Evaluation and Validation of Neo-Adjuvant Response Index (NRI) and It's Correlation with Various Predictive Biomarkers and RECIST in Locally Advanced Breast Cancer

Rahul Bamal · Chintamani · Megha Tandon ·
M. K. Mittal · Sunita Saxena

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Abstract

Background Response evaluation following neo-adjuvant chemotherapy in breast cancer is usually done without taking in to account the axillary response and the available tools like 'response evaluation criteria in solid tumors' (RECIST) have this limitation. These criteria rely solely on the response observed in the primary tumour. Neoadjuvant response index is one such attempt to have a comprehensive assessment of response both in the primary tumour and the axilla.

Methods 30 cases of locally advanced breast cancer (LABC) were assessed for response using 'Neo-adjuvant Response Index'. The index always gives score between '0' (no response or progressive disease) and '1' (pathological complete response i.e. no invasive tumor in breast as well as axilla). This index includes axillary response as well and provides a spectrum of response rather than dividing patients into simply responders and non-responders.

Results Mean reading of index was found to be 0.2925 in this study. Three patients achieved an index of 1. This index correlates significantly with the existing scales for assessing response. Hormone negative tumors were found to be more chemo responsive with higher rates of pathological complete response (pCR) while ER/PR + Her2- tumors showed a very poor response to NACT.

Conclusions Based on the observations of the present study it may be submitted that Neoadjuvant Response Index (NRI) is a reliable and simple tool that can serve as a comprehensive and accurate method of assessing response to neo-adjuvant chemotherapy as it takes in to consideration both the tumor and axillary response unlike the existing RECIST, binary system (responders are those with greater than 50 % reduction), RCB method and the available biomarkers. This study being first of it's kind in Indian population, in spite of it's limitations, could prove to be a launching ground for further reasearch and contribute substantially to the evidence base.

Keywords Neo-adjuvant response index · NRI · Locally advanced breast cancer · RECIST · LABC

Background

Breast cancer is one of the most common site-specific cancer in females with an increasing incidence in the developing world. Most of these patients in developing countries are still locally advanced at presentation requiring a multimodality approach[1, 2]. Neo-adjuvant chemotherapy (NACT) is an integral part of this multimodality treatment with its very well known advantages of making a non resectable tumour resectable, providing an in vivo chemosensitivity and an intermediate end point for assessing response to therapy [3].

Pathological complete response (pCR) after NACT is considered a strong prognostic marker of disease-free and overall survival (DFS and OS) in breast cancer and therefore serves as an important end point to compare effectiveness of various chemotherapy protocols [4, 5].

Conventionally, the response to NACT is assessed using a binary system that grades patient into responders and non-responders. This system over simplifies the response grading

R. Bamal · Chintamani (✉) · M. Tandon
Department of Surgery, VMMC and Safdarjung Hospital, New
Delhi, India
e-mail: chintamani7@rediffmail.com

M. K. Mittal
Department of Radiodiagnosis VMMC, Safdarjang Hospital New
Delhi, New Delhi, India

S. Saxena
Indian Council of Medical Research, Institute of Pathology
Safdarjang Hospital New Delhi, New Delhi, India

and valuable information is lost in the process, hence can be misleading.

Either two dimensions of the tumor are taken in to account while assessing response with responders >50 % decrease in size or only a single dimension is considered when Response Evaluation Criteria in Solid Tumours (RECIST-version 1.1) is used for the same. RECIST divides response into four categories i.e. complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). Responders in RECIST are CR + PR while non-responders are SD + PD.

The binary classification post NACT in 'pCR' and 'no pCR' (Residual Disease or RD) appears too crude and may thus be misleading. Hence, dichotomization of response as pCR or RD is overly simplistic for these objectives because RD after neo-adjuvant treatment includes a broad range of actual responses from near pCR to frank resistance.

The alternative approach to deal with this problem is assessment of Residual cancer burden (RCB) which is a measurement of the extent of residual disease (RD) taking into account both primary tumor bed and axillary lymph node features. RCB is a surrogate for distant relapse-free survival and has more prognostic power than the usual dichotomized response categories of pCR and RD or the American Joint Committee on Cancer (AJCC) staging system following NACT. Furthermore, RCB identifies a subset of patients with minimal RD (RCB-I) whose prognosis is the same as for those who achieve pCR. This extends the definition of excellent pathologic response to include those with pCR or RCB-I. But still it lacks the ability to provide a detailed panorama for understanding the response. It also has a bias that tumors that are small to start with, will obviously have small RCB and vice versa[6, 7].

Here arises the need for a neo-adjuvant response evaluation system that provides a whole spectrum of responses that can be graded efficiently providing us with in depth understanding of response rather than a binary system of classification.

This study proposes an index to assess the response to NACT, 'Neo-adjuvant Response Index-NRI'. Calculation of NRI will always yield a score between 0 and 1. A score of 0 represents no response (or even progression in exceptional cases), while a score of 1 indicates a pCR of both primary tumor and axilla [8]. This prospective study was contemplated to evaluate and validate NRI and its correlation with other biomarkers estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), Her-2/neu receptor status and also RECIST in patients with LABC.

The NRI is calculated from a breast response and an axillary response score as described by S. Rodenhuis et al.[8] The initial staging in clinical stages cT4, cT3, cT2 and cT1 is based on contrast-enhanced MRI. Following surgery, the diameter of the residual tumor as indicated by the pathology report is considered to determine the T-stage (pT). A pCR in breast (pCR Tx) is defined as the complete absence of invasive

tumor cells at microscopy, irrespective of the presence of carcinoma in situ. A 'near-pCR breast' means that only a few scattered tumor cells remain or that the residual tumor is <0.5 cm in size. The breast response score is calculated based on the change in T-stage. The axillary response score is calculated based on a simplified clinical staging system. The axillary stages at diagnosis are classified as cA3, cA2, cA1 and cA0. Following NACT and surgery, axilla is staged as pA3, pA2, pA1 and pA0. NRI is defined as the sum of the breast response score and the axillary response score, divided by the sum of achievable points. Division by total number of achievable points ensures that the NRI is always ≥ 0 and ≤ 1 . NRI of 1 represents pCR of both breast [pCR(Tx)] and axilla [pCR(Ax)], while an NRI of 0 signifies absence of any downstaging. A minor decrease in tumor size and/or axillary disease extent remained, however, compatible with an NRI of 0.

Aims and Objectives

- I. To evaluate and grade response to neo adjuvant chemotherapy using NRI and to validate its utility in patients with LABC
- II. To correlate NRI with ER, PR, AR and Her-2/neu receptor status; as well as RECIST.

Materials and Methods

The study was conducted in Department of Surgery in collaboration with ICMR (Indian Council of Medical Research) and Department of Radiology, Vardhman Mahavir Medical College and Safdarjang Hospital, New Delhi from September 2010 to January 2012.

Patients

A total of 30 histopathologically proven cases of carcinoma breast were included in the study. All the cases were staged as LABC based on AJCC criteria. [9]

Evaluation

- A detailed and thorough history was taken
- Clinical TNM staging was done

Standard preparatory investigations including Core needle biopsy for ER, PR, AR, HER2/neu receptor status were done before subjecting these patients to NACT using CAF

(cyclophosphamide, adriamycin, 5-fluorouracil) regime at three weekly intervals, response assessment was done after each cycle using clinical examination and ultrasound. A baseline contrast enhanced MRI and ultrasonographic examination of ipsilateral axilla and peri-clavicular region with guided Fine Needle Aspiration of any suspected lymphnode metastasis was performed in all cases. These were repeated after three cycles of NACT. The other investigations as recommended by the international breast cancer guidelines (National Comprehensive Cancer Network-NCCN) were performed in all the cases.

Three weeks after the third cycle, all patients underwent modified radical mastectomy using a standardized technique by the same surgical team. The specimen was re-assessed for T-size (tumor size), grade, margins, axilla and other important histopathological and biological variables. The pathological assessment including ER, PR, AR, Her2/*neu* receptor status was performed in Tumor Biology Lab, Institute of Pathology, ICMR (Indian Council of Medical Research) using a standardized procedure by the same pathology team.

Statistical Analysis The data analysis was done using the SPSS software package version 19.0 (SPSS Inc., Chicago, IL, USA).

Observations and Results

A total of 30 histopathologically proven cases of carcinoma breast were included in the study. All the cases were staged as locally advanced breast carcinoma based on AJCC criteria.

Patient and tumor characteristics of the cohort are listed in Table 1.

After NACT, 11 patients (37 %) were found to have a pA0 i.e. microscopically negative axilla out of which 5 already had a staging of cA0 (negative axilla) before NACT. Therefore pCR(Ax) was achieved in 6 patients (25 % of positive axillae before NACT) out of which 5 patients didn't achieve a pCR(Tx), hence it becomes important to include the axillary response while calculating response to NACT.

Whole spectrum of responses to NACT calculated using NRI which includes the response of breast as well as axilla is depicted in Fig. 1. 13 patients (44 %) had a score of 0 i.e. no response either for tumor or axilla while 3 patients (10 %) had a score of 1 i.e. complete pCR with no tumor in breast as well as axilla (cpCR) but out of these 3 patients 2 had cA0 (negative axilla) before NACT.

9 patients (30 %) had a score of 0.5 or more while 13 patients (43 %) had a score greater than 0.3 while the mean NRI was 0.2925. Considering at least 30 % response in order to consider patients as responders we had a response rate of 43 % in our study.

Table 1 Patient and tumor characteristics

No. of patients	30
Age, median	50 years
Age, range	31–65 years
ER:	
Positive	7
Negative	23
PR:	
Positive	7
Negative	23
Her-2/ <i>neu</i> :	
Positive	19
Negative	11
Subtype:	
ER/PR + Her2 -	4
ER/PR + Her2+	3
ER/PR- Her2 +	16
TNBC	7
Tumor stage:	
cT4	16
cT3	4
cT2	7
cT1	3
Axillary stage:	
cA3	25
cA2	0
cA1	0
cA0	5

ER, Estrogen receptor;
PR, Progesterone receptor;
TNBC, Triple negative breast cancer

Comparison of NRI with ER, PR, Her2 and AR status couldn't reach statistically significance and the desired results mainly due to small sample size. ER gave equivocal results with respect to its expression. PR-, Her2+ and AR + tumors showed a trend towards being more chemoresponsive. (Table 2)

When we look at the findings according to RECIST, 3 patients (10 %) had shown complete response (CR) while 11 patients (37 %) had shown partial response (PR). Hence, 14 patients (47 %) were responders if we include CR and PR patients in responders i.e. decrease of at least 30 % in initial tumor size (pre-NACT) on radiology with MRI being the principal modality. (Fig. 2) Mean rank of NRI was highest in CR category (29.00) followed by PR category (16.68) followed by PD category (14.25) while it was lowest in SD category (10.90) with statistically significant results ($p\text{-value}=0.012$) while comparing RECIST with NRI. (Table 2)

While looking at different tumor subtypes out of total 6 pCR(Ax) 4 were in triple negative breast cancers (TNBCs) and moreover, 5 were ER/PR - with only 1 pCR(Ax) in ER/PR + subtype of tumors. 2 pCR(Tx) as well as 2 cpCRs were in

Fig. 1 Cohort distribution based on NRI *x* axis- NRI (Neo-adjuvant response index) values, *y* axis- Number of patients

ER/PR—tumors out of total 3 in each category. Also, mean NRI is only 0.08 in ER/PR + Her2- tumor subtype. (Table 3)

Discussion

Neoadjuvant chemotherapy has become an integral part of multimodality treatment for LABC worldwide. With the advent of NACT, the axillary status even in LABC patients that are responders could be downstaged to N0 [10]. Presence of axillary metastasis is one of the most reliable predictors of outcome in breast cancer, making axillary dissection an essential part of management of a patient with LABC.

NRI is a simple instrument to assess the degree of downstaging induced by pre-operative systemic therapy in breast cancer. It is calculated from a breast response score and an axillary response score.

Definition of NRI has been designed and used by various researchers to obtain a maximum of replicability and a minimum of arbitrariness. For the breast response, reduction in T-stage was chosen rather than a decrease in geometrical volume, because the T-stage is universally accepted and available and because volume estimations strongly depend on technique and interpretation. In addition, any degree of shrinkage measured in two numbers beyond the decimal point would

indicate a non-existent precision. For the axillary response, the presence or absence of palpable lymph nodes is taken into account, although this is clearly a subjective observation. In practice, however, no other estimation of tumor mass in the axilla is routinely available. The relative weight assigned to the breast response and the axilla response has little effect on the NRI, as a sensitivity analysis confirmed. This definition of NRI also ensures that widely accepted response measure *cpCR* is incorporated in a natural way as '1' [8].

NRI uses information that can more or less be obtained from records of patients undergoing standard management for LABC. The only non-standard parameter is MRI for tumor size and if this is not available, an individualized NRI could be adopted that should yield comparable outcomes.

Pathological complete response (pCR) following NACT is considered a surrogate marker for survival and it has been suggested that patients with pCR have the best long-term outcome [4, 11, 12]. However, the response rates vary from amongst various populations and in the same population with different chemotherapy regimens and certain patient and tumor characteristics. This is because breast cancer is a heterogeneous disease from clinical, biological, genetic and molecular point of view with disparities across racial and ethnic groups [11–14]. In a recent review of nine trials of NACT on 3946 LABC patients, enormous variability in response has

Table 2 NRI (Neo-adjuvant response index) comparison with different variables using statistical tests

Variable	Statistical significance	Interpretation	Test applied
ER	Insignificant	Equivocal	Mann Whitney
PR	Insignificant	Trend towards PR—showing better response	Mann Whitney
Her2	Insignificant	Trend towards Her2- tumors showing a better response	Mann Whitney
AR	Insignificant	Trend towards AR+ showing better response	Mann Whitney
RECIST	Significant ($p=0.012$)		Kruskal Wallis

ER, Estrogen receptor; PR, Progesterone receptor; AR, Androgen receptor; RECIST, Response evaluation criteria in solid tumors

Fig. 2 Cohort distribution based on RECIST x axis- RECIST categories, y axis- number of patients PD, Progressive Disease; SD, Stable Disease; PR, Partial Response; CR, Complete Response

been reported, with 7–65 % cCR (clinically complete response) and 4–29 % pCR [15]. All these trials have been conducted in the developed world and included the operable cases of breast cancer. Therefore, this study is an attempt to get more insight into Indian population and its variables; and at the same time to find ‘an Indian solution to an Indian problem’.

In the present study, pCR was achieved in 3 patients (10 %) after NACT that is comparable to other studies with pCR rates as 12, 13, 15.7, 18.8 and upto 23 % in one of them.[4, 11, 16–18]. Apart from the achievement of pCR(Tx), one of the most important prognostic factors after NACT is the post-treatment lymph node status; previously investigators have shown the importance of pCR in positive lymph nodes in response to NACT, independent of the response of the primary tumor. According to available literature, patients that achieved a pCR in previously documented positive lymph nodes had considerably better outcomes than patients that did not, regardless of the response in the primary tumor [19, 20].

In the present study 25 patients (83.3 %) had positive axilla before NACT and 19 patients (63 %) remained with positive axilla after NACT while none of the patients with negative axillae progressed to positive axillae post NACT. pCR(Ax) was achieved in 6 patients (25 % of positive axillae before

NACT) out of which 5 patients didn’t achieve a pCR(Tx), hence it becomes important to include the axillary response while calculating the response to NACT. [Total of 11 patients (37 %) had negative axilla at post operative histopathology but 5 out of them already had a negative axilla before starting NACT]

There was no statistically significant correlation between ER status and NRI in this study; and could be attributed to a very small sample size. Available literature shows that ER status is a marker of chemosensitivity in breast cancer. Apparently, although functionally poorly understood, ER- breast carcinomas are more sensitive to anthracycline-based chemotherapy [11, 21]. (Table 3)

According to a study, PR negative tumors have significantly better response to chemotherapy and the same trend has been observed in our study [16]. *PR negative tumors had shown better response to NACT but the difference was statistically insignificant.* (Table 3)

There is insufficient evidence to use Her-2/neu receptor expression as a predictive factor in breast cancer, as many of the reviewed studies present conflicting data including studies, in whom the response of the primary tumor to treatment with anthracyclines was [17, 21–23]. A report with 40 patients showed that Her-2/neu + tumors ($n=5$) had a significantly

Table 3 pCR (pathological complete response) rates and response according to tumor subtypes

Subtype	No. of patients	pCR (Ax)	pCR (Tx)	cpCR	Mean NRI
ER/PR + Her2 -	4	0	0	0	0.08
ER/PR + Her2+	3	1	1	1	0.58
ER/PR- Her2+	16	1	1	1	0.22
TNBC	7	4	1	1	0.4
Total	30	6	3	3	

ER, Estrogen receptor; PR, Progesterone receptor; TNBC, Triple negative breast cancer; NRI-Neo-adjuvant response index
pCR (Ax), pCR in axilla; pCR(Tx), pCR in primary tumor; cpCR (complete pCR = no invasive tumor in axilla as well as breast)

increased response rate to NACT with doxorubicin, *similar to the trend shown in present study* [24] (Table 3). While on the other hand, another study had reported Her-2/neu receptor negativity being significantly associated with better response to NACT with patients receiving anthracyclines and taxanes based chemotherapy [16].

Its rare to achieve pCR in cases with ER/PR + Her2-tumors and in the present study not a single pCR was achieved in this luminal subtype neither in axilla nor in primary tumor. Mean NRI in patients with ER + and Her-2/neu receptor negative status was only 0.083 as against the overall mean NRI of 0.29. pCRs are more frequently seen in patients with triplr negative breast cancers(TNBC). In the present study also, the only cpCR with both primary and axilla positive to start with was achieved in a TNBC tumor (Table 2).

Similarly, most available studies indicate that patients with- in the ER/PR -ve cohort are significantly more likely to achieve a pCR than patients within the ER/PR + cohort and *same was the observation in present study*. [17] 5 out of 6 pCR(Ax), 2 out of 3 pCR(Tx) and 2 out of 3c pCR were achieved in ER/PR negative cohort in this study. (Table 2)

Patients with positive AR expression, before NACT, were found to be good responders and *a similar trend was observed in present study* (Table 3). Decrease in mRNA levels of Androgen Receptor (AR) gene related to the chemotherapy-induced apoptosis could serve as an important independent predictor of response to NACT. The AR may thus serve as an important independent predictor of response to NACT and may help in tailoring of the regime for a particular patient. AR appears as a promising predictive biomarker for assessing response to neo-adjuvant chemotherapy in patients with locally advanced breast cancer [25]

Immunohistochemical AR expression was evaluated on a tissue microarray of 673 core biopsies from primary breast cancer patients treated with neoadjuvant docetaxel/ doxorubicin/cyclophosphamide (TAC) chemotherapy in the prospective GeparTrio phase-III trial. *AR was detected in 53.2 % of tumors while it was detected in 13.33 % tumors in the present study*. Lowest AR expression was detected in TNBCs with 21.2 % while *none of the TNBC expressed AR in the present study*. Highest AR expression was observed in Luminal A-like tumors with 67 % while *25 % of Luminal A-like tumors in the present study expressed AR*. In AR + tumors, pCR rate was 12.8 % as compared to 25.4 % in AR-negative tumors ($P < 0.0001$). *In the present study cpCR rate was 25 % in AR-positive tumors while it was only 7.69 % in case of AR-negative tumors*. In multivariate analysis, AR independently predicted pCR, patients with an AR-negative tumor have a higher probability of achieving a pCR than those with an AR-positive one. *While in the present study AR + tumors had shown a trend towards being more chemoresponsive* (Table 3). The quoted study had used TAC chemotherapy while CAF

(cyclophosphamide/adriamycin/5-FU) chemotherapy was used in the present study [26].

The distribution of cohort using the RECIST criteria was CR(10 %), PR(36.66 %), SD(33.33 %), PD(20 %) i.e. 46.66 % of response rate(RR) with responders being CR + PR groups while 53.33 % of non-responders (SD + PD). The results were comparable with many other studies in the literature like European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group trial in 1991 using four cycles of preoperative 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) (RR=49 %) and others with similar rates (RR=50.6 % and CR=6.5 %), (RR=38.0 %) .

{cpCR in the present study amounted to the complete pCR i.e. for primary tumor (breast) as well as axilla while pCR in most of the other studies amounted to pCR of the primary tumor (breast) only as they considered the response of the primary tumor only in their studies}.

Conclusions

Amongst the various advantages of NACT is the achievement of pCR. Achievement of pCR in the primary tumor (within the mastectomy specimen) serves as an intermediate end point to assess the tumor's response to NACT and is considered a surrogate marker of tumor behaviour and outcome in breast cancers. The conventional methods of predicting and assessing response do not take into consideration pCR or response (down staging) of axilla to NACT.

NRI takes into consideration both the response of the primary tumor and the axilla in the form of breast and axillary score. It is calculated by using simple formulae that can be reproduced in any setting, at the most with some modification that should give similar results.

In the present study NRI was calculated in 30 patients of LABC using the sum of the breast response score and the axillary response score (derived as described above and in reference article), divided by the sum of maximum achievable points and statistical analysis was done to compare and correlate NRI with ER, PR, AR and Her-2/neu receptor status as well as RECIST.

Based on the observations of the present study it may be submitted that NRI is a reliable and simple tool that can serve as a comprehensive and accurate method of assessing response to NACT. Since NRI takes in to consideration both the tumor and axillary response it is more reliable and comprehensive than the existing RECIST, binary system (responders are defined as with greater than 50 % response), RCB method and the available biomarkers. This study being first of it's kind in Indian population, in spite of it's limitations, could prove to be a launching ground for further reasearch and contribute substantially to the evidence base.

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