Eliminating the breast cancer surgery paradigm after neoadjuvant systemic therapy: current evidence and future challenges

Heil, J.; Kuerer, H.M.; Pfob, A.; Rauch, G.; Sinn, H.P.; Golatta, M.; ... ; Peeters, M.J.V.

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ANNALS OF
ONCOLOGY
driving innovation in oncology

Eliminating the breast cancer surgery paradigm after neoadjuvant systemic therapy: current evidence and future challenges

J. Heil[1*†], H. M. Kuerer[2†], A. Pfob[1], G. Rauch[3,4], H. P. Sinn[5], M. Golatta[1], G. J. Liefers[6] & M. J. Vrancken Peeters[7]

[1]Department of Gynaecology/Breast Unit, Heidelberg University, Heidelberg, Germany; [2]Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, USA; [3]Institute of Biometry and Clinical Epidemiology, Charité-University Hospital Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin; [4]Berlin Institute of Health, Berlin; [5]Department of Pathology, Heidelberg University, Heidelberg, Germany; [6]Department of Surgery, Leiden University Medical Centre, Leiden; [7]Division of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

In patients with operable early breast cancer, neoadjuvant systemic treatment (NST) is a standard approach. Indications have expanded from downstaging of locally advanced breast cancer to facilitate breast conservation, to *in vivo* drug-sensitivity testing. The pattern of response to NST is used to tailor systemic and locoregional treatment, that is, to escalate treatment in nonresponders and de-escalate treatment in responders. Here we discuss four questions that guide our current thinking about 'response-adjusted' surgery of the breast after NST. (i) What critical diagnostic outcome measures should be used when analyzing diagnostic tools to identify patients with pathologic complete response (pCR) after NST? (ii) How can we assess response with the least morbidity and best accuracy possible? (iii) What oncological consequences may ensue if we rely on a nonsurgical-generated diagnosis of, for example, minimally invasive biopsy proven pCR, knowing that we may miss minimal residual disease in some cases? (iv) How should we design clinical trials on de-escalation of surgical treatment after NST?
Key words: breast cancer, individualized treatment, neoadjuvant systemic therapy, oncology, surgery

INTRODUCTION

Modern breast cancer treatment is a multimodal approach integrating surgery, radiation, and systemic treatment.[1,2] The aim is to combine and sequence these different treatments according to each patient's needs and preferences and to de-escalate treatment whenever possible while preserving oncological safety.

Today, neoadjuvant systemic treatment (NST) is used in 17%—40% of patients with early breast cancer depending on the biological subtype.[3] Indications have expanded from downstaging of locally advanced breast cancer to facilitate breast conservation, to *in vivo* drug-sensitivity testing. We have learned that different definitions of pathologic complete response (pCR = ypT0 ypN0, ypT0/is, residual cancer burden = 0, etc.) after NST are associated with a favorable prognosis.[4,5] pCR is achieved in ~20% of all patients after NST but pCR rates depend largely on breast cancer subtype[6,7] and stage.[8] Registry data show that 40% of women with HER2-positive disease achieve a pCR after NST, with the percentage

among triple-negative tumors being 23% and among luminal A tumors only 0.3%.[6,7] Recent studies for dual HER2 blockage and carboplatin regimes in triple-negative tumors revealed pCR rates up to 68% and 80%, respectively, which illustrate that pCR rates after NST might increase even further in the next years.[9,10] Primary breast tumor and axillary lymph node metastases usually respond similarly with regard to pattern and degree of response.[11—13] In this review we will mainly focus on the response in the breast to NST.

We already know that the pattern of response to NST can be used to further tailor systemic treatment: escalating treatment in nonresponders by giving further adjuvant or postneoadjuvant additional systemic treatment after surgery (capecitabine and T-DM1) improves survival—we will discuss these findings later in detail.[14,15] Contrary, de-escalating treatment in excellent responders by shortening the NST regimen when pCR is identified does not harm the oncologic safety.[15—17] This sophisticated tailoring of systemic treatment also allows for thinking of personalized locoregional treatment strategies. Putting it to the extreme: in patients with pCR after NST, it may be reasonable to leave or at least postpone breast surgery and adopt a 'watch-and-wait' approach. If breast surgery is not performed, however, the standard method of determining response to NST, being pathologic examination of the surgical specimen, is not possible. Rather, response must be

Correspondence to: Prof. Joerg Heil, Department of Gynaecology/Breast Unit, Heidelberg University, Im Neuenheimer Feld 440, 69120 Heidelberg, Germany. Tel: +49 6221 5638555

E-mail: joerg.heil@med.uni-heidelberg.de (J. Heil).

†Contributed equally.

estimated on the basis of nonsurgical tools such as imaging or minimally invasive image-guided needle biopsy or a combination of methods and predictors, but these approaches might be less reliable than surgery.

No diagnostic tool is or ever will be absolutely perfect in terms of confirming or ruling out the presence of residual cancer cells after NST in all patients; even pathologic evaluation after standard surgical approaches is not completely accurate. However, if we consider reducing or completely omitting breast surgery in patients with pCR diagnosed by a less invasive, nonsurgical method, we need to know the potential oncological consequences if residual disease is missed.

Over the past four decades, breast surgeons have conducted a series of clinical trials that have established the appropriateness of less invasive surgical approaches in subgroups of patients with breast cancer. Breast conservation has proven to have identical survival as ablative surgery in the primary surgery setting[18,19] even with slightly more local recurrences in the long run.[20] Breast conservation after NST is also oncologically safe (Figure 1). By contrast, we learned that local recurrences affects overall survival negatively, at least in historical cohorts.[21] Following this development it seems to be a logical next step to explore the possibility of omitting breast surgery in patients with a biopsy-confirmed complete response after NST.

There are limited data supporting the hypothesis that eliminating surgery after NST in patients with a complete response by physical or radiologic examination does not impair survival,[22] while a very recent meta-analysis showed worse local control rates after neoadjuvant treatment without surgery.[23] In light of these contradictory data, balancing potential risks and benefits of nonsurgical approaches is of utmost importance. Critics would rightly argue why leaving the 'safe ground' of relatively small, low-morbidity breast surgery (in contrast to other nonsurgical strategies, e.g., in patients with esophagus or rectal cancer) and to rely on potentially less reliable image-guided tools to diagnose a pathological complete response. Four main questions guide our thinking regarding 'response-adjusted surgical management' after NST: First, what are the critical diagnostic outcome measures that should be used when analyzing diagnostic tools used to identify pCR in the breast after NST? Second, which diagnostic tools can accurately confirm and rule out residual disease in the breast after NST with the least morbidity possible? Third, what oncological consequences may we expect if we miss minimal residual disease and can we accept a watch-and-wait strategy for breast cancer patients with a complete response to NST? Fourth, how should we design and perform clinical trials to gather sufficient evidence on these questions to change clinical practice?

FIRST: DIAGNOSTIC OUTCOME MEASURES

How to assess a diagnostic tool that can be used to rule out residual disease, that is, to validly diagnose a pCR? Diagnostic accuracy is important because we know that it is linked directly to oncologic outcomes.

Sensitivity

To quantify the sampling error to rule out residual disease (i.e. to predict pCR), we propose the false-negative rate (FNR; 1-sensitivity= 1 − cases with residual tumor detected by the diagnostic tool divided by all cases with residual tumor) as the primary outcome measure of such a diagnostic tool.[24–28] Ideally, a tool used to identify residual disease after NST for breast cancer would be 100% sensitive (=0% FNR), meaning that no tumor will be missed. This ideal goal is unrealistic in clinical practice—even after breast surgery. However, it may not be necessary to be 100% certain that no residual disease remains at all, particularly if adjuvant radiation treatment and/ or further systemic treatment will be delivered. As we do not know the maximum sampling error without impairing local control rates in case of omitting surgery, we deduced a minimum sensitivity of 90% (=maximum FNR of 10%) from the results of the sentinel node trials: an FNR of 10% did not translate into a worse local and overall survival in these trials.[29]

Specificity

Specificity is also relevant when considering this new paradigm shift: the diagnostic tool should validly identify as many pCR patients as possible to be clinically relevant. One may define subgroups of patients with very low probability of a false-negative diagnosis by using combinations of pCR predictors but this will result in a low specificity, that is, the number of patients with a true pCR meant to be non-pCR by the diagnostic tool (or combination of tools) is high and therefore many patients will not benefit from the diagnostic tool.

SECOND: DIAGNOSTIC TOOLS TO CONFIRM RESIDUAL DISEASE

Which diagnostic tools can accurately confirm or rule out residual disease in the breast after NST with the least morbidity possible? Multiple small prospective and retrospective trials have yielded different but in sum mediocre results regarding the diagnostic accuracy of imaging [magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) scan] in identifying residual disease after NST.[30–32] Diagnostic accuracy might also depend on tumor biology.[33] Minimally invasive image-guided biopsy has shown promise in the identification of residual disease in the breast after NST (Table 1).[24] Conflicting issues arose, however: for example, sensitivity and specificity of image-guided biopsy may be dependent on the molecular subtype, tumor heterogeneity, and/or the size of the initial and residual imaging abnormalities that may or may not be readily and accurately sampled with image-guided biopsy.[6,34] Ongoing trials are investigating the most accurate method for these minimally invasive image-guided biopsies to standardize future approaches. Previous pilot trials suggest that diagnostic accuracy might differ for different guidance procedures (sonographic versus stereotactic), needle sizes, and number of cores.[25,26,35] It will be crucial to implement a standardized
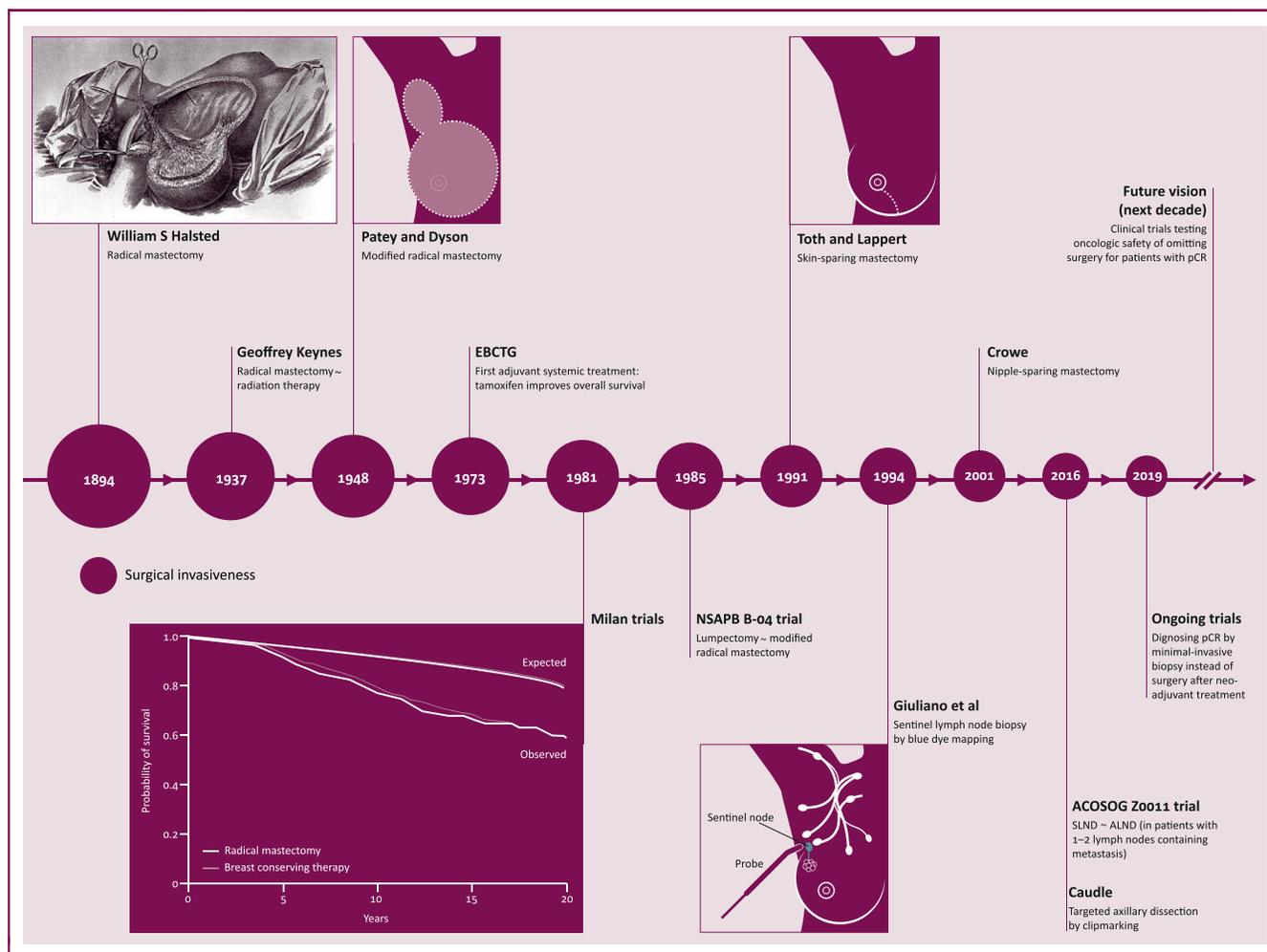
Figure 1. Timeline of oncologic breast surgery.
ALND, axillary lymph node dissection; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; pCR, pathologic complete response; SLND, sentinel lymph node dissection; ∼, equivalent outcomes between two treatments.
Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347:1227—1232.

approach based on the ongoing trials. So far, taking at least 6—12 cores (depending on the needle size) is recommended.

Future trials might also consider the use of biomarkers besides image-guided biopsies to predict pCR without surgery as they could further improve the diagnostic accuracy. Early studies showed promising results: AAGAB—a single on-treatment biomarker—could predict pCR with 78%—100% accuracy in a small sample.[36] Other studies showed that higher levels of tumor-infiltrating lymphocytes and anti-HER2 CD4+ T-helper type 1 are associated with higher pCR rates;[37,38] however, these biomarkers are not yet clinically established.

The challenge of mediocre imaging accuracy and accurate tissue sampling by minimal invasive biopsy techniques is based on different patterns of tumor response to NST: shrinkage and diffuse cell loss, and the extent of initial and residual imaging abnormalities. Shrinkage (also called tumor collapse) occurs with certain triple-negative and nonluminal HER2-positive breast cancers, which tend to respond early in the course of NST and leave little histological trace when pCR occurs. By contrast, in diffuse cell loss, tumors regress

in a much more heterogeneous fashion, leaving behind multiple scattered foci of single tumor cells after chemotherapy, typically with little or no change in overall tumor size. Luminal breast cancers and invasive lobular cancers most commonly exhibit diffuse cell loss as well as invasive ductal carcinomas with a high stroma content.[39,40] Diffuse cell loss is associated with a greater likelihood of in-breast tumor recurrence and makes the identification of residual disease after NST more difficult.[41] This may partly explain the recent finding that local control could be worse after NST.[23] By contrast, local recurrence rates in HER2-positive and triple-negative non-pCR cancers are significantly higher than in luminal breast cancers as well as in cancers with residual ductal carcinoma *in situ* (DCIS).[42]

THIRD: MISSED RESIDUAL DISEASE

Is eliminating surgical resection oncologically safe after image-guided biopsy demonstrating no residual disease?

What oncologic consequences can be expected if we miss minimal residual disease after NST and can we accept a

Table 1. Completed clinical feasibility trials utilizing percutaneous biopsy after neoadjuvant therapy to select patients for omission of breast cancer surgery (partially adapted from Kuerer et al.[24])

Group/author/PI	Eligibility criteria/lesion size criteria	Type of biopsy	Number of patients	Study unique characteristics	Performance results
MD Anderson Cancer Center/Kuerer et al.[64]	All lesions <5 cm on imaging after NST; included only TN and HER2-amplified cases	VAB and FNA; median number sampled 12 using 9 G under radiologist-defined image guidance (63% by stereotactic and 37% by ultrasound)	40	Meticulous image-guided sampling in radiology suite. Subtype-specific with highest probability of pCR (no invasive and *in situ*)	Accuracy = 98%; FNR = 5%; NPV = 95%
German Breast Group/Heil et al.[35,65]	Invasive breast cancer patients; nonmetastatic; with clinical imaging after neoadjuvant chemotherapy/no lesion size criteria	CC and VAB	164 (111 with CC and 46 with VAB)	Explorative comparison of different techniques: CC and VAB, ultrasound, and mammographic guidance	Entire cohort (N = 164): NPV = 71.3%; FNR = 49.3%; mammographic-guided VAB (n = 16): NPV = 100%; FNR = 0%
University of Heidelberg/Heil et al.[26]	Histologically confirmed, unilateral breast cancer; clinical partial or complete response to NST; target lesion visible by ultrasound/no lesion size criteria	Ultrasound-guided VAB	50	Explorative comparison of three evaluation methods of biopsy specimen pathologic representativeness	Entire cohort (N = 50): NPV = 76.7%; FNR = 25.9%; histopathological evaluation of representativeness (n = 38): NPV = 94.4%; FNR = 4.8%
University of Birmingham/Rea-Francis et al./NOSTRA PRELIM[66]	Invasive breast cancer with any receptor subtype receiving NST/no lesion size criteria	Ultrasound-guided core biopsy; four to six; mammography and stereotactic biopsy not used for malignant calcifications	22	Designed to inform biopsy protocol for larger study	Number of patients with a false-negative result (4/18 total patients)
Seoul National University College of Medicine/Lee et al.[67]	Clinical complete response to NST (=lesion size ≤0.5 cm on MRI)	Core needle biopsy (14 G) or VAB (10 G)	40	Only patients with clinical complete response includedRoutine	Overall FNR = 30.8%; FNR for ≥5 biopsy samples 10%
Royal Marsden Hospital, London/Konstantinos et al.[68]	Partial or complete imaging response	Routine VAB to aide surgical planning	53	VAB procedure outside of study context	Overall FNR = 19.3%; FNR for triple negative 0.0%

CC, core cut; FNA, fine-needle aspiration; FNR, false-negative rate; MRI, magnetic resonance imaging; NPV, negative predictive value; NST, neoadjuvant systemic treatment; pCR, pathologic complete response; PI, principal investigator; VAB, vacuum-assisted biopsy.
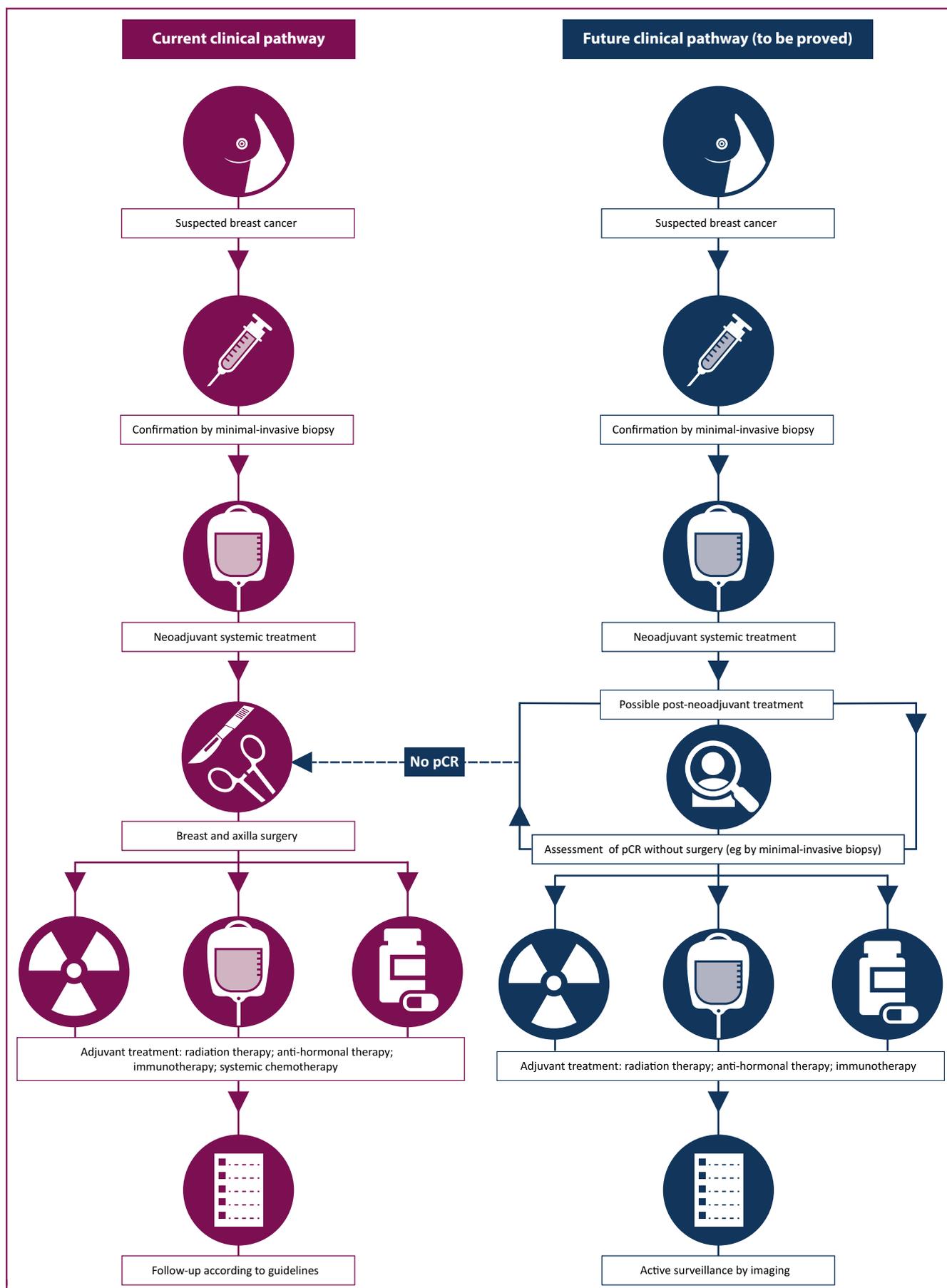
J. Heil et al.

Current clinical pathway

Future clinical pathway (to be proved)

Suspected breast cancer

Suspected breast cancer

Confirmation by minimal-invasive biopsy

Confirmation by minimal-invasive biopsy

Neoadjuvant systemic treatment

Neoadjuvant systemic treatment

Possible post-neoadjuvant treatment

No pCR

Breast and axilla surgery

Assessment of pCR without surgery (eg by minimal-invasive biopsy)

Adjuvant treatment: radiation therapy; anti-hormonal therapy; immunotherapy; systemic chemotherapy

Adjuvant treatment: radiation therapy; anti-hormonal therapy; immunotherapy

Follow-up according to guidelines

Active surveillance by imaging

Figure 2. Clinical pathway for breast cancer patients eligible for neoadjuvant systemic treatment.
pCR, pathologic complete response.

watch-and-wait strategy for breast cancer patients with a complete response after NST (Figure 2)? There is conflicting evidence on the impact of missing minimal residual disease after NST, but the fear is clear: more relapses and worse survival if residual disease is missed.[43,44] The consequences could depend on whether there is *in situ* or invasive disease, lymphovascular invasion, and on the quantity of residual disease. Moreover, we believe that missed minimal residual disease might be sufficiently controlled by either radiation treatment and/or adjuvant treatment (ongoing anti-HER2 or antihormonal therapies when applicable), which is the current standard approach, even in patients with pCR. Recent studies showed that additional systemic treatment with capecitabine and T-DM1 for triple-negative and HER2-positive patients after NST with residual disease (specified by pathological evaluation of surgery specimen) improves the overall survival and reduces the risk of recurrence.[14,15] This is of particular importance as missed residual disease in these cases might cause undertreatment (of an unclear extent) similar to missed residual disease by minimally invasive approaches before surgery. Despite highly likely, future trials need to show that the overall survival benefit for escalating the postneoadjuvant treatment in the cohorts of surgery-detected residual disease will also account for the specific subgroup of missed small cancers by minimally invasive approaches.

Worse consequences would even be anticipated if one or more key elements of standard adjuvant treatment were omitted. Nevertheless, there is no established definition for 'minimal residual disease', and exact effect estimates are not yet available. Some patients might accept a 'slightly higher' (to be defined) chance of local recurrence or tumor regrowth potentially associated with missed minimal residual disease, especially if local resection of recurrence or regrowth would yield cure rates similar to those in patients who underwent surgery without delay after NST.

Rationale for eliminating surgery

In other types of cancer, such as rectal cancer and esophageal cancer, a watch-and-wait strategy is now being used in patients with an excellent response after NST: surgery is not performed unless a local recurrence is detected.[45] Quality and quantity of spared morbidity in these cases are very much different to the morbidity of a breast surgery, although up to 20% of patients after breast conservation experience a significant reduction of long-term aesthetic outcome and consequently quality of life.[46–48] Could a no-surgery strategy therefore be acceptable in breast cancer patients in whom all available evidence points toward a complete response after NST? It seems very unlikely that breast cancer patients with an apparent complete response to NST would experience distant relapses, but minimal residual disease could be missed and might lead to local recurrence or regrowth. The frequency and the effect of missed minimal residual disease in the breast on distant relapses and death are unknown but this scenario might be comparable to patients presenting with occult breast cancer. Survival rates of women with occult breast cancer have been reportedly equivalent to other breast cancer patients.[49–52] Thus oncologic effects of missed residual disease on distant relapses and death may not be relevant in this cohort of patients as we would find local relapse in early stage and the effect of response-guided postneoadjuvant treatment might not be the same in this cohort.

How to follow patients after when breast surgery is not performed? How to define and treat a local relapse?

One important consideration in determining the appropriateness of eliminating breast surgery when no residual disease is detected on image-guided biopsy is the impact on this approach on survival rate of the patients. Is survival rate impaired when surgery is delayed if a local relapse occurs? Moreover, the appropriate adjuvant treatment after local relapse needs to be defined and may not necessarily follow standard protocols after local recurrences. These concepts would need to be studied in clinical trials (see the next section).

Finally, as early diagnosis of any local relapse may be especially relevant in patients with a nonsurgical approach after NST, we would suggest routine follow-up imaging according to local standards and add a yearly breast MRI for at least 5 (better 10) years. Performing follow-up imaging at shorter intervals than annually can also be considered in the initial nonsurgical trials. As this is a new paradigm in breast cancer treatment, however, the natural history of imaging findings without surgery will need to be reported and monitored closely while balancing safety and recommendation for additional (unnecessary) biopsies and imaging, and therefore leading to patient anxiety and other dimensions of extra costs for patients and society.

There are not enough data yet on the costs of implementing a no-surgery approach to make a valid conclusion. Nevertheless, taking a look at the costs of breast surgery and breast biopsies might be informative for this discussion: Results from 2009—2014 show that costs were US$13 190 greater for breast surgery compared with core-needle biopsy.[53]

With average costs of US$550 per MRI examination,[54] after initial annual MRI examinations for 10 years there would be a saving of US$7690 per patient. Considering the false-positive rate of 10% for breast MRI (highest among all breast imaging procedures),[33] this would require additional biopsies, and assuming the worst case, all of these false-positive cases would be followed by breast surgery: Even accounting for these surgery costs following every false-positive case, the no-surgery approach still results in savings of nearly US$600 per patient. But we do not know yet how much additional costs these false-positive cases truly add. Thus, evaluating health-economic end points will be relevant and is already part of ongoing trials.[55] Having saved a number of unnecessary surgeries is worth these efforts and might be economically reasonable, too.

FOURTH: QUESTIONS REGARDING FUTURE CLINICAL TRIAL DESIGNS

How should we design and perform clinical trials to gather sufficient evidence on the aforementioned questions to

change clinical practice? There are some practical and methodological challenges to be taken into consideration. First of all: In two important recent randomized controlled trials of de-escalation topics in breast surgical treatment, the ACOSOG Z0011 trial and the AMAROS trial, the number of events were extremely low and recruitment of patients was much more difficult than anticipated.[56,57] This suggests that clinical trials to examine de-escalation of surgical management in breast cancer patients with an excellent response to NST may be very challenging with respect to sample size. Nevertheless, we believe that we should design and support controlled clinical trials, randomized if possible, to address one major question: whether breast surgery can be safely omitted after NST in patients with an excellent, image-guided biopsy—'proven' complete response.

To answer this question, we should design a trial comparing two strategies after NST: (i) standard therapy being surgery plus radiation treatment, (ii) no breast surgery but standard radiation treatment (Figure 3). From a methodological point of view we would encourage a second randomization of radiation treatment but assume that this is not feasible and the probability of radiation therapy benefit (as for all residual tumor burden in every breast conservation) is more relevant as the potential benefit of surgery in these cases. All other adjuvant or post-NST recommendations should be applied according to actual guidelines of care. The primary end point should be locoregional or regional breast cancer recurrences. Secondary end points should include economic aspects as percentage of additional visits, biopsies, and MRIs due to omitted surgery (as discussed earlier). As patient-reported outcomes and patient-centered medicine

have increasingly evolved over the past years, we should also consider evaluating women's preferences and possible anxieties when skipping breast surgery as secondary end points.

The first no-surgery trial has already started: NCT02945579 at MD Anderson is enrolling women 40 years or older who have a pathologically confirmed stage I or II HER2-positive or triple-negative breast tumor <5 cm and for whom initial ultrasonography reveals four or fewer abnormal axillary lymph nodes. The patients receive standard neoadjuvant systemic therapy. After the neoadjuvant treatment, patients who have a pCR as assessed by image-guided biopsy forgo surgery and receive whole-breast radiation therapy. The patients are followed up for at least 5 years every 6 months by imaging. Primary outcomes are ipsilateral breast tumor recurrence-free survival after 5 years and overall survival after 5 years. This is a nonrandomized trial of a highly selected cohort of patients, however. One major task will be how to deal with randomization and patient preferences in future trials.

Given the feasibility challenges illustrated by the aforementioned recent surgical oncology trials, we need to consider a number of methodological and practical challenges in designing these clinical trials, including challenges related to potential confounders, patient recruitment, and patients switching from one arm to another.

A parallel group design would be adequate; however, the group allocation would only fix the initial treatment. Therefore, relapse as a short-term end point might be an end point that more directly captures the initial treatment effect compared with survival.

Even though controlled clinical trials are generally adequate and feasible, randomized controlled clinical trials are the gold standard. Randomizing patients to the different arms, however, will be a major challenge as patients usually want to choose their treatment if the two treatment options are very different. Not including patients who refuse to be randomized is a possibility but would cause major recruitment issues. Allowing patients to choose their treatment group is more patient centric and consistent with value-based modern health care. If patients are allowed to choose their treatment group, all variables with a potential influence on the final outcome must be carefully documented at baseline. Imbalance in the two groups with respect to these influencing variables can be accounted for by incorporating covariates in the final model or by matching the patient groups either directly by the confounders or by propensity scores. Thus conducting two (or even single) armed noninferiority trials with well-established lower 95% confidence intervals is the more appropriate study design while still being methodological sound. This approach has been successfully used to address problems with randomization in de-escalating therapy trials for women with low-risk HER2-positive breast cancer.[58,59]

Another approach to address the difficult patient accrual is considered by an ongoing study conducting a pooled analysis of internationally performed minimal invasive biopsy trials, combining small cohorts. While this might be theoretically a good approach it is highly challenging in the current situation: several small pilot trials have been
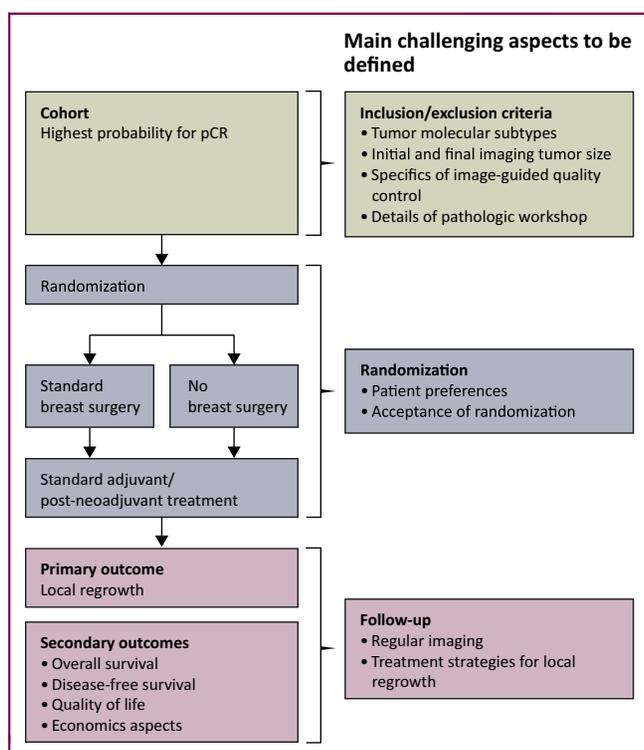

Figure 3. Trial chart and main challenging aspects.
pCR, pathologic complete response.

Table 2. Ongoing clinical feasibility trials utilizing percutaneous biopsy after neoadjuvant therapy to select patients for omission of breast cancer surgery (partially adapted from Kuerer et al.[24])

Group/author/PI	Eligibility criteria/lesion size criteria	Type of biopsy	Number of patients	Study unique characteristics	Performance results
MD Anderson Cancer Center/Kuerer et al.[63]	TN- or HER2-positive initial imaging size 5 cm and final size 2 cm and/or 90% of lesion sampled after NST; N0 or biopsy-confirmed N1 with four or less abnormal nodes on initial ultrasound	Minimum of 12× 9G VAB; image guidance dependent on radiologist decision	50	No breast surgery treatment trial	Primary end point is local recurrence with continuous monitoring and early stopping rules
Netherlands Cancer Institute/MICRA Trial Vrancken-Peeters et al.[69]	Invasive breast cancer patients; nonmetastatic; with radiologic partial or complete response on CE-MRI after NST/no lesion size criteria	Ultrasound-guided 14 G biopsies targeted around pre-NST-placed marker (four central; four peripheral)	525 (150 with partial radiologic response on CE-MRI and 375 with complete radiologic response on CE-MRI)	All breast cancer subtypes; response monitoring with CE-MRI	Primary end point is a specificity of 92% (proportion of patients with residual disease in the surgical specimen that is also confirmed by biopsy). In addition, FNR will be calculated
University of Heidelberg/RESPONDER Trial Heil et al.[61]	Invasive breast cancer after NST; clinical partial or complete response; target lesion visible on ultrasound or mammography/no lesion size criteria	Ultrasound- or mammographic-guided VAB	600	Confirmative analysis to identify a pCR using VAB	Primary end point <10% FNR. Standardization of histopathological evaluation of post-NST samples.
University of Birmingham/Rea/NOSTRA feasibility	ER-negative or HER2-positive invasive breast cancer receiving NST/lesion size must be >1 cm on ultrasound or node-positive	Ultrasound-directed biopsy, minimum of six	150	Microcalcifications will not be targeted; no upper limit of size criteria	FNR <10%
NRG/Basik and De Los Santos	Operable focal or multifocal [T1—T3, stage II and IIIA invasive ductal carcinoma with no size criteria (all receptor phenotypes)], completed NST with a clinical complete response (by clinical examination); patients must have achieved a complete or near-complete radiologic tumor response on breast imaging with mammogram, ultrasound, and MRI; patients must be undergoing breast conserving therapy; patients must have a biopsy marker placed within the tumor bed with imaging confirmation (preferably mammogram but ultrasound or MRI is acceptable) of marker placement prior to NST	6× 8—11G VAB, stereotactic	175	Multicenter cooperative group study with trimodality imaging required	NPV = 90% and FNR = 10%

CE, contrast enhanced; FNR, false-negative rate; MRI, magnetic resonance imaging; NST, neoadjuvant systemic treatment; pCR, pathologic complete response; PI, principal investigator; VAB, vacuum-assisted biopsy.

completed using different patient criteria and procedure methods to find the best method. To adapt this pooled analysis approach in the future, study cohorts and procedures must be highly standardized, which might be impossible in an international setting.

An additional challenge is that the aim of group comparison is to show the equality of the groups, not to detect differences. Equivalence trials generally require much larger sample sizes, which implies increased costs.

The high impact of the patient preference can also cause a high amount of treatment-arm switchers. For example, patients in the watch-and-wait group might become afraid of 'not doing anything' and want to undergo surgery. If switching of patients between study groups occurs, care has to be taken in defining the populations used for the primary efficacy analysis.[60] Although treatment switchers do not formally belong to the per-protocol population, which is the population of choice for equivalence trials, if the treatment-switcher group is large, it is not meaningful to exclude these patients from the analysis. Instead, treatment switchers require a careful specific analysis, and the results must be incorporated into the final results, for example, by defining time-varying on-treatment populations or by considering stratification for relevant subgroups.

Last but most important we should discuss the appropriate patient group in which this nonsurgical diagnosis of pCR and subsequently omission of breast surgery should be investigated in future trials.

Ongoing trials to identify pCR by minimally invasive biopsies are conducted among women with a partial or complete radiologic response after NST to select low-risk patients (Table 2). The role of other factors such as clinical tumor stage and involvement of lymph nodes is currently investigated in these trials.[61-63] Based on the findings of these feasibility trials, a non-surgical trial should be offered to those women with highest diagnostic accuracy and lowest possible risk of recurrence to maximize oncologic safety.

CONCLUSION

Our goal is to do no harm to patients while continuing to de-escalate surgery and increase quality of life, but achieving this goal can be challenging in breast surgical management after NST. We believe that there may exist a subgroup of breast cancer patients who derive no benefit from breast surgery after NST. However, at present, no definitive evidence is available with which to resolve our questions, and it remains a worthy challenge to conduct high-quality clinical trials necessary to develop such evidence.

REFERENCES

1. Giordano SH, Elias AD, Gradishar WJ. NCCN guidelines updates: breast cancer. *J Natl Compr Canc Netw*. 2018;16:605—610.
2. Biganzoli L, Marotti L, Hart CD, et al. Quality indicators in breast cancer care: an update from the EUSOMA working group. *Eur J Cancer*. 2017;86:59—81.
3. Murphy BL, Day CN, Hoskin TL, et al. Neoadjuvant chemotherapy use in breast cancer is greatest in excellent responders: triple-negative and HER2+ subtypes. *Ann Surg Oncol*. 2018;25:2241—2248.
4. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384:164—172.
5. Symmans WF, Wei C, Gould R, et al. Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. *J Clin Oncol*. 2017;35:1049—1060.
6. Houssami N, Macaskill P, von Minckwitz G, et al. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. *Eur J Cancer*. 2012;48:3342—3354.
7. Haque W, Verma V, Hatch S, et al. Response rates and pathologic complete response by breast cancer molecular subtype following neoadjuvant chemotherapy. *Breast Cancer Res Treat*. 2018;170:559—567.
8. Goorts B, van Nijnatten TJ, de Munck L, et al. Clinical tumor stage is the most important predictor of pathological complete response rate after neoadjuvant chemotherapy in breast cancer patients. *Breast Cancer Res Treat*. 2017;163:83—91.
9. van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19:1630—1640.
10. Santonja A, Sánchez-Muñoz A, Lluch A, et al. Triple negative breast cancer subtypes and pathologic complete response rate to neoadjuvant chemotherapy. *Oncotarget*. 2018;9:26406—26416.
11. Samiei S, van Nijnatten TJA, de Munck L, et al. Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy. *Ann Surg*. 2018. https://doi.org/10.1097/SLA.0000000000003126 [Epub ahead of print].
12. Barron AU, Hoskin TL, Day CN, et al. Association of low nodal positivity rate among patients with ERBB2-positive or triple-negative breast cancer and breast pathologic complete response to neoadjuvant chemotherapy. *JAMA Surg*. 2018;153:1120—1126.
13. Tadros AB, Yang WT, Krishnamurthy S, et al. Identification of patients with documented pathologic complete response in the breast after neoadjuvant chemotherapy for omission of axillary surgery. *JAMA Surg*. 2017;152:665—670.
14. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376:2147—2159.
15. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380:617—628.
16. van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19:1630—1640.
17. van der Voort Aea. Image-guided de-escalation of neo-adjuvant chemotherapy in HER2-positive breast cancer: the TRAIN-3 study (TRAIN-3). ClinicalTrials.gov Identifier: NCT03820063. Available at https://clinicaltrials.gov/ct2/show/NCT03820063. Accessed October 31, 2019.
18. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347:1227—1232.

19. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233—1241.

20. Riedel F, Hennigs A, Hug S, et al. Is mastectomy oncologically safer than breast-conserving treatment in early breast cancer? *Breast Care (Basel)*. 2017;12:385—390.

21. Rutgers EJ, Group EC. Quality control in the locoregional treatment of breast cancer. *Eur J Cancer*. 2001;37:447—453.

22. Ring A, Webb A, Ashley S, et al. Is surgery necessary after complete clinical remission following neoadjuvant chemotherapy for early breast cancer? *J Clin Oncol*. 2003;21:4540—4545.

23. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol*. 2018;19:27—39.

24. Kuerer HM, Vrancken Peeters M, Rea DW, et al. Nonoperative management for invasive breast cancer after neoadjuvant systemic therapy: conceptual basis and fundamental international feasibility clinical trials. *Ann Surg Oncol*. 2017;24:2855—2862.

25. Kuerer HM, Rauch GM, Krishnamurthy S, et al. A clinical feasibility trial for identification of exceptional responders in whom breast cancer surgery can be eliminated following neoadjuvant systemic therapy. *Ann Surg*. 2018;267:946—951.

26. Heil J, Schaefgen B, Sinn P, et al. Can a pathological complete response of breast cancer after neoadjuvant chemotherapy be diagnosed by minimal invasive biopsy? *Eur J Cancer*. 2016;69:142—150.

27. Heil J, Sinn P, Richter H, et al. RESPONDER - diagnosis of pathological complete response by vacuum-assisted biopsy after neoadjuvant chemotherapy in breast cancer - a multicenter, confirmative, one-armed, intra-individually-controlled, open, diagnostic trial. *BMC Cancer*. 2018;18:851.

28. van der Noordaa MEM, van Duijnhoven FH, Straver ME, et al. Major reduction in axillary lymph node dissections after neoadjuvant systemic therapy for node-positive breast cancer by combining PET/CT and the MARI procedure. *Ann Surg Oncol*. 2018;25:1512—1520.

29. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11:927—933.

30. Fowler AM, Mankoff DA, Joe BN. Imaging neoadjuvant therapy response in breast cancer. *Radiology*. 2017;285:358—375.

31. Li H, Yao L, Jin P, et al. MRI and PET/CT for evaluation of the pathological response to neoadjuvant chemotherapy in breast cancer: a systematic review and meta-analysis. *Breast*. 2018;40:106—115.

32. Rauch GM, Adrada BE, Kuerer HM, et al. Multimodality imaging for evaluating response to neoadjuvant chemotherapy in breast cancer. *Am J Roentgenol*. 2017;208:290—299.

33. Schaefgen B, Mati M, Sinn HP, et al. Can routine imaging after neoadjuvant chemotherapy in breast cancer predict pathologic complete response? *Ann Surg Oncol*. 2016;23:789—795.

34. Yates LR. Intratumoral heterogeneity and subclonal diversification of early breast cancer. *Breast*. 2017;34(Suppl 1):S36—S42.

35. Heil J, Kummel S, Schaefgen B, et al. Diagnosis of pathological complete response to neoadjuvant chemotherapy in breast cancer by minimal invasive biopsy techniques. *Br J Cancer*. 2015;113:1565—1570.

36. Bownes RJ, Turnbull AK, Martinez-Perez C, et al. On-treatment biomarkers can improve prediction of response to neoadjuvant chemotherapy in breast cancer. *Breast Cancer Res*. 2019;21:73.

37. Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol*. 2018;19:40—50.

38. Datta J, Berk E, Xu S, et al. Anti-HER2 CD4(+) T-helper type 1 response is a novel immune correlate to pathologic response following neoadjuvant therapy in HER2-positive breast cancer. *Breast Cancer Res*. 2015;17:71.

39. Loibl S, Volz C, Mau C, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. *Breast Cancer Res Treat*. 2014;144:153—162.

40. Sinn HP, Schmid H, Junkermann H, et al. Histologic regression of breast cancer after primary (neoadjuvant) chemotherapy. *Geburtshilfe Frauenheilkd*. 1994;54:552—558.

41. Chen AM, Meric-Bernstam F, Hunt KK, et al. Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. *J Clin Oncol*. 2004;22:2303—2312.

42. Swisher SK, Vila J, Tucker SL, et al. Locoregional control according to breast cancer subtype and response to neoadjuvant chemotherapy in breast cancer patients undergoing breast-conserving therapy. *Ann Surg Oncol*. 2016;23:749—756.

43. Early Breast Cancer Trialists' Collaborative Group. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol*. 2018;19:27—39.

44. Jones RL, Lakhani SR, Ring AE, et al. Pathological complete response and residual DCIS following neoadjuvant chemotherapy for breast carcinoma. *Br J Cancer*. 2006;94:358—362.

45. Thomas Jr CR. Is watch-and-wait ready for prime time?: it depends on priming of the multidisciplinary care team. *JAMA Oncol*. 2019:e185895.

46. Heil J, Czink E, Golatta M, et al. Change of aesthetic and functional outcome over time and their relationship to quality of life after breast conserving therapy. *Eur J Surg Oncol*. 2011;37:116—121.

47. Dahlback C, Ullmark JH, Rehn M, et al. Aesthetic result after breast-conserving therapy is associated with quality of life several years after treatment. Swedish women evaluated with BCCT.core and BREAST-Q. *Breast Cancer Res Treat*. 2017;164:679—687.

48. Hennigs A, Biehl H, Rauch G, et al. Change of patient-reported aesthetic outcome over time and identification of factors characterizing poor aesthetic outcome after breast-conserving therapy: long-term results of a prospective cohort study. *Ann Surg Oncol*. 2016;23:1744—1751.

49. Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med*. 2011;364:412—421.

50. Fayanju OM, Jeffe DB, Margenthaler JA. Occult primary breast cancer at a comprehensive cancer center. *J Surg Res*. 2013;185:684—689.

51. He M, Tang LC, Yu KD, et al. Treatment outcomes and unfavorable prognostic factors in patients with occult breast cancer. *Eur J Surg Oncol*. 2012;38:1022—1028.

52. Sohn G, Son BH, Lee SJ, et al. Treatment and survival of patients with occult breast cancer with axillary lymph node metastasis: a nationwide retrospective study. *J Surg Oncol*. 2014;110:270—274.

53. Kimball CC, Nichols CI, Vose JG. The payer and patient cost burden of open breast conserving procedures following percutaneous breast biopsy. *Breast Cancer (Auckl)*. 2018;12:1178223418777766.

54. Mango VL, Goel A, Mema E, et al. Breast MRI screening for average-risk women: a Monte Carlo simulation cost-benefit analysis. *J Magn Reson Imaging*. 2019;49:e216—e221.

55. Kuerer HM. Eliminating surgery after systemic therapy in treating patients with her2 positive or triple negative breast cancer. ClinicalTrials.gov Identifier: NCT02945579. Available at https://clinicaltrials.gov/ct2/show/NCT02945579. Accessed October 31, 2019.

56. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA*. 2017;318:918—926.

57. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15:1303—1310.

58. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med*. 2015;372:134—141.

59. Goldvaser H, Korzets Y, Shepshelovich D, et al. Deescalating adjuvant trastuzumab in HER2-positive early-stage breast cancer: a systemic review and meta-analysis. *JNCI Cancer Spectr*. 2019;3:pkz033.

60. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. *Stat Med*. 1999;18:1905—1942.

61. Heil J. Diagnosis of pathological complete response by vacuum-assisted biopsy after neoadjuvant chemotherapy in breast cancer (RESPONDER).

ClinicalTrials.gov Identifier: NCT02948764. Available at https://clinicaltrials.gov/ct2/show/NCT02948764. Accessed October 31, 2019.

62. van der Noordaa MEM, van Duijnhoven FH, Loo CE, et al. Identifying pathologic complete response of the breast after neoadjuvant systemic therapy with ultrasound guided biopsy to eventually omit surgery: study design and feasibility of the MICRA trial (Minimally Invasive Complete Response Assessment). *Breast*. 2018;40:76—81.

63. Kuerer H. Eliminating breast cancer surgery in exceptional responders with neoadjuvant systemic therapy. ClinicalTrials.gov Identifier: NCT02945579. Available at https://clinicaltrials.gov/ct2/show/NCT02945579; 2017. Accessed October 31, 2019.

64. Kuerer HM, Rauch GM, Krishnamurthy S, et al. Feasibility trial for identification of patients for eliminating breast cancer surgery following neoadjuvant systemic therapy. *Cancer Res*. 2017;77(74 suppl):Abstract 75-16-30.

65. Caudle AS, Yang WT, Krishnamurthy S, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. *J Clin Oncol*. 2016;34:1072—1078.

66. Francis A, Herring K, Molyneux R, et al. NOSTRA PRELIM: a non randomised pilot study designed to assess the ability of image guided core biopsies to detect residual disease in patients with early breast cancer who have received neoadjuvant chemotherapy to inform the design of a planned trial. *Cancer Res*. 2017;77(74 suppl):Abstract 75-16-14.

67. Lee HB, Kim S-Y, Kim KE, et al. Prediction of pathologic complete response by image-guided biopsy before surgery in breast cancer with complete clinical response to neoadjuvant chemotherapy: A prospective feasibility trial. *J Clin Oncol*. 2018;36(15_suppl):566.

68. Tasoulis MK, Roche N, Rusby JE, et al. Post neoadjuvant chemotherapy vacuum assisted biopsy in breast cancer: can it determine pathologic complete response before surgery? *J Clin Oncol*. 2018;36(15_suppl):567.

69. Vrancken Peeters MJ. Towards omitting breast cancer surgery in patients without residual tumor after upfront chemotherapy. Available at https://www.trialregister.nl/trial/5939. Accessed October 31, 2019.