contralateral breast carcinoma developed in twenty-one out of 57 women (36.8%). Among these 21 cases, three women presented with synchronous bilateral DCIS, six women developed synchronous contralateral invasive ductal carcinoma and seven women had a history of mastectomy performed for invasive ductal carcinoma. Five women developed recurrent DCIS in the breast previously treated with lumpectomy and radiation for primary breast cancer: there were three cases of DCIS, one case of infiltrating ductal cancer, and one case of unknown etiology.

Table 2. Suspicious findings on mammograms of patients with DCIS.

<table>
<thead>
<tr>
<th>Suspiscious findings on screening mammo grams</th>
<th>Present (n)</th>
<th>Absent (n)</th>
</tr>
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</table>
| Most lesions were diagnosed on mammography due to the presence of microcalcifications. Microcalcifications without an identifiable mass were found in 68.3% (41 out of 60) of lesions (Fig. 4) and the mass was associated with microcalcifications in 30% (18 out of 60) of cases (Fig. 5, 6).

The masses associated with microcalcifications ranged in diameter from less than 1 cm in 7 cases, more than 3 cm in 4 cases and 1-3 cm in 7 cases (Table 3, Fig. 7).

Table 3. Pattern of microcalcifications on mammography in patients with DCIS.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Microcalcification pattern</th>
<th>Frequency(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Microcalcifications with mass- Mass &lt; 1 cm</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Mass 1-3 cm</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Mass &gt; 3cm</td>
<td>7</td>
</tr>
<tr>
<td>2.</td>
<td>Microcalcifications without mass</td>
<td>41</td>
</tr>
<tr>
<td>3.</td>
<td>Mass without microcalcification</td>
<td>1</td>
</tr>
</tbody>
</table>

A remaining lesion was a 6-mm mass without microcalcifications. Hence, microcalcification is an important clue towards further elaborative evaluation of patients with DCIS.

Microcalcifications were clustered in distribution in 23 cases, ductal in 8 cases, regional in 18 cases and segmental in 10 cases (Fig. 8).
Figure 4. A 43-year-old patient with nipple discharge exhibited an ill-defined area with internal calcifications on (I) 2D-USG and clustered amorphous type microcalcifications without mass on (II) mammogram. HPE showed features of DCIS.

Figure 5. Mammograms of (I) a 34-year-old, (II) a 58-year-old and (III) a 42-year-old female with DCIS exhibiting clustered amorphous and pleomorphic microcalcifications within an ill-defined mass.

It was pleomorphic in morphology in 19 cases, amorphous in 28 cases and fine heterogeneous in 12 cases (Fig. 9).

Multicentricity was present on 37 histopathological specimens. Since this study was performed retrospectively, exact correlation between tumor sites identified pathologically and their exact location on mammograms was not possible. Post diagnosis, forty lesions underwent mastectomy. The axillary nodes were dissected in 38 cases, and all the nodes were disease free in our study. Ten cases were treated conservatively including lumpectomy and radiation therapy in seven cases and only lumpectomy in three cases. For the remaining ten lesions, the method of treatment is unknown (Fig. 10).
Figure 6. (I) Mammogram, (II) zoomed view and (III) 2D-USG view of regional pattern of distributing microcalcification with pleomorphic morphology in a 72-year-old patient with DCIS.

Figure 7. Bar diagram representing patterns of microcalcifications in DCIS.

Figure 8. Bar diagram representing distribution of microcalcifications in DCIS.

Figure 9. Bar diagram representing morphology of microcalcifications in DCIS.

3. Discussion

The wide spectrum of mammographic findings in DCIS is interesting in itself. It exhibits a significant variation in the frequency amongst patients with breast cancer. In a study conducted by Tabar et al. [4], in situ breast cancer had a prevalence of 8% (lobular and ductal types) in 384 patients with breast carcinoma. Andersson [5] reported a 15% prevalence of DCIS. This was within the 15%-20% range generally accepted for a screened population [2]. Its incidence ranged from 4% to 32% [6, 7]. Our study population had a prevalence of 28% which was likely due to the inclusion of symptomatic women in our study. About 59% of in situ breast carcinoma...
were detected by mammography in the Breast Cancer Detection Demonstration Project [8].

While identifying this disease using mammography, it is important to keep in mind that more than one site of disease may be present in the breast with DCIS, that affects the treatment. In a study conducted by Brown et al. [9], multicentricity was found in 33% of 40 patients studied. Tumor multicentricity was found to increase with tumor size in a study carried out by Lagios et al. [10]. They observed multicentricity be present in 47% (8 out of 17) of cases amongst tumors 2.5 cm in diameter or greater, whereas only 17% (4 of 24) of tumors less than 2.5 cm were multicentric. Holland et al. [11] found that occult tumor was present 2 cm beyond the clinical and radiographic margins of invasive cancer in 43% of mastectomy specimens, and it was in situ carcinoma in 63%.

In a study conducted by Rosen et al. [12], it was found that residual DCIS in a quadrant other than that containing clinically apparent, invasive cancer constituted 33% of 121 mastectomy specimens. Our data showed that the presence of multifocal disease may be apparent mammographically. Tumors with a diameter of 2.5 cm or greater were all multicentric. The specimen radiograph may be the key to radiographic identification of more than one tumor focus, especially in these smaller lesions. Thus, a very careful examination of the mammogram and specimen radiograph in patients with DCIS helps in choosing the correct treatment option. Tumor size correlates with occult invasion and multicentricity, thereby affecting the role of breast-conservation therapy in these patients [13].

Women with DCIS, who are to be considered for breast-conservation therapy, should consider mammography before biopsy to assess the extent of microcalcifications, to confirm excision of calcifications and to direct pathologic study to the appropriate area of the specimen according to the studies conducted by Schmitt et al. [2]. From 40% to 50% of breast biopsies for nonpalpable cancers were found to be performed based on calcifications alone [14].

Mammography with magnification performed after biopsy enables the completeness of the excision of microcalcifications to be confirmed. In a study carried out by Lagios et al. [13], the authors concluded that excision alone could be adequate therapy if careful clinical and mammographic follow-up was possible in lesions of 2.5 cm or smaller with pathologically negative margins. These
foci of undetected tumor are significant in women with DCIS who are to be treated conservatively, and, if untreated, leave the women at risk for invasive malignancy. Twenty-eight percent (7 out of 25) of women with DCIS who underwent only biopsy and no other treatment, developed invasive carcinoma in the breast near the biopsy site in 3-10 years according to a study conducted by Page et al. [15]. Rosen et al. [16] found that invasive cancer developed in the ipsilateral breast in 53% (8 out of 15) of patients with DCIS being followed up after biopsy. As suggested in several studies of women with pure DCIS, who were treated with conservative surgery and radiation therapy, these residual foci appeared to be radiosensitive. It was unusual to find recurrent disease in the treated breast during the follow-up periods. In a study conducted by Zafrani et al. [17], three out of 54 patients developed recurrent cancer (two cases of in situ disease) in the treated breast with a median follow-up of 55 months. Fowbles et al. [18] (University of Pennsylvania) reported on 46 women with a 5-year recurrence rate of 8%. About 78 cases of DCIS which were initially considered as invasive carcinoma, were discovered in the National Surgical Adjuvant Breast Project B-06 protocol [6]. Patients, who were treated only with excision, had a recurrence rate of 22.7%, and those, treated with excision and irradiation, had a 6.9% rate of recurrence, within a 39-month mean follow-up. However, radiation therapy may not be necessary in cases of small tumors. The recurrence rate was only 6% in a series of 71 patients with DCIS (mean tumor size of 6.7 mm) treated with excision alone [19]. Five percent recurrence rate was noted in a group of 32 women with DCIS with a mean tumor size of 22 mm who underwent similar treatment [3].

These figures, thus, emphasize the importance of accurate mammographic assessment of the extent of this tumor. It is very important to be highly suspicious of subtle masses or calcifications in judicious evaluation of the mammograms of women with DCIS who have previously been treated with lumpectomy with or without irradiation. Our study included 5 women with disease recurrence after conservative treatment with radiation. The presence of significant unrecognized residual DCIS in some patients managed conservatively may leave them at high risk for treatment failure. Multicentricity also manifests itself in synchronous and metachronous contralateral breast disease. The contralateral breast should be meticulously searched for disease as bilateral tumor is present in a significant percentage of patients [12]. In our study, bilateral pure DCIS was present in three women, invasive contralateral tumor was the presenting symptom in six women, and prior mastectomy had been performed in seven cases. Thus, 36.8% (21 out of 57 cases) of women had bilateral synchronous or metachronous disease. Westbrook and Gabbager [20] in their study on DCIS at M.D. Anderson Hospital (20-year study) showed that 12.5% of 64 women developed contralateral tumor. Rosen et al. [12] found that 39% of 121 women undergoing mastectomy for invasive cancer had contralateral noninvasive cancer, which was of intraductal variant in 24% of cases at Memorial Sloan-Kettering Cancer Center. The probability of unsuspected DCIS in the contralateral breast is high in women with previously diagnosed invasive cancer or DCIS. Thus, these patients should be carefully investigated.

In a study conducted by Wang H et al. [21], calcifications were found more commonly in DCIS than in DCIS with microinvasion (DCISM) (74% vs. 63.9%); however, the difference was not significant. The distribution of calcifications was mainly regional and segmental in DCISM cases and mainly grouped and regional in DCIS cases, resulting in a statistically significant difference between the two groups (p < 0.05). Whereas in our study, microcalcifications were clustered in distribution in 23 cases, ductal in 8 cases regional in 18 cases and segmental in 10 cases. It was pleomorphic in morphology in 19 cases, amorphous in 28 cases and fine heterogenous in 12 cases. According to Theberge I et al. [22], patients having previous breast aspiration or biopsy and increasing breast density were more strongly associated with DCIS than with invasive breast carcinoma detection rates (p-value of 0.0050 and < 0.0001, respectively) on screening mammography, hence these parameters should also be taken into consideration. van Lujit PA et al. [23]
found out that older women were more likely to have low-grade DCIS than younger women. This is comparable to our study where the mean age of diagnosis was at older age group (55.5 years). Yamada et al [24] described that a mass-like appearance of DCIS could be related to two different conditions, namely a direct manifestation of an existing soft-tissue mass, or a result of periductal fibrosis or elastosis producing an irregular or spiculated margin around a non-mass-like lesion. In our study, the mass was seen in 19 patients on mammography with one of them showing absence of microcalcification. According to Stefanie Weigel et al. [25], high overall cancer detection rates in digital mammography screening were related to high detection rates of invasive cancers, as well as DCIS. Hence, a proper screening and interpretation of mammogram is necessary for early and appropriate detection of lesions.

4. Conclusions

The spectrum of mammographic findings of DCIS is variable. Hence, a thorough and vigilant inspection of the mammogram is necessary in all patients to avoid the possibility of missing early diagnosis of this entity, since the findings are very subtle. Predominant site of involvement in patients with DCIS is the upper outer quadrant of the breast. Most cases show microcalcifications on mammograms and their early detection can help in early diagnosis, thereby offering conservative surgical approach to a patient. Microcalcifications can be present isolated or in association with a mass. These are mostly clustered in distribution followed by regional, segmental and ductal pattern of distribution. The morphology of microcalcifications is mostly amorphous, followed by pleiomorphic and fine heterogeneous types. Hence, the mammogram must be interpreted with strict vigilance and proper attention to all aspects for early and correct diagnosis of DCIS to help in proper guidance of its treatment.
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