

# A Potential Additional Variable to Consider in the Surgical Treatment of Ductal Carcinoma in Situ

Katherine Chaisson, MD,<sup>1</sup> Amy Rivere, MD,<sup>1</sup> Ralph Corsetti, MD,<sup>1,2</sup> Tova Weiss,<sup>3</sup> George M. Fuhrman, MD<sup>1</sup>

<sup>1</sup>Department of Surgery, Ochsner Clinic Foundation, New Orleans, LA <sup>2</sup>The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA <sup>3</sup>Louisiana State University Health Sciences Center, School of Medicine, New Orleans, LA

**Background:** HER2/neu is a potentially interesting variable that has been demonstrated to have a profound impact on the management of invasive breast carcinoma, and we performed this study to evaluate the differences between HER2-positive and HER2-negative ductal carcinoma in situ. The impetus for this study was our poor recruitment to the National Surgical Adjuvant Breast and Bowel Project Protocol B-43 trial that was designed to evaluate the potential role of trastuzumab in breast conservation therapy for patients with HER2-positive ductal carcinoma in situ.

**Methods:** All patients with ductal carcinoma in situ and an assessment for the HER2/neu receptor were identified. Patients with HER2-positive and HER2-negative ductal carcinoma in situ were compared to determine differences in demographic, hormone receptor status, nuclear grade, presence of necrosis, surgical procedure (lumpectomy or mastectomy), tumor size, and extent of margins. Quantitative variables were analyzed with *t* test, and nominal variables were assessed by chi square analysis.

**Results:** A total of 177 patients were identified with a mean age of 61.0 years. A total of 101 patients (57.1%) were treated with lumpectomy, and 76 had mastectomy (42.9%). Forty-four (24.9%) patients were positive, and 133 (75.1%) were negative for the HER2/neu receptor. HER2-positive tumors were larger (23.6 vs 13.8 mm,  $P=0.001$ ) and more likely to undergo mastectomy (61.4% vs 36.8%,  $P=0.01$ ).

**Conclusion:** Based on these results, an HER2-positive ductal carcinoma in situ is likely to be larger than an HER2-negative tumor, leading to more frequent use of mastectomy. This finding would explain our poor recruitment to the National Surgical Adjuvant Breast and Bowel Project Protocol B-43 trial.

**Keywords:** Carcinoma–ductal–breast, HER2/neu, mastectomy, radiation, trastuzumab

Address correspondence to George M. Fuhrman, MD, Department of Surgery, Ochsner Clinic Foundation, 1514 Jefferson Hwy., New Orleans, LA 70121. Tel: (504) 842-4070. Email: gfuhrman@ochsner.org

## INTRODUCTION

The treatment of ductal carcinoma in situ (DCIS) of the breast typically starts with complete excision of the disease by mastectomy or lumpectomy. Either approach is associated with an estimated 99% ability to prevent death from DCIS.<sup>1–3</sup> Mastectomy nearly always allows for complete excision of the breast disease but is disfiguring and often requires reconstruction to achieve an acceptable level of patient satisfaction.<sup>4,5</sup> While reconstruction can be a critically important and valuable part of the multidisciplinary management of patients with DCIS, it adds to the costs and complexities of patient management.<sup>6</sup> Alternatively, lumpectomy can provide similar overall survival rates compared to mastectomy but is associated with an increased risk of local in-breast recurrence.<sup>7–10</sup> When lumpectomy is used, radiotherapy is typically employed to reduce the risk of developing an in-breast recurrence.<sup>11,12</sup> When local breast recurrences are detected during surveillance, about half are invasive and responsible for the 1% risk of death secondary

to an invasive recurrence that might metastasize.<sup>13</sup> An understanding of these issues is critical to select the optimal approach to manage a patient with DCIS.

The use of prognostic variables at the time of DCIS diagnosis can help select the optimal treatment approach. The best example of this strategy is the use of The University of Southern California/Van Nuys Prognostic Index.<sup>14</sup> This algorithm uses 5 prognostic variables to optimize treatment for DCIS: tumor size, margin of excision width, nuclear grade, comedonecrosis, and patient age. Older patients with small tumors that are low grade, without comedonecrosis, and excised with wide margins have the lowest risk of local recurrence after excision alone. The Van Nuys Prognostic Index stratifies patient risk for local recurrence after surgery and directs management to local excision plus radiotherapy for intermediate-risk patients and to mastectomy for patients with the greatest risk.<sup>15</sup> While the 5 variables included in the Van Nuys Prognostic Index are useful, advances in the understanding of other variables

should serve to enhance the prognostic accuracy in the selection of treatment for DCIS patients.

HER2/neu is a potentially interesting variable that has been demonstrated to have a profound impact on the management of invasive breast carcinoma. Invasive breast cancers that overexpress the HER2/neu receptor demonstrate more aggressive biologic behavior and increased sensitivity to chemotherapy and are amenable to management with targeted therapies such as trastuzumab (Herceptin) and pertuzumab (Perjeta) that improve patient outcomes.<sup>16-18</sup> In DCIS, little is known about the role of the HER2/neu receptor and its potential impact on disease management.

An important fact that might have an impact on DCIS management in HER2/neu-positive patients is the observation that trastuzumab has a radiation-sensitizing effect.<sup>19</sup> This observation led to the development of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-43 trial. The NSABP B-43 trial was developed to evaluate the potential impact of the radiosensitizer trastuzumab in the management of patients undergoing breast conservation for DCIS. Patients with DCIS had their tumors evaluated by immunohistochemistry for the HER2/neu receptor. When patients' tumors were scored as 3+ for HER2/neu by subjective assessment, they were considered eligible for the trial. When scored 2+, an objective fluorescence in situ hybridization (FISH) test was performed to determine whether tumor cells overexpressed the HER2/neu receptor, and if they did, these patients were also eligible for the study. Eligible patients were then randomized to traditional treatment with external beam radiotherapy alone or the addition of trastuzumab at the beginning and end of a course of radiotherapy.

Two years after NSABP B-43 was opened at our institution, we had accrued few patients. Until NSABP B-43 was opened, we had not performed HER2/neu assessments on patients with DCIS. Therefore, we had little understanding about this cohort of patients with HER2/neu-positive DCIS. Therefore, we performed this study to determine the differences between patients with HER2-positive and negative DCIS.

## METHODS

All patients at our institution with DCIS diagnosed between 2012 and 2015 with an assessment for the HER2 receptor were identified from a prospective database, and their medical records were retrospectively reviewed. An HER2 receptor assessment was considered positive by either intense immunohistochemical membrane staining or by equivocal membrane staining but positive gene amplification by FISH test in accordance with the guidelines for determining HER2/neu status established by the College of American Pathologists.<sup>20</sup>

Data recorded were age, estrogen and progesterone receptor status, nuclear grade, presence of necrosis, surgical procedure (lumpectomy vs mastectomy), size of DCIS, and extent of margins. Estrogen and progesterone receptors were evaluated by immunohistochemical analysis of breast cancer tissue. Typically, this assessment was done on the original biopsy material (usually core needle biopsy). However, when the original biopsy was performed at an outside institution, this analysis was done on the tumor removed at the time of surgical resection. Histologic grade and the presence or absence of necrosis were also typically determined from review of the diagnostic core biopsy material or review of outside slides when the diagnosis of breast cancer was made at an outside institution. HER2-positive and HER2-negative tumors were compared, with quantitative variables analyzed by *t* test and nominal variables assessed by chi-square analysis.

## RESULTS

A total of 177 patients were identified, with 44 (24.9%) HER2 positive and 133 (75.1%) HER2 negative. The characteristics of the 2 groups are summarized in the Table. These data demonstrate that patients with HER2-positive DCIS have tumors of larger size, absence of estrogen and progesterone receptors, higher grade histology, and an increased presence of necrosis. Further, HER2-positive patients are more likely to be treated by mastectomy. In multivariate analysis, the DCIS tumor size remained significantly greater in HER2-positive patients.

**Table. Patient and Tumor Characteristics by HER2 Status**

Variable	HER2+ n=44 (24.9%)	HER2- n=133 (75.1%)	P Value
Mean age, years	60.3	61.2	0.61
Mean DCIS size, mm	23.6	13.8	0.001
Mean closest margin, mm	11.0	9.4	0.34
Estrogen receptor +, n (%)	22 (50.0)	122 (91.7)	0.0001
Progesterone receptor +, n (%)	19 (43.2)	114 (85.7)	0.0001
Low grade, n (%)	0	36 (27.1)	0.0001
Intermediate grade, n (%)	12 (27.3)	64 (48.1)	0.0001
High grade, n (%)	32 (72.7)	33 (24.8)	0.0001
Necrosis, n (%)	36 (81.8)	60 (45.1)	0.0001
Mastectomy, n (%)	27 (61.4)	49 (36.8)	0.01

DCIS, ductal carcinoma in situ.

## DISCUSSION

Based on the data from our study, HER2-positive DCIS is associated with larger areas of disease and other known poor prognostic factors. The increased use of mastectomy is likely explained by the observation that HER2-positive cancers were about twice as large as HER2-negative cancers in our study. Large areas of DCIS are difficult (and sometimes impossible) to clear with negative margins by lumpectomy. Because the goal of breast conservation is to improve aesthetics, patients requiring large lumpectomies may have opted for mastectomy with reconstruction in search of an optimal aesthetic outcome after treatment.

For the NSABP B-43 trial, we enrolled only 11 patients at our institution and 21 patients across our entire healthcare system. Of the 21 patients, 13 were HER2/neu negative and did not proceed to randomization, 5 refused randomization after consenting to enroll in the trial, and only 3 patients were HER2 positive and proceeded to randomization (2 received trastuzumab, and 1 was randomized to standard radiation therapy). The failure to recruit a large number of patients to the NSABP B-43 trial is not surprising and reflects the biology of HER2/neu-positive DCIS.

HER2/neu-positive DCIS predicts that patients will be poor breast conservation candidates compared to those with HER2/neu-negative disease. HER2/neu is potentially another poor prognostic factor to add to the Van Nuys Prognostic Index along with age, grade, necrosis, margin width, and tumor size. As patients accumulate negative prognostic factors, the treatment for DCIS evolves from the limited treatment of lumpectomy alone, to lumpectomy and radiation for intermediate risk, to mastectomy for patients with greater risk. Currently, little is known about HER2/neu as a prognostic factor for DCIS, and our study supports increased evaluation of this potentially important factor as a predictor of the need for more whole breast-focused therapy. This increased evaluation will likely start as information from the NSABP B-43 trial becomes available.

An important point is that patients with small HER2/neu-positive DCIS are excellent candidates for breast conservation. We identified patients with small tumors that were easily excised with negative margins despite their positive HER2 status who could be successfully enrolled in NSABP B-43. However, this group was small, with only 17 patients.

This information demonstrates that HER2/neu status alone is not an indication to direct patients to mastectomy. Clearly, much about HER2/neu and DCIS is not known. Once the NSABP B-43 trial data are published, routine assessment for HER2/neu for DCIS may possibly become routine. At our institution, once NSABP B-43 closed in 2015, we stopped evaluating DCIS for HER2 status. This approach may change in the future, as HER2 might provide important information in helping to plan treatment for patients with DCIS.

The radiosensitizing effect of trastuzumab is an interesting feature of the drug. The results of NSABP B-43 will be interesting to assess. If a powerful radiosensitizing drug were available, margin status might not be as critical a treatment goal because radiotherapy additionally powered by a radiosensitizing agent might provide satisfactory treatment results. Alternatively, if trastuzumab does not provide any additional treatment benefit, then patients who have a core biopsy diagnosis of HER2/neu-positive DCIS

can be informed about the increased likelihood of harboring larger areas of disease, and that information might lead some patients to bypass breast conservation and proceed directly to mastectomy.

## CONCLUSION

Currently, little is known about HER2/neu as a prognostic factor for DCIS, and our study supports increased evaluation of this potentially important factor as a predictor of the need for more whole breast-focused therapy.

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