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Clinical and pathological factors predictive of response to neoadjuvant chemotherapy in Locally Advanced breast cancer

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A B S T R A C T

This study was performed to examine the predictive factors of pathologic complete response (pCR) in locally advanced breast cancer (LABC) patients after neoadjuvant chemotherapy (NAC). LABC remains a clinical challenge, as distant metastasis develops in most patients, and they will experience disease relapse and eventual death. The identification of reliable predictive factor for neoadjuvant chemotherapy in LABC would help select those patients most likely to benefit from neoadjuvent chemotherapy. 84 LABC Egyptian patients with neodjuvant therapy regimen containing 3-6 cycles of anthracyclin based chemotherapy, followed by modified radical mastectomy (MRM) and node dissections, followed by adjuvant hormonal therapy and Radiotherapy .The patients were divided into two groups: pathological complete response (pCR) or non-pCR group. Clinico-pathological characteristics were compared and analyzed, and multivariate analyses were performed to detect the predictive factors of pCR. The pCR rate in both the breast and axilla was (8.33%), and 91.67% of the patients showed partial response. Multivariate logistic regression demonstrated that pCR was significantly associated with The absence of nodal metastasis, necrosis, lymphovascular invasion and carcinoma insitu and negative ER , PR and HER2 and the non triple negative tumors. the absence of tumor necrosis, DCIS and LVI and negative hormonal status on initial core biopsy are linked to achieving pCR.

1.0 Introduction

Locally advanced breast cancer (LABC) are considered as an advanced breast cancer. LABC is characterized by tumor size of more than 5 cm (T3), with skin and chest wall involvement (T4), or inflammatory carcinoma and/or extensive clinical lymph node (LN) involvement, as defined by the N2 and N3 categories according to American Joint Committee on Cancer (TNM classification system) Rustogi A et al., 2005, Costa SD et al., 2010 .Preoperative Neoadjuvant chemotherapy (NAC) of breast cancer (BC) improves outcomes, especially in patients with locally advanced and inflammatory cancer Bear HD., et al.2003, Fisher B., et al 1997 **.** many studies were conducted on the clinic-pathological factors that influencing outcomes , and to identify the most favorable therapeutic strategy for each group of patients and to predict the response to the treatment Del Prete S et al., 2019 **.** Neoadjuvant chemotherapy (NAC) is established as a therapeutic way for selected high-risk BCs, for example locally advanced Thompson AM et al., 2012 **.** The use of NAC in LABC is now increasing because the ability to observe the treatment effect (in-vivo) to attain higher rates of breast conserving surgery Untch M et al., 2014 **.**on the otherhand, it has not yet been clarified whether NAC would result in enhanced survival in contrast with the standard adjuvant setting in patients with BC Rubovszky G and Horváth ZJ 2017 **.** There are many methods to evaluate the tumor response to preoperative chemotherapy, clinically and pathologically, Hee Jin Lee **et al., .**The Pathological complete response (pCR) after NAT is a good predictor for long-term outcome Loibl S **et al., 2014** . on

the otherhand Liedtke Cet al., 2008, Carey LA et al., 2007 results showed that (triple negative breast cancer) TNBC and HER-2 positive subtypes has got a worse survival**.** in recent times identified biomarkers can predict a pCR Rubovszky G and Horváth ZJ 2017**.** tumor nuclear grade (NG), S-phase fraction, ploidy, estrogen receptors, and cellular changes during the course of chemotherapy Jacquillat C et al., 1990, Mauriac L et al., 1991, O'Reilly SM, et al., 1992, Brifford M, et al ., 1989, Remvikos Y et al., 1993, Silvestrini R et al., 1991, Masters JRW et al., 1987 **.**

In this study , we evaluated the role of the age of the patient, size of the tumor, nodal status, some of tumor characters like, carcinoma insitu, the presence of lymphovascular invasion, necrosis, the ER,PR HER2 status, of preoperative specimens as a predictor of response to preoperative chemotherapy

2.0 Patient and Methods

In this retrospective study, we evaluated 84 Egyptian women with LABC, whose ages ranged from 35 to 75 years, between 2003 and 2012. All study participants performed needle core biopsies (NCB), subsequently received 3-6 cycles of anthracyclin based neoadjuvant chemotherapy, followed by modified radical mastectomy (MRM) and node dissections. Modified radical mastectomy was followed by adjuvant hormonal therapy and Radiotherapy. The clinical data were collected from the patient's medical records at the National Cancer institute of Egypt. Tumor staging was done according to American Joint Committee on Cancer and the International Union of Cancer Control Edge SB and Compton CC 2010. The stage was evaluated clinically (cTNM) before neoadjuvant chemotherapy as follows – T (tumor category): the tumor size has been evaluated by either clinical examination or mammogram; N (nodal category): the regional LNs were examined clinically; and M (distant metastasis): chest radiography, abdominal ultrasound, and bone scan were performed for screening of distant metastasis.

2.1 Pathologic assessment of needle core biopsies

All of these patients were diagnosed in the Pathology Department at the National Cancer Institute of Egypt. In this retrospective study, the re-evaluation of the histopathological features of the hematoxylin and eosin stained sections of NCB was done to confirm the diagnosis, and in addition to determine the predictive factors such as(necrosis, carcinoma insitu, lymphovascular invasion). Tumors with lost cores or insufficient tumor in the cores, were excluded from the analysis.

2.2 Immunohistochemical assessment of slides

Immunohistochemistry scoring Stained slides were evaluated by two pathologists who were blinded to clinicopathological data using the Olympus CH2 Light Microscope (Hicksville, NY, USA). Assessment of the ER‐stained and PR‐stained slides was done according to the American Society of Clinical Oncology/College of American Pathologist, Hammond et al.2010 **:** positive if finding of up to 1% of tumor cells nuclei are immuoreactive, and negative if finding of less than 1% of tumor cell nuclei are immunoreactive. Her2/neu immunoreactivity was evaluated by semiquantitive scoring, using a light microscope according to Wolff et al.2007 **.** The scoring for an IHC test is from 0 to 3+. Positive cases in this study included only the 3 + score.

2.3 Assessment of response to neoadjuvant chemotherapy

Histological sections of the mastectomy specimens and axillary dissection specimens were examined, and the chemotherapeutic response was categorized as pathological complete response (pCR) : (no residual carcinoma in the breast and axiliary lymph nodes), no response (non pCR) *Penault-Llorca F et al., 2008***.**

2.4 Statistical methods

: Data were collected, tabulated, and statistically analyzed using a personal computer with SPSS version 16 program (SPSS Inc., Chicago, Illinois, USA). To analyze the descriptive statistics, we used, percentage, median, and range. For analytical measures, Odds ratio, 97% confidence interval Initial clinical tumor size, nodal status (as defined by the TNM classification system) age , carcinoma insitu, lymphovascular invasion, necrosis, the ER,PR HER2 status of the core specimens were compared with the pathologic tumor response to chemotherapy using multivariate logostic regression Values were considered statistically significant when P value of at least 0.05.

3.0 Results

In this study, patients with LABC (cT4, cN0‐N2, and cM0), were included. Table 1 summarizes the clinicopathologic features, hormonal receptor status, and Her2/neu expression. Regarding the pretreatment tumor size, 31 of 67 cases had tumors more than 5 cm in diameter (46%). Regarding LN stage, most of the cases were N1 and N2 stage, with 58 (87%) of 67 patients. In addition, LABC in our study showed in younger patients, with median age of 53 years Regarding tumor response to NAC, 7 cases out of 84

showed pCR (8.33%), and 91.67% showed partial response. Tables 2 summarize the relationship of some clinical and pathological factors to pathologic tumor response in patients with locally advanced breast cancer. The absence of nodal metastasis, necrosis, lymphovascular invasion and carcinoma insitu , negative ER , PR and HER2 (p= < 0.05) are correlated significantly with tumor response to chemotherapy . While tumor size and the age (p =0.097, p= 0.30) respectively, did not seem to correlate with pathological response in this patients' series

4.0 Discussion

The current study is aimed to investigate a number of clinicopathological characteristics that are linked with pathological treatment response in LABC cases that undergo NACT. The median age was 54 years in this research of 84 LABC patients, which was supported by other investigations. Vasudevan *et al*.,2015. showed that the median age of presentation for LABC patients was 50.58 years. Patients with LABC are more likely to have lymph node involvement, Lymph node involvement was identified in 69.04 % of LABC patients.

Other researches had similar findings, In a study of LABC patients, Barasha *et al*., 2020 discovered lymph node involvement in 78 % of cases, Saxena *et al., 2005.* discovered lymph node positivity in 80.2 percent of cases.We discovered 59 %, 55 %, and 13 % of cases as hormone receptor (ER, PR) positive, HER2 positive, , respectively, based on molecular biomarkers. These findings are in line with those of Barasha *et al., 2020* , who found 50% to be (ER, PR) positive, 9% to be HER2 positive, and 22% to be TNBC. In the current study, pCR was achieved in 7 out of 84 cases (8.33%) of LABC patients after NACT treatment. Díaz-Casas *et a., 2019l* and Patel *et al*., 2013 found a 15.2 % (63 out of 414 cases) and 14 % (7 out of 50 cases) overall pCR rate, respectively. We identified just one case with pCR had lymphovascular invasion with a p-value of 0.05, which agrees with Vasudevan *et al*.,2015. Who discovered that there was no LVI in any LABC cases that demonstrated pCR to NACT treatment, and this was statistically significant (P = 0.015). In the final histology of 13 out of 47 core biopsies (28 percent) with LVI, Patel *et al*., 2013. found no pCR. The presence of LVI on initial core biopsy is negatively correlated with pCR. In our investigation, CIS was discovered in just two cases with pCR and a p-value >0.05, indicating that the existence of CIS is chemotherapy resistant. Vasudevan *et al*.,2015.had a similar observations in which DCIS was found in just two cases with pCR (15.4 %). We discovered 4 out of 7 cases of pCR without necrosis, which could indicate a link between the absence of tumor necrosis in the first core biopsy and pCR attainment. Patel *et al*., 2015. found comparable results (P = 0.035). As a result, we came to the conclusion that tumor necrosis on initial biopsy is a key predictor of pCR to NACT After NACT treatment, we discovered positive correlation with negative hormonal status Jinhua Ding et al., 2017 showed that (ER, PR) negativity is an independent factors for predicting higher pCR . similar results were found by Kuerer,M e al who stated that Patients with a pCR were have negative ER in the initial tumors . This suggests that the absence of these tumor markers (ER, PR) may have a positive outcome on tumor response to NATC. The clinical tumor size was statistically negligible, which contradicts the findings of Barasha *et al., 2020* and Estévez and Gradishar.2004, who concluded that smaller tumors had better outcomes. Jang and Kim, 2015. also discovered that the lower the clinical T stage, the greater the therapeutic response.

As a result, evaluating several of the characteristics in the initial core biopsy, such as LVI, CIS, necrosis, and tumor biomarkers, has a considerable predective value. The present study's principal disadvantage is its small sample size, and it is also retrospective in nature., a larger number of cases are required to assess the numerous parameters linked to treatment response in LABC cases following NACT.

Table 1. Characteristics of patients atbaseline

Characteristic	pCR n=84	%
Age group <50 ≥ 50 Median Range	 3 4 54 29 - 86	30 47
Size of Tumor		
< 2.0 cm	7	8.33%
2-5cm	32	38.10%
> 5cm	28	33.33%
Not available (17)	17	20.24%
Nodal Stage		
N0	9	10.71%
N1	48	57.14%
N2	10	11.90%
Not available	17	20.24%
Carcinoma Insitu		
Absent	62	73.81%
Present	22	26.19%
Necrosis		
Absent	64	76.19%
Present	20	23.81%
Lymphovascular Invasion		
Absent	63	75%
Present	21	25%
ER		
Negative	34	40.48%
Positive	50	59.52%
PR		
Negative	37	44.05%
Positive	47	55.95%
HER2		
Negative	64	76.19%
Positive	11	13.10%
Equivocal	9	10.71%

Table 2. Logistic Regression Analysis

Characteristic	pCR(pathologic comp response) n=7	non-pCR n=77	Odds Ratio	97% Confiden Interval	*P – values*
Age group <50 ≥ 50	3 4	30 47	0.962	0.8948 - 1.03	0.30
Size of Tumor					
< 2.0 cm	1	6	0.167	0.0201 - 1.38	0.097
2-5cm	2	26			
> 5cm	4	28			
NA (17)					
Nodal Stage					
N0	5	8	0.125	0.0156 -0.999	< 0.05
N1	1	46			
N2	1	23			
Carcinoma Insitu					
Absent	5	57	0.087	0.0352	< 0.05
Present	2	20			
Necrosis					
Absent	4	60	0.066	0.0242 - 0.183	< 0.05
Present	3	17			
Lymphovascular Inva					
Absent	6	57	0.105	0.0454 0.244	< 0.05
Present	1	20			
ER					
Negative	5	29	0.172	0.0667 - 0.445	< 0.05
Positive	2	48			
PR					
Negative	4	33	0.563	0.1178 - 2.686	< 0.05
Positive	3	44			
HER2					
Negative	4	60	0.125	0.0156 - 0.999	< 0.05
Positive	2	9			
Equivocal	1	8			

5.0 Conclusion

The prevalence of ASB among pregnant women in Sirte City shown that *E coli* found to be the common isolates organism form urine culture among the pregnant women, beside other gram negative and positive bacteria, which may lead infection complications for pregnancy. This study recommend, all pregnant women should be screened by urine culture to detect asymptomatic bacteriuria at their first visit to prevent overt urinary tract infections (UTI) and other complications in both mother and fetus to prevent risks, and used the safe and effective antibiotics to reduce the dangers.

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