International Journal of Surgery Protocols 16 (2019) 5–8

Contents lists available at ScienceDirect

International Journal of Surgery Protocols

journal homepage: www.elsevier.com/locate/isjp

Accuracy of core biopsy in predicting pathologic complete response in the breast in patients with complete/near complete clinical and radiological response (Complete Responders in the Breast – CRBr) – Trial design and conduct

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ARTICLE INFO

Article history:
Received 26 March 2019
Received in revised form 21 May 2019
Accepted 24 May 2019
Available online 25 May 2019

Keywords:
Pathologic complete response
Core biopsy
Complete responders

ABSTRACT

Introduction: With the advent of taxanes and targeted agents in neoadjuvant chemotherapy (NACT) for breast cancer, the rates of pathologic complete response (pCR) have been steadily increasing. One of the roles of surgery in these women is to serve as a biopsy to confirm or negate a pCR.
Design: This is a prospective validation study. All newly diagnosed non-metastatic breast cancers, of any luminal subtype, planned for neoadjuvant chemotherapy (NACT) with a titanium clip placed in the tumor, will be screened. Eligible patients who have a complete/near complete response to NACT as seen on a mammogram and ultrasound of the breast, will undergo multiple core biopsies of the tumor bed under ultrasound guidance as an outpatient procedure. A minimum of four core biopsy specimens will be mandatory. An MRI will also be done for these patients for documentation and analysis. The core biopsy will be compared to the final histopathology report after definitive surgery.
Objectives: The objective is to study the false negative rate and accuracy of ultrasound guided core biopsies of the tumor bed in predicting pCR. Additionally, the correlation of pCR in the breast with axillary response and the incremental benefit of an MRI in predicting pCR will be evaluated.
Discussion: The concept of using image guided core biopsies to predict pCR could be useful in designing future studies aimed at avoiding redundant surgery in women with a complete response to NACT. This study is registered with Clinical Trials Registry of India (CTRI/2018/01/011122).

1. Introduction

Neoadjuvant chemotherapy (NACT) plays an important role in down staging patients with large operable or locally advanced breast cancer. It also provides an opportunity to evaluate the in vivo response of the tumor to chemotherapy. Patients achieving an excellent response, with no demonstrable invasive or in situ tumor in the breast or the axilla, are considered to have a pathologic complete response (pCR) [1]. With the advent of taxanes and targeted therapies, an increasing number of patients now achieve pCR. In HER2 positive patients, a dual blockade can improve the pCR rates to 45–51% [2,3] Fig. 1.

At present, the standard of care for patients with an excellent response to chemotherapy includes a wide local excision incorporating the center of the tumor/clip. In the absence of a standardized technique, this lumpectomy serves the purpose of a surgical excision biopsy to substantiate or negate a pCR in the breast.

Previously, clinical studies have attempted to evaluate the option of omitting surgery in women with an excellent response to chemotherapy. In these older studies, clinical exam was used as an indicator for pCR [4,5,6] We now know that clinical exam alone, or even in conjunction with a mammogram or ultrasound, is inaccurate in identifying women likely to have a pCR. Recently, the contrast-enhanced MRI has been immensely helpful in evaluating tumor response to chemotherapy. In the hands of an

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https://doi.org/10.1016/j.isjp.2019.05.002
2468-3574/

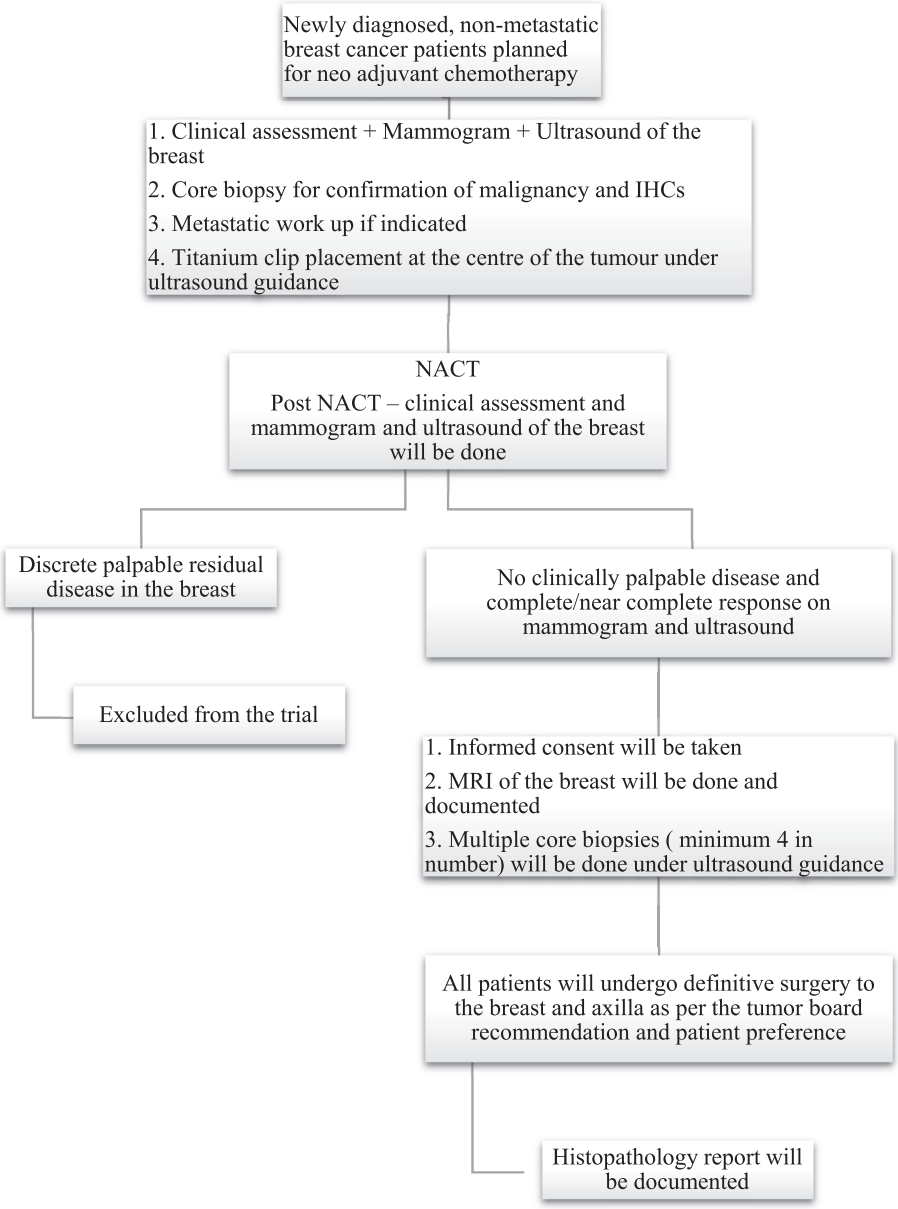

Fig. 1. Trial schema.

experienced radiologist, an MRI can improve the accuracy of predicting a pCR to about 85% [7]. Nonetheless, there is an unacceptable error rate even with the most sensitive imaging modality in predicting pCR in the breast.

The results of the above studies show that there exists a need to identify an accurate means of predicting pCR. Extrapolating from the early breast cancer studies, where triple assessment has been proven to be accurate in diagnosing breast cancer, this study proposes to use clinical exam, imaging of the breast and image guided core biopsies to predict pCR in the breast.

2. Study objectives

2.1. Hypothesis

Histopathology of ultrasound guided core biopsies taken from the tumor bed area will accurately predict pCR in the breast (brpCR) in patients with complete/near complete clinical and radiological response, post neoadjuvant chemotherapy.

2.2. Primary objective

To determine the false negative rate of ultrasound guided core biopsies in predicting pCR in the breast post neoadjuvant chemotherapy

2.3. Secondary objectives

1. Positive predictive value
2. Negative predictive value
3. The incremental benefit of MRI in predicting pCR as compared to clinical exam and a mammogram and ultrasound of the breast
4. Planned subgroup analysis in the hormone receptor negative patients

5. Exploratory analysis for correlation between pCR in the breast and pCR in the axilla

2.4. Study design

This has been planned as a single-arm feasibility study.

Patients with newly diagnosed, non-metastatic breast cancer who are planned for neoadjuvant chemotherapy will be screened for this trial, and will undergo a titanium clip placement prior to the first cycle of chemotherapy. Neoadjuvant chemotherapy schedules will be as per the discretion of the medical oncologist. Following completion of chemotherapy, as per routine protocol at our institute, a mammogram and ultrasound of the breast and axilla will be done to plan surgery. Patients with complete/near complete response to chemotherapy (definitions given below) as per a clinical exam, mammogram and ultrasound will be considered eligible. An MRI will be done for these patients, solely for the purpose of documentation, and will not influence the eligibility for recruitment into this trial. Eligible patients willing to participate in the study, will undergo multiple core biopsies under ultrasound guidance, as an outpatient procedure, using the previously placed titanium clip as the guide. A minimum of four core biopsy specimens will be mandatory.

Following this, all patients will undergo definitive surgery as per the recommendation of the tumor board and patient preference. The final histopathology report will be documented for analysis and comparison.

2.5. Definition of response

- Complete/near complete clinical response: The absence of any palpable residual disease in the breast will be considered as complete clinical response. Vague nodularity or thickening at the primary tumor site will be considered to be within the realm of near-complete clinical response.
- Complete response on mammogram: The absence of any architectural distortion or mass or calcification in the area of the primary tumor site or visualisation of only the clip at the tumor site
- Complete response on ultrasound: will be defined as 99% reduction in the volume of the mass.
- Near complete response on ultrasound: A residual tumor less than 2 cm in its largest dimension as seen on an ultrasound scan
- Complete response on MRI: Absence of gadolinium contrast enhancement or contrast enhancement less than or equal to normal breast tissue at the primary tumor site during any phase of the MRI
- Pathological complete response (pCR) in the breast: Absence of any invasive or in situ tumor in the breast

2.6. Study eligibility

Inclusion criteria:

1. Patients consenting to participate in the study
2. Women $\geq$18 years of age
3. Patients with newly diagnosed, non-metastatic breast cancer who have undergone a titanium clip placement, and have a complete/near complete response in the breast following neoadjuvant chemotherapy as seen on a clinical exam, mammogram and ultrasound of the breast

Exclusion criteria:

1. Patients undergoing upfront surgery
2. Patients with a prior history of excision biopsy
3. Pregnant/lactating women

Withdrawal criteria:

1. Patient withdraws consent

2.7. Data review and analysis

The primary objective of this study is to obtain performance measures of core biopsies as a predictor of pCR, with emphasis on the false negative rate. It is hypothesized that the false negative rate will be less than 10%. At the completion of the study, the false negative rate, accuracy, positive and negative predictive values will be calculated as per the standard formulas for the same, together with 90% confidence intervals for each statistic based on exact binomial distributions.

Since this study includes breast cancers of all luminal subtypes, we expect approximately 40% of the patients who will participate in this study to have pCR. The following table provides examples of false negative rates and corresponding 90% confidence intervals based on exact binomial distributions that might be observed in this study.

Examples of possible false negative rates in 100 eligible patients

# False negative cases	False negative rate	90% confidence interval
0/100	0%	0.00–2.95%
1/100	1%	0.05–4.66%
2/100	2%	0.36–6.16%
3/100	3%	0.82–7.57%
4/100	4%	1.38–8.92%
5/100	5%	1.99–10.23%
6/100	6%	2.65–11.50%
7/100	7%	3.33–12.75%
8/100	8%	4.04–13.97%
9/100	9%	4.78–15.18%
10/100	10%	5.53–16.37%

These estimates will be sufficiently precise to enable the design of subsequent confirmatory studies.

3. Discussion

The recent advances in NACT and targeted agents have improved the pCR rates tremendously. Consequently, about one half of the women undergoing NACT are likely to have a complete response to chemotherapy. There is evidence to suggest that women achieving pCR have improved survival outcomes compared to those with a residual tumor burden, especially in hormone receptor negative tumors [1]. In this scenario, there is a possibility, that in a select group of women with an excellent response to chemotherapy, surgery to the breast only serves the purpose of an excision biopsy to confirm pCR, with no additional oncological benefit to the patient.

There has been considerable difficulty in accurately predicting pCR via imaging modalities. Despite recent advances in MRI scans of the breast, there is still an unacceptable margin of error. Radiology alone, may prove to be inadequate to identify complete responders in the breast. Extrapolating from early breast cancer, where triple assessment including a histopathology (core/fine needle aspiration) has been very effective in accurate diagnosis,

including some form of biopsy of the tumor bed, could be the way forward toidentify women likely to have a pCR.

Pioneering studies on this subject have demonstrated encouraging results. A feasibility study at M D Anderson, [8] among women with triple negative and HER 2 positive breast cancer, suggested that image guided FNAC or vaccum-assisted core biopsies (VACB) are useful in identifying women with pCR. Combined FNAC/VACB had an accuracy of 98% and a false negative rate of 5%. Based on these results, a phase 2 trial for the omission of breast surgery has begun accrual at this centre (NCT02945579). This concept is also being explored in other contemporary trials like MICRA [9], NOSTRA [10], RESPONDER [11] and NRG-BR005 [12].

Identifying an accurate means of predicting a complete response to chemotherapy is the first step. Once achieved, it will enable the design of future trials evaluating the option of omitting surgery in such women. Just as genomic profiling has been instrumental in avoiding unnecessary chemotherapy in women who are unlikely to derive any benefit from it, image guided core biopsies could help in avoiding redundant surgery in select women who are unlikely to gain from the procedure.

4. Ethics

An institutional Ethics Committee approval was obtained for this study.

Funding

This study was funded in part by the Hyderabad Cancer Foundation, and in part by institutional funding. The funding sources had no involvement in the study design/data collection/interpretation of data or preparing the manuscript.

Declaration of Competing Interest

The authors have none to declare.

Acknowledgements

Sincere thanks to CReDO 2017 Protocol Development Workshop for their support and guidance. Special thanks to Dr Arnie Purushotham (Professor at King's College London and Director of King's Health Partners Comprehensive Cancer Care Centre), Mr Gary Clark (Ex-Vice President of Biostatistics & Data Management at Array BioPharma Inc), Dr Manju Sengar (Professor, Adult Haematolymphoid Disease Management Group, Tata Memorial Hospital, Mumbai) and Mr Subir Sinha (Scientific Officer, Statistics, Tata Medical Centre, Kolkata) for their mentorship. Lastly, we would also like to extend our thanks to Neelima Kambhayathghar and Swarnalatha Pulluri (clinical trial co-ordinators at Basavatarakam Indo American Cancer Hospial & Research Institute, India) for their help.

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