

Clinicopathological Characteristics of Triple Negative breast cancer in Suez Canal University Hospital

Maha Lotfy Zamzam¹ and Heba Mohamed Wagih²

¹Clinical Oncology & Nuclear Medicine Department, Faculty of Medicine, Suez Canal University, Egypt.

²Pathology Department, Faculty of Medicine, Suez Canal University, Egypt.

mahalZamzam@hotmail.com

Abstract: Introduction: Worldwide, breast cancer is the most common malignant tumor in females. It represents 25% of all types of cancers. Triple – negative breast cancer (TNBC) represents 15% of all breast cancers TNBC occurs in younger age, of high grade and shows a more aggressive course. In this study, we identified the frequency, clinical and pathological characteristics of TNBC in patients attending Clinical Oncology Department at Suez canal university hospital. **Methods:** A retrospective study was done between 2013 and 2016 at Clinical Oncology Department Suez Canal University hospital. Among 688 cancer breast patients, 144 women had a TNBC. Clinical and pathological features were analyzed. **Results:** 20.9% of patients had TNBC. The age range was 26-67 years. Mean age was 46 years. 59% were post menopausal. Only 8.3% of patients had a family history of breast cancer. Majority of cases were represented grade 2, T2, positive lymph nodes and stage 2. 83.3% of patients had modified radical mastectomy, 91% received adjuvant chemotherapy. 9% of patients have received neoadjuvant chemotherapy and 72.2% have received radiation therapy. **Conclusion:** TNBC group is associated with high grade, large tumor size, high stage and node positivity. Most of TNBC characteristics in our department is consistent with literature data. More research should be directed to understand the complexity of this type of breast cancer.

[Maha Lotfy Zamzam and Heba Mohamed Wagi. **Clinicopathological Characteristics of Triple Negative breast cancer in Suez Canal University Hospital.** *Cancer Biology* 2019;9(2):41-47]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). <http://www.cancerbio.net>. 7. doi:[10.7537/marscbj090219.07](https://doi.org/10.7537/marscbj090219.07).

Key words: Breast cancer, Triple negative, clinical characteristics, Suez Canal University hospital.

1. Introduction:

Worldwide, breast cancer is the most common malignant tumor in females. It represents 1.7 million new cases per year and 25% of all types of cancers (1). Each year, 40,000 women die of breast cancer, ranking it the second – leading cause of cancer deaths in American women after lung cancer (2).

Breast cancer is considered a heterogeneous tumor regarding its morphological, clinical, and biological characteristics. Recently, based on molecular and expression profile it has been divided into five distinct subgroups with different biological behavior; luminal A, luminal B, normal breast-like; Her-2 overexpressing and basal-like tumors (3). Basal-like tumors possess the most aggressive and the worse outcome. Triple negative breast cancer (TNBC) is characterized by lack of estrogen receptor (ER), progesterone receptor (PR) and HER-2/neu expression. Most TNBC belongs to basal-like group sharing biological, clinical and aggressive features (4). Surgery, anthracycline – and taxane based chemotherapy, and radiation therapy are the primary treatment modalities for patients with TNBC. No targeted therapies are approved for TNBC and patients don't benefit from hormonal or Herceptin therapy (5).

The prevalence of TNBC varies widely among different locations and races. The prevalence of TNBC among different breast cancer subtypes ranges between 9% and 27% (5, 6, 7, 8, 9, 10). TNBC tends

to occur most frequently in younger age (5, 6), it is often of ductal carcinoma type, locally advanced and with high grade (5). According to (NCI-CU) cancer 12-years registry TNBC accounts for about 13.5% of breast cancer (7).

Compared to other types of breast cancer, TNBC shows a more aggressive course with increased risk of local recurrence and metastases mainly in the lung, brain and soft tissue (8,11). However, these clinicopathological characteristics of TNBC also vary globally in the literature (5,6,7,8,9,10).

The aim of this retrospective study is to determine the frequency of TNBC and identify its clinical and pathological characteristics among patients attended clinical oncology department, Suez Canal University hospital.

Methods:

This is a retrospective study between 2013 and 2016. We analyzed the medical records at the clinical oncology department Suez Canal University hospital and 144 female patients histopathologically diagnosed with triple negative breast cancer were identified. Retrospective chart review of patients' demographics, clinical and pathological data was performed. Treatment was obtained from the patients' records. Immune histochemical (IHC) analysis to determine estrogen (ER) and progesterone receptor (PR) status was performed using standard procedures on paraffin

embedded tissue specimens stained. Over expression of HER2 status was determined positive if HER2neu was 3 + by IHC and negative if HER2 score of 0 or 1. Confirmation by fluorescence in – situ hybridization (FISH) was carried out for all those with receptor status 2+.

3. Results:

Among 688 cases of breast cancer, 144 women (20.9%) had TNBC. The age of the patients varied from 26-67 years.

The mean age was 46 years, 21.5% less than 40 years and 78.5% more than 40 years (Table 1) (Figure 1).

Majority of patients treated in our department were from Ismailia (77.8%) (Table 1). Family history was reported in only 12 patients (8,3%). Most of the patients were post menopausal 85 patients (59%), non-

smokers (93%) and didn't receive contraceptive pills (54.9%) Table (1). 56.3% had infiltrating ductal carcinoma and 61.1% had lymph node involvement. Majority of patients had high grade tumours; 50.7% grade 2 and 49.3% grade 3 (Table 2).

Majority of patients were diagnosed with stage 2 b and 3 a (39% and 27% respectively) (Table 2, Figure 2).

Most of the patients had modified radical mastectomy (83.3%) and the rate of breast conservative surgery was only 16.7%.

Adjuvant chemotherapy was administered in (131 patients) 91% of patients. 13 patients out of 144 (9%) received neoadjuvant chemotherapy, 104 out of 144 patients received adjuvant radiotherapy. Anthracyclines – based regimens were used as adjuvant or neoadjuvant in 88/144 (61.1%) of patients (Table 3).

Table (1) patients characteristics (n = 144)

Variable	No of Patients	%
Age at initial diagnosis, years		
Less than 40 years	31	21.5%
More than or equal 40 years	113	78.5%
<u>Residence</u>		
Ismailia	112	77.8%
Suez	9	6.3%
North Sinai	16	11%
Port Said	7	4.9%
<u>Occupation</u>		
Housewife	65	45.1%
Employee	45	31.3%
Retired	34	23.6%
<u>Ecog Performance Status</u>		
0	42	29.2%
1	102	70.8%
<u>Marital Status</u>		
Not married	17	11.8%
Married	127	88.2%
<u>Use of contraceptive pills</u>		
Positive	65	45.1%
Negative	79	54.9%
<u>Menopause</u>		
Premenopausal	59	41%
Postmenopausal	85	59 %
<u>Age at menarche</u>		
Before 11 years	2	1.4 %
After 11 years	142	98.6 %
<u>Smoking history</u>		
Smoker	10	7 %
Non-smoker	134	93 %
<u>Family History</u>		
Positive	12	8.3 %
Negative	132	91.7%

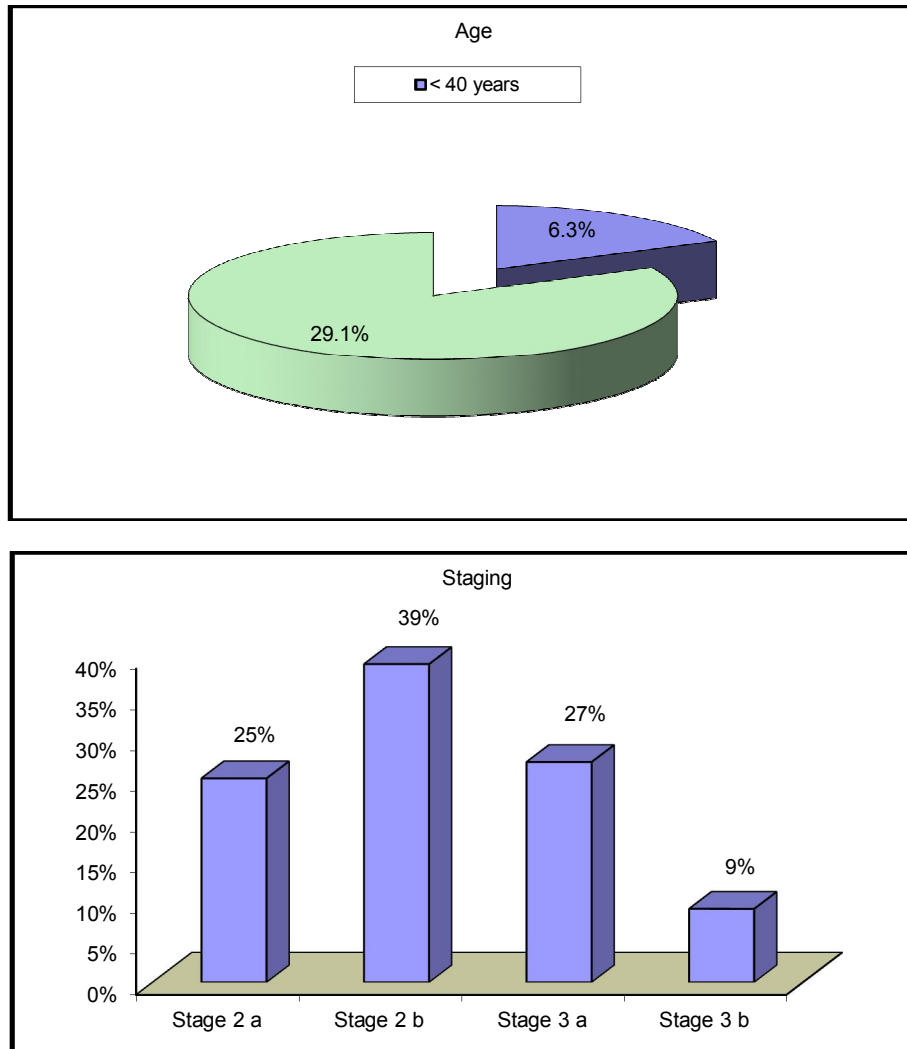
Table 2 Tumor characteristics (n=144)

Variable	No. of patients	%
Histologic type		
Infiltrating ductal carcinoma	81	56.3%
Infiltrating Lobular carcinoma	17	11.8%
Mixed (ductal/ lobular)	17	11.8%
Other types	29	20.1%
Histologic grade		
I	0	0
II	73	50.7%
III	71	49.3%
Tumor size		
T1	0	
T2	89	61.8%
T3	42	29.2%
T4	13	9%
Nodal involvement		
N0	56	38.9%
N1	66	45.8%
N2	22	15.3%
N3	0	
Staging		
Stage 1	0	
Stage 2 a	36	25%
Stage 2 b	56	39%
Stage 3 a	39	27%
Stage 3 b	13	9%
Stage 3 c	0	
Stage 4	0	

Table 3: Treatment modalities

Treatment modalities	No	%
Surgery		
Modified radical mastectomy	120	83.3%
Conservative surgery	24	16.7%
Chemotherapy		
Neoadjuvant chemotherapy	13	9%
Adjuvant chemotherapy	131	91%
Chemotherapy regimen		
Anthracyclines based	88	61.1%
Sequential Anthracyclines/ Taxans	56	38.9%
Adjuvant Radiotherapy		
Yes	104	72.2
No	40	27.8

Received among 144 cases of triple negative cancer breast



4. Discussion

Our study is a retrospective review of 144 patients with TNBC in Suez Canal University hospital over a 4 year period (2013 – 2016). We analyzed the demographics, clinical, pathological, epidemiological characteristics of TNBC patients.

Of 688 breast cancer patients, diagnosed with available IHC data, 144 patients with breast cancer were identified as having triple negative breast cancer (20.9%). This frequency is comparable to other studies (9-21%) in non – western countries, (8, 12, 13) and in western countries (9, 14, 15, 16).

The incidence of TNBC in the study done by Mondal et al and Hashmial was 18.3% and 18.6% respectively (17, 18). Compared to international data, Chinese, African Americans and Peruvians had a greater frequency of triple negative breast cancer forming an incidence of 21.5%, 21.5% and 21.3% respectively (19, 20). Also, Souad et al reported an incidence of 21.7% in a descriptive study done in

Eastern Algeria (21) while Ramprenom et al reported an incidence of 24.4% (17).

The overall rate of triple negative breast cancer in the study done by Tan et al was 17.6% (22).

The Frequency of triple negative cancer in Caucasians, UK population and Australians was found to be low forming a frequency of 12.5%, 13% and 14% respectively (23,24).

However, studies have suggested that TNBC prevalence differs between countries and races (20).

Compared to other breast cancer subtypes, TNBC develops earlier in life (20).

In our study, the mean age at diagnosis was 46 years, with most of cases \geq 40 years representing 78.5%, and 21.5 % were less than 40 years. This is similar to what is reported by many studies with the mean age of the TNBC group was 46.26 and 45 years old (25, 23). Also, the mean age of the studied group reported by Zakaria, et al was 48.95 years (26). Some studies showed different mean ages where Korea and Turkey have the youngest cohort of TNBC patients

(44-45 years) (27) while Japan was the oldest (mean age was 56 years) (4).

Gado et al reported 52 years as mean age at diagnosis and the median age at diagnosis reported by Souad, et al, was 52 years (28, 21).

The incidence rate of overall breast cancer is low in young age and this is due to the healthy estrogen surveillance in many of young women. Thus, in young cases, tumor may develop as a result of strong risk factors associated with breast cancer, as BRCA gene mutation, positive family history, irregular cycles which diminish the estrogen synthesis that causes damage of the estrogen signaling in young cases that leads to occurrence of TNBC in younger age group (29).

In our study, a positive family history was documented in 8.3% of patients which is comparable to the incidence reported by Gado et al and Souad et al 7% and 6.82% respectively (28, 21).

In Lebanon, Ghosn et al and Fakhoury reported a positive family history in 10% of patients with TNBC (8, 30). Other studies documented higher incidences of positive family history, both Kwan et al, and Fayaz et al 20% (31, 32), 28% in Phipps et al (33).

In our study, 45.1% gave history of oral contraceptives (OCP) which is comparable to 44% in Fayaz et al (36) study, versus 72% in Kwan et al (31) study, 35% in the Turkish study (27), and 55% in Phipps et al. (33) study. Only 7% of our study cohort gave history of smoking. This is comparable to 7.7% in Fayaz et al study (36) versus 49% in Kwan et al. (31).

Most of the cases were post menopausal (59%). Similar finding was reported by Pistelli and colleagues where the majority of cases (55.7%) were post – menopausal (34). This could be explained by decrease of estrogen in this period of age that leads to the development of tumor in most of the post menopausal cases. 52.5% was the frequency of post menopausal reported by Zakaria et al (26).

Other studies reported that majority of cases were premenopausal, Ajoy and Radhakrishnan 78.7% and Mandal et al 60.3% (35, 17).

The histological characteristics in this study shows that infiltrating duct carcinoma is the most frequent (56.3%). This agrees with other studies that reported the prevalence of invasive duct carcinoma as Singapore and Japan that reported 93% and 95% respectively (36, 37). Soad et al and Gado et al documented an incidence of 96.08% and 93.3% respectively, (21, 28).

Mixed ductal / lobular formed an incidence of 11.8% in this study. Also, infiltrating lobular carcinoma formed 11.8% incidence versus other studies where invasive lobular carcinoma was reported

in 2% of TNBC patients in Singapore (36), 4% in Kuwait (32), 2.3% in Italy (38).

Gado et al reported 6% incidence in their study (28). This may represent the pleomorphic subtype of lobular carcinoma (39).

Triple negative breast cancers are mainly high grade tumors (5).

In our study, grade II tumors represented 50.7% while grade III was 49.3%. No grade I tumor was detected. In the study done by Haddad Souad et al, most tumors were of high grade (53.92%) (21).

This is contrary to the study done by Gado, et al where grade II tumors represented 74% while grade III was 16% (28).

Most of cases of our study represented T₂ (61.8%), followed by T₃ (29.2%), and T₄ (4%). No one represented T₁.

This is comparable to Gado et al whom study documented predominance of T₂ tumors (28). Although Zakaria et al reported that most of cases of their study represented T₂ (67.8%) but this was followed by T₁ (15.3%), T₃ (10.2%), and T₄ (6.8%) which is different from our study (26).

Lymph node involvement was found in 61.1% of cases in our study. This is comparable to what was observed by other studies where Zakaria et al noted high incidence of node positivity 62.7% (26). Positive lymph node was 66% in the study done by Gado et al (28), while it was 69.07% in the study done by Souad et al (21). Mondal et al reported 58.15% nodal positivity (17).

Most of cases of our study represented stage 2 (64%), 2b (39%) and 2a (25%) followed by stage 3 (36%) 3a (27%) and 3b (9%). This is comparable to Zakaria et al who reported that stage II represented majority of cases (59.3%) followed by stage III (33.9%) (26).

This is different from Gado et al who reported that stage 0 – 1 represented 45% while stages III and IV represented 52.5% (28).

Fayaz et al reported 56% of patients with stages, I and II while stage III represented 37% (32).

Ajay and Radhakrishnan found that stage 3a was the commonest stage at presentation in TNBC comprising 45.3% of cases followed by stage 2b, 32% (35).

In the current study, majority of patients underwent modified radical mastectomy (83.3%) and 16.7% underwent breast conservative surgery (BCS). Ajay A et al. reported that 96% of cases with TNBC underwent MRM and 4% underwent BCS (35).

In our study, 13 patients (4%) received neoadjuvant chemotherapy followed by surgery. Main objective of neoadjuvant chemotherapy is to decrease tumor size and to increase the proportion of conservative breast surgery. It is proposed for

inflammatory or locally advanced tumours, inoperable and for operable tumors but voluminous, not accessible to conservative surgery.

TNBC have higher rates of pathological complete remission following neoadjuvant chemotherapy compared to other cancer types (11).

In our study, majority of patient to received adjuvant chemotherapy (41%). In the form of anthracycline based regimens (61.1%). This is comparable to Gado et al where the majority of patients (89%) received adjuvant chemotherapy in the form of anthracyclines based regimens (52.3%) (28).

Methods of treatment in TNBC are still limited in clinical practice due to the lack of molecular targets.

Cytotoxic chemotherapy is the standard treatment of TNBC in the adjuvant, neoadjuvant and metastatic settings because of the lack of response to tradition hormonal therapies and targeted therapies (5).

5. Conclusion

This study shows that most of TNBC characteristics in our department are consistent with literature data. It is more common among post menopausal women of age group less than 50 years, with tendency to express high grade, large tumor size, high stage and node positivity.

Our study has several limitations including lack of a comparative study of TNBC patients with other subtypes of breast cancer patients. Also, the lack of BRCA gene mutations' studies due to limited financial resources. However, it is the first study to report clinical and epidemiological characteristics of triple negative cancer breast in Suez Canal area.

More research and genetic studies should be directed to understand the complexity of this subtype of breast cancer.

Also, there is a need for national Egyptian cancer control programs for early detection of breast cancer, early treatment which improve the survival of patients.

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