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DOI:

[10.1245/s10434-017-5926-z](https://doi.org/10.1245/s10434-017-5926-z)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Kuerer, HM, Vrancken Peeters, M-JTFD, Rea, D, Basik, M, De Los Santos, J & Heil, J 2017, 'Nonoperative Management for Invasive Breast Cancer After Neoadjuvant Systemic Therapy: Conceptual Basis and Fundamental International Feasibility Clinical Trials', *Annals of Surgical Oncology*.
<https://doi.org/10.1245/s10434-017-5926-z>

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Publisher Rights Statement:

The final publication is available at Springer via <http://dx.doi.org/10.1245/s10434-017-5926-z>

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Nonoperative management for invasive breast cancer after neoadjuvant systemic therapy: Conceptual basis and fundamental international feasibility clinical trials

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Running title: Selective Omission of Breast Cancer Surgery

Financial disclosure: None of the authors has any commercial interest or conflict to disclose related to the present work.

Synopsis:

Teams of investigators from around the world are investigating the potential of selective omission of breast cancer surgery following neoadjuvant systemic therapy. Clinical trials are described and remaining challenges in the field discussed.

Abstract

With current advances in neoadjuvant systemic therapy (NST) and improved breast imaging, the potential of nonoperative therapy for invasive breast cancer has emerged as a viable option when utilizing meticulous image guided percutaneous biopsy to document pathologic complete response. Feasibility clinical trials utilizing this approach are being performed by teams of investigators from single and multi-center/cooperative groups around the world. Imaging alone after NST lacks sufficient sensitivity and specificity in predicting pCR and therefore can't be utilized for clinical selection of patients for omission of surgery. Imaging with adequate sampling after NST of the residual lesions (or around the remaining clip if a complete radiologic response occurs) appears to be essential in selecting patients with pCR to lower the false-negative rates based on initial reported feasibility studies to identify pCR without surgery that range from 5% to 49%. In this manuscript recently completed, ongoing, and planned clinical feasibility trials and a new omission of surgery trial are described. Drastic rethinking of all diagnostic and therapeutic management strategies that are ordinarily utilized for patients who receive standard breast cancer surgery is required. A roadmap of essential questions and issues that will have to be resolved as the field of nonoperative breast cancer management advances is described in detail.

Acknowledgements

Portions of this manuscript will be presented at the 18th Annual American Society of Breast Surgeons Society general plenary session on April 29th, 2017. This project was supported by the PH and Fay Etta Robinson Distinguished Professorship in Research endowment (HMK), and the National Institutes of Health (NIH) Cancer Center Support Grant (HMK, CA16672); Pink Ribbon NL (MJVP), Development Fund of the University of Birmingham for Surgical Research (DWR).

Dedication

This manuscript is dedicated to the memory of Professor Adele Francis MBChB, PhD, FRCS a visionary leading breast surgeon and clinical investigator.

INTRODUCTION

Avoidance of surgery in select breast cancer patients with excellent documented pathologic response with neoadjuvant systemic therapy (NST) by percutaneous means, if proved to be safe and effective, has the potential of decreasing post-surgical complications, improving quality-of-life, and decreasing health care costs.¹⁻⁵ Historically, attempts of omission of surgery in breast cancer patients treated with NST resulted in high rates of local-regional recurrence.² Most of these initial studies had suboptimal methodologies including use of only physical examination to determine clinical response, lack of selection of patients by disease subtype, and/or lack of utilization of enhanced image-guided biopsy to assess for pathologic response.^{2,4,6} The main impediment to potential omission of surgery for breast cancer has been the fact that standard breast imaging methods cannot accurately predict the status of the absence of residual disease after NST.^{2,3,7-9} In this manuscript, recently completed, ongoing, and planned clinical feasibility and omission of surgery after NST trials are described (Table 1) in order to summarize the state of the science of the field and develop a roadmap of essential questions to be addressed.

German Breast Group and the University of Heidelberg

From 2009-2013, 164 patients with histologically confirmed, non-metastatic, invasive breast cancer showing a clinical complete response (cCR) after NST were enrolled in this multicenter study.⁴ Core cut (CC) biopsy was performed on 116 patients, and vacuum-assisted core biopsy (VACB) on 46 patients. Biopsies were guided by

ultrasound in 144 cases and by mammography in 20 cases. The main study endpoint was the false negative rate (FNR). Overall analysis calculated a FNR of 49.3% (95% CI: (40.4%; 58.2%). However, there was no false negative result in the mammographic guided VACB (negative predictive value (NPV) 100%; FNR 0%). Overall, the study hypothesized a high potential for VACB techniques. However, insufficient diagnostic accuracy was attributed to a lack of evaluation of the representativeness of the biopsy as well as to the use of non-standardized biopsy and pathology procedures.

In order to better assess the representativeness of the biopsy, three different evaluation methods were compared at the University of Heidelberg: the subjective evaluation of the physician taking the biopsy, specimen radiography, and histopathological evaluation of the biopsy specimen.⁵ Out of 87 screened patients in 2014-15, 50 patients with complete or partial response were assigned to the study as partial responders by imaging may also result in pCR. The main study endpoint was the FNR comparing the histopathological evaluation of the biopsy with the surgical specimen. Analysis of the whole cohort yielded a FNR of 25.9% (95% CI 13.8-38.0). Given a pathologically representative VACB sample (n=38) the FNR 4.8% (95% CI 0.0-11.6), which demonstrates the high diagnostic potential of a VACB when combined with careful histologic review. Toward this end, it is of interest to determine how often residual histologic changes are and are not seen among cases with a pCR. However, the crucial challenge remains identifying reliable techniques to prevent sampling errors. Based on these results, the investigators designed a multicenter trial (RESPONDER) which will commence this year and will enroll 600 patients with breast cancer showing at

least a partial response with NST to address imaging of the target lesion (tumor and or clip) and biopsy and standardizing pathologic processing (Table 1).¹⁰

Netherlands Cancer Institute Amsterdam

The MICRA trial [(Minimally Invasive Complete Response Assessment of the breast after neoadjuvant systemic treatment (trialregister.nl – NTR6120)] is a prospective multi-center observational cohort study.¹¹ In this trial that is currently accruing, investigators at the Netherlands Cancer Institute are assessing the value of biopsies of the breast in determining pathologic response to NST in breast cancer patients. The study population consists of 525 patients with invasive breast cancer treated with NST adapted to the different subtypes (all subtypes are included); patients with proven DCIS are excluded. Group A consists of 375 women with radiologic complete response (rCR) on contrast enhanced-magnetic resonance imaging (CE-MRI). Group B consists of 150 patients with partial response (0.1 – 2.0 cm contrast enhancement and/or with $\geq 30\%$ decrease in tumor size according to the RECIST criteria) on CE-MRI.

In all patients receiving NST, a marker is placed in the center of the original tumor area in the breast. After NST and CE-MRI, 8 ultrasound-guided 14 gauge core biopsies are obtained in the region surrounding the marker (4 biopsies central near the marker within 0.5 cm and 4 biopsies 1.0 to 1.5 cm from the marker), while the patient is under general anesthesia. Immediately thereafter, breast surgery is performed. The pathology results of biopsies and surgical specimens are compared. The primary

endpoint is a specificity of >92% (meaning the proportion of patients with residual disease in the surgical specimen that is correctly confirmed by biopsy). FNR will also be calculated.

In order to selectively eliminate surgery of the axilla we developed the MARI procedure (Marking of the Axillary node with a Radioactive Iodine seed).^{12,13} By combining the MARI procedure with PET/CT staging of the axilla prior to NST we are now able to omit axillary nodal dissection in up to 80 % of our N1-2 and 3 patients.¹⁴ In line with the MICRA trial, we designed the MACRA trial (scheduled to start) to further deescalate surgery of the axilla with the intention of identifying pCR of the axilla by ultrasound guided FNA and/or biopsy of the MARI – node instead of removal of this node.

University of Birmingham, United Kingdom

NOSTRA PRELIM and NOSTRA Feasibility Trial (NO Surgery TRiAl)

NOSTRA PRELIM describes preliminary work undertaken in a diverse patient group undergoing NST at the University of Birmingham to assess the acceptability and feasibility of post-treatment tumor bed biopsy and to inform the methodology to utilize for the biopsy component in the planned NOSTRA feasibility trial.¹⁵ Patients were eligible if the tumor could be seen on US, was ≥ 1 cm, and had any receptor type. US was utilized at the end of therapy to biopsy the tumor region utilizing 4 to 6 biopsies in a total of 22 patients. The size of the initial cancers measured 1.5 cm to 6.1 cm. Two patients had a pCR, 7 patients had a partial pathologic response, 11 patients had stable disease, and 2 patients had not had surgery. There were 4 false-negative events which

resulted in correctly identifying disease in 82% of participants (18 patients). It should be noted that mammography and stereotactic biopsy were not utilized to assess concurrent malignant microcalcifications. The investigators of this preliminary investigation concluded that residual disease can be missed if there is inadequate sampling and requires that a minimum of 6 biopsies will be needed in the NOSTRA Feasibility Trial. There will be a total of 150 participants with triple-negative (TN) or HER2-positive (who have tumor size greater than 1 cm and or node positive) invasive breast cancer receiving NST in the NOSTRA feasibility study. Following NST, a minimum of six ultrasound-guided biopsies will be obtained to determine the FNR following standard surgery with an endpoint of FNR of < 10% in order to proceed to a definitive no surgery planned trial.

NRG Oncology Group (formerly the National Surgical Adjuvant Breast and Bowel Project [NSABP], Radiation Therapy Oncology Group [RTOG], and Gynecologic Oncology Group [GOG])

NRG BR005: Pilot trial evaluating core biopsy in patients with complete radiologic response after neoadjuvant chemotherapy

NRG BR005 is a multicenter cooperative group approved study that will evaluate the accuracy of image-guided biopsy of the residual tumor bed to predict pCR in 175 operable breast cancer patients undergoing NST who have a complete clinical and near complete radiological response. This study will evaluate the NPV and FNR of post-NST tumor bed biopsy as a prelude to a large multicenter study evaluating the omission of surgery for locoregional management with radiation alone in patients with excellent

response to NST. Patients with operable breast cancer of all types except lobular carcinoma and who have evidence of clinical complete response after neoadjuvant therapy will undergo trimodality imaging (mammogram, ultrasound and MRI) to assess eligibility. Patients who have a complete or near-complete imaging response, and who are candidates for breast conserving surgery will undergo VACB with removal of 6 to 8 11G biopsy core samples along with clip removal and replacement at the time of the biopsy. Axillary surgery and radiotherapy will be performed as per local standard of care. Secondary objectives include an evaluation of residual cancer burden, the number of cores performed and the NPV of a trimodality imaging algorithm. The hypothesis being tested is that the NPV will be at least 90% and the FNR < 10% in order to proceed to the phase III study of surgery avoidance. An interim analysis of the first 27 patients with detectable residual tumor at final pathology (approximately the first 135 patients in the entire study) will be performed so as to determine if the study should continue. If this threshold is not met (NPV<90%) than this approach would be deemed insufficient to identify the cohort that could safely move on to the randomized controlled trial of surgery vs no surgery.

MD Anderson Cancer Center

Feasibility trial for identification of patients for eliminating breast cancer surgery following neoadjuvant systemic therapy

The accuracy of fine-needle aspiration (FNA) and vacuum-assisted core biopsy (VACB) was determined in assessing pCR (no invasive or in situ disease) following NST.¹⁶ The sample size of 40 was determined to provide sufficient information to characterize the

diagnostic properties of VACB assuming an estimated 90% sensitivity and specificity for VACB after NST. Forty patients with clinical T1-3N0-3 limited to TN or HER2-positive breast cancer receiving NST were enrolled. The biopsy technique utilized was decided by the radiologist based on the best imaging modality for VACB based on the patient's final imaging results and performed in the breast imaging suite. Findings were compared with findings on pathologic evaluation to determine the performance of image-guided biopsy in predicting residual breast disease after NST. Nineteen patients (47.5%) had a breast pCR and the axillary node pathologic status was concordant with the breast pathologic response in 98% of cases. Combined FNA/VACB demonstrated an accuracy of 98% (95% CI, 87%-100%), false-negative rate of 5% (95% CI, 0%-24%), and negative predictive value of 95% (95% CI, 75%-100%) in predicting residual breast cancer. There were a number of other findings in this study that deserve mention: 1) the median number of 9G image guided VACB were 12 among trial participants and the false-negative results occurred in the 2 cases where the number of cores were at or below 6, 2) median initial tumor size was 3 cm and final median size 1.1 cm, 3) breast imaging consisted of only digital mammography and ultrasound (no MRI required), 4) a radiologic complete response was seen in 25% of participants and in these patients a breast pCR occurred in 80% while a partial radiologic response occurred in 75% of participants and in these patients a breast pCR occurred in 37%.

Management of the axilla among patients with a breast pCR identified by image guided biopsy after NST

Although we demonstrated that the pathologic status of the axilla correlated and was concordant with the pathologic response in the breast after NST in 98% of cases, it was

of interest for our group to analyze this scenario in a larger cohort of patients at MD Anderson.¹⁷ Data from a recent retrospective study at our institution showed that breast pCR after NST correlated with nodal pCR after NST. This study included 290 patients with TN/HER2-positive breast cancer with T1-2N0 disease and normal findings on nodal sonography at diagnosis. Of the 116 patients who had a pCR in the breast after NST, none (0%) had evidence of axillary lymph node metastases after NST. Among 237 patients with FNA/core biopsy-documented N1 disease, 89.6% of patients with a breast pCR after NST had no evidence of axillary metastases, 57.5% of patients without a breast pCR had residual axillary metastases.

*Eliminating breast cancer surgery in exceptional responders with neoadjuvant systemic therapy*¹⁸

Based on the results of the clinical feasibility trial at MD Anderson and the analysis related to nodal status among patients with a breast pCR, the clinical trial for omission of breast surgery has begun accrual.¹⁸ This single center phase 2 study in which 50 participants with TN/HER2-positive breast cancer presenting with tumors less than 5 cm with or without N1 nodal metastases are eligible following standard NST regimens (Figure). VACB will occur in responding patients provided that the tumor region is ≤ 2 cm and/or greater than 90% of the residual lesion is sampled with the minimum of 12 9G VACBs. Patients without residual disease move on to standard whole breast radiotherapy without breast surgery (Figure). Patients with initial ultrasound biopsy confirmed N1 disease are also eligible to participate in the study if VACB does not demonstrate residual breast disease as approximately 90% of these patients will also have a pCR in the lymph nodes. However, these patients will require targeted axillary

dissection to confirm no residual disease prior to radiotherapy.¹⁹ The primary endpoint for the trial is five year local-regional recurrence and will utilize continuous monitoring with ipsilateral mammography and ultrasonography every 6 months such that early stopping rules are in place.

Summary and Conclusions

Tumor response to NST is well-known to significantly impact local regional therapy by downsizing disease which facilitates breast conserving surgery and increases eligibility for limited axillary surgery in selected patients.^{13,19,20} The omission of surgery in the setting of exceptional response to NST, the ultimate breast conserving strategy, is being actively studied. The results of the clinical trials described in this manuscript have identified essential elements that are needed to ensure accuracy and safety in selecting patients for avoidance of surgery. These include the use of high quality image guidance of residual lesions after NST with an adequate sampling of residual imaging abnormalities. This will require limiting patients for this potential approach with either a complete radiologic response or near complete radiologic response for adequate pathologic assessment for residual disease. The question of which imaging modality or combination of breast imaging combined with VACB that will best ensure the lowest false-negative rates and highest negative predictive values remains to be determined and will be answered with the ongoing trials as described. Patients with the highest chance of disease eradication include those with triple negative and HER2-positive subtypes (40-60%) although patients with ER-positive disease may also become eligible (5-20%) for this approach.

The concept of nonoperative therapy of breast cancer utilizing state-of-the-art image guided biopsy to appropriately select patients for avoidance of surgery is a new arena in breast cancer management and thus there are many questions that need to be addressed. With any new paradigm consideration it will sometimes require drastic rethinking of our standard diagnostic and therapeutic management strategies. Table 2 provides a roadmap of essential questions and issues that need to be resolved as the field of nonoperative breast cancer management advances. In conclusion, safety of this approach and methods to ensure this are of prime importance.

Table 1. Completed, Ongoing, and Planned Clinical Feasibility Trials Utilizing Percutaneous Biopsy after Neoadjuvant Therapy to Select Patients for Omission of Breast Cancer Surgery

Status	Group/Author-PI	Eligibility Criteria/Lesion Size Criteria	Type of Biopsy	# Patients	Study unique characteristics	Performance Results
Completed Trials	MD Anderson Cancer Center/ Kuerer et al. ¹⁶	All lesions less than 5 cm on imaging after NST; included only TN and HER2-amplified cases	VACB and FNA; median number sampled 12 using 9G 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. ^{4,6}	Invasive breast cancer patients; non-metastatic; with clinical imaging after neoadjuvant chemotherapy/No lesion size criteria	Core cut (CC) and vacuum-assisted biopsy (VACB)	164 (111 with CC and 46 with VACB)	Explorative comparison of different techniques: CC and VACB, ultrasound and mammographic guidance	Entire cohort (n=164): NPV 71.3%; FNR 49.3%; Mammographic guided VACB (n=16): NPV 100%; FNR 0%
	University of Heidelberg/Heil et al. ⁵	Histologically confirmed, unilateral breast cancer; clinical partial or complete response to NST; target lesion visible by ultrasound/No lesion size criteria	Ultrasound-guided VACB	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./	Invasive breast cancer with any receptor subtype	Ultrasound guided core biopsy; 4 to 6; mammography and	22	Designed to inform biopsy protocol for larger study	Number of patients with a false-negative result (4 of

	NOSTRA PRELIM ¹⁵	receiving NST/No lesion size criteria	stereotactic biopsy not utilized for malignant calcifications			18 total patients)
Ongoing Trials	MD Anderson Cancer Center/ Kuerer et al. ¹⁸	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 < 4 abnormal nodes on initial ultrasound	Minimum of 12 9G VACB; image guidance method dependent on radiologist decision	50	No breast surgery treatment trial	Primary endpoint is local recurrence with continuous monitoring and early stopping rules; secondary endpoints listed in Figure
	Netherlands Cancer Institute MICRA Trial/ MACRA Trial Vrancken-Peeters et al. ¹¹	Invasive breast cancer patients; non-metastatic; with radiologic partial or complete response on CE-MRI after NST/No lesion size criteria	Ultrasound guided 14G biopsies targeted around pre-NST placed marker (4 central; 4 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 endpoint 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. ¹⁰	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 VABC	600	Confirmative analysis to identify a pCR using VACB	Primary endpoint <10% FNR. Standardization of histopathological evaluation of post-NST samples.
Planned Trials	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	Ultrasound directed biopsy, minimum of 6	150	Microcalcifications will not be targeted; no upper limit of size criteria	FNR < 10%

		positive				
	NRG/BR005 Basik and De Los Santos	<p>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)</p> <p>Patients must have achieved a complete or near complete radiologic tumor response on breast imaging with mammogram, ultrasound, and MRI</p> <p>Patients must be undergoing breast conserving therapy</p> <p>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 NST</p>	6 8-11G VACB, stereotactic	175	Multicenter cooperative group study with tri-modality imaging required	NPV= 90% and FNR= 10%

Table 2. Selective omission of breast cancer surgery following neoadjuvant systemic therapy: Essential questions and issues to resolve as the field advances

General matters

Which patients are most likely to achieve a pathologic complete response for both invasive and in situ disease?

What specific systemic therapy agents are associated with maximal chances of a pCR (no residual invasive or in situ disease) in the breast and nodes?

What is the best imaging modality or combination of imaging per breast cancer subtype to select patients for potential biopsy and elimination of surgery?

What are the potential costs and cost savings of eliminating the need for surgery?

What proportion of patients will be interested in clinical trial participation in which surgery will be avoided and what will be their willingness to participate in a single-arm versus randomization between surgery and no-surgery?

What is the optimal oncologic endpoint and study design of a single arm “no surgery” or a randomized clinical trial of surgery vs. no-surgery trials in patients with biopsy confirmed pCR?

Which are the optimal patients for consideration of eliminating surgery with respect to size and characteristics of the breast cancer, considering potential for under sampling and long term need for imaging follow-up?

Can circulating tumor cells and/or circulating DNA or other serum markers be utilized in combination with imaging to better select patients with a pCR?

Biopsy related

What is the acceptable FNR of a minimal invasive biopsy to demonstrate a pCR without influencing oncologic outcome if no surgery will be performed?

What is the optimal method of minimal invasive biopsy: core cut vs. VACB in the post-NST setting (and is this influenced by sub-type)?

What is the optimal number of core biopsies necessary to ensure the highest accuracy / lowest false-negative results (and is this influenced by sub-type)?

What is the best method with respect to sectioning for evaluating core biopsies after NST to ensure the lowest chance of missing residual carcinoma?

How much of the residual lesion(s) needs to be biopsied?

Can residual microcalcifications that are no longer associated with malignancy on biopsy be left in situ and followed?

What are objective and reliable diagnostic pathological signs of pCR of the breast in VAB specimen?

How often will there be no histopathologic evidence of biopsy related changes when pCR occurs?

Are there specific locations in the breast where optimal biopsy may not be feasible due to technical factors and how can this be overcome?

Management of the axilla

What is the best imaging tool; or combination of imaging tools for staging nodal disease prior to and following NST depending on sub-type?

Can patients with initial documented nodal metastases participate safely in clinical trials of eliminating breast surgery?

What is the correlation among exceptional responders with a pCR in the breast compared with final axillary nodal status?

Does the axilla need to be treated with radiotherapy in cases with a pCR who do not undergo surgery?

Radiotherapy issues

What is the optimal delivery method and fractionation for breast radiation when surgery is omitted (whole breast, hypofractionation, partial breast radiation)?

Which nodal fields should be treated, if any?

Should all patients receive a boost to the prior region of carcinoma?

Is radiotherapy needed when there is complete pathologic response in the breast after NST?

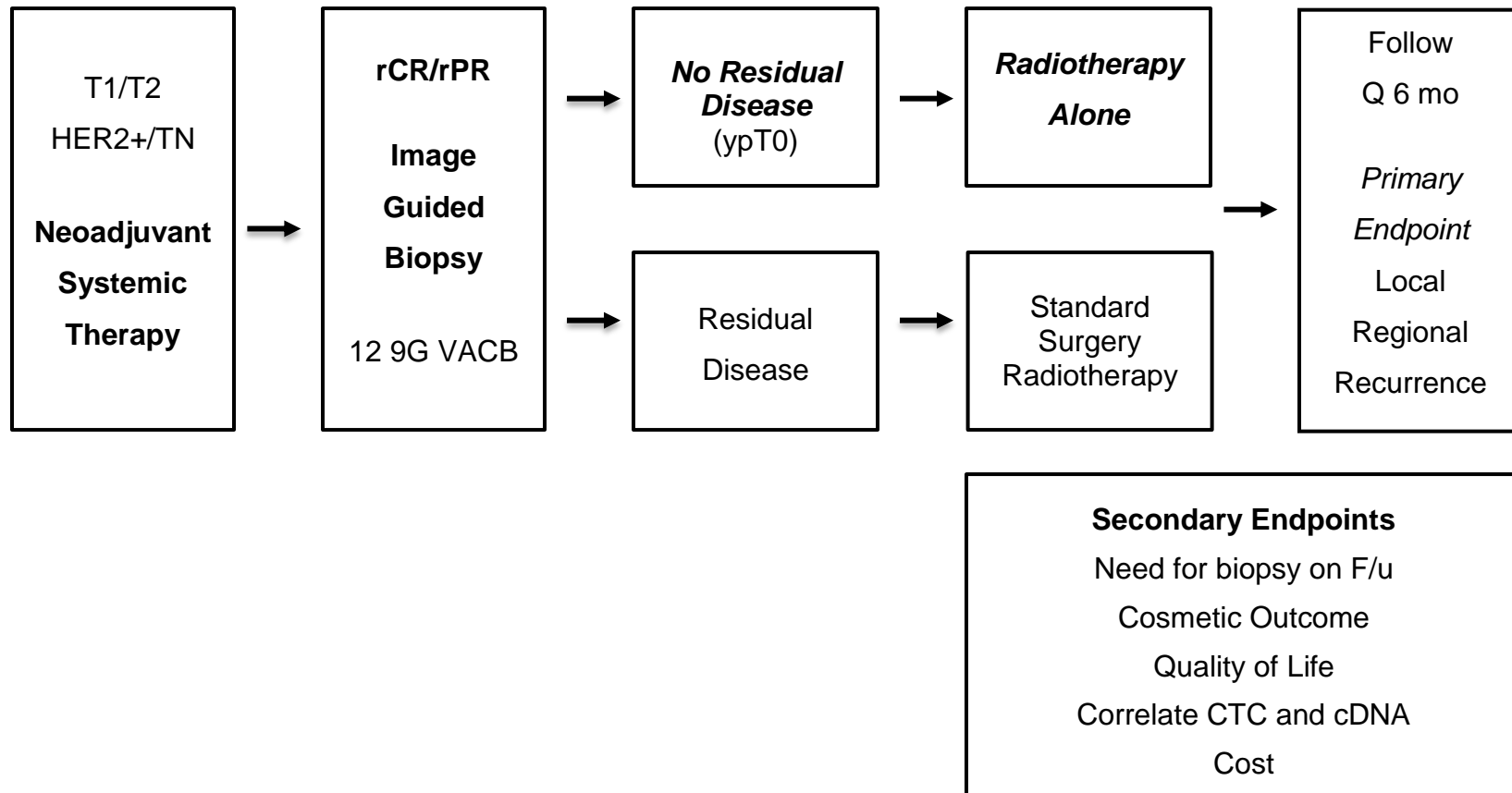
Follow-up

What is the best imaging modality for following patients who do not undergo surgery for breast cancer and how often should it occur?

What will the imaging characteristics of the breast and nodal regions among patients who do not have surgery and how often will biopsy be recommended based on imaging to rule out recurrence?

What impact will eliminating surgery have on the quality of life, decisional comfort, and cosmetic outcome for patients?

Figure. Clinical trial schema for the MD Anderson Cancer Center “Eliminating Breast Cancer Surgery in Exceptional Responders with Neoadjuvant Systemic Chemotherapy” currently accruing study.



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