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Expression of p53 and Ki67 in the Patients with Triple Negative Breast Cancer and Invasive Ductal Carcinoma

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Abstract **Background:** Breast cancer is the most common cancer (27% of all cancers) and common cause of death (16%) which occurs due to cancers among women, either in developed or developing. The aim of study is to evaluated clinicopathology figures especially Tumor markers such as Ki6 and p53 in the patients with TNBC. **Materials and Methods:** Between of 2005 to 2014, 50 patients with triple negative breast cancer and invasive ductal carcinoma referred to our Clinic. Age, sex, metastasis, Ki67, p53, laterality, treatment options and The OS were checked in the patients. **Results:** The mean age for the patients at diagnosis was 51.04, 100% female. We divided the patients based on Ki67 to two groups, 24 patients (48%) with low Ki67 (<10%) and 26 patients (52%) with high Ki67 (≥10%). Also, Seventeen patients (34%) had P53 positive. There were statistically significant correlation between of Ki-67 with p53 and laterality (P<0.05). The OS for all of patients that the mean survival for them was 39.4 months and survival rate was 67.5%. **Conclusions:** The OS in our patients was lower than other studies. Also, there is a direct correlation between Ki67 and p53 in TNBC patients that for better conclusion it needs more studies.

Keywords: *Ki67, overall survival, P53, TNBC*

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1. Introduction

Breast cancer (BC) is a heterogeneous disease and is currently divided into subtypes in accordance with the status of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) [1]. Besides having different molecular pathology and clinical manifestation, different subtypes have different response to treatments. Triple-negative breast cancer (TNBC) characterized by the absence of ER and PR expression and HER2 overexpression is mostly basal-like subgroup of breast cancers and accounts for 10%–20% of all breast cancers [2]. TNBC tumors are associated with significantly higher expression of Ki67 and p53 compared to non-TN tumors [3].

The proliferation marker Ki-67 has repeatedly been confirmed as an independent predictive and prognostic factor in early BC [4]. BC with high Ki-67 expression responds better to chemotherapy [5], but is associated with poor prognosis [6]. Also, there is significant evidence implicating that *p53* mutation as a driver plays an important role in tumorigenesis and progression of TNBC [7]. P53 mutations are more frequently observed in TNBCs compared with ER-positive breast cancers. The presence of a p53 mutation is associated with poorer prognosis in TNBC patients. The status of p53 protein expression divides TNBCs into two biologically distinct subgroups (p53-positive vs. p53-negative); p53-positive tumors have more aggressive behavior [8].

The aim of study is to evaluated clinicopathology figures especially Tumor markers such as Ki6 and p53 in the patients with TNBC.

2. Materials and Methods

2.1. Patients

Between of 2005 to 2014, 50 patients with TNBC and invasive ductal carcinoma referred to our Clinic. We surveyed age, sex, metastasis, Ki67, p53, laterality, treatment options and The OS in the patients. ER and PR positivity was defined as ≥10% positive tumor cells with nuclear staining. HER2 positivity was defined as either HER2 gene amplification by fluorescent *in situ* hybridization or scored as 3+ by IHC. In case of HER2 2(+), fluorescent *in situ* hybridization was performed to determine HER2 positivity. TNBC was defined as ER (-), PR(-), and HER2(-).

2.2. Statistics

The OS for Ki67 was plotted with GraphPad Prism 5 software and correlation between of variables was done with IBM SPSS version 19. Comparison of Ki67 with age by T-test and Ki67 with p53 or laterality, age, metastasis, histological grade, tumor size and lymph node metastasis by Chi-Square Test. P≤0.05 was statistically significant.

3. Results

The mean age for the patients at diagnosis was 51.04(±13.08), 100% female. Of 50 patients, 18 patients (36%) had metastasis and 16 patients (32%) had right breast involvement (Table 1). We divided the patients based on Ki67 to two groups, 24 patients (48%) with low Ki67 (<10%) and 26 patients (52%) with high Ki67 (≥10%). Also, Seventeen patients (34%) had P53 positive. All of the patients were treated with chemotherapy, 17 patients (34%) with tamoxifen and 29 patients (58%) with radiation.

A number of characteristics for the patients have been shown in Table 2 that we compared them with Ki-67. There were no significant correlation between of Ki-67 with age, metastasis, histological grade, tumor size and lymph node metastasis in the patients (P>0.05). There were statistically significant correlation between of Ki-67 with p53 and laterality (P<0.05) that more patients with p53 positive had high Ki-67 and more patients with low Ki-67 had p53 negative and also more patients with right breast involvement had high Ki-67 and more patients with low Ki-67 had left breast involvement. Therefore, p53 and laterality proportionally associated with the level of Ki-67.

Table 1. Characteristics for the patients with triple negative breast cancer and invasive ductal carcinoma (n=50)

Characteristics	n(%)	Mean±SD	Range
Age(year)		51.04±13.08	28-82
Sex			
Female	50(100)		
Male	0(0)		
Metastasis			
Positive	18(36)		
Negative	32(64)		
Ki67			
<10%*	24(48)		
≥10%**	26(52)		
P53			
Positive	17(34)		
Negative	33(66)		
Laterality			
Right Breast	16(32)		
Left Breast	34(68)		
Chemotherapy			
Positive	50(100)		
Negative	0(0)		
Tamoxifen			
Positive	17(34)		
Negative	33(66)		
Radiation			
Positive	29(58)		
Negative	21(42)		

* Low Ki67 ** High Ki67

Table 2. Baseline characteristics of 50 patients with triple negative breast cancer and invasive ductal carcinoma

Characteristics	Low Ki67	High Ki67#	Total	P-value
Age(Mean±SD)	50.0±12.8	51.9±13.5		P=0.6*
Metastasis, n(%)				
Positive	11(45.8)	7(26.9)	18(36)	P=0.1**
Negative	13(54.2)	19(73.1)	32(64)	
p53, n(%)				
Positive	5(20.8)	12(46.2)	17(34)	P=0.05**
Negative	19(79.2)	14(53.8)	33(66)	
Laterality, n(%)				
Right Breast	4(16.7)	12(46.2)	16(32)	P=0.02**
Left Breast	20(83.3)	14(53.8)	34(68)	
Histological Grade, n(%)				
Grade 1	1(4.2)	2(7.7)	3(6)	P=0.8***
Grade 2	13(54.2)	14(53.8)	27(54)	
Grade 3	10(41.7)	10(38.5)	20(40)	
Tumor Size, n(%)				
0.1-2	7(29.2)	4(15.4)	11(22)	P=0.2***
2.1-5	16(66.7)	17(65.4)	33(66)	
>5	1(4.2)	5(19.2)	6(12)	
Lymph Node Metastasis, n(%)				
Positive	14(58.3)	15(57.7)	29(58)	P=0.6**
Negative	10(41.7)	11(42.3)	21(42)	

#High Ki67 expression was defined as ≥10%, * T-test ** Chi-Square (Fisher's Exact Test)
*** Chi-Square (Pearson Exact Test)

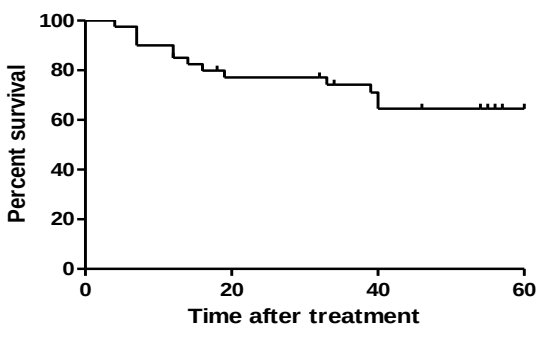

Figure 1. The 5-year overall survival for the patients with triple negative breast cancer and invasive ductal carcinoma

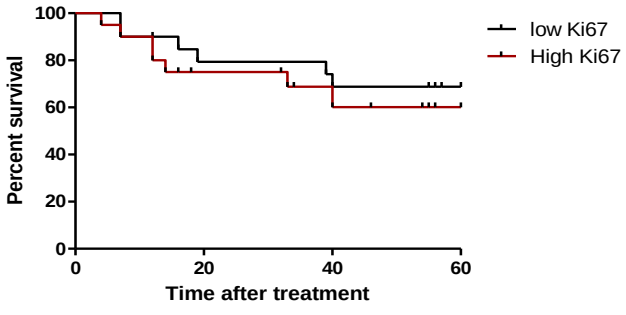

Figure 2. The 5-year overall survival for the patients with triple negative breast cancer and invasive ductal carcinoma

The Figure 1 shows the OS for all of patients that the mean survival for them was 39.4 months and survival rate was 67.5%. The Figure 2 shows the 5-year OS for the patients with low Ki67 compared to high Ki67. Survival rate for the patients with low Ki67 was 70% and mean survival was 44.8 months, but survival rate for the patients with high Ki67 was 65% and mean survival was 34.05 months. This difference between two groups was no statistically significant (p>0.05).

4. Discussion

BC is the most common cancer (27% of all cancers) and common cause of death (16%) which occurs due to cancers among women, either in developed or developing [9]. In Asia the maximum incidence is in 40 – 50 age groups. In Contrast, in western countries the increase in incidence continues as the age increases [10]. A study [11] reported that Mean age of diagnosis of TNBC was found to be 46.26 years and other study [12] showed that Median age was 50 years ranging from 27 to 67 years. Lakshmaiah KC et al. [13] reported Median age of presentation for the patients was 44.5 years. In our study, the mean age was 51.04 years and range of 28-82 years. Almost all of studies have near conclusions.

Ki67 is a nuclear antigen, which exists in proliferative cells. A number of studies have shown that the immune response of Ki67 is closely associated with the cell cycle**.** Furthermore, Ki67 may predict the pathological remission rate in BC patients following neoadjuvant chemotherapy, as an increased Ki67 level following neoadjuvant chemotherapy indicates a poor prognosis [14]. Li H et al. [15] concluded that overexpression of Ki67 expression may be an indicator of poor prognosis in TNBC and Ki67 expression was not associated with the age and also in our study, there was no correlation between of Ki67 and age.

Keam et al. [16] reported that there was no significant correlation between of Ki67 and p53, but in this study, there is a significant correlation that more patients with p53 positive had high Ki67 and more patients with low Ki67 had p53 negative and also they showed that grade III was more in the patients that In our study, grade II was more and there was no significant correlation between of Ki67 and grade and our study confirms it.

Chu et al. [17] reported that the 5-year OS was 77% for African-American women and 72% for Caucasian women but in our patents in West Iran (West Asia) is 67.5%. In other two studies [18,19] were written tat the 5-year overall survival rate for all BC subtypes is approximately 89% and this rate drops precipitously for patients with TNBC (77% to 80%). The OS in our patients is lower than other studies that probably ethnicity can affect on the OS for TNBC patients.

Keam et al. [16] showed that high Ki67 expression was significantly associated with poor OS in TNBC that our study confirms it but it isn't statistically significant (P>0.05).

There were statistically significant correlation between of Ki67 with p53 and laterality in this study that in other studies this correlation has not been checked.

5. Conclusions

The OS in our patients was lower than other studies. Also, there is a direct correlation between Ki67 and p53 in TNBC patients that for better conclusion it needs more studies.

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