www.jmscr.igmpublication.org
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v7i2.103

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Evaluation of morphological predictors for response to NACT in breast cancer

Authors
Gundimeda V R N Krishna Kanth MD, PDCC (Oncopathology)[1],
Nambiar Ajit MD, DNB, FRCPath[2*]
[1]Faculty, Department of Pathology, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda district, Telangana, India
Email: *kkanth343@gmail.com*
[2]Associate Professor, Department of Pathology, Amrita institute of Medical Sciences, Kochi, Kerala, India
*Corresponding Author
Nambiar Ajit MD, DNB, FRCPath
Email: *nambiarajit@yahoo.com*, Ph: 9567401296

Abstract
Background: *NACT is being increasingly employed to deal with breast malignancies. It is important to know the predictive value of various morphological parameters for the pathological complete response. It is also interesting to note the various changes that happen to tumor bed due to chemotherapy.*
Aims and Objectives: *1)To evaluate the importance of various morphological parameters in predicting response to NACT 2)To observe histological changes in the tumor bed after NACT.*
Materials and Methods: *A total of 108 cases where NACT was given were selected over a 3 year old period and clinical and histological parameters were assessed prior to and after NACT.*
Results: *The statistical significance for the association of various parameters is calculated and it was found that age has no influence on response to NACT where as morphological subtype, size of the tumor, grade of the tumor before NACT, Lymph node status after NACT, DCIS, tumor lymphocytic response were all found to be associated statistically with complete pathological response. Fibrosis and necrosis were the common changes that happen to the tumor bed due to chemotherapy*
Conclusions: *Even in the current era of molecular pathology, basic morphological parameters still play a pivotal role in selecting the patients for NACT.*
Keywords: *NACT (Neo adjuvant chemotherapy), PCR (Pathological complete response), NOS (Not otherwise specified), RCB(Residual cancer burden).*

Introduction

Breast cancer is the commonest malignancy in females, the incidence of breast cancer is 11.6% worldwide(1) and is 23% in india(2). NACT is an option in the management of these patients. Neoadjuvant therapy refers to the systemic treatment of locally advanced breast cancer prior to definitive surgical therapy (ie, preoperative therapy). While all systemic therapy given for nonmetastatic invasive breast cancer is intended to reduce the risk of distant recurrence, the purpose of administering it neoadjuvantly is to downstage

the tumor, allowing for less extensive surgery, improved cosmetic outcomes and reduced postoperative complications such as lymphedema. Neoadjuvant therapy also permits an early evaluation of the effectiveness of systemic therapy.[3]

The surrogate endpoint, the presence or absence of residual invasive cancer after neoadjuvant chemotherapy, is a strong prognostic factor for risk of recurrence, disease free survival and overall survival as also for further therapy.[4]

Pathological assessment is the final gold standard to judge the effectiveness of NACT. Pathological complete response (pCR) is defined differently by different systems of assessment in place. The R classification incorporated in AJCC/UICC protocols[5] and the Miller-Payne system[6] take absence of disease in the breast as a pathological complete response whereas the RCB system[7] takes into account the absence of disease both in the lymph nodes and breast proper as the definition of pCR. It is observed that different morphological parameters have different predictive value for the responsiveness to NACT. The aim of the current study is to study these variations as well as study the morphological changes that occur in the breast tissue due to chemotherapy

Materials and Methods

The study includes all the breast cancer cases which have been subjected to NACT before surgery over a 3 year period at our institute.This study includes 108 cases that were subjected to radical mastectomy after NACT.NACT regimen included 4 to 6 cycles of FEC (5-flourouracil, epirubicincyclophosphamide).The pre treatment diagnosis was based on large-bore

Core needle biopsies and none were based on FNAC.The important features like initial diagnosis consisting of morphological type and grade of invasive carcinoma,original size of the tumor based on clinical and radiological findings, the response of the tumor to chemotherapy,the variety of changes that took lace in the tumor bed due to chemotherapy, the total number of lymph nodes isolated and number of positive nodes,Size of the largest positive lymph node,foci of DCIS and tumor infiltrating lymphocytes were evaluated.

The results were tabulated and statistically analysed using Chi-square test

Results

A total number of 108 patients were included in the study.The patients were grouped according to their ages and maximum number of patients were seen in 51-60 year age group(Figure 1). Several morphological subtypes were observed in the group of patients, with Invasive ductal carcinoma –NOS constituting the majority(Figure 2).Various histological subtypes behave differently to NACT and their pathological response as er R classification is tabulated in Table 1.

Univariate analysis of various probable morhological parameters that may play a role in predicting resonse to NACT are evaluated like age,morphological subtype, size of invasive carcinoma before NACT, Grade of invasive carcinoma before NACT, lymph node status post NACT, lymphocytic response in the tumor bed, presence/ absence of DCIS. Statistical analysis using chi-square test was done and p value calculated for these various parameters.It has been found that age doesnot have any significance in predicting the response to NACT but the rest of the parameters are found statistically significant in predicting the pathological complete resonse. These findings are tabulated in table 2

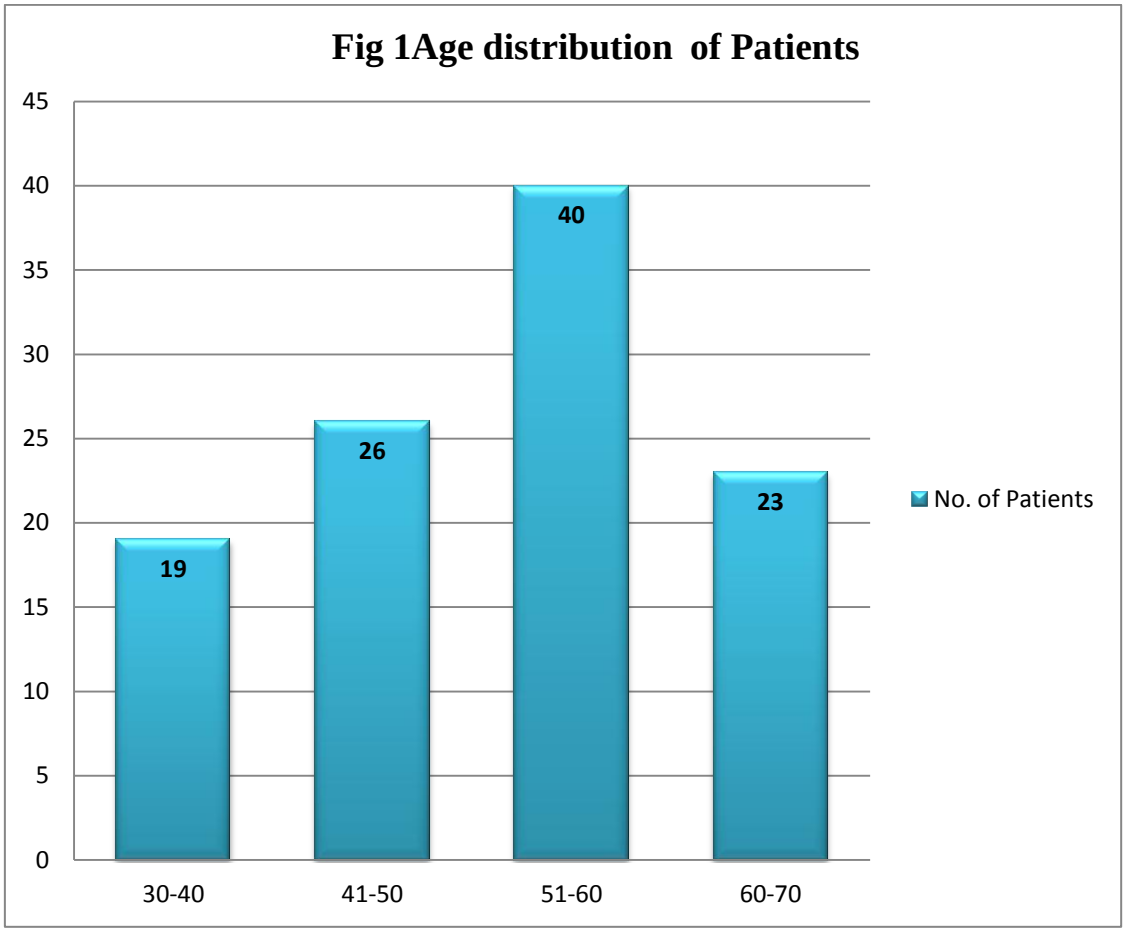
Fig 1Age distribution of Patients
45
40
35
30
25
20
15
10
5
0
19
26
40
23
30-40
41-50
51-60
60-70
No. of Patients

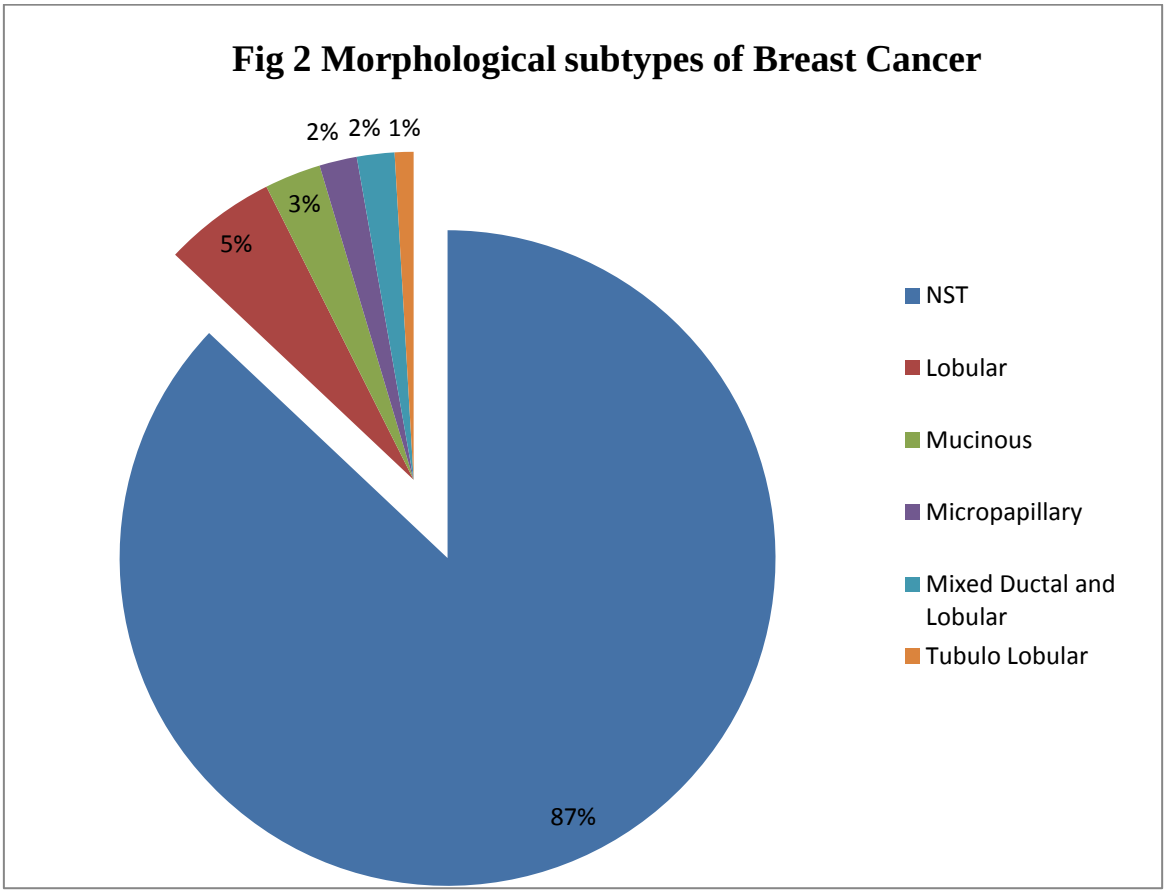
Fig 2 Morphological subtypes of Breast Cancer
2%
2%
1%
3%
5%
87%
NST
Lobular
Mucinous
Micropapillary
Mixed Ductal and Lobular
Tubulo Lobular

Table –I Response to NACT in various Morphological subtypes as per R – Classification.

Morphological subtypes	R0	R1	R2	Total (n = 108)
NST	42	10	42	94
Lobular	0	0	6	6
Mucinous	0	0	3	3
Micropapillary	0	0	2	2
Mixed Ductal and Lobular	0	0	2	2
Tubulo Lobular	0	0	1	1
Total	42	10	56	108

Table –2 Univariate analysis of response to NACT by various Morphological parameters

S.NO	Parameters		Number(%)	PCR number (%)	P value
1	Age	≤ 50	42 %	56%	0.24
		>50	58 %	35%	
2	Morphological subtype	IDC-NOS	87%	44.6%	<0.01
		ILC	5%	1%	
		Special types	8%	1%	
3	Size of IC pre NACT	≤ 5cm	52%	30.76%	<0.01
		>5cm	48%	12.5%	
4	Grade of IC pre NACT	I	3%	1%	<0.01
		II	42%	60%	
		III	55%	77%	
5	Lymph node status post NACT	N0	45%	62%	<0.01
		N1	30%	1%	
		N2	20%	1%	
		N3	5%	1%	
6	Lymphocytic response	Mild	30	20	<0.01
		Moderate	60	30	
		Marked	10	50	
7	DCIS	Present	40	15	<0.01
		Absent	60	40	

The tumor bed was showing fibrosis and hyalinisation in most of the cases (75%) necrosis (20%). The other changes noticed were lymphocytic infiltrates, giant cell reaction, hemorrhage and hemosiderin laden macrohages, fat necrosis,cholestrol clefts,multinucleated giant cells.

Discussion

Pathological complete response is one of the important predicting long time survival in Post NACT patients.

The pathological complete response rates varied from 8-30% in various anthracycline based regimens[8-12]. In the present study the pathological complete response was observed in 42 out of 108 cases constituting 39%.we did find one study with a higher pathological complete response of 40%.[13] Careful selection of the patients fit for NACT may be resonsible for the higher rates observed in our study.

The two of the most important clinical factors analysed in this study included age of the patient and the size of the tumour prior to NACT. The mean age of the patients at presentation in this study was 47 years. and the mean size of the tumor on radiological assessment was 5 cm. The age of the patient in our study was not found to have any statistical association with pathological complete response which is comparable with all the existing studieswhere in none of the studies have found positive association between age and pathological complete response[14-16]. As in our study, the other studies show that tumor size less than 5 cm (T1 or T2 tumours) were associated with better pathological complete response.[6-8]

However in some of the studies there was no significant association between tumor size with the ultimate pathological complete response.[17-18]

The most common tumor type invariabily is invasive ductal (mammary) carcinoma NST in our study and as in other studies showed maximally and stastistically significant response to NACT.[14-16] The lobular carcinomas and other special types of breast malignancies in our study did not show any significant response. Lobular carcinomas with their characteristic dense stroma probably are not condusive for response to drugs. The lower grade tumours although numerically less in our study were poor in response. The higher grade tumours showed significantly better response to NACT. This fact has borne in many studies and expectedingly faster dividing cells are more prone to chemotherapy response[14-16]. The lymphocytic response is also found as an important predictor for pathological complete resonse which is in correlation with other studies.[19]

The nodes with a complete pathological response did not show any evidence of tumor but instead showed areas of necrosis, fibrosis or even calcification in occasional cases. The pathological nodal status in studies have shown to be the major prognostic factor associated with clinical response to treatment on multivariate analysis.[20-21] Even the size of the largest lymph node with macrometastasis is associated with poor prognosis.[22]

It has also been found in the present study that residual DCIS is also an important predictor of Pathological complete response as is comparable to other studies.[23]

The morphological changes that occurred in the tumor bed after chemotherapy in our study like fibrosis,hyalinisation,necrosis are comparable to those described by Moreno etal and Hasebe etal.[24-25]

Limitations of the study

This study is based on only 108 cases, obviously more number of cases and the disease outcomes along with the survival rate may be needed to validate the results obtained in the study.

Conclusion

The present study reflects the importance of certain important histological parameters in this era of molecular pathology. This attempt has brought focus on some important histological parameters like tumor size, grade, histological type, and lymph nodal statusstill hold a key in decision making as to which group of patients are likely to get benefited from neo adjuvant chemo therapy.Our study reiterates pathological response is the gold standard for assessing the chemotherapeutic tumor response. A diligent study of the tumor bed is a cost effective methodology and importantly helps in deciding the chemotherapy drugs to be used after surgery and definitely will play the surrogate marker role for better survival.

Acknowledgements

We are thankful to all the faculty members,technical staff,Post graduates and fellows in the department of pathology, Department of Gynec oncology, AIMS, Kochi

Competing interests: None declared

Funding: None

References

1. Ferlay J, Colombet M, Soerjomataram I et al. Global and Regional Estimates of the Incidence and Mortality for 38 Cancers: GLOBOCAN 2018. Lyon: International Agency for Research on Cancer/World Health Organization; 2018.
2. Gupta A, Shridhar K, Dhillon PK. A review of breast cancerawareness among women in India: cancer literate or aware-ness deficit? Eur J Cancer 2015; 51: 2058–66
3. Outcome of neoadjuvant chemotherapy in locally advanced breast cancer: A tertiary care centre experience: Tapesh

Bhattacharyya, Suresh C Sharma, Budhi Singh Yadav, Rajinder Singh, Gurpreet Singh Indian J Med Paediatr Oncol. 2014 Jul-Sep; 35(3): 215–2204)

4. Bonnefoi, H & Litière, Saskia & Piccart, Martine & Macgrogan,. Pathological complete response after neoadjuvant chemotherapy is an independent predictive factor irrespective of simplified breast cancer intrinsic subtypes: A landmark and two-step approach analyses from the EORTC 10994/BIG 1-00 phase III trial. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 25. 10.1093/annonc/mdu118.
5. https://cap.objects.frb.io/protocols/cp-breast-invasive-18protocol-4100.pdf
6. Ogston KN, Miller D, Payne S, et al. A newhistological grading system to assess response ofbreast cancers to primary chemotherapy: prognosticsignificance and survival. Breast. 2003; 12: 320-7
7. Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V, Assad L, Poniecka A, Hennessy B, Green M, Buzdar AU, Singletary SE, Hortobagyi GN, Pusztai L. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25:4414–4422
8. van der Wall E, Rutgers EJ, Holtkamp MJ, Baars JW, Schornagel JH, Peterse JL, Beijnen JH, Rodenhuis S. Efficacy of up-front 5-fluorouracil-epidoxorubicin-cyclophosphamide (FEC) chemotherapy with an increased dose of epidoxorubicin in high-risk breast cancer patients. Br J Cancer 1996; 73 (9): 1080–5
9. Burcombe RJ, Makris A, Richman PI, Daley FM, Noble S, Pittam M, Wright D, Allen SA, Dove J, Wilson GD. Evaluation of ER, PgR, HER-2 and Ki-67 as predictors of response to neoadjuvantanthracycline chemotherapy for operable breast cancer. Br J Cancer 2005; 92 (1): 147–55.
10. Moon YW, Rha SY, Jeung HC, Yang WI, Suh CO, Chung HC. Neoadjuvant chemotherapy with infusional 5-fluorouracil, adriamycin and cyclophosphamide (iFAC) in locally advanced breast cancer: an early response predicts good prognosis. Ann Oncol 2005; 16 (11): 1778–85.
11. Sethi D, Sen R, Parshad S, Khetarpal S, Garg M, Sen J. Histopathologic changes following neoadjuvant chemotherapy in locally advanced breast cancer. Indian J Cancer 2013; 50 (1): 58–64.
12. Gharbi O, Trabelsi A, Chafai R, Zayen A, Ezzair F, Hochlef M etal.Clinical and pathological response to neoadjuvantan-thracycline based chemotherapy in women with breast cancer World J oncol 2010;1:167-7213)
13. O. M. Fayanju, I. Nwaogu, D. Jeffe, and J.Margenthaler, "Pathological complete response in breast cancer patients following neoadjuvant chemotherapy at a Comprehensive Cancer Center: the natural history of an elusive prognosticator," Molecular and Clinical Oncology, vol. 3, no. 4, pp. 775–780, 2015.
14. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status and survival in 24,740 breast cancer cases. Cancer 1989;63:181–187
15. Rosen PP, Groshen S, Kinne DW et al. Factors influencing prognosis in node-negative breast carcinoma: analysis of 767 T1N0M0/T2N0M0 patients with long-term follow-up. J ClinOncol 1993;11:2090–2100. Abstract/FREE Full Text
16. Fisher B, Slack NH, Bross ID et al. Cancer of the breast: size of neoplasm and prognosis. Cancer 1969;24:1071–1080
17. Tewari M, Pradhan S, Singh U, Singh TB, Shukla HS: Assessment of predictive

markers of response to neoadjuvant chemotherapy in breast cancer.Asian J surg 2010,33(4):157-67

18. Pu RT, Schott AF, Sturtz DE, Griffith KA, Kleer CG. Pathological features of breast cancer associated with complete response to neoadjuvant chemotherapy: importance of tumor necrosis. Am J surg Pathol 2005:29:354-58
19. Carsten Denkert, Sibylle Liobletal Tumor associated lymphocytes as an independent predictor of response to NACT in breast cancer, J clinoncol 28(1)105-113,2010
20. Bonadonna G, Valagussa P, Brambilla C, Ferrari L, Moliterni A, Terenziani M and Zambetti M (1998) Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. J ClinOncol 16: 93–100
21. Cameron DA, Anderson ED, Levack P, Hawkins RA, Anderson TJ, Leonard RC, Forrest AP and Chetty U (1997) Primary systemic therapy for operable breast cancer – 10-year survival data after chemotherapy and hormone therapy. Br J Cancer 76: 1099–1105
22. E. R. Fisher, J. Wang, J. Bryant, B. Fisher, E. Mamounas, and N. Wolmark, "Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-18," Cancer, vol. 95, no. 4, pp. 681– 695, 2002
23. Jones RL, Lakhani SR, Ring AE etal Pathological complete response and residual DCIS following NACT for breast carcinoma Br J cancer 2006 Feb 13;94(3):358-62
24. Moreno A, Escobedo A, Benito E, Serra JM, Guma A, Riu F. Pathological changes related to CMF primary chemotherapy in breast cancer. Pathological evaluation of response predicts clinical outcome Breast cancer Res Treat 2002,75:119-25.
25. Hasebe T, Tsuda H, Hirohashi S, Shimosato Y, Tsubono Y, Yamamoto H etal Fibrotic focus in infiltrating duct cell carcinoma of the breast :A significant histopathological parameter for predicting the long term survival of the patients. Breast cancer Res Treat 1998;49:195-208.