Ann Surg Oncol
DOI 10.1245/s10434-012-2640-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Microinvasive Breast Cancer: ER, PR, and HER-2/neu Status and Clinical Outcomes after Breast-Conserving Therapy or Mastectomy

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ABSTRACT

Background. Contemporary clinical outcomes of microinvasive breast cancer (MIBC), defined as no focus >1 mm, are not well characterized. We document the immunophenotype, incidence of axillary metastases, and rate of recurrence in a well-defined case series.

Methods. We reviewed 83 consecutive patients with MIBC from 1997 to 2005. Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2/neu) receptor status were assessed. The cumulative incidence of local recurrence (LR) and nodal/distant recurrence was calculated. Predictors of recurrence were identified and effect estimates determined.

Results. Fifty-two patients (63 %) underwent breast-conserving therapy (BCT) and 31 (37 %) underwent mastectomy. Sixty-one percent had ER-positive disease and 49 % had HER-2/neu-positive disease. Three (4 %) of 68 patients with sentinel node mapping or axillary dissection had single node micrometastases, and none had macrometastases or multiple nodes involved. Median follow-up was 6.4 years, with 6 LRs, 2 regional nodal recurrences, and 2 concurrent local/distant recurrences. The 5-year cumulative incidence of recurrence (local, nodal, or distant) was 5.3 % (95 % confidence interval [CI] 2.0–13.4) for all patients, and among BCT patients, the 5-year cumulative incidence of LR was 4.2 % (95 % CI 0.7–12.7). HER-2/neu overexpression was not associated with recurrence ($P = 0.46$). Close/positive margins (≤2 mm) were significantly associated with an increased risk of LR after BCT or mastectomy (hazard ratio 8.8; 95 % CI 1.6–48.8; $P = 0.003$).

Conclusions. MIBC has a favorable prognosis, and HER-2/neu overexpression, although highly prevalent, is not significantly associated with recurrence. Axillary metastases at diagnosis are small and infrequent. The cumulative incidence of LR after BCT is acceptable; however, our data confirm that negative margins (>2 mm) are required for optimal BCT outcomes.

The American Joint Committee on Cancer (AJCC 7th edition) defines microinvasion as no focus larger than 1 mm.[1] Older studies reporting clinical outcomes of microinvasive breast cancer (MIBC) have used heterogeneous definitions of microinvasion.[2–9] This has resulted in a controversy surrounding optimal prognostication and management of MIBC. More recent publications describing small numbers of patients using current AJCC criteria for microinvasion have assessed local and regional recurrence with mean follow-up ranging from 36 to 107 months (Table 1).[10–12]

None of the studies to date has evaluated the prognostic impact of breast cancer subtype, as approximated by

Presented in part at the American Society for Radiation Oncology (ASRO) 52nd annual meeting, 2010, San Diego, CA.

First Received: 11 April 2012

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Published online: 07 September 2012

TABLE 1 Published studies of clinical outcome of DCIS with microinvasion using the AJCC definition of microinvasion [a]

Study	Institution, study period	No. of cases	BCT	Follow-up (mo)	Local failure[b]	Distant failure[c]
This study, 2012	Harvard, 1997–2005	83	63 %	77 (median)	Crude 6/88; 5-y 2.6 %	0 %
Parikh, 2010[10]	Yale, 1973–2004	72	100 %	107 (median)	Crude 6/72; 10-y L-RFS 90.7 %	10-y D-RFS 97.9 %
Vieira, 2010[11]	New York University, 1993–2006	21	55 %	36 (mean)	0 %	0 %
Kwon, 2010[12]	Seoul, Korea, 2000–2006	120	53 %[d]	61 (median)	Crude 3/120; 5-y RFS 97.2 %	Crude: 1/120

DCIS ductal carcinoma-in situ, *AJCC* American Joint Committee on Cancer, *BCT* breast-conserving therapy (breast-conserving surgery and radiotherapy), *L-RFS* local recurrence-free survival, *D-RFS* distant recurrence-free survival, *RFS* recurrence-free survival

[a] AJCC 6th edition, invasive carcinoma no larger than 0.1 cm

[b] Isolated local failure as first failure is reported unless otherwise indicated

[c] Isolated distant metastasis as first failure is reported unless otherwise indicated

[d] Only 56.6 % of patients treated with BCT received adjuvant whole-breast radiotherapy

estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2/neu) receptor status in patients with MIBC. Immunoprofile is a prognostic indicator for both LR and distant recurrence in invasive carcinomas.[13,14] Patients with small (T1a or T1b), HER-2/neu-positive, node-negative tumors are at increased risk of recurrence.[15,16] Studies of ductal carcinoma-in situ (DCIS) have provided conflicting results on whether overexpression of HER-2/neu is associated with local recurrence (LR).[17–19] It is unclear whether HER-2/neu overexpression has similar prognostic significance in MIBC.

The role of axillary staging in MIBC is not well defined, with the rate of axillary metastases ranging 0–11 %.[20,21] Identifying a relationship between breast cancer immunophenotype and risk for local and/or distant recurrence may help determine which patients might benefit more from axillary staging and whether axillary staging is warranted in all cases.

The purpose of this study was (1) to determine the ER, PR, and HER-2/neu immunoprofile of microinvasion, comparing DCIS with the microinvasive profile, (2) to determine the incidence of axillary metastases at diagnosis, and (3) to evaluate long-term outcomes after treatment of MIBC with a particular focus on identifying risk factors for LR and distant recurrence.

METHODS AND MATERIALS

Patient Selection

Eighty-three consecutive women diagnosed with microinvasive breast carcinoma from 1997 to 2005 were identified in the Brigham & Women's Hospital Department of Pathology database. Mammography was the most common method of cancer detection in this cohort of patients. Mammographic findings were available for 82 of the 83 patients. Calcifications were present in 69 of mammograms. The extent of calcifications was not routinely quantified, and therefore we could not provide this information in our study. Postlumpectomy mammography was also not routinely performed. A minimum 5-year follow-up was chosen to allow adequate time for recurrence events while ensuring that the current guidelines for definition of microinvasion ($\leq$0.1 cm) had been used in the initial diagnosis. Patients with prior malignancy were excluded. This study was approved by the Dana-Farber/Harvard Cancer Center institutional review board.

Treatment

Fifty-two patients (63 %) received breast-conserving therapy (BCT; lumpectomy and whole-breast radiotherapy), and 31 (37 %) underwent mastectomy. The decision to perform a sentinel lymph node dissection or axillary lymph node dissection was at the discretion of the surgeon and was performed in 68 (82 %) of 82 patients. All patients treated with conservative surgery received adjuvant radiotherapy with tangents only. Only 1 patient received postmastectomy radiotherapy (to the chest wall alone) to treat a deep margin positive for microinvasion and DCIS. The decision to receive adjuvant endocrine therapy (tamoxifen and/or an aromatase inhibitor) or chemotherapy was made by the treating medical oncologist. Forty-eight percent of patients received adjuvant endocrine therapy, and 4 patients (5 %) received adjuvant chemotherapy with either a doxorubicin- or a taxane-based regimen. No patient received HER-2/neu-targeted therapy.

Pathologic Analysis

All cases of microinvasion were confirmed by a breast pathologist at Brigham & Women's Hospital. Each focus was measured individually, and multiple foci of microinvasion were not added together. All BCT specimens were serially sectioned and sequentially submitted in their entirety when approximately <5 cm in greatest dimension, and at least all fibrous tissue was submitted for excisions >5 cm. Suspicious lesional tissue within mastectomy specimens was extensively sampled.

Immunohistochemical Studies

ER, PR, and HER-2/neu receptor expression status was determined by immunohistochemistry (IHC) for both the in situ and invasive components. ER and PR were reported as positive if ≥1 % of nuclei stained and negative if <1 % of tumor cells stained. HER-2/neu was reported as negative if scored as 1+ or 2+, or reported as negative. Tumors were considered HER-2/neu-positive if scored as 2–3+, 3+, or reported as positive (without a score). HER-2/neu fluorescence in situ hybridization was not performed. Microinvasion was not always present on deeper levels used for IHC studies, and in these cases, the receptor profile for the in situ component alone was reported.

Evaluating Margin Status

Our institution defines a negative margin as >3 mm for BCT; however, 2 mm is used by many other institutions and in most publications, so for this analysis, we chose >2 mm as a negative margin for BCT specimens and mastectomy specimens to permit comparison with other institutional data. Specifically, BCT specimens were routinely oriented and all margins inked accordingly and reported. For mastectomy specimens, the distance to posterior margin (fascia) was reported routinely.

Evaluating Extent of Disease

The extent of DCIS was reported two ways: by using the ratio of number of blocks of DCIS divided by total slides examined, and by estimating the number of centimeters of DCIS disease present by using a DCIS volume algorithm comprising the number of blocks of DCIS multiplied by 0.4 cm.[22]

Clinical End Points

The primary end point was time to first recurrence including local, nodal, or distant recurrence. The secondary end points included the time to ipsilateral LR, time to regional/nodal or distant metastases, and the rate of axillary metastases at initial diagnosis. Regional/nodal and distant metastases were grouped together as a single end point in order to maximize power to detect a significant association between pathologic tumor characteristics and non-LR.

Statistical Analysis

We used Fisher's exact test to identify differences in proportions and the Wilcoxon rank sum test to identify differences in median values. The cumulative incidence of recurrence included local, nodal, and distant recurrence. The cumulative incidence of LR was estimated with nodal/distant recurrence as a competing event; the cumulative incidence of nodal/distant recurrence was estimated with LR as a competing event. Time to recurrence was measured from the date of breast cancer diagnosis. Patients were censored at the date of second malignancy ($n = 1$), contralateral breast cancer ($n = 2$), or date of last breast cancer follow-up. Univariate predictors of LR were identified by the log rank test, and the effect estimates were determined by Cox proportional hazard regression. DCIS extent was analyzed as a continuous variable; DCIS grade was dichotomized as grade 3 versus grades 1 and 2. The number of foci of microinvasion was analyzed as multiple versus single.

RESULTS

Clinical and Pathologic Characteristics

Patient and tumor characteristics are listed in Tables 2 and 3. Race was self-reported by patients at the time of hospital registration and was available for 95 % (79 of 83) of patients in this study. Most patients were white ($n = 73$); 3 patients were black, 2 were Hispanic, and 1 was Asian.

Overall, 61 % (25 of 41) of microinvasion was ER positive (Table 2). Of the 30 cases that had complete hormone receptor information for both the DCIS and invasive components, ER- and PR-positive microinvasive disease was 100 % concordant in both microinvasion and DCIS (60 %, 18 of 30). ER-negative microinvasive disease was 83 % concordant (10 of 12 cases) between in situ and invasive disease with 2 discrepant cases of ER-negative microinvasion having low level of ER-positive in situ component (between 1 % and 10 %). No ER-negative microinvasion was seen associated with high levels of in situ expression of ER (>10 %).

Forty-nine percent (20 of 41) of microinvasion was HER-2/neu positive (Table 2). There was 100 % concordance

TABLE 2 Baseline characteristics for 83 patients

Characteristic[a]	BCT ($n = 52$)	MX ($n = 31$)	Total ($n = 83$)	P (BCT vs. MX)
Age, y, median (IQR)	55.8 (46–61)	49.0 (42–55)	53.9 (44–60)	0.04
ER or PR (microinvasive)				0.68
Positive	14 (58 %)	11 (65 %)	25 (61 %)	
Negative	10 (42 %)	6 (35 %)	16 (39 %)	
Unknown	28	14	52	
HER-2/neu (microinvasive)				0.28
Positive	10 (42 %)	10 (59 %)	20 (49 %)	
Negative	14 (58 %)	7 (41 %)	21 (51 %)	
Unknown	28	14	42	
ER or PR (DCIS)				0.71
Positive	31 (74 %)	16 (70 %)	47 (72 %)	
Negative	11 (26 %)	7 (30 %)	18 (28 %)	
Unknown	10	8	18	
HER-2/neu (DCIS)				0.15
Positive	13 (37 %)	13 (57 %)	26 (45 %)	
Negative	22 (63 %)	10 (43 %)	32 (55 %)	
Unknown	17	8	25	
Endocrine therapy				
Yes	29 (56 %)	11 (35 %)	40 (48 %)	0.07
No	23 (44 %)	20 (65 %)	43 (52 %)	
Chemotherapy				
Yes	2 (4 %)	2 (6 %)	4 (5 %)	0.58
No	51 (96 %)	29 (94 %)	79 (95 %)	

BCT breast-conserving therapy, *MX* mastectomy, *IQR* interquartile range, *ER* estrogen receptor, *PR* progesterone receptor, *HER-2/neu* human epidermal growth factor receptor 2, *DCIS* ductal carcinoma-in situ

No patient received trastuzumab. Percentages may not total 100 because of rounding

[a] Denominator excludes cases where the receptor status was unknown

between HER-2/neu status for the 30 cases where HER-2/neu status was known for both microinvasion and DCIS. Other studies published to date reporting invasive carcinomas >0.1 cm in size also report a high rate of concordance between the HER-2/neu status of the invasive and in situ carcinoma.[23,24] Given the overall high concordance between in situ and microinvasive carcinoma for ER, PR, and HER-2/neu, when microinvasion was not observed on additional levels for IHC, the receptor status was reported for the in situ component and used in subsequent analyses ($n = 28$).

Axillary Nodal Staging

The rate of axillary lymph node metastases is shown in Table 4. Of the 68 patients who had axillary staging, none had macrometastases, 3 (4 %) had micrometastases (defined as 0.02–0.2 cm), and 4 (6 %) had isolated tumor cells (defined as <0.02 cm). Of the 4 patients with isolated tumor cells, 3 were found via IHC only, and 1 was found via both IHC and hematoxylin and eosin staining.

Clinical Outcomes

At median follow-up of 6.4 years, there were 10 recurrences including 6 local, 2 regional/nodal, and 2 concurrent local and distant recurrences (Table 5). Eight of the 10 had an initial axillary staging procedure. Two (of 6) patients with local-only failure did not. There were no isolated distant metastases as first events, and no deaths occurred during follow-up. The 5-year cumulative incidence of any recurrence was 5.3 % (95 % confidence interval [CI] 2.0–13.4) for all patients, 4.2 % (95 % CI 1.1–15.7) for patients who underwent BCT, and 7.0 % (95 % CI 1.8–25.3) for patients who underwent mastectomy. The 5-year cumulative incidence of isolated LR was 2.6 % (95 % CI 0.5–8.1), and for nodal/distant recurrence it was 2.7 % (95 % CI 0.5–8.4). Among patients treated with BCT, the 5-year cumulative

TABLE 3 Pathologic characteristics

Characteristic	BCT ($n = 52$)	MX ($n = 31$)	Total ($n = 83$)	P (BCT vs. MX)
DCIS margins				0.17
Negative (>2 mm)	36 (71 %)	26 (84 %)	62 (76 %)	
Close (≤2 mm)	13 (25 %)	3 (10 %)	16 (20 %)	
Positive (at ink)	2 (4 %)	2 (6 %)	4 (5 %)	
Unknown	1	0	1	
Invasive margins				0.37
Negative (>2 mm)	52 (100 %)	30 (97 %)	82 (99 %)	
Close (≤2 mm)	0	0	0	
Positive (at ink)	0	1 (3 %)	1 (1 %)	
No. of foci of microinvasion in a specimen				0.65
Multiple	31 (62 %)	17 (57 %)	48 (60 %)	
Single	19 (38 %)	13 (43 %)	32 (40 %)	
Unknown	2	1	3	
Nuclear grade of DCIS				0.17
1	3 (6 %)	0	3 (4 %)	
2	17 (33 %)	6 (19 %)	23 (28 %)	
3	32 (62 %)	25 (81 %)	57 (69 %)	
DCIS subtype				0.07
Comedo	25 (48 %)	22 (71 %)	47 (57 %)	
Cribriform	26 (50 %)	12 (39 %)	38 (46 %)	
Micropapillary	3 (6 %)	4 (13 %)	7 (8 %)	
Papillary	2 (4 %)	0	2 (2 %)	
Solid	31 (60 %)	19 (61 %)	50 (60 %)	
Unknown	1	0	1	
LVI				0.25
Positive	1 (2 %)	2 (6 %)	3 (4 %)	
Indeterminate	1 (2 %)	0	1 (1 %)	
None	50 (96 %)	29 (94 %)	79 (95 %)	
Extent of DCIS, cm, median (IQR)	2.2 (1.1–3.8)	4.4 (3.2–7.2)	3.2 (1.4–5.1)	0.001
Ratio of slides with DCIS out of total slides examined, median (IQR)	0.33 (0.2– 0.5)	0.53 (0.5–0.7)	0.40 (0.3–0.5)	<0.001

BCT breast-conserving therapy, *MX* mastectomy, *DCIS* ductal carcinoma-in situ, *LVI* lymphovascular invasion, *IQR* interquartile range

[a] Percentages may not total 100 because of rounding

incidence of LR was 4.2 % (95 % CI 0.7–12.7). There were no recurrences among the 3 patients with axillary micrometastases. However, 1 patient with micrometastases and 1 patient with isolated tumor cells received chemotherapy.

There were 35 patients who underwent initial breast-conserving surgery who required repeat excision; 6 of the 35 patients eventually had mastectomy rather than BCT. There was no association between repeat excision and LR, yet our study was not powered to detect such an association; there were 5 LRs among the 35 who underwent repeat excision and 3 LRs among those who did not undergo repeat excision.

There was no significant association between HER-2/neu status and breast cancer recurrence ($P = 0.46$). There were 5 recurrences among 36 HER-2/neu-negative patients (2 local only, 2 local and distant, 1 nodal; 5-year cumulative incidence 2.9 %; 95 % CI 0.4–18.6) and 3 recurrences among the 33 HER-2/neu-positive patients (2 local only, 1 nodal; 5-year cumulative incidence 6.8 %; 95 % CI 1.7–24.6). Of the 33 patients with HER-2/neu-positive disease, only 2 received systemic therapy, and none received trastuzumab. Among 24 ER-negative patients, there were 3 recurrences (2 local only and 1 nodal; 5-year cumulative incidence 4.3 %; 95 % CI 0.6–27.1). There were 6 recurrences (3 local only, 2 local and distant, 1 nodal) among the 52 ER-positive patients (5-year cumulative incidence 4.2 %; 95 % CI 1.1–15.7). Of the 52 patients with ER-positive breast cancer, 32 received hormone therapy and none received chemotherapy. Of those who experienced recurrence, 2 had received hormone therapy. There was no significant association between ER status and breast cancer recurrence ($P = 0.93$).

TABLE 4 Axillary nodal assessment

Assessment	BCT ($n = 52$)	MX ($n = 31$)	Total ($n = 83$)
Sentinel LN biopsy	33 (63)	20 (67)	53 (64)
Axillary LN dissection (completion or initial)	8 (15)	14 (45)	22 (27)
Total no. lymph nodes examined			
Sentinel LN biopsy	2 (1–6)	3 (1–8)	2 (1–8)
Axillary LN dissection	11 (5–19)	11 (5–20)	11 (5–20)
Total patients with either SLND or ALND	39 (75)	29 (94)	68 (82)
Macrometastases (>2 mm)	0	0	0
Micrometastases (≤2 mm)	1 (3)	2 (7)	3 (4)
Isolated tumor cells (≤0.2 mm)	2 (5)	2 (7)	4 (6)

BCT breast-conserving therapy, *MX* mastectomy, *LN* lymph node, *SLND* sentinel lymph node dissection, *ALND* axillary lymph node dissection

Data are presented as *n* (%) or median (range)

TABLE 5 Site of first recurrence at a median follow-up of 6.4 years

Event type	BCT ($n = 52$)	MX ($n = 31$)	Total ($n = 83$)
No. of total recurrences	6	4	10
Local only	5	1	6
Isolated regional nodal	0	2	2
Local and distant	1	1	2
Distant only	0	0	0
No. of additional events			
Second malignancy	0	1	1
Contralateral breast cancer	2	0	2
Death	0	0	0

BCT breast-conserving therapy, *MX* mastectomy

Although the margins for the invasive component were almost always negative (99 %), 5 % had positive DCIS margins and 20 % had close DCIS margins (≤2 mm) margins. Close/positive margins (compared to negative margins) with both BCT and mastectomy were significantly associated with an increased risk of LR (hazard ratio [HR] 8.8; 95 % CI 1.6–48.8; $P = 0.003$). Among those treated with BCT, close/positive margins were associated with LR with borderline significance (HR 4.9; 95 % CI 0.8–30.0; $P = 0.06$) (Table 6). Twenty percent (3 of 15) of patients with close/positive margins experienced recurrence locally after BCT, compared with 6 % (2 of 36) of patients with negative margins after BCT. No patient with mastectomy and negative margins experienced local recurrence, but 1 (of 5) with a close/positive margin experienced recurrence.

Forty percent of patients had one focus of microinvasion, and 60 % of patients had multiple foci of microinvasion. On univariate analysis, the number of foci of microinvasion (HR 3.4; 95 % CI 0.6–18.7; $P = 0.13$) was not a significant predictor of LR.

Patients who underwent mastectomy were younger and had more extensive DCIS than patients who underwent BCT. Although patients with mastectomy had on average twice the volume of DCIS present (4.4 cm vs. 2.2 cm), DCIS extent was not a significant predictor of LR (HR 1.1; 95 % CI 0.8–1.4; $P = 0.64$). We presume patients with higher volumes of disease were recommended mastectomy at initial presentation or ended up undergoing mastectomy after multiple excisions.

Microinvasion was associated with high-nuclear-grade DCIS in 69 % of cases, frequently with comedo (57 %) and solid (60 %) subtypes. High-nuclear-grade DCIS was more prevalent in MIBC than in cases of DCIS alone at our institute (69 % in MIBC vs. 39 % in DCIS alone).[17] DCIS grade was not associated with LR (HR 0.7; 95 % CI 0.1–3.7; $P = 0.65$).

TABLE 6 LR by margin status

DCIS margin	Close/positive margins (≤2 mm)	Clear margins (>2 mm)	*P* (log rank test)	HR (95 % CI)
BCT and MX	4/20	2/62	0.003	8.8 (1.6–48.8)
BCT	3/15	2/36	0.057	4.9 (0.8–30.0)
MX only	1/5	0/26	–[a]	–[a]

LR local recurrence, *DCIS* ductal carcinoma-in situ, *HR* hazard ratio, *CI* confidence interval, *BCT* breast-conserving therapy, *MX* mastectomy

Data are expressed as no. of LR/total

[a] Too few events to estimate

DISCUSSION

This study is unique in its detailed pathologic analysis, and to our knowledge, it is the largest series reported to date in a U.S. population with a median follow-up of >5 years. Our contemporary study period reflects current diagnostic and treatment practices, and all patients treated with conservative surgery received adjuvant radiotherapy. The 5-year cumulative incidence of LR was 2.6 % for the entire cohort and 4.2 % after BCT. There were no deaths and no isolated distant failures.

The rate of axillary metastases at diagnosis was low with no macrometastases and 4 % with micrometastases. This is lower than the 6–11 % rate of axillary metastases (>0.2 mm) reported in other studies of MIBC.[20,21,25] This lower rate may be attributable to dedicated breast pathology review and enhanced detection of minimal regions of microinvasion, or it could reflect our sentinel node evaluation procedure, which does not include routine keratin IHC.

Close/positive margins (≤2 mm) were associated with an increased risk of LR compared to negative (>2 mm) margins, both overall ($P = 0.003$) and within the subgroup treated with BCT ($P = 0.06$). These data highlight the importance of both a careful pathologic evaluation of high-grade DCIS for the presence of microinvasion, careful evaluation of margin status, and achievement of negative margins at the end of surgical treatment. Most patients in the study self-identified as white. Of the patients who experienced recurrence, 7 were white and 1 was black. Because of the homogeneity of self-reported race in this study, we could not draw any conclusions regarding association between race and recurrence.

HER-2/neu overexpression is significantly higher in microinvasion (49 %) compared with both invasive carcinomas >0.1 cm (10–15 %) and DCIS (20 %).[17,26,27] Despite the higher prevalence, there was no association with recurrence or nodal metastases in our series. MIBC patients have a favorable outcome compared with HER-2/neu-positive tumors—between 0.1 and 1.0 cm (T1a–b), which has a 5-year recurrence-free survival of 77.1 %.[16] This difference in outcome justifies the continued pathologic distinction between DCIS with microinvasion and T1a–b invasive breast cancer and their differing management.

Several limitations in our series should be noted. In our analysis of risk factors for recurrence, we could not perform multivariate analysis because of the small number of events and the potential for statistical overfitting of the model. There was heterogeneity in treatment, with some patients receiving BCT and others mastectomy, which may particularly influence the LR estimates. We addressed this by providing the results for both mastectomy and BCT. We could not determine the receptor status for every case. One (of 3) patients with axillary nodal metastasis received chemotherapy, and 4 patients received chemotherapy, none of whom experienced recurrence. We have insufficient distant recurrences in the first 5 years of follow-up to suggest that additional treatment such as chemotherapy might improve outcomes. We wondered whether the rate of axillary metastases may be influenced by the number of foci of microinvasion and biologic subtype, but our study was not powered to address this important question. Finally, with longer follow-up, there are likely to be additional recurrences.

In conclusion, MIBC has a favorable prognosis, and HER-2/neu overexpression, although highly prevalent, is not significantly associated with recurrence. The cumulative incidence of LR after BCT is acceptable; however, our data confirm that negative margins (>2 mm) are required for optimal BCT outcomes. We currently recommend careful and extensive pathologic evaluation of tissue excised, excision to achieve negative margins, and radiotherapy in BCT. Consideration for sentinel node evaluation is reasonable, although axillary metastases at diagnosis are small and infrequent, and they do not predict for recurrence.

ACKNOWLEDGMENT We thank Barbara Silver for editing and research support.

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