Not All Ductal Carcinomas in Situ Are Created IDLE (Indolent Lesions of Epithelial Origin)

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Context.—Mammographic screening has increased the incidence of ductal carcinoma in situ (DCIS), but this has not been accompanied by a decline in the incidence of invasive carcinoma (IC). Consequently, the surgical treatment of DCIS has recently been questioned, with some advocating only surveillance (with or without neoadjuvant endocrine therapy) after a core biopsy diagnosis of DCIS.

Objectives.—To examine the predictive value of a core biopsy diagnosis of DCIS, particularly the upgrade rate to IC, and to identify associated factors.

Design.—Using the pathology database, we identified 2943 cases of DCIS diagnosed on core biopsy from 2000 to 2015, of which 229 cases (8%) later had the stage upgraded to IC.

Results.—Ages ranged from 25 to 90 years (mean, 59 years). The DCIS presented with calcifications in 151 of 229 cases (65.9%), was widespread in 26 of 151 cases (17%), had a mass or density present in 70 of 229 cases (31%), with heterogeneous echogenic features in 44 of those 70 cases (63%), and an enhancement upon magnetic resonance imaging in 8 of 229 cases (3.5%). Of the 229 cases, the DCIS grades were as follows: low in 29 cases (13%), intermediate in 79 cases (36%), and high in 121 cases (53%). Of the 229 cases, necrosis was present in 152 (66.4%) and was comedo necrosis in 99 cases (43%). Of the 229 cases of IC, the tumor stage was as follows: microIC in 36 (16%), T1a in 119 (52%), T1b in 35 (15%), T1c in 28 (12%), T2 in 8 (3%), and T3 in 3 cases (1%). Axillary lymph nodes were staged in 167 patients as follows: N0, 141 cases (84%); N0(i+), 14 cases (8%); and N1, 12 cases (7%). The 12 N1 cases were subclassified by T stage as follows: T1a, 1 case (8%); T1b, 4 cases (33%); T1c, 2 cases (17%); T2, 4 cases (33%); and T3, 1 case (8%). The IC cases of stage upgrading were predominantly smaller than 2 cm (218 of 229; 95%), and more than two-thirds were smaller than 0.5 cm (155 of 229; 95%), most of which were accompanied by extensive DCIS.

Conclusions.—Approximately one-half of the upgrades were associated with high-grade DCIS, especially with comedo necrosis; nevertheless, the other one-half of the upgrades were due to low- and intermediate-grade DCIS and should not be underestimated. There were few positive results from axillary lymph node biopsies, but they occurred in 3% (7 of 218) of the carcinomas smaller than 2 cm. Our findings indicate that caution is needed when DCIS cases diagnosed by core biopsy are treated nonsurgically with surveillance (with or without neoadjuvant endocrine therapy), given the number of cases (229 of 2943; 8%) that are upgraded to IC and those with axillary lymph node metastases (12 of 167; 7%).


The advent of mammographic screening led to a dramatic increase in the incidence of ductal carcinoma in situ (DCIS), but that has not been paralleled by a decrease in invasive carcinoma.1 These conflicting phenomena have been attributed to overdiagnosis and overtreatment, defined as the identification and treatment of lesions that may never affect the patient adversely.2 The natural history of untreated DCIS is to progress to invasive carcinoma over decades, as shown by some historic studies3–7 and as further supported by modern molecular studies.8,9 Mortality from DCIS after treatment is low, and contemporary therapies have shown improved outcomes.10,11 Current DCIS treatment includes surgical excision (lumpectomy or mastectomy) with or without radiation and endocrine therapy.12

The heterogeneous disease of DCIS is graded using a 3-tiered system of low, intermediate, and high grades. Although some carcinomas may progress rapidly and affect the patient, the low-grade and, perhaps, some intermediate-grade DCIS cases are thought to comprise the carcinomas that may either never progress or do so at a much slower pace.13 Thus a “one size fits all” treatment may not be the right approach for DCIS. Consequently, it has been proposed that certain low-grade DCIS cases could be retermed indolent lesions of epithelial origin and be treated less aggressively.14
To address that issue, multiple clinical trials from several different countries have been implemented to attempt to treat predominantly low- to intermediate-grade DCIS.15–17 The Low Risk DCIS (LORD; NCT02492607) trial is a phase III, noninferiority trial randomizing 1240 women older than 46 years with a core biopsy diagnosis (performed for screen-detected calcifications) of low-grade DCIS to either active surveillance or standard surgery and adjuvant treatment.15–17 The Low Risk DCIS (LORIS; ISRCTN27544579) trial is a phase III, noninferiority trial randomizing 932 women older than 46 years to active surveillance or surgery, with the broader inclusion of a core biopsy (performed for screen-detected calcifications) of low-grade DCIS without randomizing women older than 40 years with a core biopsy.

The introduction of breast core biopsies more than a decade ago brought with it the risk of sampling error. Such errors are especially relevant today in the setting of these surveillance clinical trials. Particularly, the upgrade rate to invasive carcinoma, and to identify any associated factors that meet criteria for inclusion in surveillance clinical trials.

### MATERIALS AND METHODS

Using the computerized hospital diagnostic pathology database, we searched for all cases with a core biopsy diagnosis of DCIS from 2000 to 2015 using keywords breast, core, and DCIS. The search found 2943 cases of DCIS diagnosed on core biopsy; 229 of those cases (8%) had invasive carcinoma upon excision. Clinical and radiographic features of the 229 cases were gathered. The hematoxylin-eosin-stained slides of the core biopsies were reviewed to confirm the diagnosis of pure DCIS. Excision hematoxylin-eosin slides were also reviewed to verify the diagnosis of invasive carcinoma, biopsy site changes, and any other pathologic findings. The DCIS was graded as low, intermediate, or high nuclear grade using a 3-tiered system.28 Invasive carcinomas were graded as well, as intermediate or poorly differentiated, using the Nottingham grading system.29 Extensive DCIS was defined as comprising at least 25% of the area involved by invasive carcinoma as well as in the surrounding breast or as DCIS associated with a small (less than a centimeter) invasive carcinoma.30 Clinical and pathologic features examined included age; presenting features of DCIS (calcifications, mass, enhancement); imaging modality; extent of calcifications; biopsy needle gauge; surgical procedure; biomarkers estrogen receptor (ER), progesterone receptor (PR), and HER2/neu (HER2); and axillary lymph node involvement.

### RESULTS

The patients’ ages ranged from 25 to 90 years (mean, 59 years). By imaging, the DCIS either presented as calcifications (151 of 229; 65.9%), a mass or density (70 of 229; 31%), or an enhancement (8 of 229, 3.5%). The calcifications were found to be widespread in 26 of 151 cases (17%). All calcifications and magnetic resonance imaging biopsies were sampled with 9- to 14-gauge needles. Ultrasound-guided biopsies were performed using 14- to 18-gauge needles. Most of the sonographic masses (44 of 70; 63%) were read as having heterogeneous echogenic features.

The DCIS on core biopsy was classified as low grade in 29 of 229 cases (13%), as intermediate grade in 79 of 229 cases (34%), and as high grade in 121 of 229 cases (53%) (Table 1). Necrosis was seen in 152 of 229 cases (66.4%), with comedo-type necrosis in 99 of 229 cases (43%). The DCIS was stratified by imaging modality as shown in Table 1.

When evaluated by surgical procedure, the DCIS was stratified as follows: low grade in 23 of 29 cases (79%), with lumpectomy versus mastectomy in 6 of 29 cases (21%); intermediate grade in 51 of 79 cases (65%), with lumpectomy versus mastectomy in 28 of 79 cases (35%); and high grade in 60 of 121 cases (49.5%), with lumpectomy versus mastectomy in 61 of 121 cases (50%). Examining the invasive carcinomas on excision specimens revealed extensive DCIS in 120 of 229 cases (52%), which, when classified by stage, occurred in 115 of 155 (74%) of the microinvasive and T1a carcinoma cases versus 41 of 74 (55%) of the PT1b to pT3 carcinomas. After excluding cases of microinvasion (36 of 229; 15.7%), the grades of the invasive carcinomas on the 193 excision specimens were as follows: well differentiated in 25 cases (13%), moderately differentiated in 100 cases (52%), and poorly differentiated in 68 cases (35%) (Table 3). Stratifying the 229 invasive carcinomas by tumor stage, the results were as follows: microinvasive in 36 cases (16%), T1a in 119 cases (52%), T1b in 35 cases (15%), T1c in 28 cases (12%), T2 in 8 cases (3%), and T3 in 3 cases (1%) (Table 2). When tumor size and grade were evaluated by imaging modality, similar proportions were seen for each

**Table 1. Ductal Carcinoma In Situ (DCIS) Grade on Biopsy by Sampling Modality and Procedure**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Low, No. (%)</th>
<th>Intermediate, No. (%)</th>
<th>High, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
<td>95 (41)</td>
<td>6 (21)</td>
<td>61 (50)</td>
<td>.05</td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>134 (59)</td>
<td>23 (79)</td>
<td>51 (65)</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>8 (3.5)</td>
<td>2 (7)</td>
<td>2 (3)</td>
<td>.05</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>70 (31)</td>
<td>17 (59)</td>
<td>22 (18)</td>
<td></td>
</tr>
<tr>
<td>Mammography</td>
<td>151 (66)</td>
<td>10 (34)</td>
<td>46 (58)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: MRI, magnetic resonance imaging.
stage and grade for both ultrasound- and mammographic-guided biopsies (Table 2).

Correlation of the grade of DCIS on core biopsy to the grade of the invasive carcinoma on excision was performed as shown in Table 3. Biomarker results of the 229 invasive carcinomas were as follows: ER was positive in 186 cases (81%); 41 cases (18%) were HER2+, and 17 cases (7%) were triple negative (ER-/PR-/HER2-). Twenty-two cases were both ER+ and HER2+. The ER and HER2 status, divided by the grade of DCIS on core biopsy, is shown in Table 3.

The 167 patients who underwent axillary lymph node dissection had the following findings: N0 in 141 cases (84%), N0(i+) in 14 cases (8%), and N1 in 12 cases (7%). When stratified by T stage, the 12 N1 cases were as follows: T1a, 1 case (8%); T1b, 4 cases (33%); T1c, 2 cases (17%); T2, 4 cases (33%); and T3, 1 case (8%). When stratified by grade, the 12 invasive carcinomas were as follows: moderately differentiated, 4 cases (33%); and poorly differentiated, 8 cases (67%). By DCIS grade on core biopsy, the 12 N1 cases included 9 high grade (75%), 2 intermediate (17%), and 1 low grade (8%) case (Table 4).

The next part of our analysis entailed applying inclusion and exclusion criteria from the various clinical trials to assess the feasibility of those trials (Table 5). We began by identifying any potential candidates for the LORD trial, which required a core biopsy diagnosis of low-grade DCIS performed for incidental or screened calcifications.16 Of the 29 low-grade DCIS cases, only 4 (14%) of the cases qualified. In that subset, the size of the upgraded invasive carcinomas ranged from microinvasive to 0.5 cm (mean, 0.4 cm). Two of the 4 cases (50%) were well differentiated, and the other 2 (50%) were moderately differentiated. No lymph node metastases were identified. Application of the LORIS criteria (low- or intermediate-grade DCIS on core biopsy, performed for calcifications of any size)15 identified 37 of 229 cases (16%) of DCIS (low grade, 5 [14%]; intermediate grade, 32 [86%]) with invasive carcinoma size on excision ranging from microinvasive to 1.9 cm (mean, 0.6 cm), and grades for the 33 pT1a tumors and larger were as follows: well differentiated, 10 cases [30.3%], moderately differentiated, 21 cases [63.6%], and poorly differentiated, 2 cases [6.1%]). Although all axillary lymph node results were negative in this subset, isolated tumor cells were identified in 5 of the 37 cases (14%). We also applied the COMET criteria (low- or intermediate-grade ER+/PR+/HER2- DCIS without necrosis),17 and 15 cases qualified (low-grade, 6 cases [40%]; intermediate-grade, 9 cases [60%]), with invasive carcinoma size on excision ranging from microinvasive to 1.5 cm. The grades of those 15 invasive carcinomas were well differentiated, 6 cases (40%); moderately differentiated, 7 cases (47%); poorly differentiated, 2 cases (13%). Again, axillary lymph node metastases were absent, but isolated tumor cells were identified in 2 of the 15 patients (13%).
DISCUSSION

Recently, the management of non–high-grade DCIS has been questioned, prompting a number of trials to consider nonsurgical treatment of some subsets of patients with DCIS. These studies are based on observations that many cases of low- and even intermediate-grade DCIS are being radiographically detected at a point that may never affect the patient’s clinical prognosis. However, an important assumption of those trials is that the core biopsy diagnosis is an accurate reflection of the severity of a patient’s disease. Despite improvements in core biopsy sampling, with sophisticated imaging modalities and larger-gauge, vacuum-assisted needles, there is, nevertheless, a not-insignificant rate of upgrading from DCIS to invasive carcinoma from core biopsies to excisions reported in the literature. Our study consisted of 2934 cases of DCIS diagnosed on core biopsies during 15 years and identified 229 cases in which the stage was upgraded to invasive carcinoma upon excision. That is an upgrade rate of 8%, which is within the range reported in the literature (0%–59%).

Risk factors for a stage upgrade in DCIS diagnosed on core biopsy to invasive carcinoma upon excision reported in the literature include high-grade DCIS and the presence of necrosis. Indeed, we found approximately one-half of the upgrades in our series were associated with high-grade DCIS, especially when associated with comedo necrosis. However, the other one-half was due to a combination of low- and intermediate-grade DCIS. Consistent with that finding, a previous study of 895 patients with DCIS on core biopsy and subsequent excision reported 35% of the upgrades were from low- and/or intermediate-grade DCIS. Therefore, low- to intermediate-grade DCIS does not ensure a lack of upgrade to invasion upon excision.

Based on imaging, most upgrades in our series, approximately two-thirds of the cases, were performed because of the presence of calcifications, and the rest were due to a mass; enhancement comprised a rare reason for upgrade. Interestingly, most low-grade DCIS cases in our series were identified by ultrasound for a mass lesion because of mass-forming DCIS, invasive carcinoma, or DCIS involving a mass lesion, such as an intraductal papilloma or radial scar. These lesions were also more likely treated by lumpectomy. In contrast, most of the high-grade DCIS cases were identified by stereotactic biopsy for calcifications and were treated approximately equally by lumpectomy and mastectomy.

One-third of the 229 upgraded cases had a mass detected radiographically, some of which were also clinically apparent. This is not surprising, given that evidence of a mass radiographically or clinically has been a consistently reported, positive predictor of upgrade from DCIS on core biopsy to invasive carcinoma upon excision. Multifocality and personal history of carcinoma were also exclusion criteria for one or more of the trials and excluded 14 and 3 patients, respectively, from our series.

An 11-gauge, vacuum-assisted device has been reported as being superior to smaller, 14-gauge needles in terms of...
upgrading rates.19,31 A greater proportion of our upgraded cases were biopsied for calcifications and were performed using 9- to 11-gauge needles. However, when compared with the total number of cases of DCIS on biopsies upgraded at excision versus those not upgraded at excision performed by mammography and ultrasound, there were in fact a smaller percentage of upgraded cases in the mammography group, consistent with the finding that a larger needle has superior sampling capability and lesser chance of sampling error. When tumor size and grade of invasive carcinoma were evaluated by imaging modality, similar proportions were seen at each stage and grade for ultrasound and mammography (Table 2).

The upgraded invasive carcinomas were predominantly (218 of 229; 95%) smaller than 2 cm, and more than two-thirds (155 of 229; 67%) were smaller than 0.5 cm. Excluding the microinvasive carcinomas, the mean size of an invasive carcinoma was 0.76 cm. Importantly, only rare cases of T2 and T3 tumors occurred, and only 3% (7 of 218) of cases smaller than 2 cm showed axillary lymph node positivity; those 2 situations could have the most devastating clinical consequences if missed and will be discussed further below. We observed a direct relationship between invasive carcinoma grade and size, with the well- and moderately differentiated carcinomas clustering around 0.5 cm, whereas the poorly differentiated carcinomas were larger. Many cases (186 of 229; 81%) had ER+ results, even more so, in those cases upgraded from low-grade DCIS. The opposite trend was seen for HER2, with a greater percentage of the high-grade DCIS cases resulting in HER2+ invasive carcinomas. Interestingly, when isolating the HER2+ cases, the low-grade lesions were positive for both ER and HER2, 5 of 6 cases (83%) of intermediate-grade cases were positive for both ER and HER2, and one-half of the high-grade lesions upgraded to invasive carcinoma (15 of 33; 45%) were positive for both.

Twelve patients in our study had a T2 or T3 tumor and/or positive sentinel lymph nodes. When those cases were analyzed, all of them would have been excluded from the observation trials for at least 1 of the risk factors discussed above (mass, multifocality, necrosis). However, unlike our results, a recent study of 296 patients who met criteria for the LORD trial identified up to 58 patients with invasive carcinoma upon excision, emphasizing that there is a risk of sampling error. When those cases were upgraded to invasive carcinoma (15 of 33; 45%) were positive for both ER and HER2, and one-half of the high-grade lesions upgraded to invasive carcinoma (15 of 33; 45%) were positive for both.

In summary, approximately one-half the upgrades in our study were due to low- and intermediate-grades of DCIS; therefore, this diagnosis of DCIS on core biopsy should not be underestimated or underestimated as being an indolent lesion. Axillary lymph node positivity was rare but affected 3% (7 of 218) of the carcinomas smaller than 2 cm. Our findings indicate that caution must be exercised when treating DCIS diagnosed upon core biopsy diagnosed with nonsurgical surveillance (with or without neoadjuvant endocrine therapy), given the rate of upgrade to invasive carcinoma (8%; 229 of 2943) and the rate of axillary lymph node metastases (7%; 12 of 167) occurring from sampling error in identifying a small invasive carcinoma in the setting of diffuse, heterogeneous, or multifocal lesions or calcifications. These findings have therapy-changing implications from adding axillary lymph node sampling to chemotherapy, including anti-HER2 agents.

References


