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Research Article

**CLINICOPATHOLOGICAL AND RADIOLOGICAL
FEATURES OF TRIPLE NEGATIVE BREAST CANCER:
A CROSS SECTIONAL STUDY FROM A TERTIARY CARE
CENTER**Dr Naila Jabeen¹, Dr Musarat Jehan Baloch², Dr Adina Anwar³, Dr Sabir Hussain⁴¹ Lecturer Radiology Department Ojha Campus DUHS² Liaquat University Hospital Hyderabad/Jamshoro³ Lecturer Dow Institute of Medical Education, DIMC, DUHS⁴ MD Resident Radiology Department Ojha Campus DUHS**Article Received:** February 2020 **Accepted:** March 2020 **Published:** April 2020**Abstract:**

Objective: To assess the clinicopathological and radiological findings of triple negative breast cancer in our setting.

Methodology: A cross sectional descriptive study was conducted between March 2019 to January 2020 at Dow Institute of Radiology, Dow University of Health Sciences, Ojha Campus. All patients 18 years or older who presented for a mammography and diagnosed for triple negative breast cancer were included while patients who were being treated at the time of the study, or had breast conserving surgery were excluded from the study. Data was recorded in a pro forma and was analyzed using SPSS version 24. Mean age (SD) at diagnosis, breast density, & other variables were presented as mean while the categorical data was presented as percentage. A p-value of 0.05 was considered statistically significant.

Results: A mean age (SD) at diagnosis of 59.6 (6.4) years was observed. A frequency of 214 (19.1%) was reported for triple negative breast cancer. 1/3rd patients had grade II while 3/4th had grade III tumors. One-half of the patients had lobulated masses, one-third were irregular while only a minority were oval shaped. There were no calcifications observed. Patients with triple negative breast cancer were more likely to have advanced disease and younger populace ($p < 0.001$).

Conclusion: The study findings indicate that triple negative breast cancer are associated with more aggressive clinicopathological and radiological findings. Further large scale studies are needed to truly understand the role played by molecular variation in breast cancer in relation to the prognosis and treatment outcome.

Keywords: Breast carcinoma; mammography; radiology; triple negative breast cancer; ultrasound.

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INTRODUCTION:

The clinical behavior of breast cancer among patients varies to a great extent which is due to heterogeneity in breast cancer molecular biology which is dependent upon many factors including how well the tumor is differentiated, how invasive it is, the presence of hormone receptors i.e. Estrogen, Progesterone and the amplification of HER-2/neu protein [1-2]. Triple negative breast cancer (TNBC) is one of the subtypes of breast cancer that is estrogen and progesterone receptor negative as well as absence of HER-2/neu protein [3]. It carries an aggressive course and is associated with a poor survival rate and prognostic outcome. They are responsible for 16.3% of the cases of breast cancer in our population [4-5].

Endocrine and anti HER-2/neu treatment options are not effective against the treatment for triple negative breast cancer as they do not have the receptors which is usually the target for these pharmacotherapeutic agents [6]. Moreover, they are usually found in younger patients leading to more emotional and psychosocial damage. The protocol of standard treatment of TNBC is usually excision surgery which is usually undertaken in combination with adjuvant radiation therapy and chemotherapy [7]. Nevertheless, the overall clinical outcome of TNBC is poorer compared to the cancer which tests positive for hormone receptors. The biomarkers regarded as significant in TNBC include p53 and Ki-67 [8]. Breast carcinoma that has a high activity of Ki-67 have a better response to chemotherapeutic agents. Moreover, the overall survival rate for breast cancer groups that are p53 positive are lower compared to p53 negative breast cancer. Tumors expressing high Ki-67 are associated with a poorer survival rate as well as survival that is relapse free [9].

The ability to identify this subtype of breast cancer early by imaging either by mammography or ultrasound can have an impact in initiating its outcome by formulating a treatment plan faster. In Pakistan, triple negative breast cancer is responsible for 17.2% of the cases [10]. Mammography is commonly used to screen and diagnose breast cancer. Moreover, ultrasound is used in the cases where a mammogram is inconclusive. Very limited studies exist that have evaluated the radiographic features of triple negative breast cancer to date and we have none from a developing country like Pakistan. Therefore, the aim of the study was to determine the main mammography profile, ultrasound and clinicopathological features of triple negative breast cancer in our setting.

METHODOLOGY:

This was a cross sectional and descriptive study conducted at Dow Institute of Radiology, DUHS, Ojha Campus between March 2019 to January 2020.

Study was approved by the ethical committee of the institutional review board, DUHS, and informed written consent was obtained from all patients prior to the study. A non-probability convenience sampling technique was applied to recruit patients in the study. All patients 18 years or older who presented for a mammography and ultrasound at our radiology center with a diagnosis of triple negative breast cancer were included in the study. Patients with recurrent breast cancer disease, those who had not undergone mammography in our setting, those who had their anti cancer treatment started prior to a mammography report, or those with breast implants, or with a history of breast conserving surgery were excluded from the study. Sample size was calculated using a previous local study by Badar F, et al, where he reported a frequency of triple negative breast cancer in Pakistan to be 16.6%. Keeping a confidence interval of 95%, sample proportion of 16.6%, a population size of a million, margin of error to be 5%, a sample size of 213 was obtained using a calculator on select statistics website [12].

Histopathological and radiological assessment

The study included clinically diagnosed and histologically verified breast cancer cases having complete details of the receptor status. As per the departmental protocol, a 16G trucut biopsy was used and 3 to 4 core samples were obtained. Samples were fixed using formalin and were sent for histopathological analysis. All surgical specimens were immunohistochemically analyzed to determine the estrogen and progesterone receptors status. Her2/neu was confirmed on FISH analysis whenever required i.e. IHC +2.

All mammograms were read and reported by a radiologist having more than 3 years of experience in breast imaging and biopsy. The radiologist was blinded to the study objective to minimize bias. Following features of TNBC were evaluated on mammogram; no abnormality, masses, asymmetry, calcification, etc. Moreover, ultrasound features that were assessed included; no abnormality, masses, shape, size, etc.

Statistical analysis

Data was entered and recorded in a predefined pro forma and statistical package for social sciences (SPSS) version 24 was used to analyze the data. Mean age (SD) at diagnosis, breast tissue density, size of tumor and certain other variables were presented as mean and standard deviation while the categorical data i.e. parity, menopausal status, age groups, grade and tumor size, ultrasound and mammography findings were presented as frequency and percentage. The demographic, clinicopathological, and radiological findings were further stratified into groups and comparison was made between triple negative and other subtypes of

breast cancer in our population. The chi squared test was used to calculate the significance. A p-value of 0.05 was considered statistically significant.

RESULTS:

Out of the 1121 patients who were diagnosed with breast cancer at our hospital setting from March 2019 to January 2020, 214 (19.1%) tested negative for hormone receptor and HER-2/neu protein. The mean age at diagnosis (standard deviation) was 59.6

(6.4) years. The patients belonged to diverse ethnic origins, majority being Urdu speaking and Sindhi. The different demographic and clinical profile is given in table 1. The mean tumor size reported was 2.36 (2.2) centimetres. There was no patient with grade I breast cancer, one-third were grade II, while 3/4th of the study population had grade III tumors at the time of diagnosis. See table 1 for details.

Table 1: Demographic and clinicopathological characteristics of patients with triple negative breast cancer

Characteristics	Frequency n (%)
Age	
30-45	34 (15.9%)
46-60	89 (41.6%)
61 years and older	91 (42.5%)
Marital Status	
<i>Unmarried</i>	24 (11.2%)
<i>Married</i>	157 (73.4%)
<i>Separated/Divorced</i>	12 (5.6%)
<i>Widowed</i>	21 (9.8%)
Menstrual Status	
<i>Premenopausal</i>	13 (20%)
<i>Postmenopausal</i>	52 (80%)
Parity	
<i>Nulliparous</i>	22 (11.6%)
<i>1 child only</i>	56 (29.5%)
<i>2-3 children only</i>	51 (26.8%)
<i>4 or more children</i>	61 (32.1%)
Lymph node status	
<i>Positive</i>	87 (54.4)
<i>Negative</i>	70 (44.6)
<i>Missing/Not tested</i>	7/16
Tumor Size	
<i>T1 (<2)</i>	71 (33.2%)
<i>T2 (2 to 5)</i>	111 (51.9%)
<i>T3 (>5)</i>	19 (8.9%)
<i>Missing</i>	13 (6.1%)
Tumor Grade	
<i>Grade I</i>	0 (0.0%)
<i>Grade II</i>	66 (30.8%)
<i>Grade III</i>	148 (69.2%)
Histological subtype	
<i>Invasive ductal carcinoma</i>	192 (89.7%)
<i>Invasive lobular carcinoma</i>	7 (3.3%)
<i>Invasive micropapillary carcinoma</i>	1 (0.5%)
<i>Tubular carcinoma</i>	0 (0.0%)
<i>Metaplastic carcinoma</i>	10 (4.7%)
<i>Invasive Mucinous carcinoma</i>	4 (1.9%)

The majority of the patients were diagnosed with invasive ductal carcinoma while only 11.3% had other histological subtypes (See table 1 for details). The density of the breast tissue of patients with diagnosed breast

cancer was observed with the majority of the patients having scattered fibroglandular tissue; 91 (42.5%) and heterogeneously dense tissue; 109 (50.9%). Only 6 (2.8%) had fatty tissue and 8 (3.7%) patients had dense breast tissue on mammography. See figure 1.

Density of Breast Tissue in Patients with Triple Negative Breast Cancer

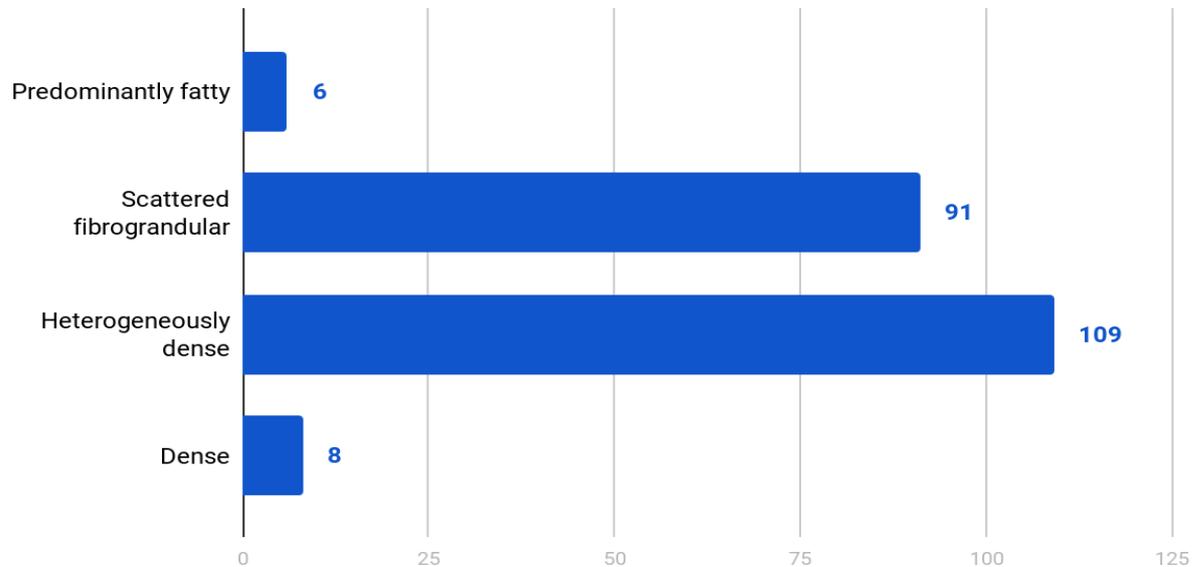


Figure 1: Mammography findings for patients with triple negative breast cancer

When evaluating the radiological findings, we reported that the majority of the patients had detectable masses on imaging. One-half of the patients had lobulated masses, one-third were irregular while only a minority were oval shaped. There were no calcifications observed. The majority of the patients i.e. about 40% cases were hypovascular and a similar ratio of cases had spotty signals. See details in table 2.

Radiological Features	Frequency n (%)
Shape of mass	
<i>Oval</i>	35 (16.4%)
<i>Lobulated</i>	104 (48.6%)
<i>Irregular shape</i>	60 (28%)
<i>Indistinct</i>	15 (7%)
Vascularity	
<i>Avascular</i>	19 (8.9%)
<i>Spotty signals</i>	86 (40.2%)
<i>Hypovascular</i>	91 (42.5%)
<i>Hypervascular</i>	18 (8.4%)
Findings	
<i>Masses</i>	194 (90.7%)
<i>Non mass lesions</i>	20 (9.3%)
Posterior echoes	
<i>Accentuating echoes detected</i>	81 (37.9%)
<i>No change detected</i>	100 (46.7%)
<i>Attenuating echoes detected</i>	33 (15.4%)

Age was significantly associated with the molecular subtype of breast cancer. Patients with triple negative breast cancer were younger compared to patients with other subtypes of breast cancer ($p=0.000$). Similarly, we observed

a link between triple negative breast cancer and tumor grade, $p=0.002$. Other variables were not significantly different.

Table 3. Association of triple negative breast cancer and independent demographic, clinicopathological and radiological variables

Independent Variable	Triple negative breast cancer (n=214)	Other breast cancer (n=358)	P-value
Age			
30-45 years	34 (15.9%)	61 (17.0%)	0.000
46-60 years	91 (42.5%)	98 (27.4%)	
61 years or older	89 (41.6%)	199 (55.6%)	
Parity			
Nulliparous	22 (11.6%)	123 (39.4%)	0.08
Parous	168 (88.4%)	190 (60.7%)	
Menopausal Status			
Premenopausal	34 (15.9%)	61 (17%)	0.843
Postmenopausal	180 (84.1%)	297 (83%)	
Tumor Grade			
Grade I	0 (0.0%)	3 (0.8%)	0.002
Grade II	66 (30.8%)	177 (49.4%)	
Grade III	148 (69.2%)	178 (49.7%)	
Tumor Size			
<2 cm	71 (33.2%)	125 (34.9%)	0.221
2 cm to 5 cm	111 (51.9%)	180 (50.3%)	
>5 cm	19 (8.9%)	53 (14.8%)	

DISCUSSION:

The estrogen and progesterone hormone receptors (ER and PR) together with HER2 (HER-2/neu) oncoprotein play a vital role in the pathogenesis of human breast carcinoma. Approximately 50-85% and 15-20% of breast malignancies exhibit ER or PR and HER-2/neu positivity, respectively and are referred to as hormone receptor-positive cancers [13, 14]. Breast cancer that tests negative for estrogen receptors, progesterone receptors, and HER-2/neu protein are regarded as triple negative cancer [reference]. Hormone positive tumors are well-differentiated and are more likely to have a better prognosis while the hormone receptor negative malignancy has a poor prognosis [6]. Determination of estrogen, progesterone, and HER-2/neu receptors status is helpful in selecting the patients most likely to receive benefit from endocrine therapy, and provide prognostic information on recurrence and survival since their expression is related to the degree of tumor differentiation.

The present study evaluated the clinicopathological and radiological findings of triple negative breast

cancer cases. We reported a frequency of 19.1% i.e. 214 patients who were diagnosed with triple negative breast cancer in our setting. Previous studies have reported the prevalence of triple negative breast cancer to be 12% to 17.5%, which is comparable to the findings of the present study [ref]. In a local study by Badar F. et al, the frequency of patients diagnosed with triple negative breast cancer at Shaukat Khanum memorial cancer hospital and research center, Lahore, Pakistan, was 16.6% [11].

We found in our study that there was a preponderance of Grade 3 tumors in the category of triple negative at the rate of 68.10% with only 31.90% cases of Grade 2 tumors (p -value < 0.001). It is well established that triple negative breast cancer is known to have a poorer prognosis and is characterized by high grade (G3) and thus an aggressive behavior as reported in literature [11-16]. Similarly the prognostic significance of triple-negative breast cancer was explored in a cohort of 1,601 patients with breast cancer. It was found that subjects with triple negative cancer had an increased likelihood of distant recurrence (hazard ratio, 2.6; 95% confidence interval, 2.0-3.5; $P < 0.0001$) and

death (hazard ratio, 3.2; 95% confidence interval, 2.3-4.5; $P < 0.001$) within 5 years of diagnosis as compared to other subjects in the cohort. [15-16]

The radiological features were evaluated by means of ultrasound and mammography in patients with triple negative breast cancer. In the present study it was reported that the majority of the patients had detectable mass i.e. 90.7% on mammography. While assessing the ultrasound characteristics, we observed that there were only a minority of cases where the breast tissue was dense, and the majority were composed of fibro glandular (42.5%) or heterogeneously dense (50.9%). The triple negative breast cancers were usually observed as lobulated or irregularly shaped lesions. Posterior echoes in the majority of the patients were accentuated and vascularity was also detectable in the majority of the cases.

Our data is in accordance with the earlier data where radiological findings were discussed and evaluated specific to triple negative breast cancer. [17-18]. In previous studies, the findings on mammography and ultrasound were compared with the hormone receptor status and the over amplification of HER-2/neu cancers. The radiological features of triple negative cancers reported in their studies were similar to those observed in the present study. Moreover, earlier data by Ko, et al, indicated that only a minority of the patients with triple negative cancer had calcification compared to those with hormone receptor positive cancer or HER-2/neu overamplification ($p < 0.0001$) [19]. The study further speculated that triple-negative breast cancer was associated with rapid conversion to invasive carcinoma without major in situ components or to a precancerous stage; therefore, these types of cancers often lack calcifications on imaging.

A local study by Fatima et al, reported that there was no association between menopausal status and stage of breast cancer in patients with triple negative breast cancer. The report indicated that triple negative breast cancer was significantly associated with older age groups of first birth and frequency of parity [10].

The present study focused on the clinicopathological findings of only the triple negative breast cancer in our setting, evaluating the prime and most common features associated with this aggressive cancer. Our results are comparable to the very limited data. We hope that this study can act as a catalyst for future research and provide a foundation to conduct further studies on a much larger sample size.

CONCLUSION:

The present study indicates that the frequency of triple negative breast cancer is increasing with distinctive features detected on ultrasound and mammography. Since the triple negative breast cancer is associated with poorer prognosis and survival rate, their early detection and prompt treatment can subsequently lead to a better patient outcome.

Conflict of interest: none declared.

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Author's contribution: All authors contributed equally and substantially.

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