Original Investigation

Imaging Features of Patients Undergoing Active Surveillance for Ductal Carcinoma in Situ

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Abbreviations and Acronyms

DCIS
ductal carcinoma in situ

ER
estrogen receptor

IDC
invasive ductal carcinoma

PR
progesterone receptor

Rationale and Objectives: The aim of this study was to describe the imaging appearance of patients undergoing active surveillance for ductal carcinoma in situ (DCIS).

Materials and Methods: We retrospectively identified 29 patients undergoing active surveillance for DCIS from 2009 to 2014. Twenty-two patients (group 1) refused surgery or were not surgical candidates. Seven patients (group 2) enrolled in a trial of letrozole and deferred surgical excision for 6–12 months. Pathology and imaging results at the initial biopsy and follow-up were recorded.

Results: In group 1, the median follow-up was 2.7 years (range: 0.6–13.9 years). Fifteen patients (68%) remained stable. Seven patients (32%) underwent additional biopsies with invasive ductal carcinoma diagnosed in two patients after 3.9 and 3.6 years who developed increasing calcifications and new masses. In group 2, one patient (14%) was upstaged to microinvasive ductal carcinoma at surgery. Among the patients in both groups with calcifications ($n = 26$), there was no progression to invasive disease among those with stable (50%, 13/26) or decreased (19%, 5/26) calcifications.

Conclusions: Among a DCIS active surveillance cohort, invasive disease progression presented as increasing calcifications and a new mass following more than 3.5 years of stable imaging. In contrast, there was no progression to invasive disease among cases of DCIS with stable or decreasing calcifications. Close imaging is a key follow-up component in active surveillance.

Key Words: Carcinoma, intraductal, noninfiltrating; carcinoma, ductal, breast; mammography; breast carcinoma in situ; breast neoplasms.

INTRODUCTION

Since the widespread adoption of screening mammography, the detection of ductal carcinoma in situ (DCIS) has steadily increased, now representing 20%–30% of all new breast cancer diagnoses (1–5). Although DCIS is very common, the natural history of the disease is not well known because complete surgical excision is currently the standard of care (6). However, there is strong circumstantial evidence that 50%–85% of DCIS cases will never progress to invasive disease (7–11), and if DCIS does progress, it is unlikely to shift to a higher nuclear grade (7,12,13). This finding has prompted growing concerns regarding DCIS overdiagnosis and overtreatment with a desire for alternative management strategies (1,2,7,8,14).

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Active surveillance is a management strategy for low-risk DCIS, which avoids surgical excision, may utilize hormonal therapy to suppress growth, and emphasizes imaging follow-up to detect whether progression to invasive disease occurs (15–17). Active surveillance is based on the premise that not all DCIS cases are life threatening and that many patients may die with the disease than from the disease, especially those with competing mortality risks (15,18–20). The safety and effectiveness of active surveillance have been identified as a key research need by the Patient-Centered Outcomes Research Institute (21) and the National Institutes of Health Panel on the Diagnosis and Management of Ductal Carcinoma In Situ (22). There is only one published manuscript of active surveillance outcomes, which demonstrated feasibility among a well-informed patient population but an increased risk of invasive cancer at surgical excision (15). There are three active surveillance trials in progress. The LOw Risk DCIS (LORD) trial in Europe compares annual mammography to usual care among women with low-grade DCIS with the primary outcome of ipsilateral invasive cancer (17). In England, the LOw RISk DCIS (LORIS) trial is comparing annual mammography to usual care among non–high grade DCIS with the primary outcome of ipsilateral invasive cancer-free survival

(16,23). In the United States, the Comparison of Operative to Monitoring and Endocrine Therapy (COMET) trial is comparing endocrine therapy with biannual mammography vs usual care with ipsilateral invasive cancer diagnosis as the primary outcome (24).

Active surveillance programs for DCIS will rely upon imaging findings to identify eligible patients and to monitor if invasive disease develops. However, there are very limited data describing the imaging features during the initial assessment and changes during monitoring that prompted biopsy or were associated with progression to invasive disease. Therefore, the purpose of the present study was to describe the initial and longitudinal imaging appearance of patients undergoing active surveillance for DCIS.

MATERIALS AND METHODS

Case Selection

Institutional review board approval with a waiver of informed consent was obtained for this Health Insurance Portability and Accountability Act-compliant study. We searched our breast imaging and pathology reports from January 1, 2009, to April 30, 2014, to retrospectively identify all patients diagnosed with DCIS ($n = 418$) undergoing active surveillance ($n = 29$), defined as deferring definitive surgery in favor of imaging and clinical follow-up. New active surveillance patients who underwent at least one follow-up examination were eligible for inclusion. Patients who initiated active surveillance before the study period but continued during the study period were eligible for inclusion. Two groups were identified among the 29 patients. In group 1, 22 patients were either not optimal surgical candidates because of medical comorbidities or refused surgery because of personal preference. Patients were self-selected, informed of standard treatment options for DCIS, and counseled regarding the risks and uncertainties of nonstandard of care therapy. Patients were offered surgical excision at each follow-up appointment. The remaining seven patients (group 2) were enrolled in a single-arm trial, unrelated to the present study, which deferred definitive surgery for 6–12 months during treatment with letrozole for patients with newly diagnosed estrogen receptor (ER)-positive DCIS (25).

Medical Record Review

Pathology results from the initial core needle biopsy were reviewed for tumor grade, ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 status. The decision to perform any subsequent biopsies and surgical excisions of the same site as well as the pathology results were recorded. For group 1, progression to invasive ductal carcinoma (IDC) was the primary end point, signaling the end of active surveillance. For group 2, all patients underwent definitive surgery per protocol and upstage to IDC was the primary end point. For both groups, any hormonal therapy (eg, tamoxifen and letrozole) was recorded. The follow-up duration was calculated from the initial diagnosis of DCIS to either the last breast imaging study, the breast cancer clinic visit, or the date of definitive surgery during the study period.

Imaging Review

All cases were reviewed collectively by three fellowship-trained breast imagers with 1, 16, and 23 years of breast imaging experience who were aware that the cases represented DCIS but were unaware of any follow-up results. Diagnostic imaging studies starting from the time of the initial DCIS diagnosis to the last follow-up were reviewed and consensus BI-RADS descriptors were recorded (26). The imaging follow-up in group 1 was nonstandardized, but all patients underwent at least a yearly two-dimensional mammography with a directed ultrasound (50%, 11/22) or a magnetic resonance imaging (MRI) (55%, 12/22) performed at the discretion of the surgical oncologist or radiologist. In group 2, all patients were scheduled for mammography and MRI according to the study protocol.

RESULTS

Patient and DCIS characteristics are shown in Table 1. In group 1, 86% (19/22) of the patients presented with mammographic calcifications with a mean long-axis length of 3.4 cm (range: 0.3–8.0 cm). The calcification morphologies were amorphous (21%, 4/19), pleomorphic (74%, 14/19), or linear (5%, 1/19), and their distribution was regional (16%, 3/19), grouped (32%, 7/19), linear (16%, 3/19), or segmental (32%, 6/19). The two cases of DCIS identified on high-risk screening MRI presented with clumped morphologies and multiple or regional distributions. All patients with available pathology data were ER positive (91%, 20/22; receptor status was unavailable in two cases). The majority of the patients were placed on hormonal therapy with either letrozole ($n = 9$, 41%) or tamoxifen ($n = 7$, 32%). In group 2, all patients presented with calcifications and the mean long-axis length was 4.7 cm (range: 2.6–10.4 cm). The calcifications were pleomorphic (71%, 5/7) or linear (29%, 2/7) in morphology and linear (43%, 3/7), segmental (29%, 2/7), or grouped (29%, 2/7) in distribution.

A flowchart of the active surveillance cohort outcomes is shown in Figure 1. For group 1 patients there was a median follow-up of 2.7 years (range: 0.6–13.9 years). The majority of patients (68%, 15/22) developed no new suspicious findings on follow-up imaging (median: 2.1 years, range: 0.6–5.9 years) and did not undergo any additional biopsies. The remaining seven patients developed a change or changes on imaging that prompted 11 additional biopsies (Table 2), most commonly because of an increase in calcifications (45%, 5/11) or the development of a new mass (64%, 7/11). This occurred after a median of 3.3 years (range: 0.7–6.8 years) of active surveillance. Although most biopsies (82%, 9/11) demonstrated no evidence of disease progression (ie, histology from subsequent biopsies yielded only DCIS, atypia, or false-positive benign findings), there were two cases of IDC. Both cases initially presented