Assessment of pathological response to neoadjuvant chemotherapy in patients with breast carcinoma using Sataloff system

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SUMMARY

Background: *Neoadjuvant chemotherapy is frequently administered to patients with breast carcinoma. Response to chemotherapeutic regime can be assessed clinically as well as by pathological examination of the breast tissue. It is essential to accurately categorize the patients with residual disease according to the standard guidelines for pathological evaluation of breast specimens after neoadjuvant chemotherapy. The present study was undertaken to assess the histomorphological changes in mastectomy specimens and axillary lymphatic nodes of patients receiving neoadjuvant chemotherapy, grade the pathological response using Sataloff system and to compare the clinical and pathological response after neoadjuvant chemotherapy.* **Methods:** *Present prospective study included a total of 31 patients with locally advanced breast carcinoma, diagnosed with infiltrating ductal carcinoma, not otherwise specified on biopsy specimen and subsequently treated with 2 to 6 cycles of neoadjuvant chemotherapy. Pathological response to neoadjuvant chemotherapy was assessed in breast and axillary lymphatic nodes according to Sataloff criteria.* **Results:** *Clinical response observed was complete (cCR) in four cases (12.9%), partial response (cPR) in 24 cases (77.4%), and no response (cNR) in three cases (9.7%). Based on tumor response, breast and lymph nodes were graded as pathological complete response (pCR), pathological partial response (pPR), and pathological no response (pNR) in five (16.1%), 18 (58.1%) and eight (25.8%) cases respectively using Sataloff criteria. Ductal carcinoma in situ and lymphovascular invasion were seen in 11 (35.4%) and 16 cases (51.6%), respectively.* **Conclusion:** *The pathological assessment of tumor response remains the gold standard, as neither the clinical nor the radiological responses are sensitive predictors of tumor response after treatment. However pathological examination is quite challenging and demands sufficient experience along with detailed clinical and radiological data of pre- and postoperative neoadjuvant chemotherapy for precise response evaluation.*

KEY WORDS: *Pathology; Lymph; Carcinoma; Breast*

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INTRODUCTION

Breast cancer is amongst the most commonly diagnosed cancer in females and also one of the leading causes of cancer-related deaths worldwide. As per the estimations made by global cancer statistics for year 2012, breast carcinoma accounts for 25% of all new detected cancers and it also accounts for the 15% of all cancer related deaths among females (1). Neoadjuvant chemotherapy (NAT) was first introduced in early 1980 (2) and was aimed for women with inoperable, locally advanced breast carcinoma in order to down-size the tumor to attain operable size. Later, NAT was extended to women with operable and earlier stage breast carcinoma in order to become eligible for breast conservation surgery and achieve better outcome (3, 4). It also offered the advantage due to minimizing micrometastases (5), and possibility of assessment of the treatment efficacy *in vivo* (6) - allowing modification of chemotherapeutic agent in patients with insignificant response (3) and insight in the benefit of the same NAT regime if continued postoperatively. However, the survival benefit offered by NAT was negligible (5, 7).

Response to chemotherapeutic regime can be assessed clinically as well as by pathological examination of the breast tissue. Pathological response is an important prognostic indicator (8), particularly the complete pathologic response which is associated with improved longer term outcome (9). Residual disease may vary from almost complete response with minimal disease to no response or even disease progression after chemotherapy (9). Moreover, the presence and extent of residual tumor determines the rate of local recurrence and plays a decisive role for the need of further loco-regional and systemic therapy (10, 11). Histopathological evaluation of chemotherapy response is regarded as gold standard (5, 12). Hence, it is essential to accurately categorize the patients with residual disease according to the standard guidelines for pathological evaluation of breast specimens after NAT. There are several pathological response evaluation systems being used, most of which are shown to correlate with the outcome and newer ones that are continuously evolving. However, a well-established standardized system is still deficient (3, 13). In the case of insufficient experience of the pathologist, pathological examination of such specimens may be quite challenging.

The present study was undertaken to assess the histo-morphological changes in specimens retrieved after mastectomy and axillary lymph nodes from patients receiving NAT, and to grade the pathological response using Sataloff system and compare their clinical and pathological response.

METHODS

Present prospective study was conducted on 31 patients between January 2015 and May 2017, who had tumors larger than >2 cm or locally advanced breast carcinoma, diagnosed as infiltrating ductal carcinoma (IDC, ductal NOS) on biopsy specimen and subsequently treated with 2 to 6 cycles of NAT comprising of either anthracycline based regimes (CAF-cyclophosphamide, adriamycin and 5-Flurouracil or FEC-5 Flurouracil, epirubicin, and cyclophosphamide) or combination of anthracycline and taxane regime (TAC-Paclitaxel, adriamycin and cyclophosphamide), and followed by mastectomy. Patients with previous history of lumpectomy,

chemotherapy, radiotherapy, distant metastasis and diagnosed other than IDC on biopsy, were excluded. Complete clinical and radiological details pertaining to location, size and axillary lymphadenopathy were obtained to stage the tumor before NAT. Assessment of the size of tumor was made radiologically wherever possible. Written consent from all the patients and clearance from institutional Ethical Committee were obtained.

After completing NAT the clinical response was evaluated using WHO criteria (14) that defines complete response (cCR) as complete absence of detectable disease, partial response (cPR) as >50% reduction in maximal dimension of tumor, progressive disease (cPD) as increase in tumor size by more than 25%, stable disease (cSD) as no increase in tumor size more than 25%, and no response (cNR) as scenarios that do not fulfill any of the above criteria.

Post-NAT mastectomy specimens were subjected to meticulous gross examination for tumor, tumor bed, and axillary lymph nodes. Information regarding pre-NAT tumor size and location where correlated in every case. The Modified Bloom Richardson (MBR) grading of pre-chemotherapy biopsy and post-chemotherapy mastectomy specimen was done on hematoxylin and eosin stained sections. In Sataloff system response to treatment is assessed for primary tumor in breast and lymph nodes. Primary tumor response categories TA, TB, TC, and TD refers to therapeutic effect amounting to total or near total, >50%, <50% and no effect, respectively. Likewise, for lymph nodes metastasis response categories NA, NB denotes node negative status with and without therapeutic effect whereas NC and ND imply to node positive status with and without therapeutic effect, respectively. Response to NAT was assessed in breast and axillary lymph nodes according to Sataloff criteria (15). Pre-NAT biopsy was also assessed in each case. Cases graded as TA, NA and TA, NB were taken as pCR, cases showing TD tumor response in breast with any combination of lymph node response were taken as pNR, whereas TB and TC tumor response in breast with any combination of lymph node response were considered pPR. Presence of lymphovascular invasion (LVI) and ductal carcinoma *in situ* (DCIS) were noted.

The response to neoadjuvant chemotherapy on breast and lymph nodes was calculated and expressed as numbers and percentages. The association of different clinical and pathological factors with tumors responses was estimated using test of proportion (χ^2 test) and level of significance at $p<0.05$.

RESULTS

In the present study the median age of the patients with breast carcinoma was 50 years and most commonly affected age range was 41-50 years. The range of the pre-NAT tumor size on clinical assessment was 2.5 – 8 cm. On clinical staging highest number of patients were in stage IIIB (64.5%), followed by IIIA, IIIC and IIA as shown in Table 1. Clinical responses observed were complete response (cCR) in 4 cases (12.9%), partial response (cPR) in 24 cases (77.4%), no response (cNR) in 3 cases (9.7%) and none of the cases showed tumor progression (Table 2). Gross examination of post-NAT mastectomy specimens showed fibrotic rubbery tumor bed (Figure 1a) of variable size in 7 cases. Discrete tumor mass with or without identifiable tumor bed (Figure 1b) was identified in remaining cases. In the present series the MBRgrade II tumors were the commonest accounting for 87.1% (27/31 cases) and remaining 4

Age range (years)	33 - 70 years
Median age	50 years
Family history	Six positive cases (19.4%)
Pre-NAT tumor size range	2.5 – 8 cm
Tumor stage	T2- 2 (6.5%) T3- 10 (32.3%) T4- 19 (61.3%)
Lymph node stage	2 (6.5%) 18 (58.1%) 8 (25.8%) 3 (9.7%)
TNM Stage	2 (6.5%) 6 (19.4%) 20 (64.5%) 3 (9.7%)
Pre NAT Tumor type	Infiltrating ductal carcinoma (NOS) (n=31)
Pre NAT Tumor grade	MBR 1- 4 (12.9%) MBR 2- 27 (87.1%) MBR 3- 0
Type of surgery	Modified radical mastectomy (n=31)

NAT- Neoadjuvant chemotherapy, MBR- Modified Bloom Richardson

Table 1. Patient information and pre-NAT clinical details

Clinical response	cCR- 4 (12.9%) cPR- 24 (77.4%) cNR- 3 (9.7%)
Pathologic response	pCR- 5 (16.1%) pPR- 18 (58.1%) pNR- 8 (25.8%)
Post-NAT tumor grade	MBR 1- 4 (12.9%) MBR 2- 26 (83.9%) MBR 3-1 (3.2%)
Lymph node metastasis	24 cases (77.4%)
Lymphovascular invasion	16 cases (51.6%)
Ductal carcinoma in situ	11 cases (35.4%)
TNM Stage	2 (6.5%) 6 (19.4%) 20 (64.5%) 3 (9.7%)
Pre NAT Tumor type	Infiltrating ductal carcinoma (NOS) (n=31)
Pre NAT Tumor grade	MBR 1- 4 (12.9%) MBR 2- 27 (87.1%) MBR 3- 0
Type of surgery	Modified radical mastectomy (n=31)

NAT- Neoadjuvant chemotherapy, cCR-clinical complete response, cPR- clinical partial response, cNR- clinical no response, pCR- pathologic complete response, pPR- pathologic partial response, pNR- pathologic no response, MBR- Modified Bloom Richardson

Table 2. Post-NAT clinical and pathological findings

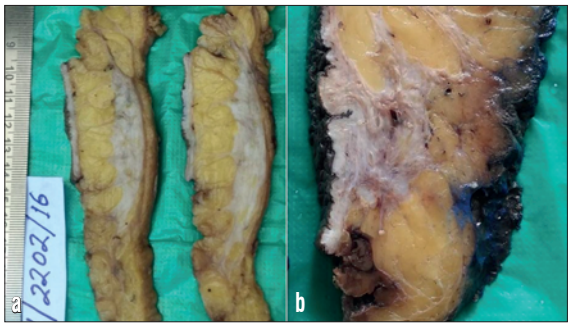

Figure 1. Gross photograph of a case of a) pathological complete response showing dense fibrotic scar tissue and no grossly visible tumor present and b) pathological partial response showing fibrous scar

cases were of grade I (12.9%). There was no significant change in tumor grading in post-NAT specimens when compared to pre-NAT biopsies. An increase in MBR grade was observed in one case after NAT and was reported as grade II on pre-NAT biopsy (Tables 1 and 2).

On evaluation of pathological tumor response in breast as per criteria of Sataloff system TA, TB, TC, TD was seen in 7 (22.6%), 7 (22.6%), 9 (29.0%), and 8 (25.8%) cases respectively (Table 3). Lymph nodes were assessed in all 31 cases. An average number of lymph node assessed was 12.8. In total of 24 cases metastatic deposits to lymph node was present. Results of evaluation of tumor response in lymph nodes according to Sataloff criteria were shown in Table 3.

After compilation of tumor response grades for breast and lymph nodes, pCR, pPR, pNR was seen in 5 (16.1%), 18 (58.1%), and 8 (25.8%) cases (Table 2). Table 4 shows various clinical and pathological factors in different pathologic response groups. DCIS and LVI was seen in 11 (35.4%) and 16 cases (51.6%), respectively.

Out of 5 pCR cases, two had minimal residual tumor in breast which accounted for <5% of tumor surface. These foci showed cytoplasmic eosinophilia and nucleolar prominence (Figure 2a). Fibro-elastotic vascular stroma (Figure 2b), hyalinization, stromal edema, calcification, foamy histiocytes, large areas of necrosis, cholesterol crystals, and lymphocytic aggregates were seen in these cases. One case showed foci of DCIS (Figure 2b), and none had LVI. All these cases were of MBR grade II. Two of the five cases were of stage IIA and remaining three cases were of stage IIIA.

Sixteen and 2 cases of pPR were of MBR grade II and I, respectively. In one case increase in tumor grade was observed. Tumor response was seen in the form of sheets of foamy histiocytes, fibrosis, elastosis (Figure 3a), necrosis, dyscohesive tumor cells (Figure 3b), shrinking effect (Figure 3c), cytoplasmic eosinophilia, vacuolization (Figure 3d), nucleolar prominence, mucinous change, bizarre cells, multinucleation, calcification, cholesterol crystals, and lymphocytic infiltration. In two cases there was no tumor in the breast (TA) but there were foci of metastatic deposits and treatment related changes in lymph nodes and hence these were categorized as pPR. LVI and DCIS were seen in 11 and 6 cases, respectively. Sixteen out of 18 cases showed metastatic deposits in the lymph nodes, and of these eight cases showed treatment related changes. In two cases no tumor deposits or treatment changes were seen in lymph nodes.

Six cases of pNR were MBR grade II and two cases were MBR grade I. These cases had high tumor cellularity (Figure 4a) and minimal to no tumor response was seen. LVI (Figure 4b) and DCIS was seen in 5 and 4 cases, respectively. Lymph nodes showed metastasis in all the cases and response related changes were seen in three cases only. In none of the cases transformation of tumor to other tumor type was noted.

Sataloff criteria (Breast)	Pathological response category in Breast and number of cases*	Sataloff criteria (Lymph node)	Pathological response category in Lymph node and number of cases*
Total or near total therapeutic effect	(T-A) 7 (22.6%)	Evidence of therapeutic effect, no metastasis	(N-A) 1 (3.2%)
>50 % therapeutic effect, but less than T-A	(T-B) 7 (22.6%)	No nodal metastasis or therapeutic effect	(N-B) 6 (19.4%)
<50 % therapeutic effect	(T-C) 9 (29%)	Evidence of therapeutic effect, but metastasis present	(N-C) 14 (45.2%)
No therapeutic effect	(T-D) 8 (25.8%)	Metastatic disease, no therapeutic effect	(N-D) 10 (32.2%)

*Total number of patients n=31

Table 3. Distribution and categorization of tumor response in breast and lymph node according to Sataloff system

	pCR (5/31)	pPR (18/31)	pNR (8/31)	p value
Patient age				
<50	4 (80%)	6 (33.3%)	2 (25%)	p=0.11
>50	1(20%)	12 (66.6%)	6 (75%)	
Tumor stage				
IIA	2 (40%)	0	0	p=0.001
IIIA	3 (60%)	3 (16.7%)	0	
IIIB	0	12 (66.6%)	8 (100%)	
IIIC	0	3 (16.7%)	0	
Tumor size				
<5cm	2 (40%)	4 (22.2%)	3 (37.5%)	p=0.42
> 5cm	3 (60%)	14 (77.8%)	5 (62.5%)	
DCIS				
Present	1 (20%)	6 (33.3%)	4 (50%)	p=0.52
Absent	4 (80%)	12 (66.7%)	4 (50%)	
LVI				
Present	0	11 (61.1%)	5 (62.5%)	p=0.04
Absent	5 (100%)	7 (38.9%)	3 (37.5%)	
Lymph node metastasis				
Present	0	16 (88.9%)	8 (100%)	p=0.0001
Absent	5 (100%)	2 (11.1%)	0	
Fibroelastotic vascular stroma				
Present	5 (100%)	15 (83.3%)	0	p=0.0001
Absent	0	3 (16.7%)	8 (100%)	
Lymphocytic infiltration				
Moderate	5 (100%)	12 (66.7%)	6 (75%)	p=0.59
Severe	0	6 (33.3%)	2 (25%)	

pCR- pathological complete response, pPR- pathological partial response, pNR- pathological no response, DCIS- ductal carcinoma in situ, LVI- lymphovascular invasion

Table 4. Overview of clinical and pathological factors in different pathological tumor response groups

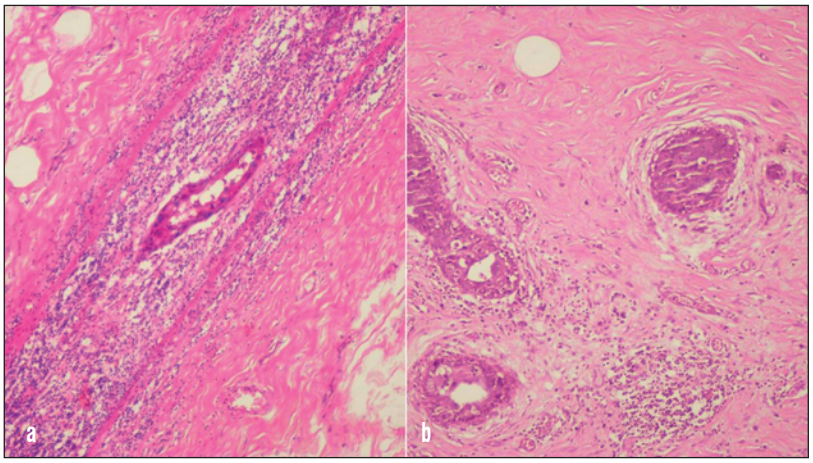

Figure 2. Microphotograph of pathological complete response showing a) focus of minimal residual tumor, b) focus of DCIS and fibroelastoticstroma (hematoxylin-eosin, magnification ×200)

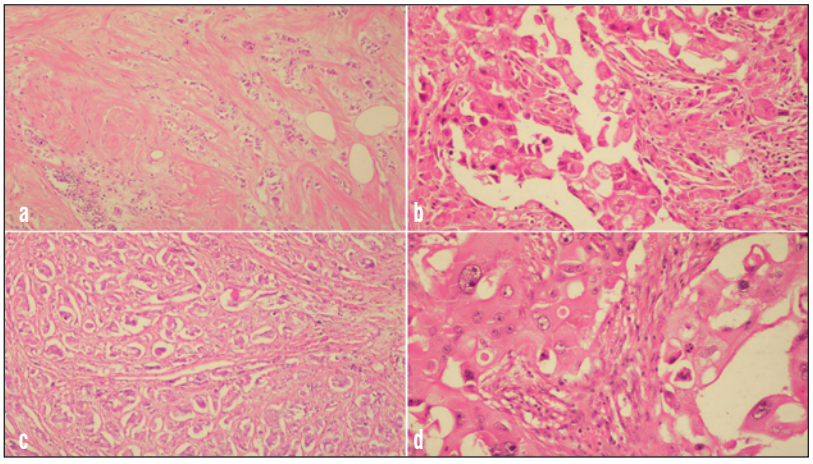

Figure 3. Microphotograph of pathological partial response (hematoxylin-eosin) showing a) prominent fibro-elastotic stroma and residual tumor cells (magnification ×100), b) tumor dyscohesion, cytoplasmic vacuolization, and sheets of foamy cells (magnification ×200), c) marked shrinking effect (magnification ×100) and d) chemotherapy related changes marked by cytomegaly, abundant cytoplasm with marked eosinophilia, cytoplasmic and nuclear vacuolization, prominent nucleoli (magnification ×400)

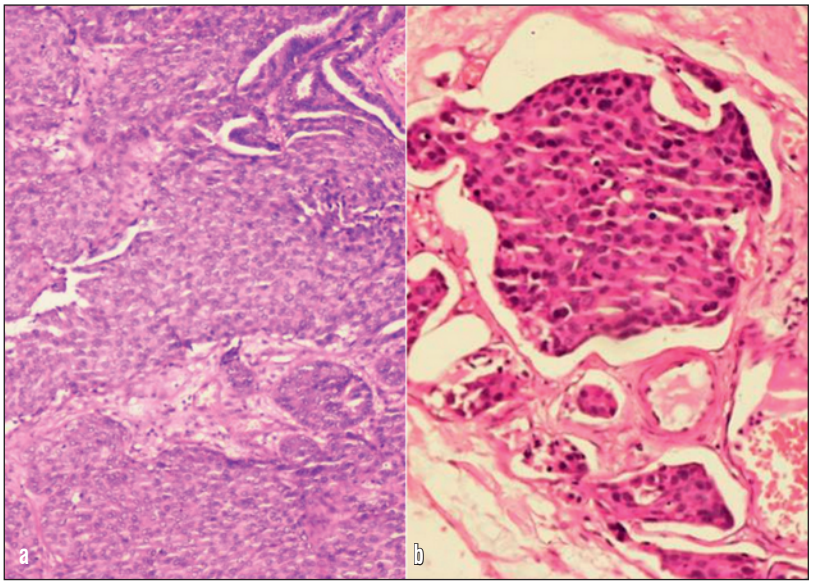

Figure 4: Microphotograph of pathological no response (hematoxylin-eosin) showing a) no alteration in tumor cellularity (magnification ×100) and b) prominent lymphovascular emboli (magnification ×200)

On statistical analysis, significant association was seen between the type of pathologic response and advanced tumor stage (p=0.001), lymph node metastasis (p=0.0001), lymphovascular invasion (p=0.04) and fibroelastotic stroma (p=0.0001).

DISCUSSION

The goal of the NAT is to achieve better pCR rate with improved outcome. As multiple tumor response evaluation systems are in existence, the definition of pCR remains controversial and further add to the challenges associated with reporting of such specimens (16, 17). Some systems grade tumor response from breast tissue alone (GEPARDO, Miller and Payne, Response criteria of Japanese Breast Cancer Society, and NASBP-18) while others consider both breast tissue and lymph nodes (Chevallier and Sataloff classification) (16). According to Sataloff system definition of pCR (category TA, NA and TA, NB) is complete absence of tumor or minimal residual tumor comprising of <5% of tumor surface in breast and no evidence of metastasis to lymph node with or without treatment related changes.

Several authors share the opinion that definition of pCR must consider the lack of disease in breast tissue as well as in the lymph node as persistence of residual disease in lymph nodes is associated with worse prognosis (17). Whether or not the presence of DCIS alone in patients with pPR affects the overall survival is yet to be established (8, 10, 17).

Highest number of patients in our study were in stage IIIB accounting for 64.5 (20/31), followed by IIIA in 19.4% (6/31). In the study by Shintia et al. (18) majority of patients were also in stage IIIB (97.62%) and only one case belonged to stage IIIA (2.38%). All our patients had infiltrating ductal carcinoma (NOS) which was also the commonest type in the study of Shintia (18) and Vasudevan (12).

Clinical partial remission was observed as commonest clinical response category seen in 77.4%, cCR was seen in 12.9% and cNR was seen in 9.7% cases. Literature shows that partial clinical and pathological response is the commonest category accounting for 60-80% and complete response category being less prevalent ranging from 3-30% cases (19). Shintiaet al. (18) also reported partial response in majority of the cases (78.57%) and no response in only 14.28% during clinical response assessment. However, in the study performed by Sethi et al. commonest clinical response category (60%) was comprised of patients with stable disease showing no response to NAT, whereas cPR was observed in only 30% cases (20).

In the present study pathological response was assessed using criteria of Sataloff system where pCR was observed in 16.1% (5/31) cases, pPR in 58.1% (18/31 cases) and pNR in 8 cases (25.8%). In a study by Vasudevan (12), pCRwas observed in 27.1% and pPR in 70.9% cases. Smith et al. (21) and Baer et al. (22) reported pCR in 19-31% cases, 10% cases by Chin et al. (23) and 40% was reported by Fayanju et al. (24). In another study conducted by Shintia et al. (18) reported rate of pNR, pPR and pCR was 35.71%, 59.53% and 4.76%, respectively. This variation in the reported frequencies of different pathologic response categories is partially attributable to the use of different evaluation criteria for response assessment by different authors. Shintiaet al. evaluated pathological response using modified Miller-Payne (MP) system wherein tumor cellularity and percentage of apoptosis were assessed by terminal

deoxynucleotidyl transferase mediated deoxyuridine triphosphate *in situ* nick end labeling (TUNEL) for comparison of reduction in cellularity between pre-NAT and post-NAT specimens. As routine hematoxylin and eosin staining does not enable unequivocal recognition of very early DNA fragmentation hence TUNEL technique was employed for its detection. It was later concluded that modified MP system improves the grading of pathological response. However, no correlation was found between apoptosis and clinical response. Authors have recommended the use of modified MP system, as tumor size reduction does not accurately represent the number of cell death (18). In the present study the assessment of pathological response is performed by using criteria of Sataloff system. Penault-Llorca et al. compared pCR rate by Sataloff and Chevallier system which accounted for 13.6% and 14.3%, respectively (25). In the study by Rousseau (26) efficacy of 18F-fluoro-deoxyglucose positron emission tomography (FDG, PET) was evaluated in tumor response assessment. Pathological tumor response was assessed by Sataloff system and results were compared in 64 patients. Patients with grade A (10 cases) and B (26 cases) tumor response were defined as responders and grades C or D (28 cases) as non-responders.

In the present study no significant difference in the tumor MBR grading was observed in pre- and post-NAT tumors, that was similar to the observations made by Frierson et al. (27) and Vasudevan (12). Sharkey et al. (28) observed differences in tumor grade in one third of their patients. It was also observed that out of five cases of pCR, two patients were of stage IIA, and remaining three patients were of stage IIIA. The size of the tumor was <5 and >5 in 2 and 3 cases, respectively. None of the patients had LVI and only one had foci of DCIS. Vasudevan (12) mentioned that clinically stage T2 tumor, low grade tumor and younger patients had better response to chemotherapy. Although pCR is associated with good prognosis, yet small percentage will still develop recurrence (5, 29).

The experience of the pathologist regarding handling of the NAT specimens and standardization of the evaluation process and reporting can affect the results (30). A multidisciplinary approach has been recommended for evaluation of these cases in order to increase the efficacy of assessment of breast cancer (13). For accurate gross and microscopic evaluation an adequate clinical information regarding clinical presentation, pre-NAT location and size, biopsy/ cytological diagnosis, presence of calcification, tumor markings (if any), NAT regime, and clinical or radiological response should be available (6).

NAT is now used as standard treatment for breast cancer. The pathological assessment of tumor response remains the gold standard, as neither the clinical nor the radiological responses are sensitive predictors of tumor response after treatment. However, pathologic examination is quite challenging and demands sufficient experience along with clinical and radiological details of pre- and post-NAT tumors for response evaluation. Moreover, existence of several reporting systems for response assessment and lack of standardized one has limited the reproducibility and uniformity among institutions.

Declaration of Interests

Authors declare no conflicts of interest

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