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Selective Elimination of Breast Surgery for Invasive Breast Cancer
A Nonrandomized Clinical Trial

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IMPORTANCE Neoadjuvant systemic therapy (NST) has been associated with pathologic complete response (pCR) in up to 60% of breast cancers (BCs). The findings of this trial question the necessity of surgery.

OBJECTIVE To report preplanned 5-year efficacy outcomes evaluating radiotherapy alone without breast surgery in patients selected with image-guided vacuum assisted biopsy (VAB).

DESIGN, SETTING, AND PARTICIPANTS This single-arm, prospective, phase 2 nonrandomized clinical trial was conducted at 7 US medical centers and included women 40 years or older with cT1-2N0-1M0 *ERBB2*-positive (formerly *HER2*-positive) or triple-negative invasive BC who showed residual breast lesions after NST of less than 2 cm on imaging. Enrollment was from March 6, 2017, to November 9, 2021. Data analysis was from October to December 2024.

INTERVENTION Image-guided VAB of the tumor bed (9G with a minimum of 12 cores) was performed after standard NST. Patients with clinically node-negative disease at diagnosis and no residual cancer in the breast on post-NST VAB underwent whole-breast radiotherapy with a boost without breast or axillary surgery. Patients with initial documented nodal disease and a breast pCR on VAB underwent targeted axillary dissection, while those with residual cancer when undergoing VAB had standard breast and axillary surgery. Patients were monitored with physical examinations and mammography every 6 months.

MAIN OUTCOME MEASURES The primary outcome was ipsilateral breast tumor recurrence.

RESULTS Fifty patients (median [IQR] age, 62 [55-77] years) were enrolled and underwent post-NST VAB. Twenty-nine (58%) and 21 (42%) patients had *ERBB2*-positive and triple-negative invasive BC, respectively. Breast pCR on VAB was identified in 31 patients (62%; 95% CI, 47.2%-75.34%), and axillary pCR was identified among all 8 patients with initial nodal metastases and breast pCR on VAB who underwent targeted axillary dissection. At a median follow-up of 55.4 (IQR, 44.0-63.5) months, the ipsilateral breast tumor recurrence rate was 0%, and disease-free and overall survival rates were 100% for patients without breast surgery.

CONCLUSIONS AND RELEVANCE The results of this nonrandomized clinical trial that reported preplanned 5-year outcomes suggest that omission of breast surgery in select patients after NST may be feasible, with no recurrences seen. More confirmatory studies are necessary before this new approach alters surgical practice.

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Supplemental content

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Globally, 2.3 million women receive a diagnosis of breast cancer (BC) annually. For more than a century, surgical resection has been the standard primary treatment for nonmetastatic invasive BC. Approximately 60% of patients with triple-negative BC (TNBC) and *ERBB2* (formerly *HER2*)-positive BC who are treated with neoadjuvant systemic therapy (NST) have a pathologic complete response (pCR), which indicates an excellent long-term prognosis. This high pCR rate has raised questions regarding the necessity of breast surgery for patients without residual disease after NST.

Identifying a pCR to NST can be accurately determined through percutaneous image-guided vacuum-assisted core biopsy (VAB).[1,2] A multicenter and, to our knowledge, first-in-the-field phase 2 trial was conducted to investigate whether radiotherapy alone without breast surgery is sufficient for local control in patients with a VAB-determined pCR. Results at 2 and 3 years showed no local or distant recurrences without surgery[3,4]; in this article, we report the preplanned 5-year updated results.

Key Points

Question What is the ipsilateral breast tumor recurrence rate among patients with breast cancer with exceptional response to neoadjuvant systemic therapy (NST) as determined by image-guided percutaneous biopsy, treated with radiotherapy alone and no breast surgery?

Findings In this inaugural nonrandomized clinical trial of 50 patients with breast cancer who did not undergo breast surgery after NST, the ipsilateral breast tumor recurrence rate was 0% at a median (IQR) follow-up of 55.4 (44.0-63.5) months.

Meaning The findings of this trial suggest that selective avoidance of breast surgery after NST may be feasible and may inform additional warranted clinical trials in breast cancer treatment de-escalation research.

Methods

Study Design and Patients

This was a prospective, single-arm, multicenter trial that included women older than 40 years who were not pregnant with pathologically confirmed nonrecurrent, unicentric invasive cT1-2N0-1M0 TNBC or *ERBB2*-positive BC who received clinically standard non–immunotherapy-based NST regimens. Initial NST regimens administered were previously detailed in the 2-year interim analysis.[3] The institutional review boards of the participating centers approved this prospective clinical trial (NCT02945579); the protocol is available in Supplement 1. Patients provided informed consent, and the trial followed the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) reporting guideline. Data analysis was from October to December 2024. The trial design, patient details, and outcome measures have been previously published.[3,5,6]

Procedures and Treatments

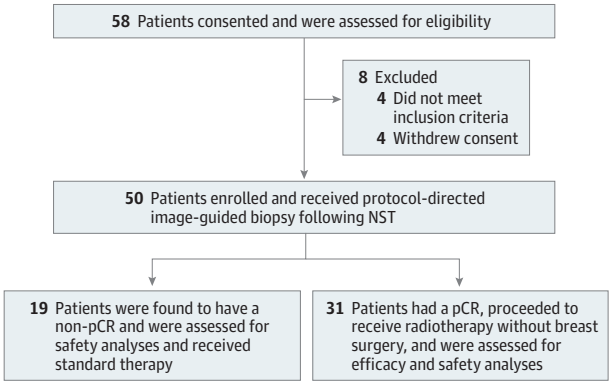
After NST, patients underwent breast imaging that documented the residual breast lesion at less than 2 cm, and the radiologist determined the best imaging guidance for biopsy. Breast biopsy could be done under stereotactic or ultrasonography guidance. One biopsy with a minimum of 12 VAB cores was obtained with a 9G needle that targeted the previously placed clip and any residual abnormality and was extensively examined histologically. After VAB, a new marker clip was placed to facilitate identification of this area for surgery (if residual disease was found) or the radiotherapy boost planning and imaging follow-up (for patients with a pCR).

If no invasive or in situ disease was detected, breast surgery was not performed. Patients with residual disease underwent standard breast and nodal surgery. Patients with initial documented nodal disease and a breast pCR were eligible for breast surgery omission if they underwent targeted axillary dissection and no residual nodal disease was found. All other patients did not undergo axillary surgery. All patients received standard whole-breast radiotherapy. For clinically node-negative patients, the prescription dose was 40.05 Gy in 15 fractions delivered to the whole breast (inclusion of the low axilla was optional). The prescription dose for the tumor bed boost was 14 Gy. For patients with axillary nodes involved, the radiation oncologist had the option of treating the breast and draining nodal basins with 50 Gy in 25 fractions followed by a boost of 14 Gy. All treatment plans were presented for central peer review at MD Anderson Cancer Center. Patients had their medical history recorded and received physical examinations and mammography every 6 months for 5 years. Abnormalities detected on mammography or physical examination had additional imaging, and biopsy was required to confirm the absence or presence of an ipsilateral breast tumor recurrence (IBTR) or nodal recurrence. Blood was collected for measuring circulating tumor cells (CTCs) using the CellSearch System (Menarini-Silicon Biosystems)[7] and circulating tumor DNA (ctDNA)–targeted sequencing (Thermo Fisher Scientific) at baseline, 6 months, and 1 year for patients with a pCR treated at MD Anderson Cancer Center Texas Medical Center.

End Points

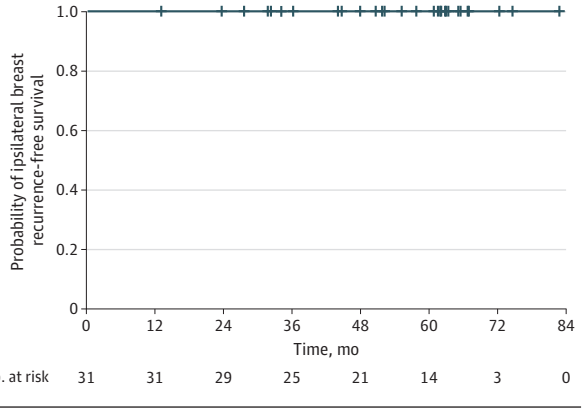
The primary outcome was IBTR, which was defined as the time from documentation of a pCR among patients who did not have breast surgery at 6 months and at 1, 2, 3, and 5 years until IBTR or death or the last contact date. The 5-year planned outcomes are reported in this article. Protocol-specified secondary outcomes included in this article are disease-free and overall survival, the presence of CTCs and ctDNA at baseline pCR and 6 and 12 months, the updated total number of patients recommended for image-guided biopsy on follow-up, and updated responses to validated patient-reported outcome measures: the Decisional Regret Scale, Breast Cancer Treatment Outcome Scale, and FACT-B+4. Scoring for patient-reported outcomes measures was described previously.[5] Secondary end points that were reported in the 2-year planned interim analysis of outcomes article include the tolerability of the biopsy procedure, the number of patients for whom biopsy demonstrated residual disease, and biopsy quantification of remaining disease at surgery among patients with a non-pCR image-guided biopsy,[3]

Figure 1. Trial Flow Diagram



pCR indicates pathologic complete response; NST, neoadjuvant systemic therapy.

Figure 2. Ipsilateral Breast Recurrence-Free Survival Among Patients With an Image-Guided Vacuum-Assisted Biopsy Pathologic Complete Response After Neoadjuvant Systemic Therapy and Treated Without Surgery



Statistical Analysis

Detailed operating characteristics for trial design, continuous data safety monitoring with formal bayesian stopping rules, and statistical analyses plans have been previously described and are available in the protocol document (Supplement 1).[3,5] In brief, target enrollment of 50 patients was set to ensure that there would be approximately 30 patients who would have a pCR after NST assuming an estimated pCR rate in this particular study population of 60% based on prior publications in the field.[8] The study consisted of a feasibility phase and an expansion phase. Time-to-event outcomes, including IBTR and overall survival, were estimated using the Kaplan-Meier method together with 95% CIs if appropriate. At each survey point, patient-reported outcome (PRO) scores were summarized using descriptive statistics. Linear mixed-effects models with intrapatient correlation were used to evaluate changes in PRO scores over time, with receipt of biopsies during the surveillance period included as a time-dependent covariate.[5] Statistical significance was set at $P < 05$. SAS (version 9.4; SAS Institute), S-Plus (version 8.2; Tibco Software), and R (version 3.4.4; R Foundation) were used for all analyses.

Results

Patients

Fifty women, 21 (42%) with TNBC and 29 (58%) with *ERBB2*-positive BC, enrolled and underwent VAB following NST (**Figure 1**) between March 6, 2017, and November 9, 2021. The last patient follow-up date was December 9, 2024. The median (IQR) age of participants was 62 (55-77) years. Baseline patient and tumor characteristics were described previously.[3] In brief, subtypes were either *ERBB2*-positive estrogen receptor (ER) or progesterone receptor (PR)-positive in 18 patients (36%), *ERBB2*-positive ER and PR-negative in 11 patients (22%), and TNBC in 21 patients (42%). Disease stage was T1 in 25 patients (50%), T2 in 25 patients (50%), and N1 in 9 patients (18%) based on image-guided nodal biopsy and clip placement before NST.

Response to NST and Image-Guided Biopsy Results

The mean (SD) final tumor size on post-NST imaging was 0.90 (0.81) cm, and 17 patients (34%; 95% CI, 21.2%-48.8%) had a complete radiologic response. VAB revealed a pCR in 31 patients (62%; 95% CI, 47.2%-75.4%), all of whom subsequently received protocol-directed radiotherapy without breast surgery. Characteristics of patients with and without receipt of breast surgery are presented the eFigure in Supplement 2. Patients with initial documented nodal disease and a VAB-determined breast pCR post-NST (n = 8) underwent targeted axillary dissection, with no residual nodal disease identified.

IBTR Rate and Disease-Free and Overall Survival

During follow-up among patients who did not receive breast surgery, 6 monthly protocol-directed imaging identified 11 patients (35.5%) who were recommended breast (n = 9) or nodal (n = 2) biopsy. In each biopsy, no cancer recurrence was identified, and results were histologically benign and concordant with imaging findings. For these 31 patients, the median follow-up time was 55.4 months (IQR, 44.0-63.5 months), the 5-year IBTR rate was 0% (**Figure 2**), and the 5-year disease-free and overall survival rates were 100%.

CTC and ctDNA Results

CTCs were evaluated in a total of 33 blood samples collected from 13 patients at baseline pCR identification, 6 months, and 12 months. Two patients had CTCs detected at baseline, 2 had CTCs detected at 6 months, and 1 had CTCs detected at 12 months; no patient had CTCs detected at more than 1 point. ctDNA was measured using targeted sequencing in 30 plasma samples collected from 12 patients at the same points. Two patients had TP53 ctDNA detected at baseline, of whom 1 had an absence and the other persistence of ctDNA at 6 and 12 months. No patient with CTCs detected had ctDNA detected, and vice versa. The detection of CTCs or ctDNA could not be correlated with outcomes, as no patients with a breast pCR had a cancer recurrence.

Trial Participant PROs

Updated PROs are presented in the eTable in Supplement 2. Patients reported relatively high levels of comfort with their initial decision to participate in the trial and forego breast surgery, with a mean (SD) baseline Decisional Regret Scale score of 15.2 (15.9) out of 100. Over time, decisional comfort significantly increased. At 5 years, the mean (SD) Decisional Regret Scale score was 2.5 (3.8), significantly lower than baseline. Overall health-related quality of life, including physical, social/family, emotional, functional, and breast cancer–specific well-being, significantly increased over time. The mean (SD) FACT-B+4 composite score was 120.7 (14.9) out of 148 at baseline compared with 126.7 (10.6) at 5 years (P = .04). Arm-specific quality of life was high at baseline (mean [SD], 19.6 [1.0] out of 20) and remained stable over time (P = .18). At baseline, patients reported minimal differences between breasts with respect to cosmesis, pain, edema, and function, with a mean (SD) overall Breast Cancer Treatment Outcome Scale score of 1.1 (0.1). Overall, there was a slight increase in perceived differences between breasts over time. This was primarily driven by changes in cosmesis, with subscores at 5 years indicating greater asymmetry than at baseline (mean [SD], 1.8 [0.6] vs 1.1 [0.2]; P < .001). In contrast, there were no significant long-term differences in breast function, pain, or edema (5-year subscore vs baseline subscore).

Discussion

In this nonrandomized clinical trial, radiotherapy alone without breast surgery produced excellent oncologic and PROs in highly selected patients with an image-guided VAB-determined pCR after NST in this inaugural trial in the field. These anticipated results with a doubling of the median follow-up from the first reported 2-year interim analysis[3] suggest that this new technique used to select patients for omission of breast surgery provides additional evidence of durability in outcomes, as there have yet to be any recurrences as of last follow-up. These findings are promising, as potential missed disease without surgery in such patients would be expected to generally recur early.

In the present study, CTCs and ctDNA were measured in only a subset of patients with a pCR in the trial in the Texas Medical Center, and their presence could not be correlated with outcomes, as no patients had a cancer recurrence; therefore, these results can only be interpreted as exploratory. There is a paucity of literature regarding the prognostic value of CTC detection among patients with early BC who have a pCR after NST. Although the presence of CTCs before NST administration was associated with a decreased survival in the GeparQuattro trial, the presence of them after therapy were not associated with worse disease-free or overall survival.[9] Similarly, O'Toole et al[10] found that patients with a pCR after NST had persistence of CTCs and concluded that enumeration of CTCs is unlikely useful in selecting patients who might avoid surgery. A recent meta-analysis on the prognostic value of ctDNA detection in patients with early BC who are undergoing NST demonstrated that the presence of ctDNA before and after receipt of NST was associated with worse recurrence and overall survival but not associated with obtaining a pCR.[11] The authors called for use of this measure in prospective clinical trials as a potential risk stratification factor. The potential value of ctDNA use in the emerging field of omission of surgery after NST remains to be determined.

The current 5-year PROs were consistent with our previously reported 3-year interim PRO results.[5] This report includes longer follow-up, with the addition of 5-year PRO scores, and data for more patients at other points. The finding of high decisional comfort at baseline aligned with a study of women with early BC who were treated with standard-of-care surgery and adjuvant therapies.[12] Our observation that health-related quality of life improved over time aligned with findings from a randomized trial comparing adjuvant conventional and hypofractionated radiotherapy that also used the FACT-B+4 to evaluate PROs.[13] In contrast to our finding that cosmetic asymmetry slightly worsened over time, Weng and colleagues[13] observed no significant long-term difference in this Breast Cancer Treatment Outcome Scale subscore. As the patients in our trial did not undergo breast surgery, it is possible that they had heightened awareness of the cosmetic effect of radiotherapy on the affected breast.

Early clinical trials that challenge traditional dogma regarding established standard treatments are difficult to perform and controversial to undertake, as clinicians and patients may be apprehensive. While lumpectomy and axillary surgery are usually straightforward, the overall documented complication rates for this surgical procedure are not insubstantial. Complications in the form of infection, bleeding, chronic pain, paresthesia, seroma, lymphedema, and unsatisfactory cosmetic and psychological outcomes can affect quality of life and may occur (often with several occurring in the same patient) about 30% of the time.[14]

Over the last several decades, BC surgery has progressively been safely de-escalated moving from radical mastectomy through breast-conserving therapy and axillary node dissection to sentinel node biopsy, eliminating sentinel node biopsy in select patients, and even allowing for less surgery for node-positive BC after NST[9,15-19] Most recently, selective elimination of surgery for some patients with ductal carcinoma in situ with active monitoring instead of standard surgery has shown that patients did not have a higher incidence of developing invasive BC at 2 years compared with patients receiving standard treatment.[20]

Limitations

The limitations of this phase 2 trial design have been described.[3,5] Briefly, these included the small number of patients and limited follow-up time of 55.4 months. *ERBB2*-postive hormone receptor–positive cancers may recur later, although this is also the case with standard surgery.

Conclusions

In this nonrandomized clinical trial with stringent eligibility and meticulous protocol-directed procedural requirements, radiotherapy alone without breast surgery produced excellent

oncologic outcomes and PROs in highly selected patients with TNBC and *ERBB2*-positive BC with an image-guided VAB-determined pCR to NST. Additional clinical trials are necessary. The trial reported in this article has been expanded with an additional cohort (Supplement 1), and there is active accrual in the South Korean OPTIMIST trial (NCT05505357-KBCSG-24) recruiting patients. The methods used in the current study taken together with additional results from future studies could represent the commencement of a paradigm shift in the surgical management of BC after NST.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kuerer, Valero, Lucci, Shaitelman, Hunt, Rauch.
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