Eliminating breast surgery for invasive breast cancer in exceptional responders to neoadjuvant systemic therapy: a multicentre, single-arm, phase 2 trial

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Summary

Background Neoadjuvant systemic therapy (NST) for triple-negative breast cancer and HER2-positive breast cancer yields a pathological complete response in approximately 60% of patients. A pathological complete response to NST predicts an excellent prognosis and can be accurately determined by percutaneous image-guided vacuum-assisted core biopsy (VACB). We evaluated radiotherapy alone, without breast surgery, in patients with early-stage triple-negative breast cancer or HER2-positive breast cancer treated with NST who had an image-guided VACB-determined pathological complete response.

Methods This multicentre, single-arm, phase 2 trial was done in seven centres in the USA. Women aged 40 years or older who were not pregnant with unicentric cT1–2N0–1M0 triple-negative breast cancer or HER2-positive breast cancer and a residual breast lesion less than 2 cm on imaging after clinically standard NST were eligible for inclusion. Patients had one biopsy (minimum of 12 cores) obtained by 9G image-guided VACB of the tumour bed. If no invasive or in-situ disease was identified, breast surgery was omitted, and patients underwent standard whole-breast radiotherapy (40 Gy in 15 fractions or 50 Gy in 25 fractions) plus a boost (14 Gy in seven fractions). The primary outcome was the biopsy-confirmed ipsilateral breast tumour recurrence rate determined using the Kaplan-Meier method assessed in the per-protocol population. Safety was assessed in all patients who received VACB. This study has completed accrual and is registered with ClinicalTrials.gov, NCT02945579.

Findings Between March 6, 2017, and Nov 9, 2021, 58 patients consented to participate; however, four (7%) did not meet final inclusion criteria and four (7%) withdrew consent. 50 patients were enrolled and underwent VACB following NST. The median age of the enrolled patients was 62 years (IQR 55–77); 21 (42%) patients had triple-negative breast cancer and 29 (58%) had HER2-positive breast cancer. VACB identified a pathological complete response in 31 patients (62% [95% CI 47·2–75·4]). At a median follow-up of 26·4 months (IQR 15·2–39·6), no ipsilateral breast tumour recurrences occurred in these 31 patients. No serious biopsy-related adverse events or treatment-related deaths occurred.

Interpretation Eliminating breast surgery in highly selected patients with an image-guided VACB-determined pathological complete response following NST is feasible with promising early results; however, additional prospective clinical trials evaluating this approach are needed.

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See Online for appendix

Introduction

In patients with breast cancer, rates of pathological complete response to neoadjuvant systemic therapy (NST) have increased dramatically over the past 25 years.[1–3] In patients with triple-negative breast cancer and HER2-positive breast cancer, rates of pathological complete response to NST have been reported to be approximately 60–80%. This raises the possibility that some patients who receive NST might not require breast and nodal surgery, particularly if they did not receive adjuvant local therapy with radiotherapy.

In 2018, we published the results of a prospective trial showing that image-guided vacuum-assisted core biopsy (VACB) of the primary breast tumour bed following NST can identify patients who are very likely to have had a pathological complete response.[4] The requirement that the residual suspicious disease needed to be less than 2 cm on breast imaging after NST allowed for maximal targeted sampling ability. Several other published studies have since tested the hypothesis that image-guided biopsy can accurately identify patients with a pathological complete response. Published rates of false-negative results on VACB for detection of residual disease following NST range from 5% in a study from our group (in which all patients with false-negative findings had only minimal microscopic disease)[4] to 40% or more in other studies.[5–8] The success of image-guided VACB is highly dependent on careful selection of appropriate

Research in context

Evidence before this study

We searched PubMed for studies published in English from database inception to Aug 1, 2022, on omission of breast cancer surgery following neoadjuvant systemic therapy (NST). Searches were intentionally broad and included the terms "breast cancer" AND "radiation" AND "neoadjuvant chemotherapy" AND ("surgery" OR "biopsy" OR "complete response" OR "pathologic complete response"). We identified several retrospective and a few prospective single-institution and multi-institutional studies evaluating radiotherapy as the definitive local modality after NST. These studies collectively showed unacceptably high locoregional failure rates. These poor outcomes were due to restricted or no use of rudimentary breast imaging techniques, the inability of breast imaging to accurately identify patients who would have a pathological complete response, and poor of knowledge of the molecular subtypes most likely to be associated with an exceptional response. We have recently shown that image-guided vacuum-assisted core biopsy (VACB) can accurately identify patients likely to have a pathological complete response after NST. Other studies using different eligibility and biopsy techniques have shown less robust performance. One previous retrospective study used core biopsy to select patients who might have a pathological complete response after NST. In that study, which showed a high local failure rate in patients who underwent radiotherapy but not surgery after NST, core needle biopsies were done randomly by non-image-guided biopsy of the breast at the time of axillary surgery following NST. Thus, the overall quality of the previous evidence was moderately low (level 3–4). No data from long-term, prospective studies or modern, randomised trials were found.

Added value of this study

To our knowledge, this study is the first modern, prospective trial of omission of surgery in patients with early-stage breast cancer (triple-negative breast cancer and HER2-positive breast cancer) who are exceptional responders to NST as indicated by state-of-the art breast imaging-guided VACB. Compared with previous trials, this modern trial had improved systemic therapy and selective image-guided VACB with stringent histological processing. The protocol-specified early results of this trial suggest that this new potential treatment approach appears promising.

Implications of all the available evidence

Long-term data to corroborate the early results of this trial, taken together with previous historical results and other results from prospective, single-centre, multi-institutional, and cooperative group trials, are necessary before this novel de-escalated treatment approach can become standard of care in this patient population.

patients and meticulous standardised techniques.[8,9] False-negative rates have been shown to decrease to 0–5% when the procedure is restricted to patients with unicentric triple-negative breast cancer or those with HER2-positive breast cancer and when it is done with the following technical parameters: representative tissue sampling, use of multimodality breast imaging, removal of at least six core biopsy samples, documented clip removal, standardised histopathological processing and examination, and use of larger-gauge (≥9G) VACB needles.[6,8,10]

Here, we present results of the first planned prospective outcome analysis of a multicentre, single-arm, phase 2 trial of the elimination of breast surgery in patients with localised HER2-positive breast cancer and triple-negative breast cancer who were presumed to have a pathological complete response on the basis of no evidence of residual tumour following percutaneous image-guided VACB after completion of NST.

Methods

Study design and participants

This prospective, multicentre, single-arm, phase 2 trial was done in seven centres in the USA (appendix p 2) and had two phases: a feasibility phase (to assess the study procedures in the first six enrolled patients in the first 6 months of follow-up) and an expansion cohort phase. Women aged 40 years or older who were not pregnant with pathologically confirmed, non-recurrent, unicentric, invasive breast cancer who desired breast-conserving therapy who had received initially planned clinically standard NST regimens were eligible for inclusion. Patients were required to have HER2-positive breast cancer (defined as a score of 3+ on immunohistochemistry or amplified on fluorescence in situ hybridisation [FISH]) or triple-negative breast cancer (defined as <10% of cells positive for oestrogen or progesterone receptor and a HER2 score of 0–2+ on immunohistochemistry or non-amplified on FISH), clinical T1 or T2 disease (≤5 cm largest tumour diameter on breast imaging), clinical N0 or N1 disease with no more than four abnormal-appearing axillary lymph nodes on initial nodal sonography, and no clinical or pathological evidence of distant disease. Any suspicious lymph nodes had to be biopsied percutaneously before initiation of NST to determine if nodal metastatic disease was present. If metastatic disease was present, a clip was placed in the biopsied node to facilitate later identification and retrieval. Patients were not eligible for inclusion if they were participating in a clinical trial of NST that required surgical excision of the primary tumour and lymph nodes, they had clinical or pathological evidence of skin involvement or distant metastases, they had a previous diagnosis of invasive breast cancer or ductal carcinoma in situ in the ipsilateral breast, they had clinical evidence of progression of disease in more than 20% of the breast

or new evidence of nodal metastases on NST, or final breast imaging after completion of NST showed a residual mass lesion, density, suspicious microcalcifications, or enhancement of more than 2 cm. The full list of inclusion and exclusion criteria are in the protocol (appendix). The protocol was amended twice to include the activation of two separate currently accruing studies (cohort B [amendment on Oct 30, 2019] evaluating endocrine therapy and ablative radiotherapy in hormone receptor-positive HER2-negative breast cancer; and cohort C [amendment on and May 28, 2020] evaluating omission of radiotherapy in patients with HER2-positive breast cancer or triple-negative breast cancer receiving standard surgery; appendix). All patients provided written, informed consent to participate approved by the institutional review board of each participating site. The study was done in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki.

Procedures

Patients received clinically standard NST regimens as recommended by their medical oncologist. After completion of the NST regimen, patients underwent mammography and sonography, and the radiologist determined the best imaging guidance for biopsy.

Breast biopsy could be done under stereotactic or ultrasound guidance on the basis of clinical evaluation of the radiologist performing the biopsy, and a minimum of 12 VACB cores were obtained with a 9G needle, targeting the previously placed clip, provided that there was no clip migration, and the other cores acquired circumferentially around the remaining region of distortion, mass, or residual microcalcifications. After VACB, a new marker clip was placed in the area of the tumour bed to facilitate identification of this area for surgery (if residual disease was found) or for radiation boost planning and imaging follow-up (in patients with a pathological complete response). Core biopsy specimens were immediately fixed in formalin and embedded in paraffin and extensively examined (appendix p 2).

Patients without histological evidence of residual disease in the breast did not have breast surgery. Patients with residual disease had standard breast and nodal surgery, and any residual disease was quantitated. Patients with initial documented nodal disease and a breast pathological complete response were eligible to participate if, after completing NST, they had targeted axillary dissection and no residual nodal disease was found.

All patients received external-beam whole-breast irradiation (40 Gy in 15 fractions or 50 Gy in 25 fractions) plus a mandatory boost (14 Gy in seven fractions, which began on the day following completion of whole-breast irradiation; appendix pp 2–3).

Patients were monitored for adverse events during the biopsy and for 14 days after the procedure. All adverse events were reported according to the Common Terminology Criteria for Adverse Events (version 4.0). Patients had a history and physical examination every 6 months after completion of radiotherapy. Surveillance mammography was required at the 6-month follow-up visit and then every 6 months for a total of 5 years. Abnormal findings on imaging follow-up or clinical examination were investigated with additional imaging modalities (eg, ultrasound and MRI) as directed by the radiologist. Findings that remained suspicious after additional imaging required biopsy to confirm the presence or absence of ipsilateral breast tumour recurrence. Biopsy was also required in patients with an increase in the size of calcifications or of a residual mass or asymmetry, a change in calcifications morphology to a more aggressive morphology according to the Breast Imaging Reporting and Data System (BIRADS) lexicon, or development of a new mass or asymmetry (an area of focal fibroglandular tissue that does not have the discrete borders of a mass visible only in one projection).

For more on **BIRADS** see https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Bi-Rads

Outcomes

The primary endpoint was the rate of biopsy-confirmed ipsilateral breast tumour recurrence in patients who did not undergo breast surgery at 6 months and at 1, 2, 3, and 5 years. In this Article we report the 2-year planned interim outcomes and subsequent analyses will take place in approximately 1–3 years as dictated by the protocol. Ipsilateral breast tumour recurrence-free survival, the primary endpoint of the expansion cohort phase, was defined as the time from confirmation of pathological complete response to the time of ipsilateral breast tumour recurrence or death, whichever occurred first, or the time of last contact. Planned secondary endpoints reported in this Article are the number of patients in whom final biopsy revealed residual disease; the quantification of residual disease in the surgery specimens; and the number of patients for whom image-guided biopsy of the ipsilateral breast or axillary nodes was recommended during follow-up. Three prespecified secondary endpoints are not reported in this Article: (1) recording of VACB results compared with surgery in patients who proceeded to routine surgery, which is not reported because no patients received routine surgery; (2) patient-reported outcome measures (Decisional Regret and Breast Cancer Treatment Outcomes Scales and Functional Assessment of Cancer Therapy 4 questionnaires) at baseline, 6 months and 1, 3, and 5 years, because these outcomes are planned to be reported in a separate manuscript after more mature data are collected and analysed to assess for change over time; and (3) correlating circulating tumour cells and circulating tumour DNA collected after NST, at 6 months, and at 1 year in patients with a pathological complete response, which are not reported because sample analyses have not been completed. Overall survival was a protocol-defined exploratory planned outcome measure.

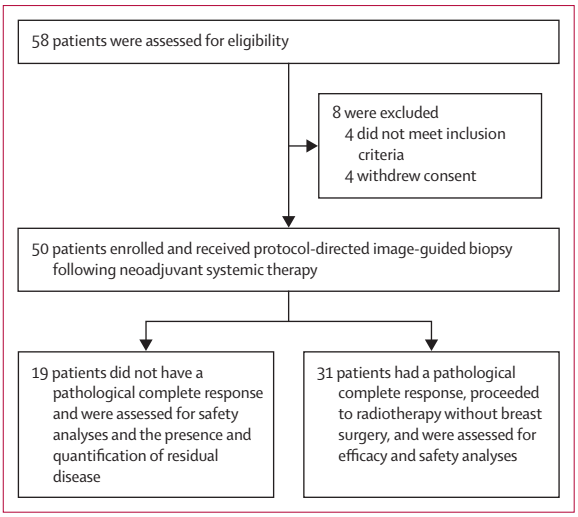

Figure: **Trial profile**

	Patients (n=50)
Age, years	62 (55–77)
Sex	
Male	0
Female	50 (100%)
Race	
Asian	2 (4%)
Black or African American	10 (20%)
White	38 (76%)
Ethnicity	
Hispanic	6 (12%)
Not Hispanic	41 (82%)
Not reported	3 (6%)
Disease stage*	
T1N0M0	19 (38%)
T1N1M0	6 (12%)
T2N0M0	22 (44%)
T2N1M0	3 (6%)
Largest tumour size, cm*	2·28 (0·92)
Histology	
Ductal	48 (96%)
Mixed ductal and lobular	2 (4%)
Clinical-pathological subtype	
HER2-positive and positive for oestrogen receptor, progesterone receptor, or both	18 (36%)
HER2-positive and negative for oestrogen receptor and progesterone receptor	11 (22%)
Triple negative	21 (42%)
Initial NST regimen	
AC+T	19 (38%)
AC+TC	2 (4%)
TH	5 (10%)
THP	4 (8%)
TCH	2 (4%)
TCHP	18 (36%)

Data are median (IQR), n (%), or mean (SD). AC+T=doxorubicin and cyclophosphamide followed by paclitaxel. AC+TC=doxorubicin and cyclophosphamide followed by paclitaxel and carboplatin. NST=neoadjuvant systemic therapy. TCH=docetaxel, carboplatin, and trastuzumab. TCHP=docetaxel, carboplatin, trastuzumab, and pertuzumab. TH=paclitaxel with trastuzumab. THP=docetaxel, trastuzumab, and pertuzumab. *T category and largest tumour size based on largest breast tumour diameter on imaging; N category based on sonography of lymph nodes with image-guided biopsy if imaging demonstrated abnormalities.

Table 1: **Baseline patient and disease characteristics and initial NST regimens**

Statistical analysis

Previously published results have shown that approximately 60% of patients with triple-negative breast cancer and HER2-positive breast cancer have a pathological complete response after NST.[1] Thus, the target enrolment was set at approximately 50 patients in an attempt to ensure that approximately 30 patients with a pathological complete response to NST who subsequently received definitive radiotherapy were included in the analysis. In the feasibility phase of the study, if none of the first six patients with a pathological complete response had ipsilateral breast tumour recurrence during the first 6 months after the pathological complete response, the proposed treatment regimen (radiotherapy without surgery) would be considered feasible. If one or more of the first six patients had ipsilateral breast tumour recurrence during the 6-month follow-up, the proposed treatment regimen would be considered unsafe, and the protocol would be halted by the Data Safety Monitoring Committee. Patients enrolled during the feasibility phase of the study were rolled over into the expansion cohort phase. The stopping rules for the expansion phase are summarised in the appendix (pp 3–4).

Student's *t*-test or Wilcoxon test and ANOVA or Kruskal-Wallis test were used to compare continuous variables between different patient groups. The χ^2 test or Fisher's exact test were used to assess associations between two categorical variables.

Time-to-event outcomes, including ipsilateral breast tumour recurrence-free survival and overall survival, were estimated using the Kaplan-Meier method.[11] The analysis population included all patients enrolled or treated per protocol. Post-hoc analyses were analyses by hormone receptor status, nodal status, and radiological complete response comparisons with breast pathological complete response status after NST. Statistical significance was set at p less than 0·05. SAS (version 9.4), S-Plus (version 8.2), and R (version 3.4.4) were used for all analyses. This study is registered with ClinicalTrials.gov, NCT02945579.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 6, 2017, and Nov 9, 2021, 58 patients consented to participate (figure). Four (7%) patients did not meet the eligibility criteria (their final tumours were too large on imaging), and four (7%) patients withdrew consent. Fifty (86%) patients (all women; median age 62 years (IQR 55–77) were enrolled and had protocol-directed image-guided VACB following NST. Breast biopsy was done under stereotactic guidance in 43 (86%) patients and under ultrasound guidance in seven (14%) patients. The last patient follow-up date was July 28, 2022.

Baseline patient characteristics are summarised in table 1. The mean initial largest tumour size was 2·28 cm (SD 0·92). Nine (18%) patients had biopsy-proven nodal metastases at baseline. 29 (58%) patients had HER2-positive breast cancer, and 21 (42%) had triple-negative breast cancer. Initial NST regimens received are listed in table 1.

The mean final tumour size following NST was 0·90 cm (SD 0·81) on imaging (table 2). 17 patients (34% [95% CI 21·2–48·8]) had a complete radiological response. The mean number of VACB specimens obtained was 15·24 (SD 5·05; table 2). Examination of VACB specimens showed that 19 (38%) patients had residual disease, and 31 (62% [95% CI 47·2–75·4]) patients had a pathological complete response in the breast (table 2).

The biopsy procedure was well tolerated. Grade 1 complications occurred in two (4%) of 50 patients. One patient had nausea during the procedure that resolved without intervention. In the other patient, the VACB device malfunctioned, but the problem was rectified, allowing for the procedure to be completed successfully. No serious adverse events or deaths occurred.

At a median follow-up of 26·4 months (IQR 15·2–39·6), there were no ipsilateral breast tumour recurrences in the 31 patients who had a pathological complete response on VACB after NST, and no other recurrence events or deaths were observed (both ipsilateral breast tumour recurrence-free survival and overall survival were 100%; appendix p 5).

In a prespecified secondary endpoint analysis, seven (37%) of the 19 patients with residual disease identified on image-guided VACB had no residual disease at the time of breast surgery and 12 (63%) patients had residual disease (table 2). The mean size of the residual breast disease in these 12 patients was 9·00 mm (SD 5·03) for invasive cancer and 2·33 mm (2·09) for ductal carcinoma in situ. None of these 12 patients were found to have nodal metastases.

In the prespecified secondary analyses of ipsilateral breast and nodal recommendation and performance of biopsy based on breast imaging follow-up, nine (29%) of 31 patients with no residual disease identified on image-guided VACB were recommended to have image-guided breast or nodal biopsy: six patients had biopsy recommended once, two patients had biopsy recommended twice, and one patient had biopsy recommended three times. Three patients received recommendations for biopsy at 6 months, four received recommendations at 12 months, three received recommendations at 24 months, one received a recommendation at 36 months, and one received a recommendation at 48 months. Two patients had contralateral breast biopsies recommended. Indications for biopsy included new or increasing architectural distortion in seven patients, enhancement in three patients, new calcifications in one patient, and a suspicious axillary lymph node in one patient. In each case, biopsy findings were benign and concordant with the imaging findings (benign lymphoid tissue in one patient; fibrosis, scar, or necrosis in eight patients; fibroadenoma in two patients; and a papilloma in one patient).

In the post-hoc analyses of outcomes by hormone receptor status, no difference was detected in the rate of breast pathological complete response by tumour hormone receptor status, with a pathological complete

	All patients (n=50)	Breast pathological complete response, no breast surgery (n=31)*	No breast pathological complete response, standard breast surgery (n=19)†	p value‡
Clinical pathological subtype				
HER2 positive	29 (58%)	16 (55%)	13 (45%)	0·24
Triple negative	21 (42%)	15 (71%)	6 (29%)	..
Initial biopsy-proven node-positive disease				
Yes	9 (18%)	8 (89%)	1 (11%)	0·14
No	41 (82%)	23 (56%)	18 (44%)	..
Initial largest tumour size, cm§	2·28 (0·92)	2·32 (1·03)	2·22 (0·72)	0·86
Complete radiological response				
Yes	17 (34%)	14 (82%)	3 (18%)	0·06
No	33 (66%)	17 (52%)	16 (48%)	..
Final tumour size on breast imaging after NST, cm	0·90 (0·81)	0·78 (0·88)	1·09 (0·67)	0·12
Number of 9G cores removed on VACB	15·24 (5·05)	14·67 (5·2)	16·16 (4·79)	0·10
Residual disease at breast surgery among patients with disease detected on VACB after NST				
None	..	..	7 (37%)	..
Invasive disease only	..	..	6 (32%)	..
DCIS only	..	..	4 (21%)	..
Both invasive disease and DCIS	..	..	2 (11%)	..
Size of residual disease at breast surgery in patients with disease detected on VACB after NST, mm				
Invasive disease	..	..	9·00 (5·03)	..
DCIS	..	..	2·33 (2·09)	..

Data are n (%) or mean (SD). DCIS=ductal carcinoma in situ. NST=neoadjuvant systemic therapy. VACB=vacuum-assisted core biopsy. *ypT0 (no residual invasive disease or DCIS); these 31 patients had a pathological complete response, proceeded to radiotherapy without breast surgery, and were assessed for efficacy and safety endpoints. †The 19 patients with residual disease were assessed for safety endpoints and the presence and quantification of residual disease per protocol. ‡Wilcoxon test was used to compare continuous variables between different patient groups; the χ^2 test or Fisher's exact test was used to assess associations between two categorical variables. §Based on breast imaging.

Table 2: **Breast pathological complete response status by disease features, treatment response, and VACB details and findings**

response recorded in 15 (71%) of 21 patients with triple-negative breast cancer compared with 16 (55%) of 29 patients with HER2-positive disease (p=0·24; table 2). Seven (39%) of 18 patients with HER2-positive and hormone receptor-positive disease had a pathological complete response compared with nine (81%) of 11 patients with HER2-positive and hormone-receptor negative disease (p=0·052). Nine (18%) of 50 patients had image-guided biopsy proved N1 disease (table 1). All nine patients had a nodal conversion from percutaneous biopsy positive to histological node negative after NST diagnosed by targeted axillary dissection (mean number of nodes excised 2·2 [SD 1·5]). One of these nine patients did not have a breast pathological complete response and was noted to have residual ductal carcinoma in situ on VACB; therefore, this patient received standard lumpectomy. All eight patients who presented with nodal metastases and had a pathological complete response in the breast by VACB (table 2) also had a nodal pathological complete response confirmed on targeted axillary dissection. No significant difference in pathological complete response rates were found based on complete radiological response (14 [82%] of 17 patients) versus incomplete radiological response (17 [52%] of 33 patients; p=0·06); three (18%) of 17 patients had a complete radiological response but no breast pathological complete response.

Discussion

In this multicentre trial investigating the elimination of the need for breast surgery in patients with a pathological complete response on image-guided VACB of the tumour bed after NST, there were no local-regional or distant recurrences at the first reported planned 2-year analysis, with a median follow-up of 26·4 months. Although early, these results are important because recurrences in patients with triple-negative breast cancer or HER2-positive breast cancer with residual disease after NST would tend to occur early within the first few years.

Of note, our study had stringent clinical and imaging eligibility requirements, and patients with initial node-positive disease had to have fewer than four abnormal-appearing nodes on initial ultrasound examination, and any abnormal lymph node had to be biopsied and clipped before NST to ensure removal and testing with targeted axillary dissection. More than half of the patients without a complete radiological response following NST had a breast pathological complete response.

Patients in this study were specifically selected on the basis of their exceptional response to NST, which resulted in an overall high pathological complete response rate of 60%. These stringent entry criteria, along with technical improvements on previous studies,[1,4,8,9] probably contributed to the successful outcome of this study.

The concept of attempting to omit surgical therapy in patients with invasive breast cancer who have clinical complete response is not new.[1] Many of the ground-breaking studies in the field were initiated for patients who presented with locally advanced breast cancer and tested omission of radical breast surgery after NST in those who would receive radiotherapy.[12–14] Subsequent studies were hindered by limited use of any breast imaging and or older breast imaging techniques, and no use of use of image-guided breast biopsy to identify patients most likely to have a pathological complete response.[1,15–17]

As shown in our study, even modern breast imaging technologies perform poorly in the identification of patients with no residual disease after NST, which occurred in three patients thought to have a complete radiological response. Most patients in this study with a VACB-determined breast pathological complete response did not have a radiological complete response. This information suggests the fundamental necessity of image-guided biopsy for ensuring appropriate patients are selected for future trials of omission of breast surgery. Measurement of minimal residual disease from liquid biopsies with correlation with pathological complete response is one of the secondary aims of this study, and these samples are still being collected and the data will be reported in a later manuscript.

Until around 35 years ago, all patients with a breast abnormality routinely underwent surgical excision for diagnosis of cancer versus benign disease. Image-guided stereotactic needle biopsy was introduced to identify patients who needed therapeutic surgery for removal of malignant disease.[18] The number of cores taken and analysed in this trial (a mean of 15·24) to accurately identify a breast pathological complete response has been considered high by some clinicians. However, removal of this amount of tissue or more is routine, and a recommended multidisciplinary guideline to assess B3 breast lesions categorised as of uncertain malignant potential found during screening mammography.[19] In this regard, conceptually, the technique of appropriate sampling with image guided VACB used to evaluate lesions of uncertain malignant potential detected on breast imaging to avoid surgery for diagnosis appears similar in nature to the techniques used in this trial to assess for potential residual malignant disease after NST to circumvent the need for breast surgery.[19] The concept of core biopsy to select patients who might have a pathological complete response after NST was retrospectively investigated by Clouth and colleagues.[20] The main issue with their study, which was published in 2007, was that the core needle biopsies were done by random non-image-guided biopsy of the breast at the same time as the axillary dissection following NST, which reflects the techniques of a previous treatment era.

The management of the axillary nodes for breast cancer after NST in our trial and future clinical trials testing the safety and efficacy of avoiding breast cancer surgery remains an ongoing area of research. Patients with N0 or N1 disease were included in this trial because we have

previously found that breast pathological complete response is highly correlated with nodal status after NST in patients with triple-negative breast cancer and HER2-positive breast cancer, and the risk for missing nodal metastases without axillary surgery in this cohort is extremely low.[21] In our previous study of 527 patients,[21] we found 100% of patients with a breast pathological complete response also had a nodal pathological complete response. 69 (90%) of 77 patients with N1 disease with a breast pathological complete response had a nodal pathological complete response. The nine patients in our trial with biopsy-confirmed N1 disease preferred to avoid any breast surgery if VACB showed a pathological complete response because a small, targeted axillary dissection scar would be mostly hidden in the axilla. The study by Tadros and colleagues[21] provided the rationale for management of the axilla in clinical trials for omission of breast surgery when image-guided VACB showed a breast pathological complete response. Subsequent studies might choose to avoid any axillary staging surgery and proceed to radiotherapy in patients with a VACB-determined breast pathological complete response and initial N1 disease.

There is a paucity of evidence on the frequency of recommendations for breast biopsy in patients who have undergone routine breast cancer surgery. The largest nationwide population-based cohort study by van la Parra and colleagues[22] reports a 5-year overall incidence of breast biopsy of 14·7% and a 10-year incidence of 23·4% in 41 510 patients aged 64 years or younger; in 80 369 patients aged 66 years or older the 5-year incidence was 11·8% and the 10-year incidence was 14·9%.[22] The estimated 5-year contralateral breast biopsy rate was 10·4% in patients aged 64 years or younger and 7·7% in those aged 66 years or older.[22] Omission of surgery in exceptional responders to NST is a new field, and thus high-sensitivity imaging follow-up is required to detect early signs of possible recurrence.[23] This new approach might have resulted in higher rates of recommendations for biopsy in our trial. Surveillance imaging and management of imaging findings in exceptional responders with omission of breast surgery is a developing and evolving field.

The presence of residual invasive disease after NST is well established to have an adverse effect on disease-free survival, and receipt of escalated additional adjuvant systemic therapy might be warranted in such cases.[1–4] Of note, standard breast-conserving surgery based on post-NST tumour response, rather than the original footprint of the disease at diagnosis, might result in missed residual disease. Similarly, lymph node surgery after NST is associated with a low but recognised risk of a false-negative result. These issues are due to imaging limitations, challenges with surgical localisation procedures in patients receiving breast-conserving surgery, and inadequate histological processing of tissues. The consideration of missed residual disease is important in the developing area of omitting surgery for breast cancer after NST. Although the absolute magnitude of potential benefit of additional adjuvant systemic therapy in patients with a false-negative VACB pathological complete response who respond exceptionally and did not receive surgery after NST would be expected to be low because they would probably have a low residual cancer burden, it will need to be addressed and quantified in future trials.

Several limitations of this study merit discussion. This was a high-risk, small, phase 2 trial with short, although protocol-specified, early follow-up. Radiotherapy could merely delay and not prevent ipsilateral breast tumour recurrence; HER2-positive hormone receptor-positive cancers even with a pathological complete response might recur later, and thus longer follow-up is needed to validate these early promising findings. Adoption of this strategy outside centres of excellence with high-volume breast imaging centres might be challenging because of the reliance on meticulous nodal assessment using ultrasound and extensive image-guided VACB assessment of the tumour bed following NST. Although VACB is minimally invasive and was overall well tolerated with no serious complications, the technique is not an entirely benign intervention, and additional work is needed to determine whether or not the VACB approach is truly preferable to segmental mastectomy for some patients. Assumptions that cost, morbidity, and patient acceptance are far better for VACB than for segmental mastectomy will need to be adequately studied and addressed along with other potential de-escalation strategies (NCT02945579; cohort C of this trial).

In summary, although this was a small, non-randomised study, the planned analysis of short-term results is highly promising because none of the patients who avoided breast surgery have had a recurrence. The ultimate form of breast conservation is exclusion of any breast surgery following NST. This early report suggests feasibility of this approach, and this field is rapidly advancing. As occurred in the historical development of surgery de-escalation trials, additional clinical trials will be needed to validate our findings before elimination of surgery in exceptional responders can be considered a standard of care.

Contributors

HMK, BDS, WTY, VV, and GMR conceived and designed the trial, collected data, and interpreted data; these authors have accessed and verified the underlying data. YS and HL did the statistical design of the study. HMK, YS, and HL analysed the data and generated the tables and figures. HMK drafted the manuscript. HMK, YS, BDS, HL, SK, VV, EJD, AL, and GMR interpreted data and revised the manuscript. AL, JCB, EJD, and RLW were key members of the multidisciplinary team who evaluated and treated patients on the trial and assisted with data acquisition and interpretation. All authors had access to all the data. All authors read and edited the manuscript and approved it for final submission. HMK and GMR had full access to all data and the final responsibility for the decision to submit for publication.

Declaration of interests

HMK reports consulting fees from Merck; honorarium from Physicians Education Resources; payment as an Editor from the New England Journal of Medicine Group; royalties from McGraw-Hill Professional and Elsevier Publishing; and leadership role in National Surgical

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Data sharing

Data collected for this study, including deidentified individual participant data and a data dictionary defining each field in the set, will be made available to others on acceptance of an official request to MD Anderson Cancer Center, Houston, TX, USA, after Institutional Review Board approval for release. The study protocol is available in the appendix of this Article, and other related documents can also be made available to others on request to MD Anderson Cancer Center. The data shall be available beginning with publication and can be shared as an electronic or physical file after explicit approval of the study investigators and a signed data usage agreement between the participating institutions as required.

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