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PATHOLOGICAL EVALUATION OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER

Pathology

Payal Sanjay Desai Resident, Md Pathology, American International Institute Of Medical Sciences, Udaipur.

Swarneet Bhamra Assistant Professor, Department Of Pathology, American International Institute Of Medical Sciences, Udaipur.

Quresh Bambora Head Of Oncology Department, American International Institute Of Medical Sciences, Udaipur.

Preeti Agrawal Professor And Head Of Department Of Pathology, American International Institute Of Medical Sciences, Udaipur.

Garima Mehta Hon. Professor, Department Of General Surgery, American International Institute Of Medical Sciences, Udaipur

ABSTRACT

Background: Breast cancer is globally known to be the most commonly diagnosed cancer in women. Among various modes of advanced therapies available surgery remains the prime modality aided by chemotherapy, hormonal therapy and radiation. With the increasing use of neoadjuvant chemotherapy for breast conservation, it becomes necessary for a pathologist to have the thorough knowledge of possible changes rendered by the therapy. **Aim:** To assess the tumor and lymph node response in breast carcinoma after paclitaxel based chemotherapy. **Settings and Designs** : A Cross sectional study carried out in the Histology section of Pathology department in American International Institute of Medical Sciences, Udaipur. **Methods:** Study was conducted over the period of 4.5 years from January 2019 to May 2023. Clinical and tumor characteristics of patients with breast carcinoma (n=47) were assessed preoperatively. Post- NACT breast cancer specimens (modified radical mastectomy and breast conservation surgery) received in the histopathology section of our institute were analysed grossly and slides were prepared. The response in tumor and lymph node was graded into pathological complete response (pCR), pathological partial response (pPR), and pathological no response (pNR). **Statistical Analysis:** Statistical analysis was done using Pearson's Chi square test. **Results:** Our studies showed a pCR of 23.4% , pPR of 70.2% and pNR of 6.4%. Clinically small sized tumors (2–5 cms) showed a pCR of 6.0% (p value 0.001). Mean age at presentation was 49.9 yrs. 97.8 % of cases were invasive ductal carcinoma NOS of which 23.9% cases showed complete response (p value <0.001) . Only 2.1% of the cases were mucinous carcinoma and all of them showed partial response. Ductal carcinoma in situ and lymphovascular invasion were found to be resistant to chemotherapy (p value 0.015). **Conclusion:** The study concludes that histopathology is a gold standard method to assess the chemotherapeutic tumor response. Tumor grades can be downgraded after neoadjuvant chemotherapy.

KEYWORDS

Breast cancer, Neoadjuvant chemotherapy, Tumor response, Histopathology

INTRODUCTION

Breast cancer is the most common malignancy among women globally. It is a leading cause of global cancer incidence with estimated 2.3 million new cases , representing 11.7% of all cancer cases [1,2]. It is rare in women younger than age 25 and incidence rapidly increases after the age of 30. Family history also plays a major role as women having first-degree relative with breast carcinoma have 2 or 3 times higher risk of developing cancer compared to general population. Other risk factors include early menarche, nulliparity, late menopause, influence of exogenous oestrogen's, ionising radiation and genetic predisposition [3]. Breast cancer is not a single disease and comprises several entities ranging from ductal carcinoma in situ (DCIS) to a widespread metastatic disease. Clinical presentation and investigations such as mammography and fine-needle aspiration cytology (FNAC) often help in the diagnosis of breast cancers. However, histopathological examination remains the better predictor for an accurate diagnosis of breast cancers [4]. In addition, immunohistochemical markers aid in classification and are often used to guide the therapy of the disease process [5].

Because of extensive advances made in the field of oncology, various modes of therapy of breast cancers are available at present including surgery, radiotherapy, chemotherapy, and, more specifically, targeted hormonal and tumor receptors therapy. Surgery that may include mastectomy or, breast-conserving surgery (lumpectomy), still remains the prime modality of therapy for most of the operable breast cancers [6].

In advanced disease, prior to surgery, radiation therapy is used to reduce the tumor size. In early breast cancers, to facilitate breast conservation, chemotherapy is more commonly used both as a neoadjuvant chemotherapy and/or postoperative chemotherapy [7]. The pathologist evaluates the residual tumor both in the breast and lymph nodes. Therapy and prognosis depend on the various clinical and histopathological factors, including tumor size, type of tumor, hormonal receptor status and the type of therapy provided. This ensures the role of pathologists in the correct diagnosis as well as grading of the tumor with a correct histopathological interpretation for an effective and planned regimen of the therapy increasing prognosis and chances of survival of the affected patients rendering better clinical outcome and an effective patient care [8].

MATERIALS AND METHODS

This was a Cross sectional study conducted over the period of 4.5 years from January 2019 to May 2023 in American International Institute of Medical Sciences, Udaipur. The study included 47 patients diagnosed with locally advanced breast cancer with axillary lymph node involvement who had taken chemotherapy cycles of Paclitexal based chemotherapy (adriamycin, cyclophosphamide, and paclitaxel) followed by surgery that included either modified radical mastectomy (MRM) or breast conservation surgery (BCS) with axillary lymph node dissection. These post-NACT breast cancer specimens were received in the histopathology section of our institute. Tumor size was measured grossly. Pre-therapeutic clinical size of the tumor was noted from the previous radiological investigations and records of the patients. Slides were prepared from the required sections and stained with Hematoxylin and Eosin (H&E). Histologic type of cancer was identified microscopically. Tumor was graded on the basis of Bloom Richardson grading system (Table 1) [9]. Lymphovascular invasion (LVI) and DCIS components were mentioned separately.

Table1: Bloom Richardson Grading

	Score 1	Score 2	Score 3
Tubule formation	>75%	10-75%	<10%
Nuclear Pleomorphism	Mild	Moderate	Marked
Mitotic figures	<7/10 HPF	8-14/10HPF	>15/10HPF

Histopathological response to the chemotherapy was graded on the basis of the parameters used by Chevalier in his study.

According to Chevalier system of grading [10],
Grade 1: Disappearance of all tumor either on macroscopic or microscopic assessment.
Grade 2: Presence of in situ carcinoma in the breast, invasive tumor

and no tumor found in the lymph nodes.
Grade 3: Presence of invasive carcinoma with stromal alteration such as sclerosis or fibrosis.
Grade 4: No or few modifications of the tumoral appearance.

Pathological complete response (pCR) was assigned to Grade 1, pathological Partial response (pPR) was assigned to Grade 2 and 3 and pathological No response was assigned to Grade 4 of Chavelier system of grading.

All data set were analysed with the software of SPSS v 14 for windows. Baseline sociodemographic characteristics and microscopic findings were compiled as numbers and percentages.

Response to neoadjuvant chemotherapy was also found and expressed as numbers and percentages. Possible risk factors affecting tumor and lymph node response were tested using tests of proportions (Pearson's chi square test) and p value was calculated. P value of <0.005 was considered as cut off value of significance.

RESULTS

The present study included 47 cases. Basic sociodemographic parameters like age, sex and family history were noted for all the cases and are mentioned in the [Table 2]. Tumor size noted at the time of presentation (clinical size) were divided into three divisions of upto 2cm, 2 to 5 cm and more than 5 cm. Response obtained after chemotherapy and graded histopathologically is also mentioned in [Table 2].

Table 2: Basic sociodemographic parameters

Parameter		Number of cases	Percentage
Age	Upto 39	9	19.2
	40 to 59	28	59.6
	60 and above	10	21.2
Sex	Female	47	100
	Male	0	0
Family history	Yes	11	23.4
	No	36	76.6
Clinical size	Upto 2 cm	8	17.0
	2 to 5 cm	28	59.6
	more than 5 cm	11	23.4
Tumor response	Complete response (pCR)	11	23.4
	Partial response (pPR)	33	70.2
	No response (pNR)	3	6.4

Post NACT tumor size measured grossly was also divided into three categories of upto 2 cm, 2 to 5 cm and >5cm [Table 3]. Various characteristics noted on microscopy like Bloom Richardson grade, DCIS component, lymph-vascular invasion and lymph node metastasis are given in [Table 3].

Table 3: Post NACT Gross and Microscopy findings of the specimens

Characteristic		Number of cases	Percentage
Tumor size post NACT (out of 36)	upto 2 cm	16	44.4%
	2 to 5 cm	12	33.3%
	>5 cm (T3)	8	22.2%
Bloom Richardson grade in partial response (pPR) (out of 33)	Grade I	5	15.1%
	Grade II	14	45.4%
	Grade III	14	48.5%
Bloom Richardson grade in no response (pNR) (out of 3)	Grade II	1	33.3%
	Grade III	2	66.7%
DCIS component	Present	13	27.7
	Absent	34	72.3
LVI	Present	11	23.4
	Absent	36	76.6
Lymph node metastasis	Present	20	42.5%
	Absent	27	57.5%

(DCIS: Ductal Carcinoma In Situ; LVI: Lymphovascular Invasion)

Influence of factors like age, family history, clinical size, histologic type of cancer, DCIS component and LVI on type of tumor response was analysed along with corresponding p values. Majority of the cases (54.5% of complete response and 63.6% of partial response) were from the age group of 40 to 59 years. However tumor with no response showed no age preponderance. Family history of breast cancer was present in only 18.2% of complete response , 24.2% of partial response and 33.3% of no tumor response cases. Most of the cases with complete and partial response presented with clinical size of 2 to 5 cm (pT2) while most of the cases with no response presented clinically with tumor size less than 2 cm (pT1). Histologic type of cancer in all of the cases with complete and no response were of Invasive Ductal Carcinoma, NOS; only 1 (3%) case with partial response was of Mucinous carcinoma. All of the cases with no response and majority of cases with complete (72.7%) and partial (69.7%) response did not show DCIS component.

Majority of the cases from complete(100%), partial (69.7%) and no response (66.7%) had no lymph-vascular invasion [Table 4].

Table 4: Factors affecting tumor response

Characteristic		Tumor complete response (pCR) (n = 11)	Tumor partial response (pPR) (n = 33)	Tumor no response (pNR) (n = 3)	P value
Age	Upto 39	2 (18.2%)	6 (18.2%)	1 (33.3%)	0.851
	40 to 59	6 (54.5%)	21 (63.6%)	1 (33.3%)	
	60 and above	3 (27.3%)	6 (18.2%)	1 (33.3%)	
Family history	Yes	2 (18.2%)	8 (24.2%)	1 (33.3%)	0.840
	No	9 (81.2%)	25 (75.8%)	2 (66.7%)	
Clinical size	Upto 2 cm	5 (45.5%)	1 (3%)	2 (66.7%)	0.01
	2 to 5 cm	6 (54.5%)	21 (63.7%)	1 (33.3%)	
	More than 5 cm	0	11 (33.3%)	0	
Histologic type	IDC NOS	11 (100)	32 (97%)	3 (100%)	<0.001
	Mucinous carcinoma	0	1 (3%)	0	
DCIS	Yes	3 (27.3%)	10 (30.3%)	0	0.532
	No	8 (72.7%)	23 (69.7%)	3 (100%)	
LVI	Yes	0	10 (30.3%)	1 (33.3%)	0.111
	No	11 (100)	23 (69.7%)	2 (66.7%)	

Similarly factors affecting lymph node complete and partial response are mentioned in [Table 5].

Table 5: Factors affecting lymph node response

Characteristic		Lymph node complete response (n=27)	Lymph node partial response (n=20)	P value
Age	Upto 39	4 (14.8%)	5 (25%)	0.530
	40 to 59	16 (59.2%)	12 (60%)	
	60 and above	7 (26%)	3 (15%)	
Family history	Yes	8 (29.6%)	3 (15%)	0.242
	No	19 (70.4%)	17 (85%)	
Clinical size	Upto 2 cm	4 (14.8%)	4 (20%)	0.790
	2 to 5 cm	14 (51.8%)	11 (55%)	
	More than 5 cm	9 (33.3%)	5 (25%)	
DCIS	Yes	8 (29.6%)	4 (20%)	0.840
	No	19 (70.4%)	16 (80%)	
Type of cancer	IDC NOS	20 (74%)	14 (70%)	0.015
	Mucinous carcinoma	0	1 (5%)	
	pCR	7 (26%)	4 (20%)	
LVI	Yes	7 (26%)	4 (20%)	<0.001
	No	20 (74%)	16 (80%)	

(DCIS: Ductal Carcinoma In Situ; LVI: Lymphovascular Invasion)

DISCUSSION

Basic Sociodemographic characters:

In our study mean age of patients at diagnosis was 49.9 years. In a study conducted by Vasudevan et al [11] mean age of presentation was 50.8 years and as per study carried out by Mansa et al [12] it was 50 years. However study conducted by Hemavathi et al [13] showed the peak incidence in 4th decade.

The mean clinical tumor size at the time of presentation in this study was 3.60 cm which was concordant with the studies by Vasudevan et al (3.75cm) and Manasa et al (3.70 cm). This was discordant to the results of Hemavathi et al which had mean tumor size of 1.5 cm.

Most common type of cancer seen in this study was Invasive duct

carcinoma (74.5%) which was in concordance with studies conducted by Manasa et al, Hemavathi et al and Sheereen et al [14].

Response to chemotherapy

Present study showed a pCR of 23.4% which was very near to the studies conducted by Manasa et al (18%), Vasudevan et al (27%) and Sheereen et al (17.9%). Cases with no response were only 6.4% in this study which was concordant with study conducted by Manasa et al (6%) and discordant with the studies conducted by Vasudevan et al (0) and Sheereen et al (66.7%) [Table 6].

Table 6: Comparison of Response to chemotherapy

Response	Present study (n= 47), n(%)	Manasa et al (n = 50)	Vasudevan et al (n = 48)	Sheereen et al (n = 39)
pCR	11 (23.4)	9 (18)	13 (27)	7 (17.9)
pPR	33 (70.2)	38 (76)	35 (73)	6 (15.4)
pNR	3 (6.4)	3 (6)	0	26 (66.7)

There was a prominent decrease in the tumor grade as per our study which was discordant with the studies of Vasudevan et al and Fisher et al [15].

DCIS component was noted in 27.3% of pCR and 30.3% cases of pPR which showed good response to the chemotherapy. This was in concordance with studies conducted by Hemvathi et al and Galal et al [16].

All of the cases with pCR had no lymphovascular invasion and 25.9% cases had lymph node metastasis. Hence, absence of lymphovascular invasion is also a factor for good therapeutic response. This was seen in concordance with study conducted by Vasudevan et al.

CONCLUSION

Our study concludes that histopathological evaluation of the post chemotherapeutic specimens in Breast cancer is a gold standard method for assessment of tumor response. Certain factors like age, presenting size of tumor, type of cancer, DCIS component, lymphovascular invasion and lymph node metastasis can be considered while predicting the tumor response. Tumor grades can be downgraded after neoadjuvant chemotherapy according to the present study. However as most of the studies including the present one have maximum cases of Invasive ductal carcinoma, NOS , further research is required to find out the factors affecting the chemotherapy response in other histologic types of breast cancer.

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