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Analysis of Stereotactic Biopsies Performed on Suspicious Calcifications Identified within 24 months after Completion of Breast Conserving Surgery and Radiation Therapy for Early Breast Cancer: Can Biopsy Be Obviated?

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Abstract

Background—To determine the cancer yield of stereotactic biopsy of suspicious calcifications identified within 24 months after breast conservation therapy (BCT)

Methods—Retrospective review of stereotactic biopsies performed during 2009–2013 for suspicious calcifications in the ipsilateral breast of patients who completed BCT

Results—94/2773 (3.4%) had stereotactic biopsies for suspicious calcifications in the ipsilateral breast; 7/94 (7.4%) had DCIS (6) or invasive (1) cancer; 5/7 occurred in the same breast quadrant as the primary. All 7 originally had negative surgical margins (≤ 2 mm); 6 received whole breast irradiation, and 2 received adjuvant chemotherapy+endocrine therapy. Median time to detection was 11 months (range, 6–20 months). There was a strong association between calcification morphology (particularly pleomorphic) and likelihood of malignancy ($p=0.008$).

Conclusions—Stereotactic biopsy of calcifications identified within 24 months post-BCT has a 7% cancer yield. Tissue biopsy should be performed rather than imaging followup alone when breast calcifications have suspicious morphology.

Monica L. Huang, MD – Nothing to disclose.

Lumarie Santiago, MD – Nothing to disclose.

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Keywords

breast cancer; breast conservation; calcifications; mammography; stereotactic biopsy

INTRODUCTION

Breast conservation therapy (BCT) (breast-conserving surgery [BCS] followed by breast radiation therapy [RT]) is widely accepted as the treatment of choice for early-stage breast cancer. Large prospective studies showed no significant difference in rates of distant metastasis or survival between women undergoing mastectomy and women undergoing BCT.^{1–3} Nonetheless, women treated with BCT are at risk for locoregional recurrences or second ipsilateral breast cancer with incidence of 1–2% per year for 10 years.⁴ Early detection of breast cancer local recurrence provides a significant survival advantage.

Mammography complementary with breast physical examination is the current standard of care for surveillance after BCT. New calcifications identified on mammography after BCT may represent ipsilateral tumor recurrence, a second breast cancer or benign treatment sequelae.^{5,6} For diagnosis of suspicious calcifications detected only on mammography, tissue can be sampled with stereotactic biopsy, a minimally-invasive procedure. Although previous studies have suggested adequacy of annual mammographic surveillance due to low rates of ipsilateral breast cancer recurrence within 2 years after completion of BCT, to our knowledge there are no published studies on the rate of malignancy of suspicious calcifications detected on digital mammography within two years of BCT.^{7,8} Previous published small series did not focus on the early post-BCT period and were predominantly based on film screen mammography.^{9–15} Identification of early-developing suspicious calcifications helps to select appropriate patients to undergo stereotactic biopsy.

The primary aim of our study was to determine the cancer yield of stereotactic biopsy of suspicious calcifications identified within 24 months after BCT. The secondary aim was to determine whether mammographic features of early-developing suspicious calcifications in the post-BCT breast are associated with likelihood of malignancy.

MATERIALS AND METHODS**Study Population**

We performed a retrospective review of the electronic imaging database at a single institution to identify patients who underwent stereotactic biopsy between 1/1/2009 and 12/31/2013 for new suspicious calcifications (i.e., designated a BIRADS 4 or 5 by the original interpreting radiologist) in the conservatively-treated breast within 24 months after BCT. All patients had surgery at our institution. Patients with RT completed at our institution or at an outside facility but adequately documented in our electronic medical records were included. We excluded patients who did not complete post-BCS RT. We also did not include patients in which other mammographic abnormalities such as mass, asymmetry or architectural distortion were identified and resulted in ultrasound and/or MRI

workup and biopsies. Institutional Review Board approval was obtained, and the requirement for informed consent was waived.

Imaging and Biopsy Techniques and Interpretation

Diagnostic mammography included standard craniocaudal (CC), mediolateral oblique (MLO), and lateromedial (LM) views and additional CC and LM spot compression magnification views were performed using full-field digital mammography units (Lorad Selenia Hologic). All mammograms were reviewed independently according to the American College of Radiology BI-RADS (Breast Imaging Reporting and Data System) mammography lexicon by 3 radiologists, fellowship-trained in breast imaging (B.E.A., R.P.C., and P.H.).¹⁶ The following mammographic features were analyzed: presence/absence of mass, architectural distortion, or asymmetry; size, morphology, and distribution of calcifications; and location of calcifications relative to the surgical scar. For calcifications, morphology was categorized as round, coarse heterogeneous, amorphous, fine pleomorphic, or fine linear/fine linear branching, and distribution was categorized as diffuse, regional, grouped, linear, or segmental.

All biopsies were performed using a stereotactic approach with the patient on a prone table (Lorad Multicare Platinum, Hologic). Core needle samples were obtained using a 9-G vacuum-assisted biopsy system (ATEC Pearl, Hologic). Routine specimen radiographs and post-procedure mammograms were obtained to confirm that the target calcifications were adequately sampled.

Data Collection and Analysis

The following data were collected from electronic medical records: patient age; dates of surgery, RT completion, and calcification detection; time interval between completion of each treatment and calcification detection; surgical procedure, RT method, and adjuvant therapy; primary tumor TNM stage, tumor grade, hormonal status, and surgical margin status; and findings on pathologic examination of the stereotactic biopsy specimen. In patients with benign histopathology at stereotactic biopsy, imaging studies from the following 2 years were reviewed to assess lesion stability.

Statistical analysis was performed using R, version 3.3.1 (<http://www.R-project.org>). Fisher's exact tests for statistical significance were used to assess associations between clinicopathologic variables and tumor recurrence. For variables significant in bivariate analysis, univariate logistic regression was analyzed to predict likelihood of malignancy. P values less than 0.05 were considered statistically significant.

RESULTS

From 2009–2013, 2773 patients in our institution completed BCS+RT; of these 2773 patients, 94 (3.4%) were included in this study. The index, or more dominant, lesion was included in the analysis for the 6 of 94 patients who underwent 2 stereotactic biopsies each. Primary malignant tumors were invasive ductal carcinoma (IDC) in 9 patients, IDC with ductal carcinoma in situ (DCIS) in 33, invasive lobular carcinoma (ILC) in 5, mixed IDC and ILC in 6, mixed IDC and ILC with DCIS in 2, invasive mucinous carcinoma in 2, and

DCIS in 37. The post-BCT stereotactic biopsies showed malignant histopathology in 7 of 94 patients for a cancer yield of 7% (and 7/2773, 0.3% patients overall) and benign histopathology in 87 of 94 patients (93%).

For the 7 malignant cases, the mean patient age was 54 years (range, 38–73 years). Histopathologic findings from the stereotactic biopsies were high-grade IDC with DCIS in 1 patient, high-grade DCIS in 4, intermediate-grade DCIS in 1, and low-grade DCIS in 1. All 7 patients had negative (≥ 2 mm) margins after BCS for the first malignancy. None of these cases had a first malignancy with an extensive intra-ductal component. Whole breast irradiation was performed in 6 patients, and accelerated partial breast irradiation (APBI) was performed in 1. Two of the 7 post-BCT patients had undergone adjuvant chemotherapy and hormonal therapy when the suspicious calcifications were identified. In 5 of 7 cases, the calcifications were located in the scar or same quadrant as the primary lesion and were of similar histopathology. In the other 2 cases, the calcifications were located in a separate quadrant and were of different histopathology: 1) a patient with IDC with lobular features developed high-grade DCIS post BCT, and 2) a patient with ILC developed high-grade DCIS post BCT (Fig. 1).

For the 87 benign cases, the mean patient age was 58 years (range, 32–82 years). In 61 cases, the pathologic diagnosis was related to post-therapeutic effect; the specific findings included fat necrosis, stromal fibrosis, atrophic duct/lobule, and foreign body reaction. Other benign lesions were fibrocystic change in 12 biopsies, fibroadenoma in 9, ductal hyperplasia in 3, intraductal papilloma in 1, and benign breast tissue in 1. Two-year follow-up mammograms and clinical history were available in 84 of 87 patients with none of them found to have developed ipsilateral recurrence or second breast cancer.

Segmental mastectomy or lumpectomy was performed in all 94 patients. For this cohort of 94 patients, median time from BCS to calcification detection was 14 months (range, 7–24 months), and median time from RT completion to calcification detection was 10 months (range, 2–24 months). Median times to detection of calcifications after BCS and RT were 12 months (range, 11–23 months) and 11 months (range, 6–20 months), respectively, for malignant cases and 14 months (range, 7–24 months) and 9 months (range, 2–24 months), respectively, for benign cases.

The relationship between mammographic and histopathologic features of the suspicious calcifications, all of which were classified as BI-RADS 4, is shown in Table 1. Mean size of calcifications was 10.9 mm (range, 2.0–80 mm) for the entire group of 94 cases, 10.8 mm (range, 2.0–80.0 mm) for the benign cases, and 15.4 mm (range, 6.0–30.0 mm) for the malignant cases. Median number of specimens obtained from stereotactic biopsy was 7 (range, 4–24), and median number of specimens with calcifications was 4 (range, 1–11).

There was a strong association between morphology of calcifications and the likelihood of malignancy ($p=0.008$); malignancy was found in 0/7 (0%) biopsies of round, 2/47 (4%) biopsies of coarse heterogeneous calcifications, 3/38 (8%) biopsies of amorphous calcifications, and 2/2 (100%) biopsies of fine pleomorphic calcifications (Table 2). The likelihood of developing a second malignancy after BCT was not significantly associated

with primary tumor size, stage, hormonal receptor status, surgical margin, method of RT, endocrine treatment or with location or distribution of new calcifications ($p = 0.20$ for each) (Table 2).

DISCUSSION

The development of new calcifications in the post-BCT breast, which has a reported prevalence ranging from 7–28%, presents a diagnostic dilemma.^{6,12,13} Post-treatment changes diminish the sensitivity of mammography, resulting in compromised differentiation between benign and malignant calcifications. New calcifications may represent local recurrence, new cancer, or benign post-treatment process.¹⁷ Recommendation for biopsies of new calcifications not only has a financial impact but also an emotional one.¹⁷ Our study showed that the cancer yield for stereotactic biopsy of suspicious calcifications that developed within 24 months after BCT was 7%. Previously-reported rates of malignancy on biopsy of suspicious calcifications that are clinically-occult and not associated with another new mammographic abnormality such as a mass in the conservatively-treated breast range from 0–100% with a total number of 64 patients biopsied reported across seven series.^{9–15} Our malignancy rate was at the lower range at 7%, most probably because of different inclusion criteria in which we analyzed only suspicious calcifications that developed relatively early in the post-BCT surveillance period while the other series included calcifications that developed over a more extended time frame.

Our study also showed a strong association between the morphology of the calcifications and the likelihood of malignancy ($p=0.008$). Previous studies have examined the usefulness of mammographic features of calcifications in predicting malignancy; Giess et al and Günhan-Bilgen et al reported that all malignant calcifications in the post-BCT breast manifested as pleomorphic calcifications.^{12,13} Our results agree with these previously-reported findings in that we found that all cases of pleomorphic calcifications in our cohort were malignant.^{12,13,18} Additionally, in our study, 0% of round, 4% of coarse heterogeneous and 8% of amorphous calcifications represented new disease. Our results align with the increasing rate of malignancy based on BI-RADS morphology as reported in a meta-analysis by Rominger et al that showed malignancy rates of 9% for round calcifications, 13% for coarse heterogeneous, 27% for amorphous, and 50% for pleomorphic.¹⁹

Dershaw described that recurrence within the first 5 years after treatment most often appears at or near the site of original tumor and occurs because of failure to eradicate the original carcinoma, whereas tumor developing after 5 years often grows elsewhere in the breast and appears in a new tumor form.¹⁷ Our cohort of patients who developed a second malignancy had wider negative surgical margins ($>2\text{mm}$) by current standards with 2 of the 7 patients also having undergone adjuvant chemotherapy with endocrine therapy. Our data is similar to Dershaw's report in that all malignant calcifications that developed adjacent to the surgical bed were of histopathology similar to that of the primary tumor, whereas malignant calcifications that developed elsewhere were of different histopathology.¹⁷

Previous reports have shown that interpretation of new calcifications in the treated breast should not be influenced by the presence or absence of calcifications in the original tumor

because the calcification status of the original tumor does not necessarily match that of recurrent disease.^{12,14} Our data agree with these reports: 3 of 7 second malignancies in our series did not have a primary malignancy that presented with calcifications. Therefore, any suspicious calcifications in the treated breast should be subjected to tissue diagnosis regardless of the appearance of the original tumor.

There remains no consensus on the timing and frequency of post-BCT mammographic surveillance because of the paucity of supporting data. Indeed, this is the subject of a large, multicenter trial comparing annual versus biannual mammography (the Mammographic surveillance in breast cancer patients aged 50 years or older ISRCTN48534559).²⁰ In our study, time to detection of calcifications overlapped between benign and malignant cases. Previous studies have also shown overlap between benign and malignant cases in time to detection of calcifications, therefore, suggesting that time to calcification detection is not a good predictor of histopathology.^{6,12,13} Nonetheless, our study revealed that most of the second malignancies (4 of 7 cases) were identified within 12 months after completing RT, which indicates that the current American Society of Clinical Oncology (ASCO) guidelines of an initial surveillance mammogram between 6–12 months after RT seems appropriate.²¹ It is important to clarify that these 7 malignant cases out of the 2733 total number of patients who completed BCS+RT amount to a detection rate of 2.5 per 1000 mammograms but do not include additional cases that would have been detected as other new abnormalities on mammography (e.g., mass, focal asymmetry, architectural distortion).

This study has some limitations including the small patient sub-population and the inherent selection bias of a retrospective design. Additionally, since post-BCS, pre-RT mammography was not routinely performed at our institution, we cannot exclude residual calcifications after BCS; however, all cases in our study had pathologically-proven, widely-negative primary tumor resection margins. Also, the frequency of surveillance mammography after BCT depended on individual clinician preference (ranging from 6–12 months post-BCT), and this variation may have influenced the time to detection of calcifications. Finally, patients undergoing ABPI are recognized to have a higher rate of local breast recurrence than those undergoing external beam radiotherapy (ELIOT and TARGIT trials), although the comparative numbers undergoing ABPI here were too small to unduly influence overall recurrence rate.^{22,23}

In conclusion, we found that stereotactic-guided vacuum-assisted biopsy of suspicious calcifications developing within 24 months after BCT resulted in a cancer yield of 7%. Similarly to the general population, the management of new calcifications in the post-BCT population should be dictated by morphology. Therefore, even in the setting of adjuvant therapy, tissue biopsy should not be obviated in lieu of follow up imaging when calcifications have morphology that is suspicious by BI-RADS guidelines.

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Figure 1.

A 61-year-old woman had a group of amorphous calcifications detected on follow-up mammography 11 months after breast-conserving surgery (BCS) for invasive lobular carcinoma in the right lower outer quadrant. She had been treated with accelerated partial breast irradiation after BCS. (A) Craniocaudal and (B) spot compression magnification mammograms show grouped amorphous calcifications in the right lower inner quadrant. Biopsy yielded high-grade ductal carcinoma in situ. A skin marker indicates the postsurgical scar with associated seroma located in the right lower outer quadrant. A post biopsy clip shows the site of a prior ultrasound-guided biopsy with benign findings in the right upper outer quadrant.

TABLE 1

Relationship between mammographic features and pathologic findings of new calcifications identified within 24 months after completion of breast conservation therapy (n=94)

Mammographic features		Pathologic findings		
Distribution	Morphology	Benign	Malignant	Total
Diffuse	Amorphous	1	0	1
Regional	Punctate/round	2	0	2
	Amorphous	1	0	1
	Coarse heterogeneous	4	0	4
Grouped	Round	5	0	5
	Amorphous	31	3	34
	Coarse heterogeneous	40	2	42
	Fine pleomorphic	0	2	2
Linear	Amorphous	2	0	2
	Coarse heterogeneous	1	0	1
Total		87	7	94

TABLE 2

Relationship between clinicopathologic features and cancer rate in patients with new suspicious calcifications identified within 24 months after completion of breast conservation therapy (n=94)

Feature	No. of patients with cancer/total no. of patients	% of patients with cancer	P value
<i>Primary cancer</i>			
Size, mm *			0.76
20	2/37	5	
>20	1/24	4	
Stage			0.52
0	4/32	13	
I	1/34	3	
II	2/22	9	
III	0/5	0	
IV	0/1	0	
Hormonal status			
ER			0.35
Positive	4/73	5	
Negative	3/21	14	
PR			0.71
Positive	4/62	6	
Negative	3/31	10	
Unknown	0/1	0	
HER2			0.26
Positive	1/15	7	
Negative	2/49	4	
Unknown	4/30	13	
Margin width, mm			1.00
<2	0/7	0	
2	7/87	8	
<i>Treatment</i>			
Radiation			0.30
APBI	1/5	20	
WBI	6/89	7	
Received risk-reduction therapy for ER-positive tumors			0.21
Yes	2/57	4	
No	2/16	13	
<i>New calcifications</i>			
Location			1.00
Scar	3/41	7	
Same quadrant as scar	2/31	7	
Different quadrant from scar	2/22	9	

Feature	No. of patients with cancer/total no. of patients	% of patients with cancer	P value
Morphology			<i>0.008</i>
Round	0/7	0	
Coarse heterogeneous	2/47	4	
Amorphous	3/38	8	
Fine pleomorphic	2/2	100	
Distribution			1.00
Diffuse	0/1	0	
Regional	0/7	0	
Grouped	7/83	8	
Linear	0/3	0	

BCS = breast-conserving surgery, ER = estrogen receptor, PR = progesterone receptor, APBI = accelerated partial breast irradiation, WBI = whole breast irradiation

* Note: patients with DCIS excluded