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Pattern of Failure and Treatment Results in Triple Negative Breast Cancer Patients

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Abstract

Background: Triple negative breast cancer (TNBC) tends to present aggressively with rapid progression and poor survival. **Methods:** We retrospectively reviewed patients' files to define TNBC patients' characteristics, predictive and prognostic factors, pattern of recurrence and survival. **Results:** 965 cases were identified. 147 patients (15.2%) were TNBC. 71.1% patients were premenopausal. T2, T3, T4 tumors represented 46.1%, 32% and 14.1%, respectively. N0, N1, N2, N3 disease represented 18.5%, 50.9%, 27.8% and 2.8%, respectively. Stages II, III & IV constituted 34.1%, 44.2% and 15.5%, respectively. 31.5% patients received neoadjuvant chemotherapy with 17.7% complete pathological response. 19.5%, 35.9%, 44.6% patients had unknown, ≤20 and >20 Ki67, respectively. Among non-metastatic patients (n = 108), 21.3% patients developed relapse with median time to relapse of 11 months. 78.3% of them had visceral (88.3% lung) metastasis, 13% bone metastasis, 21.7% brain metastasis and 13% LRR. There is significantly high risk of relapse in patients with large tumor size [T4: 66.75%, T3: 22.9%, T2: 16.7%, T1: 0% ($p = 0.002$)], positive LNs [N3: 100%, N2: 37.9%, N1: 15.1%, N0: 4.3% ($p < 0.001$)] and Ki67 [>20: 31.6% versus 10.8% for Ki67 ≤ 20 ($P = 0.007$)]. Multivariate analysis revealed only T4 and N2-3 were significantly associated with high probability for relapse ($P = 0.022$ & 0.038). The 3-year DFS and OS were 73.2% and 75% respectively. For metastatic patients (n = 20), the m PFS was 7 months and m OS 1.5 years. **Conclusion:** Our data confirms the aggressive nature of TNBC with significant risk of relapse for patients with large tumor and positive lymph nodes. Maintenance metronomic capecitabine, neoadjuvant/adjuvant immunotherapy could be beneficial for non-metastatic patients. Lungs and brain were the most common sites of distant failure with poor survival that necessitates administration of molecular biomarkers (BRCA mutations, PD-L1 expression and microsatellite instability) for patients' selection for novel targeted therapy.

Keywords

Metastatic Breast Cancer, Triple Negative, Pattern of Failure

1. Introduction

Breast cancer is the most common malignancy among women. It is clinically categorized into three basic therapeutic groups including estrogen-receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-amplified, and triple-negative breast cancers (TNBC) [1] [2].

TNBCs account for approximately 12% - 16% of all breast cancer cases (Voduc *et al.*, 2010) [3]. These tumors are negative for ER, progesterone-receptor (PR) and HER2, tend to occur at younger age and present aggressively with rapid growth and progression [4].

The vast majority (80%) of TNBC is in the basal-like subtype but not all basal like tumors are triple negative as defined by gene expression profiling [5].

Generally, TNBCs are poorly differentiated tumors with poor prognosis except for medullary carcinoma and adenoid cystic carcinoma which tend to have favorable outcomes [6].

Due to lack of receptor expression, TNBCs are not candidates for hormonal or targeted therapies and chemotherapy is the mainstay of treatment. TNBC patients have improved disease-free survival (DFS) and overall survival (OS) with neoadjuvant chemotherapy especially in those with tumor size > 2 cm or positive lymph nodes who had achieved complete pathological response (pCR) [7]. In addition, TNBC patients who did not achieve pCR to neoadjuvant chemotherapy have a poorer outcome relative to patients with receptor positive disease. It is presumed that the residual tumor after neoadjuvant treatment may relapse soon and cause poor survival [8].

These tumors generally tend to relapse after standard adjuvant chemotherapy regimens earlier than hormone receptor positive types and have a higher tendency for visceral, soft tissue and central nervous system metastasis [9]. The peak risk of recurrence is within two to three years after diagnosis. However, after this peak risk period, the risk of recurrence declines rapidly, and recurrences seldom occur thereafter [10]. We still need to understand more about TNBCs to improve outcome of this unlucky group of patients [11].

We conducted this retrospective study to define patients' and tumor characteristics, therapeutic approaches and patterns of recurrence, predictors for recurrence and survival outcomes (DFS and OS) in TNBC patients.

2. Patients and Methods

We retrospectively reviewed the medical records and files of breast cancer patients treated at Clinical Oncology Department Faculty of Medicine Alexandria University Hospital, Ayadi Almostakbal Oncology Center, and Damanhur On-

cology Institute, Egypt during the period between January 2013 and December 2017. Patients with pathologically proven TNBC who had adequate data and follow-up were included in the study.

Inclusion criteria: 1) female patients, 2) age ≥ 18 years old, 3) Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 2, 4) pathologically proven invasive carcinoma (ductal, lobular, metaplastic, others), 5) stage I-IV, 6) triple negative breast cancer. TNBC was defined by immunohistochemistry (ER –ve (<1%), PR –ve (<1%) and Her2/neu was considered negative if it scored 0 or 1, if it scored 2 complementary DISH test was done and considered negative if Her2/CEP17 ratio < 2 and the average Her2 copy number < 4 signals/cell).

Exclusion criteria: 1) patients who didn't receive chemotherapy, 2) in situ carcinoma without invasive component, 3) positive or unknown receptor status, 4) male patients, and 5) incomplete file data.

We collected data regarding patient, tumor, and treatment characteristics as well as follow-up data. Patient characteristics included: age at diagnosis, menopausal status, and body mass index. Tumor characteristics included: tumor size (cm), number of dissected and involved lymph nodes, clinical and pathologic stage grouping, histological type, tumor grade, presence or absence of lymphatic vascular invasion (LVI) and Ki-67 (%).

Treatment characteristics included: type of surgery either modified radical mastectomy or breast conservative surgery, axillary dissection, or sentinel lymph node biopsy.

Chemotherapy: adjuvant or neo adjuvant, type and number of chemotherapy cycles. Radiation therapy: received or not, dose and fractionation.

In addition, follow-up data regarding the failure pattern, incidence, timing, and sites whether local (breast or chest wall), regional (axillary, supraclavicular or internal mammary lymph node), or distant failure.

3. Data Analysis

Data was analyzed using IBM SPSS statistics (version 22). Data was presented as number and percentage for qualitative variables, median and interquartile range (IQR) for quantitative variables. Comparison between groups was done using chi-square test, Mann whitney test, Krauskal wallis tests according to the type of variable and number of groups. Multivariate logistic regression analysis was conducted to verify predictors of relapse however multivariate linear regression analysis was done for predictors of the overall survival. Kaplan Meir analysis was conducted to illustrate disease free survival and factors associated with it using Log-rank test. Significance was judged at 5% level of significance.

OS was calculated as the time from the initial pathological diagnosis to death from any cause or lost follow up. DFS was defined as the period from the initial pathological diagnosis to recurrence, metastasis, or breast cancer related death.

4. Results

A total of 965 breast cancer cases were identified between 2013 and 2017, 147 of

them had TNBC with an incidence of 15.2%. 19 patients were excluded due to incomplete file data and a total of 128 TNBC patients were analyzed. The tumors', patients' and treatment characteristics are presented in Table 1. The median age of patients at diagnosis was 43 years (range: 25 - 79 years). 71.1% of study patients were premenopausal, 67/128 (52.3%) were overweight and 51/128 (39.8%) were obese.

Table 1. Patients, tumor and treatment characteristics.

	Tumor stage	Non metastatic tumor n = 108 (84.5%)	Metastatic tumor at presentation n = 20 (15.5%)	Total (n = 128) (%)
Age in years	less than 40	34 (31.5)	8 (40.0)	42 (32.8)
	40 to 60	63 (58.3)	12 (60.0)	75 (58.6)
	More than 60	11 (10.2)	0	11 (8.6)
Menopausal s	Premenopausal	73 (67.6)	18 (90.0)	91 (71.1)
	Postmenopausal	35 (32.4)	2 (10.0)	37 (28.9)
BMI	Less than 25	8 (7.4)	2 (10.0)	10 (7.8)
	25 to <30	57 (52.8)	10 (50.0)	67 (52.3)
	30 or more	43 (39.8)	8 (40.0)	51 (39.8)
Tumor size	T1	10 (9.3)	0	10 (7.8)
	T2	54 (50.0)	5 (25.0)	59 (46.1)
	T3	35 (32.4)	6 (30.0)	41 (32.0)
	T4	9 (8.3)	9 (45.0)	18 (14.1)
Lymph node	N0	20 (18.5)	0	23 (18.1)
	N1	55 (50.9)	14 (73.7)	67 (52.8)
	N2	30 (27.8)	5 (26.3)	34 (26.7)
	N3	3 (2.8)	1 (5.0)	4 (3.1)
Stage	I	7 (5.5%)	IV = 20 (15.5%)	
	II	44 (34.4%)		
	II	57 (44.6%)		
LVI	Yes	104 (69.3)	20 (100)	124 (96.9)
	No	4 (3.7)	0	4 (3.1)
K1 67	Not done	21 (19.4)	4 (20.0)	25 (19.5)
	less than 20	44 (50.6)	2 (12.5)	46 (35.9)
	More than 20	43 (49.4)	14 (87.5)	57 (44.6)
Tumor grade	I	1 (0.9)	0	1 (0.8)
	II	41 (38.0)	7 (35.0)	48 (37.5)
	III	66 (61.1)	13 (65.0)	79 (61.7)
Histopathology	IDC	94 (87.1)	13 (65.0)	107 (83.6)
	ILC	8 (7.4)	1 (5.0)	9 (7.0)
	Others	6 (5.5)	6 (30.0)	12 (9.4)

Continued

Surgery	MRM	71 (65.7)	0	
	BCS	37 (34.3)	0	
	ALND	100 (92.6)	0	
	SLN	8 (7.4)	0	
Neo adjuvant chemotherapy 34/108 (31.5%)	CR	6 (17.6%)		
	PR	24 (70.6%)		
	No response	4 (11.8%)		
Types of chemotherapy	FAC	14 (12.9%)		14 (11%)
	AC and Taxol	94 (87%)	20 (100%)	114 (89%)
	Platinum/Gem	0 (0%)	20 (100%)	20 (15.6%)
	Taxotere	0 (0%)	12 (60%)	
	Xeloda	0 (0%)	6 (30%)	
Adjuvant XRT	NO	10 (9.3%)	20 (100%)	30 (23.4%)
	conventional	56 (51.8%)	0	56 (43.8%)
	hypofractionation	42 (38.9%)	0	42 (32.8%)

BMI: body mass index, LVI: lymphovascular invasion, XRT: external beam radiotherapy, MRM: modified radical mastectomy, BCS: breast conservative surgery, ALND: axillary lymph node dissection, SLN: sentinel lymph node, CR: complete response, PR: partial response.

The majority of patients were diagnosed with stage II & III (34.1% & 44.2%, respectively) and 20 patients (15.5%) had stage IV disease at initial presentation. 18.1%, 52.8%, 26.8%, and 2.4% of patients had N0, N1, N2, and N3 disease, respectively. Most of the patients had T2 and T3 tumors (46.1% and 32%). The most common histological type was infiltrating duct carcinoma (83.6%). Lymphatic vascular invasion and grade III were identified 96.9% and 61.7% of patients respectively.

74/108 (68.5%) of patients underwent upfront surgery followed by adjuvant chemotherapy compared to 34/108 (31.5%) of patients who received neoadjuvant chemotherapy. 6/34 patients (17.7%) achieved pCR to neoadjuvant chemotherapy. 71/108 (65.7%) of patients had modified radical mastectomy, while breast conservative surgery was done in 37/108 (34.3%) patients, 92.6% had axillary lymph node dissection and no surgery for those with stage IV disease (15.6%). AC followed by Taxol received in 92.6% (100/108) patients. Adjuvant radiotherapy was administered to 98/108 (90.7%) patients (51.8% conventional and 38.9% hypofractionation and 9.3% no radiotherapy). Regarding Ki67, 25/128 (19.5%) of patients had unknown Ki67, 46/128 (35.9%) patients had Ki67 score ≤ 20 compared to 57/128 (44.6%) of patients with score > 20.

4.1. Pattern of Failure and Survival Analysis

For non-metastatic patients (n = 108), the median duration of follow up was 4.5 years (range: 2.1 - 8.2 years). 23/108 (21.3%) patients developed relapse and died

during follow up (21.3%). In addition, 10 patients (9.3%) lost follow up. 91.3% (21/23) of recurrences developed 6 - 24 months after diagnosis, 8.7% patients (2/23) relapsed between 2 - 2.5 years, no relapses occurred after 2.5 years with a median time for recurrence of 11 months.

The estimated 3-year DFS and OS were 73.2% and 75%, respectively. The 5-year DFS and OS were 69.5% and 70%, respectively (Figure 1 and Figure 2). The median DFS was 5.3 years, 3.2 years, 3.0 years for stages I, II and III, respectively (P = 0.001) (Table 2).

Most of relapsed patients 82.6% (19/23) had visceral metastasis with or without bone metastasis, 13% (3/23) of patients developed bone metastasis, 21.7% (5/23) had brain metastasis and 13% (3/23) developed locoregional recurrences.

For metastatic patients at presentation (n = 20), the median follow-up duration was 1.6 years (range: 1.4 - 2.2). 85% of patients (17/20) had visceral metastasis with or without bone metastasis, 25% (5/20) had brain metastasis and 10% (2/20) had bone metastasis. All those patients died or lost follow up, the median progression free survival (m PFS) was 7 months (range: 3 - 10 months), and the median OS was 1.6 years. The 3-year OS was 0% (Figure 2).

For the whole group of metastatic patients (n = 43), lungs were the commonest site of distant metastasis detected in 38/43 (88.3%) patients, followed by liver and brain metastases in 24/43 (55.8%) and 10/43 (23.2%) patients, respectively. Bone metastasis developed in 13.9% (6/43) patients and loco regional recurrence occurred in 7% (3/43) patients. The median PFS and OS were 7.4 months and 16 months, respectively.

For the whole group of patients (n = 128), the 3 and 5-year OS were 63.3% and 58.6%, respectively.

4.2. Predictors of Relapse among Non-Metastatic Studied Patients (n = 108)

On univariate analysis, there was a significantly higher probability of relapse in patients with large tumor size, positive lymph node and high Ki67. The risk of relapse for T4, T3, T2 and T1 were 66.75%, 22.9%, 16.7%, and 0%, respectively (p value = 0.002). Regarding lymph node metastasis, the risk of relapse was 4.3%, 15.1%, 37.9% and 100% for N0, N1, N2 and N3, respectively (p value ≤ 0/001). In addition, 18/57 (31.6%) patients with high Ki67 > 20 relapsed compared to 5/46 (10.8%) patients with Ki67 ≤ 20 (p value = 0.007). While there were no statistically significant differences in the risk of relapse regarding age groups, menopausal state, BMI, tumor grade, LVI, tumor histology, type of surgery (MRM or BCS), radiotherapy fractionation (conventional or hypofractionation), neoadjuvant or adjuvant chemotherapy despite our finding that none of the 6 patients who achieved pCR after neo adjuvant chemotherapy experienced relapse during the follow up period (Table 3).

Multivariate analysis revealed that only large tumor size and high node positivity were significantly associated with higher probability for relapse (p value = 0.022 and 0.038, respectively) (Table 4).

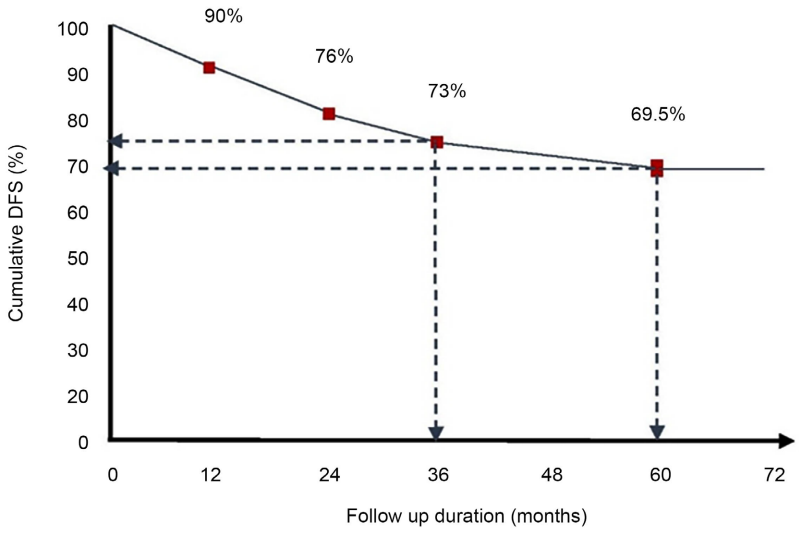

Figure 1. Kaplan Meier curve for disease free survival among studied non metastatic triple negative breast cancer patients.

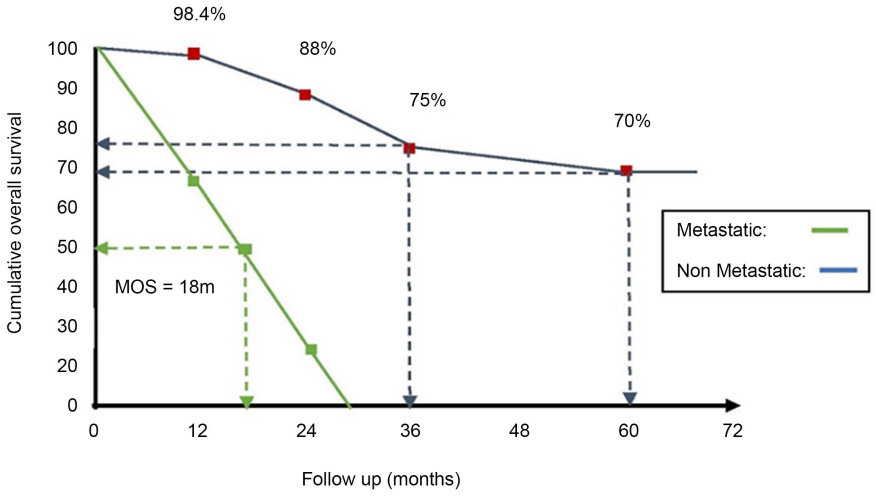

Figure 2. Kaplan Meier curve for overall survival among metastatic and nonmetastatic triple negative breast cancer patients.

Table 2. Disease free and overall survival according to tumor stage.

	Stage I n = 7	Stage II n = 44	Stage III n = 57	Stage IV n = 20	Total (n = 128)	p value
OS						
Min-max	3.4 - 8.2	1.5 - 6	0.5 - 5.5	0.7 - 1.5	1 - 8	<0.005*
Median (IQR)	5.3 (3.4 - 5.3)	3.4 (2.7 - 4)	3.2 (1.6 - 4)	1.5 (0.75 - 1)	3.4 (2)	
Three-year survival	8 (100%)	35 (79.5%)	42 (73.7%)	0 (0))	85 (65.9)	<0.001*
DFS (n = 108) *						
Min-max	3.4 - 8.2	1.5 - 6	0.5 - 5.5			0.001*
Median (IQR)	5.3 (4.1 - 7.1)	3.2 (2.8 - 4.0)	3.0 (1.8 - 4)			

OS: Overall survival, DFS: Disease free survival.

Table 3. Factors associated with higher probability of relapse among non-metastatic patients.

		No relapse (n = 85) (%)	Relapse (n = 23) (%)	P value
Age	<40y	28 (82.4)	6 (17.6)	0.391
	40 to 60y	47 (74.6)	16 (25.4)	
	>60y	10 (90.9)	1 (9.1)	
Menopausal	Premenopausal	58 (79.5)	15 (20.5)	0.784
	Postmenopausal	27 (77.1)	8 (22.9)	
BMI	<25	7 (87.5)	1 (12.5)	0.798
	25 to ≤30	44 (77.2)	13 (22.8)	
	>30	34 (79.7)	9 (20.9)	
Tumor size	T1	10 (100)	0 (0)	0.002*
	T2	45 (83.3)	9 (16.7)	
	T3	27 (77.1)	8 (22.9)	
	T4	3 (33.3)	6 (66.7)	
LN	N0	19 (95.0)	1 (5.0)	<0.001*
	N1	48 (87.3)	7 (12.7)	
	N2	18 (60.0)	12 (40.0)	
	N3	0 (0)	3 (100)	
LVI	Yes	82 (78.8)	22 (21.2)	1.000
	No	3 (75.0)	1 (25.0)	
K167 (n = 87)	≤20	40 (90.9)	4 (9.14)	0.007*
	>20	29 (67.4)	14 (32.6)	
Tumor grade (n = 107)	II	33 (80.5)	8 (19.5)	0.694
	III	51 (77.3)	15 (22.7)	
pathology (n = 108)	IDC	73 (77.7)	21 (22.3)	1.000
	ILC	7 (87.5)	1 (12.5)	
	other	5 (83.4)	1 (16.6)	
Chemotherapy	FAC	10 (71.5)	4 (28.5)	0.629
	AC and Taxol	75 (79.8)	19 (20.2)	
	Neoadjuvant	29 (85.3)	5 (14.7)	0.391
	Adjuvant	56 (75.7)	18 (24.3)	
Radiotherapy	conventional	44 (78.6)	12 (22.4)	1.000
	Hypofractionation	32 (76.2)	10 (23.8)	
	No	9 (90.0)	1 (10.0)	

BMS: body mass index, LVI: lymphovascular invasion, IDC: infiltrating duct carcinoma, ILC: infiltrating lobular carcinoma.

Table 4. Multivariate logistic regression analysis for predictors of relapse among studied patients (n = 108).

	B	P value	Adjusted Odds ratio	95% C.I. Odds ratio	
				Lower	Upper
KI67 (1)	−0.850	0.256			
T	1.189	0.022	3.282	1.187	9.074
N	1.177	0.038	3.244	1.068	9.852

4.3. Predictors of OS among Studied Patients (n = 128)

Stage was the only significant predictor for overall survival. The 3-year overall survival was 100%, 79.5%, 73.7% and 0% for stages I, II, III and IV, respectively ($P \leq 0.001$). The median OS was 5.3y, 3.4y, 3.2y and 1.5y for stages I, II, III and IV, respectively ($p \leq 0.005$).

5. Discussion

TNBC is considered an aggressive molecular subtype with rapid tumor recurrence, distant metastasis, and lack of targeted therapy [12]. We hypothesized that understanding the patterns of failure may help in decision of future treatment and follow up directions based upon the most likely sites of failure.

In this study, we found that 15.2% of our patients were TNBC. Worldwide TNBC constitute about 10% - 20% of all breast cancer cases, but some studies showed a higher prevalence in India and Ghana and only one study in Iran reported a lower prevalence [13] [14] [15].

Several studies had confirmed that those patients generally experienced an aggressive clinical course, with increased risk of disease progression and worse OS despite initial response to chemotherapy [16]. This poor prognosis may be due to the aggressive behavior and/or lack of the targeted therapy [17].

This was in concordance with our study as the majority of our patients were diagnosed with stage II & III (34.1% and 44.2%) and 20 patients (15.5%) had stage IV at initial presentation. In addition, grade III was identified in 61.7% patients, LVI was detected in 96.7% patients, high Ki 67 > 20 in 44.6%, and positive LN metastasis in 82.6% patients.

21.3% (23/108) patients developed relapse, all of recurrences developed within 2.5 years from diagnosis which is consistent with literature data where most of relapses occur during the first 3 years. On the contrary among non-TNBC patients, the recurrence risk was mostly constant over the period of the follow up [18] (Stuart *et al.*, 2019).

Positive lymph node metastasis, high Ki67 > 20 and large tumor size were significantly associated with higher risk of relapse (p value ≤ 0.001, 0.007 and 0.002, respectively). The estimated 3 and 5-year DFS were 73.2%, 69.5% respectively, while 3 and 5-year OS were 75%, 69.5%, respectively. For metastatic patients, the median OS was 1.6 years, and the 3-year OS was 0%. The 3-year OS for the whole patients was 63.3%.

Ovcaricek *et al.*, evaluated the prognostic factors and survival in triple negative breast cancer patients. The 5-year DFS and OS were 68.2% and 74.5%, respectively. High recurrence rate was observed in the first 3 years following the diagnosis with clear decline over the next 3 years. In the univariate analysis age (<65y versus >65y), nodal status, tumor size (>2 cm versus <2 cm) and LVI were found to have a significant impact on DFS as well as on OS. In the multivariate analysis age (HR = 1.79; 95% CI = 1.14 - 2.82; p value = 0.012) and nodal status (HR = 2.71; 95% CI = 1.64 - 4.46; p value < 0.001) retained their independent prognostic value [19].

Regarding loco regional recurrence rates in TNBC following either breast conserving therapy (BCT) or mastectomy. Some reports showed low incidence of 3% - 8%, other series have shown higher rates in the range of 10% - 20% [20] [21] [22] [23] [24]. Our results showed low incidence of locoregional recurrence of 2.8% (3/108). However, locoregional recurrences are usually under reported when distant metastases are present.

Xiuzhi Zhu *et al.*, (2020) evaluated the prognostic and predictive potential of Ki-67 in triple-negative breast cancer. OS and DFS were compared between the two groups (low and high Ki 67). They concluded that, the most relevant cutoff value for Ki-67 was 30% (p = 0.008). At the cutoff point of 30%, worse DFS and OS were observed in the Ki-67 high group [25].

Several studies reported lung metastasis as the most frequent site of distant failure (18.5%), higher rate of brain metastasis (10.9%) and lower incidence of bone only involvement (9.3%) [26] [27]. Similarly, our data showed that lungs were the most distant failure site representing 29.7% (38/128) followed by liver metastasis 18.7% (24/128), brain metastasis 7.8% (10/128), and bone involvement 4.7% (6/128).

Neoadjuvant chemotherapy is considered the standard of care for TNBC patients (foulks *et al.*, 2010) [28] with tumor size ≥ 2 cm or positive lymph node metastasis and pCR is considered as a surrogate for overall survival [28] [29]. If pCR was achieved, patients with TNBC have similar survival as non-TNBC (P = 0.24). In contrast, patients with residual disease have worse OS compared with non-TNBC (P < 0.0001) [30].

In our study only 31.5% patients received neoadjuvant chemotherapy compared to 69.5% patients who received adjuvant treatment. Only 17.6% achieved pCR which is lower than most of published studies (pCR 22% - 40%) [30]. The difference could be explained as some of our patients had surgery after only 4 cycles of chemotherapy and didn't complete the whole course before surgery, others didn't receive taxanes and non-received platinum agents, and most of patients who received neo adjuvant treatment were locally advanced.

In the Keynote 522 study, adding pembrolizumab to chemotherapy in the neoadjuvant/adjuvant setting statistically improved the pCR, 64.8% (95% CI, 59.9 to 69.5) in the pembrolizumab-chemotherapy group and 51.2% (95% CI, 44.1 to 58.3) in the placebo-chemotherapy group (estimated treatment difference, 13.6 percentage points; 95% CI, 5.4 to 21.8; P < 0.001) and the risk of death

or disease progression reduced by 37% with pembrolizumab (HR, 0.63; 95% CI, 0.43 - 0.93) [31].

In the SYSUCC phase III study, metronomic capcitabine maintenance (650 mg/m^2 twice daily continuously for one year) after standard adjuvant treatment for TNBC improved the 5-year DFS (85% vs. 76%, HR, 0.56; 95% CI, 0.37 to 0.90; p value = 0.016). However, 5-year OS was not significantly different between two groups (85% vs. 81%, HR, 0.74; 95% CI, 0.47 to 1.18; p = 0.203) [32].

In the metastatic settings, Final analysis of IMpassion130 (Iwata *et al.*, 2020) demonstrated that, after a median follow-up of 18.8 months, the median OS was 25.4 months with atezolizumab/nab-paclitaxel vs 17.9 months with placebo/nab-paclitaxel in patients with PD-L1–positive TNBC (HR, 0.67; 95% CI, 0.53 - 0.86). The 3-year OS rates were 36% vs 22%, respectively [33].

Also, pembrolizumab or placebo in combination with different chemotherapy treatments (keynote 355) significantly improved PFS in patients with CPS ≥ 10 1st line metastatic setting. Median PFS was 9.7 months (95% CI: 7.6, 11.3) in the pembrolizumab plus chemotherapy arm and 5.6 months (95% CI: 5.3, 7.5) in the placebo arm plus chemotherapy (HR 0.65; 95% CI: 0.49, 0.86; one-sided p value = 0.0012) [34].

Unfortiounatly, none of our patients received adjuvant metronomic capcitabine, atezolizumab/nab-paclitaxel nor pembrolizumab in neoadjuvant, adjuvant, or metastatic settings.

Approximately, 20% - 30% of TNBC patients had BRCA mutations which may be translated into benefit from platinum agents or PARP inhibitors in metastatic and adjuvant/ neoadjuvant settings. None of our patients had been evaluated for this mutation [35] [36] [37].

Limitations of this study were the relatively small number of TNBC patients included in the analysis due to exclusion of patients with incomplete file data, the retrospective study design, and the different treatment protocols in each center.

6. Conclusions

This study confirms the aggressive nature of TNBC that warrants close follow-up for non-metastatic patients during the first 2 - 3 years of diagnosis especially for those with large tumor size and positive lymph nodes. Maintenance metronomic capecitabine, neoadjuvant/adjuvant immunotherapy could be beneficial for non-metastatic patients.

Lungs and brain were the most common sites of distant failure with poor survival that necessitates administration of the new molecular biomarkers testing (BRCA1, 2 mutations, PD-L1 expression and microsatellite instability) for better patients' selection for novel targeted therapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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