Original Article

Correlation of clinico-pathologic and radiologic parameters of response to neoadjuvant chemotherapy in breast cancer

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Abstract

CONTEXT: As of today, there is no validated standard method to assess clinical response of breast cancer to neo-adjuvant chemotherapy (NACT). Some centers use clinical dimensions while others use radiological measurements to evaluate response according to RECIST criteria. **AIMS:** The aim was to correlate and compare the clinical, radiological, and pathological parameters for assessing the tumor response in patients of breast cancer receiving NACT. **SETTINGS AND DESIGN:** Single institution, prospective nonrandomized study conducted over a 2-year period. **MATERIALS AND METHODS:** Patients with diagnosed breast cancer were assessed for response to NACT prior to surgery using clinical and radiological techniques. This was correlated with pathological reponse which was assessed by measuring gross dimensions and Miller-Payne grading of response to chemotherapy. **STATISTICAL ANALYSIS USED:** Spearman's rho nonparametric. **RESULTS:** Fifty two patients completed the evaluation (out of 313 cases of ca breast treated during the same period) with a median age of 52.5 years. We noted a 26.9% clinical complete response (CR) and 19.2% had pathological CR. Clinical evaluation had a sensitivity and specificity of 73.5% and 88.5% respectively compared to 14.2% and 100% respectively for radiological assessment. **CONCLUSIONS:** Clinical assessment of response to NACT shows a higher sensitivity compared to radiological assessment. However the overall low sensitivity and specificity rates of clinical assessment mandate a search for a better method of evaluation.

Key Words: Breast Cancer, pathological criteria, primary chemotherapy, radiological assessment, RECIST criteria, response assessment

Introduction

Complete histological response following neo-adjuvant chemotherapy (NACT) for breast cancer has great prognostic value.[1,2] The significance of a lesser degree of histological response in terms of prognosis is also colossal as a major percentage of patients fall under the category of partial responders.[3-7]

In spite of the differences in the criteria adopted to measure and report the pathological findings after primary noninvasive treatment, most groups have shown a similar correlation between residual disease found at surgery and patient outcome.[7]

Till date, no parameter/s has/have been validated to assess clinical or pathological response of breast cancer to NACT. The change in clinical dimensions of tumor, as assessed during serial clinical breast examination, is used to evaluate the response to therapy in accordance with RECIST criteria.[8] Radiological measurements (by ultrasonogram [USG], mammography, CT scan or MRI) have also been used for response assessment as a logical extension to (more accurately) measure the tumor size in certain centers. Radiological imaging is resource intensive and the additional expenses involved limit the utility of this option in developing countries.

There is a relative lack of comparative studies to tell us whether these parameters are true reflection of total viable tumor size. In such a vacuum, clinicians sometimes resort to radiological measurements, often assuming them to be more accurate. This is bolstered by the fact that there is a dearth of literature comparing serial clinical assessment to radiological evaluation. Still as the availability of such facilities grows, there is increasing marketing pressure to utilize these more often in such repetitive tasks.

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The primary aim of this study was to correlate and compare the clinical, radiological, and the gold standard pathological parameters in assessing the tumor response to NACT. The secondary aim was to assess rates of complete clinical and pathological response in patients of breast carcinoma being treated with NACT.

Thus the present study was aimed at correlating and comparing the conventional methods of assessment to pathological parameters of response.

Materials and Methods

This study was planned as a prospective nonrandomized study to be conducted over a period of 24 months (March 2005 to March 2007). Eligible patients included those with breast cancer over the age of 18, who were taken up for initial chemotherapy and followed by surgery. Prior history of treatment for cancer of breast was an exclusion criterion. Diagnosis was established in all patients by cytopathology and tru-cut biopsy.

After obtaining informed written consent, eligible patients were enrolled to receive serial clinical and radiological (USG or CT scan) measurements before initiation of treatment and after three cycles of chemotherapy.

Lesions were measured clinically and radiologically in two dimensions each time at diagnosis and then after three cycles of NACT. The second assessment was done just prior to surgery. The product of two dimensions was used to assess and categorize the response to chemotherapy using standard UICC criteria.[9,10] Categorization of response was done independently for clinical and radiological measurements. For this study clinical complete response has been defined as the absence of any palpable tumor in the breast. Specimen assessment included size at time of grossing and histological grading of response to chemotherapy using Miller-Payne criteria (MPC) [Table 1] by a pathologist.[11]

Hormone receptor status for estrogen receptor (ER), progesterone receptor (PR), and Her-2/neu (erb-2) was evaluated in most patients using immunohistochemical stains (IHC).

Pathological response was then classified as pathological Nil Response (pNR) for grade 1 MPC response; pathological Partial Response (pPR) for grade 2, 3, or 4 MPC responses and pathological Complete Response (pCR) for grade 5 MPC response.

Results

A total of 313 patients of breast cancer were treated during the study period in our department. Of these, 102 were found eligible for inclusion in this study. Sixty-four patients consented for inclusion in the evaluation protocol but only 52 patients completed the evaluation [Figure 1].

Patients included in this study had a median age of 52.5 years (range 29-75 years). Sixty one percent were postmenopausal; 50% had Taxol based chemo, 46% had Anthracycline-based chemo and 4% had CMF chemotherapy. The median number of chemotherapy cycles before surgery was 3 (range 2-6).

Majority (94.2%) of the patients had an infiltrating ductal carcinoma. Complete receptor status details were not available for eight patients. Of the remaining 44 patients, 17 were triple negative while only two were triple positive. Eighteen patients were positive for either ER or PR or both.

A total of 14 (26.9%) patients had clinical complete response (cCR). It is interesting to note that of these 14 patients, only 6 patients (42.9%) had a correlating pathological complete response (pCR). Conversely, of the 10 patients with pCR (19.2%), only 6 (60%) had correlating cCR. Of the remaining four, two had clinical partial response (cPR), one had clinical stable disease (cSD), and one, in fact, had clinical progressive disease (cPD) [Table 2]; in other words clinical evaluation had a sensitivity of 60% and specificity of 80.9%.

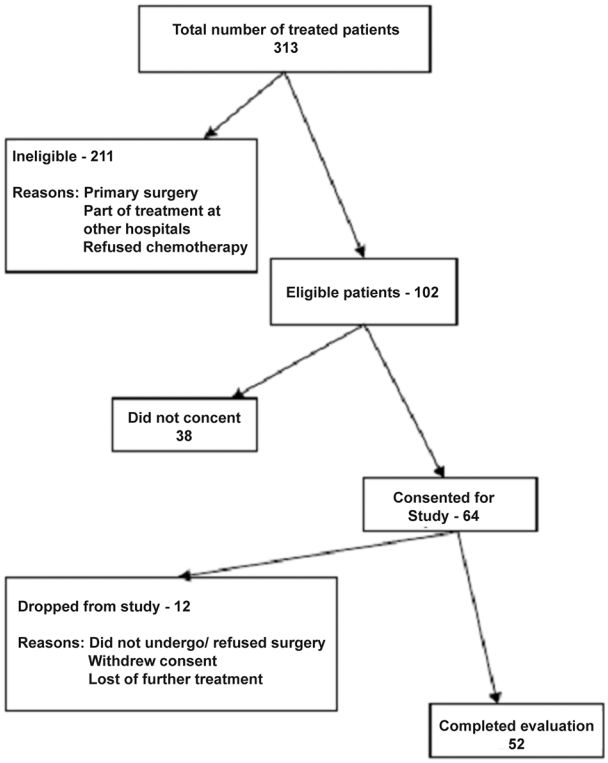

Figure 1: Schema showing patient recruitment

Interestingly only 7.1% patients (3/42) were noted to have a complete response radiologically, but all these had a pCR [Table 3]. This translated into a specificity of 100% and sensitivity of 37.5% (3/8 patients).

The pathological assessment for response grading to chemotherapy according to MPC is shown in Table 4.

We have grouped the MPC grades IV and V as the group showing good pathological response. Of patients who achieved a cCR, 78.6% (11/14) cases had a correlating grade V or grade IV response; this is in contrast to the radiologically assessed complete response rate which was seen in only 3 patients, all of whom had a grade V response (100%). Thus we see that of the 26 cases of good responders pathologically,

Table 1: Miller-Payne criteria (MPC) for grading response of solid tumors to chemotherapy

Grade	Description
1	No change or some alteration to individual malignant cells but no reduction in the overall cellularity
2	A minor loss of tumor cells but overall cellularity still high; up to 30% loss
3	Between an estimated 30% to 90% reduction in tumor cells
4	A marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumor cells
5	No malignant cells identifiable in sections from the site of tumor; only vascular fibro-elastic stroma remains often containing macrophages. However, DCIS may be present

Table 2: Correlation of clinical and pathological response to NACT

Clinical response category	Pathological response category			Total
	pCR	pPR	pNR	
cCR	6	8	0	14
cPR	2	21	2	25
cSD	1	6 (+1)*	2	9 (+1)*
cPD	1	1	1	3
Total	10	36 (+1)*	5	52

*One patient underwent surgery without presurgical measurements and hence the clinical response category of that patient is not known and is assumed in the stable disease group

Table 3: Correlation of radiological and pathological response to NACT

Radiological (R) response category	Pathological response category			Total
	pCR	pPR	pNR	
R CR	3	0	0	3
R PR	4	24	2	30
R SD	0	6	2	8
R PD	1	0	0	1
Total	8	30	4	42*

*Ten patients underwent surgery without presurgical radiological assessment and hence the radiological clinical response category is unknown in this group

11 were predicted by a complete clinical response, while of the 23 good responders available for the radiological assessment group, only 3 could be predicted [Table 5]. Those who had a radiological CR also had a clinical CR [Table 6]. Thus, while using histological assessment as standard criteria for pathological response, clinical evaluation had a sensitivity and specificity of 73.5% and 88.5% respectively compared to 14.2% and 100% respectively for radiological assessment.

Clinical response groups (as per UICC criteria) had a higher correlation to MPC histological response grade [Table 5] compared to radiological assessment suggesting that clinical evaluation is more sensitive in predicting degree of response pathologically, whereas radiological assessment, though more specific for complete response, is not as sensitive.

Discussion

The current rationale for NACT is based on its usefulness in quickly evaluating the likely benefit of new approaches to treatment and tailoring to the biological characteristics of the individual tumor.[3,5,12]

This approach has the advantage of enabling *in vivo* assessment of tumor sensitivity to chemotherapy. The complete clinical and pathological response of a primary breast cancer to NACT has been shown to be important prognostic factor in survival of these patients.[7,13] A critical component of this strategy is to use improved methods for monitoring tumor response to treatment. Patients who do not demonstrate an initial response, or who cease to respond to therapy, would have the option to change to other available agents to maximize response or can choose straight to go for surgery. Evidence is emerging that pathological response after NACT can be used as a surrogate endpoint for survival.[5,7,13] In spite of the differences in the criteria adopted to measure and report the pathological findings after primary noninvasive treatment, most groups have shown a similar correlation between residual disease found at surgery and patient outcome.[7]

Using current standard chemotherapy regimens, approximately 70-90% of patients demonstrate at least a 50% reduction in tumor size clinically. However, only 10-20% patients demonstrate a complete pathological response.[3-7] Furthermore, the clinical response to neo-adjuvant chemotherapy, which is commonly reported, does not always adequately reflect the pathological response.[14] We found a clinical complete response rate of 26.9%, and a path CR rate of 19.2% in our study.

Physical examination is often considered unsatisfactory for assessment of the response of locally advanced breast cancer to primary medical treatment. Feldman *et al.* reported that 45% of complete clinical responders had macroscopic tumor at histological examination; inversely, 60% of patients without any histological gross residual tumor had an incomplete clinical response.[1] In the series of 49 patients studied by Cocconi *et al.*, physical examination overestimated tumor regression in 23% of cases and underestimated the response in 9%.[15] In our series pCR was noted in 42.9% (6/14) of patients who had cCR. Thus we overestimated the occurrence of complete response in 57.1% (8/14) by clinical examination. Conversely, in as many as 40% (4/10) patients in our study, physical examination underestimated occurrence of pCR.

The accuracy of physical examination has been reported to be mediocre because palpation of a fibrotic and necrotic mass may mimic a residual tumor mass. In other cases, the apparent clinical regression may be due to patchy (and therefore incomplete) eradication of cancer cells or resolution of peritumoral inflammation.

Correlation of routine clinico-radiological criteria used to assess response clinically with the final pathological response rates is not well established. This is due to combination of factors: One, dearth of literature on the subject; two, lack of uniformity in techniques of grading and assessing clinical and pathological response rates; and three, inter observer variability even if the same clinical and/or pathological criteria are adopted.[5,9,16-18]

Several studies in the past have attempted to study the accuracy of CT scan or ultrasound to measure the tumor response but the results have been controversial.[19-21] Operator dependence has been one of the factors quoted to be responsible for interfering with the accuracy. Modification of tumoral echogenicity induced by chemotherapy has been also quoted as one of the factors. This density diminution

Table 4: Grading of pathological response according to MPC

Miller-Payne's grade	No. of patients (*n*)	Percentage
I	6	11.5
II	10	19.2
III	10	19.2
IV	14	26.9
V	12	23.1

Table 5: Correlation of clinical response category and radiologic response categories to histological good response according to Miller-Payne's criteria (MPC)

	Total number	Complete response
MPC grade IV and V for clinical responders	26	11/14
MPC grade IV and V for radiologic responders	23	3/3

Table 6: Correlation of clinical and radiological response to NACT

Clinically assessed response category	Radiologically assessed (R) response category					Total
	R CR	R PR	R SD	R PD	Unknown	
cCR	3	8	q	0	3	14
cPR	0	17	3	0	5	25
cSD	0	3	4	1	1	9
cPD	0	1	1	0	1	3
Unknown	0	1	0	0	0	1
Total	3	30	8	1	10	52

may interfere and cause misrepresentation of measurements because of the decreased contrast ratio between tumoral and normal tissue.

Balu-Maestro found ultrasound to be poorly reliable in evaluating the size of residual tumor after chemotherapy, correlating in only 43% of cases.[22] In other series ultrasound was found to be superior to physical examination and mammography especially when the tumor was hypoechoic.[23,24] Akashi-Tanaka *et al.* compared the results in 42 cases of clinical examination, mammography, ultrasound, and presurgical CT after four courses of chemotherapy with the results of histopathology.[19] In our study, clinical response, as judged by serial clinical measurements, correlated better with good histopathological response (assessed taking MPC grade IV and V together) [Table 5].

There are several flaws to this study: One, it is a prospective observational study with a small sample size and not designed with a statistical power to it; two, there were several missing values for radiological assessment of response; and three, clinical and radiological measurements were done by different clinicians each time.

In spite of the inherent flaws, our observations show that serial clinical assessment was better of the two methods to predict extent of histopathological response. In other words, routine (and serial) use of radiological imaging (USG and CT), to measure tumor size and to monitor its response to NACT, is no better than careful clinical assessment.

It is pertinent to mention here that in situations where we need to ascertain the possibility of pathCR, to possibly decide on less surgery or no surgery, radiological examination will score over physical examination because of better specificity (100% vs. 88.5% respectively).

However, it is important to note that both methods of assessment of response (clinical and radiological) suffer from poor sensitivity rates, and although radiological assessment seemed to have a 100% specificity rate, the low observed complete responses on radiological assessment render this value open to question. A larger sample size may provide more conclusive evidence regarding superiority of one method over another by providing adequate power to it. There are a number of recent studies which have evaluated the role of various other imaging modalities (PET, MRI, Doppler USG, optical tomography, etc.) in assessing the response to neo-adjuvant chemotherapy in carcinoma breast.[25-30] Of these Magnetic resonance imaging (MRI) holds promise in future, as it not only provides accurate information about the degree of response but also the pattern of response. Although it is still not widely available and is costly, but in future with increased experience of its use in this setting, it will prove to be very useful.

Conclusion

It is shown in the present study that clinical assessment of response to NACT, shows a higher sensitivity compared to radiological assessment. However the overall low sensitivity and specificity rates of clinical assessment mandate a search for a better method of evaluation.

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