Predictors of microinvasion and its prognostic role in ductal carcinoma in situ

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Abstract

BACKGROUND: We sought to determine factors predicting microinvasion and the prognostic role it plays in patients with ductal carcinoma in situ (DCIS).

METHODS: A retrospective cohort study of 205 consecutive patients presenting to the Yale Breast Center, New Haven, CT, was performed.

RESULTS: Fifty-one (24.9%) patients had microinvasion on pathology. Patients with microinvasion had larger areas of DCIS and were more likely to have high-grade DCIS of the comedo and solid type associated with necrosis and microcalcifications. On multivariate analysis, none of these factors were independent predictors of microinvasion. With a median follow-up of 8.5 years, there was no difference in the recurrence rate or 5-year actuarial survival between those with microinvasion vs those with pure DCIS.

CONCLUSIONS: Microinvasion was associated with more extensive DCIS, higher grade, comedo or solid histology, necrosis, and microcalcifications although none of these were found to be an independent predictor of microinvasion. Furthermore, the presence of microinvasion does not seem to significantly increase the risk of recurrence or decrease survival.

Ductal carcinoma in situ (DCIS) is a heterogeneous, preinvasive carcinoma confined within the basement membrane of the ducts of the mammary gland. Because of the advent of screening mammography over 3 decades ago, the incidence of DCIS has increased significantly. DCIS accounted for approximately 84% of the 57,650 new diagnoses of in situ carcinoma of the breast in the United States in 2011. If left untreated, DCIS may progress to invasive breast cancer although the mechanism of this transition is not well understood. With current treatments, including surgery with or without radiation and/or hormonal therapy, the prognosis for DCIS is generally favorable.

DCIS with microinvasion (DCISM) is a DCIS subtype with an extension of cancer cells beyond the basement membrane. The American Joint Committee on Cancer defines DCISM as DCIS with 1 or more areas of invasion, each measuring less than 1 mm in diameter. DCISM is uncommon, accounting for less than 1% of all breast cancers. Given the rarity of DCISM, its natural history is poorly understood, and treatment recommendations are not well established.

We analyzed the clinicopathologic factors and outcomes associated with DCISM compared with DCIS. Our objective was to elucidate predictors of microinvasion and...
determine the prognostic role of microinvasion in patients with DCIS.

Methods

A retrospective cohort study of 205 consecutive female patients presenting to the Yale Breast Center, New Haven, CT, with DCIS from 2000 through 2003 was performed. Patients with evidence of invasive carcinoma greater than 1 mm on biopsy or surgical pathology were excluded. DCISM was defined as the presence of either “microinvasion” or “possible microinvasion” as indicated on the surgical pathology report. The diagnosis of microinvasion is sometimes difficult, and all slides were reviewed by a board-certified pathologist at Yale. Clinicopathologic patient data including age, race, tumor grade, tumor size, histologic subtype, the presence of necrosis or microcalcifications, and the presence of microinvasion were collected. Additionally, we collected patient follow-up data regarding recurrence and death.

Statistical analyses were performed using IBM SPSS Statistics Version 19.0.0 (IBM, Armonk, NY). Bivariate analyses were performed using the Fisher exact test for categoric variables and the Mann-Whitney U test for continuous variables. Multivariate analysis used a logistic regression model in SPSS. Variables that were significant at the \( \alpha = .05 \) level (\( P < .05 \)) were included in the model. Our study endpoints included recurrence (locoregional and/or distant) and overall survival. Survival analyses were performed using the Kaplan-Meier estimator. This study was approved by the Human Investigation Committee at the Yale University School of Medicine.

Results

Descriptive statistics

Of the 205 patients who presented with DCIS, 51 (24.9%) had evidence of possible microinvasion on final pathology. The median age of all patients was 53.0 years (range 35.8 to 88.9 years). Among our patient cohort, 149 (72.7%) were treated with breast-conserving surgery, and 47 (22.9%) were treated with mastectomy. On bivariate analysis, several variables were associated with the DCISM subtype (Table 1). Patients in the DCISM cohort had a larger median tumor size than patients in the DCIS cohort (15 vs 9 mm, \( P < .001 \)). Those with DCISM were more likely to have grade 3 DCIS compared with those without microinvasion (55.1% vs 30.9%, \( P = .003 \)). Patients with DCISM were more likely than patients with pure DCIS to present with a solid (56.9% vs 39.0%, \( P = .034 \)) or comedo (78.4% vs 38.3%, \( P < .001 \)) histologic subtype, associated necrosis (76.5% vs 48.1%, \( P = .001 \)), and microcalcifications (90.2% vs 69.5%, \( P = .003 \)). In addition, there was a trend toward white women having a higher rate of microinvasion than black women (26.9% vs 8.7%, \( P = .061 \)).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DCISM (n = 51)</th>
<th>DCIS (n = 154)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (y)</td>
<td>54.9 154</td>
<td>56.7 154</td>
<td>.799</td>
</tr>
<tr>
<td>White (%)</td>
<td>47 (92.2) 51</td>
<td>128 (83.1) 154</td>
<td>.061</td>
</tr>
<tr>
<td>Black (%)</td>
<td>2 (3.9) 51</td>
<td>21 (13.6) 154</td>
<td>.003</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>1 (2.0) 51</td>
<td>0 (0) 154</td>
<td>.003</td>
</tr>
<tr>
<td>Tumor size, median (mm)</td>
<td>15 51</td>
<td>9 154</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grade (%)</td>
<td>1 (2.0) 51</td>
<td>15 (12.2) 154</td>
<td>.003</td>
</tr>
<tr>
<td>2</td>
<td>21 (42.9) 51</td>
<td>70 (56.9) 154</td>
<td>.222</td>
</tr>
<tr>
<td>3</td>
<td>27 (55.1) 51</td>
<td>38 (30.9) 154</td>
<td>.222</td>
</tr>
<tr>
<td>Histologic subtype (%)</td>
<td>40 (78.4) 51</td>
<td>59 (38.3) 154</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Comedo</td>
<td>29 (56.9) 51</td>
<td>60 (39.0) 154</td>
<td>.034</td>
</tr>
<tr>
<td>Solid</td>
<td>11 (21.6) 51</td>
<td>50 (32.5) 154</td>
<td>.160</td>
</tr>
<tr>
<td>Cribriform</td>
<td>19 (37.3) 51</td>
<td>43 (27.9) 154</td>
<td>.222</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>39 (76.5) 51</td>
<td>74 (48.1) 154</td>
<td>.001</td>
</tr>
<tr>
<td>Microcalcification</td>
<td>46 (90.2) 51</td>
<td>107 (69.5) 154</td>
<td>.003</td>
</tr>
</tbody>
</table>

In light of the strong associations between certain clinicopathologic variables (tumor grade, solid histologic subtype, comedo histologic subtype, the presence of necrosis, and the presence of microcalcifications) and DCISM, we adjusted for these factors in our multivariate logistic regression analysis. None of these variables remained significant on multivariate analysis.

Outcomes analysis

Among our patient cohort, the median follow-up was 8.5 years after the diagnosis of DCIS. Fourteen (6.8%) patients had a recurrence of disease during this follow-up period. There was no significant difference in the likelihood of recurrence in DCISM compared with DCIS without microinvasion (5.9 vs 7.1, \( P = 1.000 \)). On Kaplan-Meier analysis, there was no difference in the 5-year actuarial time to recurrence between the 2 groups with \( P = .202 \) (Fig. 1).

Comments

In our analysis of 205 women with either DCISM or DCIS alone, we found that DCISM was not associated with any patient demographic factors such as age and race but was associated with a variety of histopathologic characteristics including a higher tumor grade, a larger extent of DCIS, solid and comedo histologic subtypes, the presence of necrosis, and associated microcalcifications. However, none of these factors remained independently associated.
with the presence of microinvasion on multivariate analysis. None of the patients (whether with microinvasion or without) who had a sentinel node biopsy in our cohort had evidence of metastases. Furthermore, the presence of microinvasion was not associated with an increased risk of recurrence or decreased overall survival when compared with DCIS without microinvasion. These findings may have implications on the clinical significance of microinvasion in DCIS.

Microinvasion was associated with a larger DCIS tumor size, a higher tumor grade, and comedo histology. These 3 tumor characteristics, in addition to positive margins, were found to be predictors of local recurrence after treatment of DCIS, as reported in a meta-analysis by Wang et al with pooled random-effects risk estimates of 1.63, 1.81, 1.71, and 2.25, respectively. Additionally, tumor size is an independent predictor of local recurrence in the Van Nuys Prognostic Index, a simple scoring system used to guide therapeutic management of DCIS. Although we did not observe a difference in recurrence rates between DCISM compared with DCIS, it is possible that with longer follow-up the patients with DCISM will have higher rates of recurrence than patients with DCIS given the strong associations between DCISM and predictors of local recurrence.

Certain histopathologic features have been associated with DCISM, which corroborate the findings we present here. Several studies have reported an association between comedo histopathology and DCISM. We found that, in addition to a comedo histologic subtype, DCISM was associated with an increased incidence of solid histopathology when compared with DCIS alone. In a related study by Parikh et al on consecutive DCIS patients presenting to our institution from 1973 to 2004 but limited only to those who were treated with both breast-conserving therapy and subsequent radiotherapy, no significant associations were observed between overall histopathologic subtype and the presence of microinvasion. The differences in our observations are likely caused by differences in patient selection because we included all patients with DCIS regardless of treatment modality and further evaluated individual subtypes of DCIS.

From a pathologic perspective, it is thought that there is a continuum from atypical ductal hyperplasia to DCIS and, finally, to invasive ductal carcinoma (IDC). The molecular basis of this transition remains poorly understood. Studies show that the malignant epithelium of atypical ductal hyperplasia, DCIS, and IDC are very similar at the genome and transcriptome levels, suggesting that the genetic changes that modulate invasive-ness are likely present in tumor cells before they acquire DCISM morphology. In a recent study, Ma et al observed extensive changes in gene expression in the stroma associated with DCIS, suggesting that stroma adjacent to tumor progresses alongside the tumor epithelium even before tumor invasion. DCISM lies at the cusp of the transition between DCIS and IDC, with tumor invasion beyond the ductal basement membrane but in amounts insufficient to qualify as IDC. More pathologic studies are needed to better characterize the molecular basis of the DCIS to DCISM to IDC transition. To our knowledge, the genetic features of DCISM have yet to be studied independently from DCIS.

Our findings from outcomes analyses are consistent with the notion that DCISM is generally associated with a good prognosis, with no differences between DCISM and DCIS in terms of disease recurrence and overall survival. A study by Murphy et al found that the presence of sentinel node metastases in patients with DCIS or DCISM did not have prognostic significance with respect to local recurrence or survival. However, in a study by de Mascarel et al, in which patients with DCISM were divided into 2 groups, those with less extensive microinvasion (type 1) and more extensive microinvasion (type 2), a significant difference in metastasis-free and overall survival was observed.

There remains a need for a consensus definition for DCISM. The 7th edition of the American Joint Committee on Cancer staging system defines DCISM as DCIS with 1 or more areas of invasion each less than 1 mm in diameter. However, DCISM had been defined by other authors as microinvasion less than 2 mm in the greatest dimension. As mentioned earlier, de Mascarel et al identified 2 types of DCISM, with type 1 including invasion of surrounding stroma by single tumor cells and type 2 including invasion by tumor cell clusters forming nongradable foci. A consensus definition of DCISM would allow for standardization of the reporting of DCISM associations and outcomes in the literature.

In our analysis, we classified patients with “microinvasion” or “possible microinvasion” denoted on surgical pathology report as part of the DCISM group. Our DCISM rate of 24.9% is higher compared with previously reported rates of 13.5% and 18.3%. This may be a reflection
of differences in the definition of what constitutes microinvasion as well as the difficulty in making a definitive diagnosis of microinvasion in certain cases. It should be noted that we included “possible microinvasion” in our definition, whereas other studies may have relied on a definitive diagnosis.

In conclusion, our study suggests that histopathologic features of DCISM differ from those in pure DCIS. DCISM is associated with a higher grade, a larger extent of DCIS, comedo and solid histopathology, and the presence of necrosis and microcalcifications on histology. We found that the presence of microinvasion was not significantly associated with recurrence or worse overall survival in patients with DCIS. This may be related to the small number of events noted in our population, and a larger sample and/or longer follow-up periods may be warranted to better capture the potential effect of DCISM on patient outcomes.

References