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A Clinical Feasibility Trial for Identification of Exceptional Responders in Whom Breast Cancer Surgery Can Be Eliminated Following Neoadjuvant Systemic Therapy

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Abstract

Objective—To determine the accuracy of fine-needle aspiration (FNA) and vacuum-assisted core biopsy (VACB) in assessing the presence of residual cancer in the breast after neoadjuvant systemic therapy (NST).

Summary Background Data—Pathologic complete response (pCR) rates after NST have improved dramatically, suggesting that surgery might be avoided in some patients. Safe avoidance of surgery would require accurate confirmation of no residual invasive/in situ carcinoma.

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Methods—Forty patients with T1-3N0-3 triple-negative or HER2-positive cancer receiving NST were enrolled in this single-center prospective trial. Patients underwent ultrasound-guided or mammography-guided FNA and VACB of the initial breast tumor region before surgery. Findings were compared with findings on pathologic evaluation of surgical specimens to determine the performance of biopsy in predicting residual breast disease after NST.

Results—Median initial clinical tumor size was 3.3 cm (range, 1.2–7.0 cm); 16 patients (40%) had biopsy-proven nodal metastases. After NST, median clinical tumor size was 1.1 cm (range, 0–4.2 cm). Nineteen patients (47.5%) had a breast pCR and were concordant with pathologic nodal status in 97.5%. Combined FNA/VACB demonstrated an accuracy of 98% (95% CI, 87%–100%), false-negative rate of 5% (95% CI, 0%–24%), and negative predictive value of 95% (95% CI, 75%–100%) in predicting residual breast cancer. VACB alone was more accurate than FNA alone ($P = 0.011$).

Conclusions—After NST, image-guided FNA/VACB can accurately identify patients with a breast pCR. Based on these results, a prospective clinical trial has commenced in which breast surgery is omitted in patients with a breast pCR after NST according to image-guided biopsy.

Keywords

breast cancer; breast imaging; neoadjuvant; prospective clinical trial; surgery

The impact of avoidance of surgery in select breast cancer patients, if proved to be safe and effective, has the potential of decreasing short and long-term postsurgical complications, improved quality-of-life, and decreasing health care costs. Among patients with breast cancer, rates of pathologic complete response (pCR) to neoadjuvant systemic therapy (NST) have improved dramatically in the past decade, especially among patients with triple-negative breast cancer and HER2-positive breast cancer receiving improved NST.¹ Rates of pCR in these groups of patients can be up to 60%, which raises the question of whether breast and nodal surgery are required for all patients, particularly those who will receive adjuvant radiotherapy.^{2,3} Historically, attempts have been made to omit surgical resection in breast cancer patients treated with NST, but these attempts resulted in high rates of local-regional recurrence.¹ These historical studies had methodologic features now known to be suboptimal, including use of only physical examination to determine clinical response, lack of selection of patients by disease subtype, and/or lack of utilization of enhanced image-guided biopsy to assess for pathologic response.¹ The main impediment to potential omission of surgery for breast cancer has been the fact that standard breast imaging methods cannot accurately predict the status of residual disease after NST.^{1,4–7}

This prospective single-center trial was designed to assess the accuracy of image-guided fine-needle aspiration (FNA) and vacuum-assisted core biopsy (VACB) of the initial breast tumor region in assessing the presence or absence of residual breast carcinoma after NST. For this study compared with previous reported studies from our group and others, a pCR was defined as absence of invasive carcinoma and ductal carcinoma in situ.^{1,8} This endpoint was selected and defined in this protocol as optimal for patients enrolled in clinical trials where surgery is to be omitted as no residual invasive or DCIS would be required in this clinical scenario. The results of the present study were utilized to design a clinical trial that

has recently begun accrual at MD Anderson designed to test the safety of selective omission of surgery in breast cancer patients who are exceptional responders to NST as determined by percutaneous image-guided biopsy and who will undergo standard radiotherapy.⁹

METHODS

Patients and Procedures

Patients were eligible for this single-center study if they had image-guided core biopsy-confirmed triple-negative or HER2-positive (3+ score on immunohistochemical analysis or HER2 amplification on fluorescence in situ hybridization) clinical T1-4N0-3M0-1 breast cancer and were receiving NST with planned surgery during 2015 to 2016. Informed consent was obtained before patients were enrolled in this trial that was registered with the NIH ClinicalTrials.gov (NCT02455791), and was approved by our institution's Institutional Review Board.

Patients received standard NST regimens (anthracycline- and/or taxane-based with the addition of HER2-targeted therapy for patients with HER2-positive disease). At diagnosis and after NST, patients had breast imaging that included mammography and whole-breast and regional nodal sonography (with biopsy of any suspicious nodes) per institutional protocol. Imaging findings were carefully reviewed by dedicated breast radiologists to identify residual imaging abnormalities and determine the optimal method for imaging-guided biopsy. Features recorded included the presence and size of residual mass/architectural distortion and microcalcifications in the tumor bed. A radiologic complete response in the breast was defined as no residual imaging abnormality other than the presence of the clip placed in the cancer at the time of the initial biopsy.

After NST and prior to standard surgery, responding patients (imaging complete/partial response) underwent ultrasound-guided or mammography-guided combined FNA and VACB (FNA/VACB) of the site of the treated breast cancer in the breast imaging suite from 10 days prior to and up to the same day of definitive surgery. FNA was performed with 2 passes and VACB was performed using a 9G needle (Eviva/ATEC breast biopsy system, Hologic, Bedford, MA; Fig. 1). The FNA material was used to prepare smears that were stained with Papanicolaou and modified Giesma stains and subjected to conventional cytopathological examination. If no residual imaging abnormality was identified following NST, the clip placed in the breast cancer at the time of the initial biopsy, together with the region immediately surrounding the clip, was sampled, followed by the placement of a new clip to document removal of the original clip and/or sampling of the treated breast cancer. In accordance with protocol requirements, all expected and unexpected adverse events, regardless of grade or treatment attribution, were recorded and graded using the NCI's Common Toxicity Criteria for Adverse Events, version 4.0.

The results of the pathologic evaluation of the FNA and VACB specimens were compared with the results of standard evaluation of the surgical specimen, which included acquisition of radiographs of the intact specimen and 5-mm specimen slices to ensure complete histologic sampling of the initial tumor bed. The breast specimen and nodes were processed

and dedicated breast pathologists documented the presence or absence of residual carcinoma (noninvasive and invasive), the size of any residual disease, and any changes due to therapy.

Statistical Analysis

The design of this prospective study assumed that approximately 60% of patients would have residual carcinoma (invasive and/or DCIS) after NST. The sample size of 40 was determined to provide sufficient information to characterize the diagnostic properties of VACB, yielding on average 95% confidence intervals (CI) for the false-negative rate and negative predictive value of (0.03–0.30) and (0.60–0.96), respectively, with an estimated assumed 90% sensitivity and specificity for VACB. The findings from the pathologic review of the preoperative FNA and VACB specimens were compared to the findings from the pathologic review of the breast surgical specimen to identify cases in which biopsy failed to detect residual disease when residual disease was actually present. A pCR (ypT0) was defined as no evidence of residual invasive or in situ carcinoma in the breast surgical and biopsy specimen; cases showing invasive, in situ, or suspicion for residual carcinoma were coded as positive. The accuracy, sensitivity, specificity, false-negative rate, and positive and negative predictive values were calculated for FNA alone, VACB alone, and the combination of FNA and VACB. Statistical analyses were carried out using statistical software R version 3.2.5¹⁰ and were calculated using exact (Clopper–Pearson) confidence limits for the binomial proportion. The exact McNemar test was applied to test for marginal homogeneity¹¹ among the paired assessment based on FNA alone and VACB alone. All tests were 2-sided with statistical significance conferred at the 0.05 level.

RESULTS

Patient and Tumor Characteristics

Table 1 lists patients and tumor characteristics and protocol outcome measures for the 40 patients with invasive ductal carcinoma who enrolled in and completed the study. The median age of the patients was 50.5 years. The median initial clinical tumor size was 3 cm (range, 1.2–7 cm) based on physical examination and breast imaging. Thirty-six patients (90%) had clinical T1 or T2 tumors. Sixteen patients (40%) had FNA/core biopsy-proven axillary nodal metastases. Twenty-six patients (65%) had triple-negative breast cancer, and 14 (35%) had HER2-amplified disease.

Response to NST

Nineteen patients (47.5%) had a pCR in the breast defined as no residual invasive or in situ breast carcinoma. A pCR in the breast occurred in 13 of 26 patients (50%) with triple-negative tumors and 6 of 14 patients (42.9%) with HER2-positive tumors ($P = 0.78$). Patients with HER2 and ER-negative cancers were more likely to have a pCR in the breast compared with patients with HER2 and ER-positive cancers, although this did not reach statistical significance (80% vs. 22%, respectively; $P = 0.09$). There were no statistical significant baseline differences between those patients who did and did not achieve a pCR with respect to median age ($P = .80$), race/ethnicity ($P = 0.40$), clinical T stage ($P = 0.31$), or presence of confirmed nodal metastases ($P = 0.35$). Median largest tumor size after NST based on physical examination and breast imaging was 1.1 cm (range, 0–4.2 cm). Eight patients

(20%) had a radiologic complete response in the breast. Among the patients with a radiologic complete response in the breast, 87.5% had a breast pCR. Importantly, 12 of 19 patients (63.2%) who had a breast pCR did not have a radiologic complete response in the breast. Thirty-nine of 40 patients (97.5%) had concordant breast pathologic response and pathologic nodal status; 1 patient with a breast pCR had a single positive lymph node with micrometastases (1 mm) on final pathologic evaluation.

Accuracy of Image-guided Biopsy in the Detection of Residual Carcinoma

Fifteen patients (37.5%) had ultrasound-guided FNA/VACB, and 25 (62.5%) had stereotactic-guided FNA/VACB. On VACB, the median number of cores removed was 12 (range, 4–14). Table 2 summarizes the performance of FNA, VACB, and the combination of FNA and VACB in predicting residual breast disease after NST. The combination of FNA and VACB correctly identified the pathologic status of the breast in 39 of 40 patients and had an accuracy of 98% (95% CI, 87%–100%), a false-negative rate of 5% (95% CI, 0%–24%), and a negative predictive value of 95% (95% CI, 75%–100%). VACB alone was significantly more accurate than FNA alone ($P = 0.012$).

FNA alone had an accuracy of 73% (95% CI, 56%–85%), a false-negative rate of 52% (95% CI, 30%–74%), and a negative predictive value of 63% (95% CI, 44%–80%). In contrast, VACB alone correctly identified the pathologic status of the breast in 95%, had a false-negative rate of 10% (95% CI, 1%–30%), and a negative predictive value of 90% (95% CI, 70%–99%) with only 2 patients having residual disease identified in the surgical specimen but not detected in the VACB specimens. These patients had only 4 and 6 VACB specimens obtained, whereas the median number of VACB specimens obtained for the remaining patients in the study was 12 suggesting that the tumor bed was under sampled (Table 1). The false-negative cases occurred in 1 patient with a triple-negative breast cancer and 1 patient with a HER2-amplified tumor, both had a partial radiologic response with final residual lesions measuring 3.1 and 2.5 cm on imaging, and overall pathologic findings demonstrated < 3% tumor cellularity in a tumor bed measuring 1.3 cm and 1.8 cm, respectively. In 5 patients, all residual disease was removed in the VACB specimens, that is, disease was present in the VACB specimens but not in the breast surgical specimen.

Table 3 characterizes the performance of mammography, ultrasound, and the combination of image-guided FNA/VACB with mammography and ultrasound in predicting residual breast disease after NST. These results demonstrate that imaging has decreased accuracy, specificity, and positive-predictive value compared with image-guided biopsy in detecting residual disease. Utilizing the combination of imaging and image-guided biopsy in determining residual disease would correctly identify patients without residual disease in only 7 of 19 (36.8%) patients who actually had a pCR.

Biopsy-related Adverse Events

Patient tolerance of the biopsy procedure was excellent, and there were no vasovagal episodes. Adverse events of image-guided biopsy occurred in 8 patients (20%; bleeding at puncture site in 4, hematoma in 3, and bruising in 1) and did not exceed grade 1 in any patient.

DISCUSSION

This initial feasibility trial demonstrated that state-of-the-art image-guided biopsy after NST of the initial tumor bed region and removal of the initial biopsy clip when no residual imaging abnormality is identified can accurately identify most patients with no residual invasive or in situ disease in the breast following NST. This study also demonstrated the strong correlation between pathologic response in the breast and pathologic status of the axillary lymph nodes. Further, the findings showed that although FNA biopsy is an accurate method for initial diagnosis, it has a very high false-negative rate (52%) in the detection of residual disease in the breast following NST, a finding most likely related to the therapy associated tumor bed fibrosis that can result from NST. The initial design of the trial included FNA as a potential accurate procedure for sampling the prior tumor bed after NST as multiple areas can simultaneously be sampled with this technique. In contrast, VACB had a much lower false-negative rate of only 10%, and the 2 patients with false-negative findings on VACB were patients who underwent limited sampling which suggests that the false-negative finding was most likely due to sampling error. This information is useful for planning future similar feasibility trials to be followed by definitive studies where surgery will be omitted. Based on the results of this feasibility trial a minimum of 12 9G image-guided VACBs of the initial tumor bed region is required for the participation in the recently opened eliminating breast cancer surgery in exceptional responders with neoadjuvant therapy trial at our institution.⁹

For several other malignant diseases, including some stages of esophageal, anal, laryngeal, prostate, cervical, and lung carcinomas, sequential and/or concurrent chemoradiation as a definitive local treatment has been proven effective.¹ Efficacy of this approach is thought to be due to the ability of radiotherapy to eradicate microscopic disease particularly in documented responding tumors. The concept of eliminating surgery in breast cancer patients with an exceptional response to NST is not new, but earlier studies of this approach resulted in high rates of local-regional recurrence as they relied on clinical evaluation of response to NST, an approach now known to be inaccurate in predicting the presence or absence of residual disease in breast cancer.¹ A recent large multicenter trial performed in Germany by Heil et al showed that biopsy had a false-negative rate of 49% in the identification of patients with a pCR after NST.^{12,13} A number of features of that trial most likely contributed to the high false-negative rate, including the inclusion of all breast cancer subtypes; no tumor size/imaging criteria for participation; inadequate tumor bed tissue sampling (size and number of biopsies utilized and only 30% had VACB; in 37% of patients, no clip was placed at the initial cancer site prior to NST to guide adequacy of sampling); and use of image-guided stereotactic biopsy in only 10% of cases.^{12,13}

One question that has been raised in discussions regarding omission of surgery after NST is: how should the axillary lymph nodes be handled following NST if no breast surgery is planned? In our initial study reported herein, in 97.5% of patients the pathologic response in the breast correlated with the axilla, and the 1 patient with a breast pCR but disease in the axilla had only minimal residual micro-metastatic nodal disease. These findings are concordant with data from a recent retrospective study at our institution that showed that breast pCR after NST correlated with nodal pCR after NST.¹⁴ This study included 290

patients with triple-negative or HER2-positive breast cancer with T1-2N0 disease and no suspicious findings in the regional nodal basins during initial sonographic evaluation at diagnosis. Of the 116 patients who had a pCR in the breast after NST, all (100%) had no evidence of axillary lymph node metastases after NST. In the same series, among 237 patients with FNA/core biopsy-documented N1 disease, 89.6% of patients with a breast pCR after NST had no evidence of axillary metastases, 57.5% of patients without a breast pCR had residual axillary metastases.

Previous studies have shown that in breast cancer patients who undergo NST followed by surgery and radiotherapy, a pCR in patients with triple-negative and HER2-positive subtypes after NST is associated with a very low risk of local-regional recurrence as well as excellent long-term disease-free and overall survival.^{3,8,15,16} The findings from those studies, taken together with the findings from the initial feasibility study reported here, have led to a recently opened clinical trial at our institution evaluating the omission of breast surgery after NST in patients with a breast pCR confirmed by image-guided biopsy after NST.⁹ The trial is open to patients with triple-negative or HER2-positive breast cancer with tumor size less than 5 cm at the time of diagnosis in whom image-guided biopsy demonstrates no residual carcinoma. Patients will not undergo breast surgery after NST but will receive whole-breast radiotherapy. The primary end-point for this initial study is ipsilateral breast recurrence-free survival.

In conclusion, our data support the hypothesis that it is possible to accurately identify patients who are exceptional responders to NST with well-sampled image-guided biopsy. This method can identify patients with a pCR who may also be considered potential optimal candidates for consideration of participation in prospective clinical trials designed to test omission of surgery after NST. Notwithstanding, additional single and multicenter trials testing this methodology are planned or have commenced in the USA with the NRG Oncology Group (formerly the National Surgical Adjuvant Breast and Bowel Project [NSABP], Radiation Therapy Oncology Group [RTOG], and Gynecologic Oncology Group [GOG]; NRG Study BR005) and internationally which will need to replicate the results of the current study before this approach can be broadly utilized in clinical trials of omission of surgery. Imaging expertise including proper education regarding sampling of the tumor bed will be critical and best performed at specialized centers where there is meticulous collaboration among the multidisciplinary teams in order to safely select patients. As the field begins to further test this methodology for breast cancer patients treated with NST, essential additional endpoints for the study will include the impact on avoidance of surgical complications, patient quality of life, and overall health care-related costs.

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FIGURE 1.

A 44-year-old woman with a palpable triple-negative invasive ductal carcinoma who was enrolled in and completed the study. (A) Craniocaudal and (B) lateromedial left mammograms at diagnosis show a 4.6-cm irregular high-density mass (white arrows) with a ribbon-shaped clip (dashed arrow). C, Corresponding longitudinal gray-scale ultrasound image shows a 4.9-cm hypoechoic lobular mass (arrow). D, Ultrasound image after the completion of NST shows a flattened tumor bed (arrow) with a clip (dashed arrow). Stereotactic biopsy was performed with the removal of the clip. (E) Craniocaudal and (F) lateromedial left mammograms after biopsy demonstrate residual focal asymmetry with a new rod-shaped clip (arrow) at the biopsy site. Specimen radiographs (G) of the core biopsy specimens confirm the removal of the ribbon-shaped clip (dashed arrow). Pathologic evaluation of the core biopsy specimens showed no evidence of residual carcinoma. H, Specimen radiographs from needle-localized segmental mastectomy confirm the removal of the residual focal asymmetry and the clip (arrow). Pathological evaluation of the breast surgical specimen confirmed pCR.

TABLE 1

Patient and Tumor Characteristics

Characteristic	Value
Median age (range), yrs	50.5 (26–76)
Race/ethnicity, no. (%)	
White	22 (55)
Black	8 (20)
Hispanic	9 (22.5)
Asian	1 (2.5)
Initial largest median tumor size, (range), cm	3 (1.2–7)
Initial clinical T category, no. (%)	
T1	12 (30)
T2	24 (60)
T3	4 (10)
Initial cytologically or histologically confirmed nodal metastases, no. (%)	16 (40)
Histology, no. (%)	
Ductal	40 (100)
Lobular	0 (0)
Other	0 (0)
Nuclear grade, no. (%)	
1	0 (0)
2	2 (5)
3	38 (95)
Tumor receptor subtype, no. (%)	
HR+/HER2+	8 (20)
HR–/HER2+	6 (15)
HR–/HER2–	26 (65)
Breast pCR (ypT0) (no residual invasive or DCIS), no. (%)	
Overall	19 (47.5)
Triple-negative	13 (50)
HER2-positive	6 (42.9)
Breast pCR (ypT0/Tis) (no residual invasive but with residual DCIS), no. (%)	
Overall	21 (52.5)
Triple-negative	15 (57.6)
HER2-positive	6 (42.9)
Breast and nodal pCR (ypT0N0), no. (%)	
Overall	18 (45)
Triple-negative	12 (46.2)
HER2-positive	6 (42.9)
Concordance of pathologic response in breast and pathologic nodal status	39 (97.5)*
Concordance of radiologic complete response in breast and pCR in breast, no. (%)	
Radiologic complete response	8 (20)

Characteristic	Value
Radiologic complete response and pCR	7 (87.5)
Lack of radiologic complete response	32 (80)
Lack of radiologic complete response but confirmed pCR	12 (37.5)
Final largest median tumor size after NST, (range), cm	1.1 (0–4.2)
Final biopsy guidance, no. (%)	
Stereotactic	25 (62.5)
Ultrasound	15 (37.5)
Number of samples taken on VACB, median (range)	12 (4–14)
Adverse events from breast biopsy, no. (%)	
Hematoma, grade 1 resolved	3 (7.5)
Bleeding at puncture site, grade 1 resolved	4 (10)
Bruising, grade 1 resolved	1 (2.9)

* One patient with a breast pCR had 1 positive micro-metastatic axillary node (1 mm) and 14 negative axillary nodes.

DCIS indicates ductal carcinoma in situ; HR, hormone receptor.

TABLE 2

Performance of Image-guided FNA, VACB, and the Combination of FNA and VACB in Predicting Residual Breast Disease After NST*

Measure	Test or Combination		
	FNA	VACB	Combination
Accuracy, %	73 (56–85)	95 (83–99)	98 (87–100)
Sensitivity, %	48 (26–70)	90 (70–99)	95 (76–100)
Specificity, %	100 (82–100)	100 (82–100)	100 (82–100)
False-negative rate, %	52 (30–74)	10 (1–30)	5 (0–24)
Positive-predictive value, %	100 (69–100)	100 (82–100)	100 (83–100)
Negative predictive value, %	63 (44–80)	90 (70–99)	95 (75–100)

* Values in parentheses are 95% CIs.

TABLE 3

Performance of Mammography, Ultrasound, and the Combination of Image-guided FNA/VACB With Mammography and Ultrasound in Predicting Residual Breast Disease After NST*

Measure	Test or Combination			
	Mammography	Ultrasound	Combination Mammography and Ultrasound	Combination Imaging and Image-guided Biopsy
Accuracy, %	73 (56–85)	73 (56–85)	68 (51–81)	70 (53–83)
Sensitivity, %	90 (70–99)	95 (76–100)	95 (76–100)	100 (84–100)
Specificity, %	52 (29–76)	47 (24–71)	37 (16–62)	37 (16–62)
False-negative rate, %	10 (1–30)	5 (0–24)	5 (0–24)	0 (0–16)
Positive-predictive value, %	68 (48–84)	67 (47–83)	63 (44–79)	64 (45–80)
Negative predictive value, %	83 (52–98)	90 (55–100)	88 (47–100)	100 (59–100)

* Values in parentheses are 95% CIs.