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

Maha Lotfy Zamzam[1] and Heba Mohamed Wagih[2]

[1]Clinical Oncology & Nuclear Medicine Department, Faculty of Medicine, Suez Canal University, Egypt.
[2]Pathology 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.

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

1. Introduction:

Worldwide, breast cancer is the most common malignant tumour 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 over expressing and basal-like tumors (3). Basal-like tumors possesses 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 clincopathological 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%
Residence		
Ismailia	112	77.8%
Suez	9	6.3%
North Sinai	16	11%
Port Said	7	4.9%
Occupation		
Housewife	65	45.1%
Employee	45	31.3%
Retired	34	23.6%
Ecog Performance Status		
0	42	29.2%
1	102	70.8%
Marital Status		
Not married	17	11.8%
Married	127	88.2%
Use of contraceptive pills		
Positive	65	45.1%
Negative	79	54.9%
Menopause		
Premenopausal	59	41%
Postmenopausal	85	59 %
Age at menarche		
Before 11 years	2	1.4 %
After 11 years	142	98.6 %
Smoking history		
Smoker	10	7 %
Non-smoker	134	93 %
Family History		
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

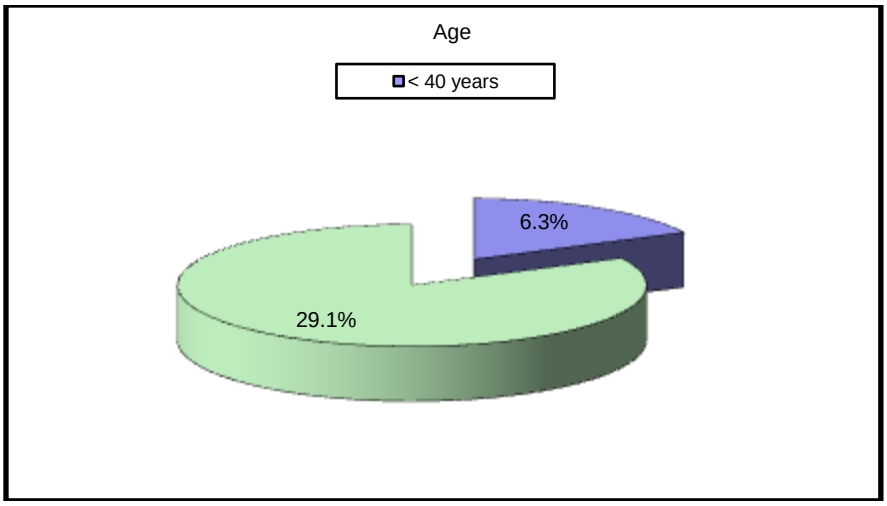

Figure (1): Age distribution

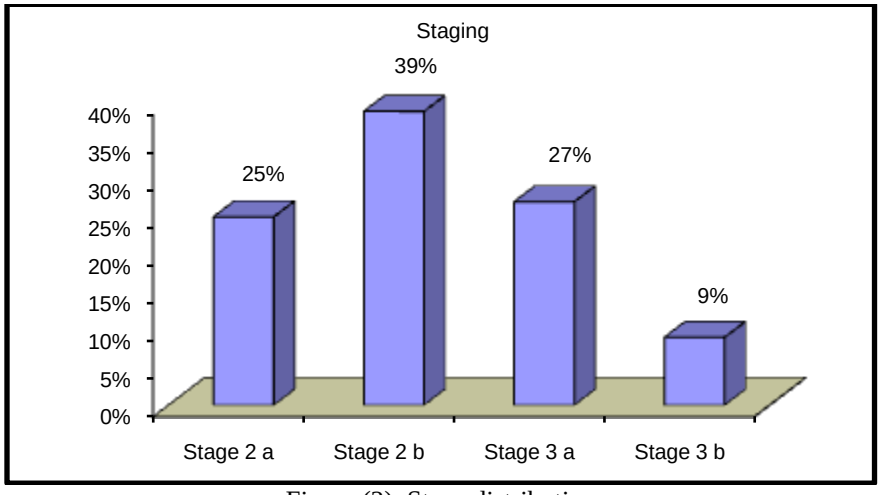

Figure (2): Stage distribution

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 Hashmietal 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 canceris low in young age and this is due to the healthy estrogen surveillance in many of young women. Thus, is 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 al20% (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 colleages where the majority of cases (55.7%) were post – menopousal (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 agree 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 T_2 (61.8%), Followed by T_3 (29.2%), and T_4 (4%). No one represented T1.

This is comparable to Gado et al whom study documented predominance of T_2 tumors (28). Although Zakaria et al reported that most of cases of their study represented T_2 (678%) but this was followed by T_1 (15.3%), T_3 (10.2%), and T_4 (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 2 a (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 Radhaknishnan 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 strandard 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.

References

1. Ferlay J., Soerjomataram I., Di Kshit R., et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in Globocan 2012. International Journal of Cancer, 136 (5), 2015.
2. Parkin DM, Bray f, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin. 2005 Mar-Apr; 55(2):74-108.
3. Perou C.M., Sorlie T., Eisen M.B., et al. Molecular portraits of human breast tumours. Nature, 406 (6797):747-52, 2000.
4. Thike AA, Cheok Py, Jara-Lazaro AR, et al. Triple – negative breast cancer: clinicopathological characteristics and relationship with basal – like breast cancer. Mod pathol. 2010:23 (1):123-33.
5. Dent R, Trudeau M, Pritchard KI, et al. Triple negative breast cancer: clinical features and patterns of recurrence. Clin. Cancer Res. 2007, 13;4429-34.
6. Rakha EA, El-Sayed M, Green A, et al. prognostic markers in triple-negative breast cancer. Cancer. 2007; 109:25-32.
7. Mohamed G. Breast cancer In: Mokhtar, N., Salama, A. Badawy, O., Khorshed, E., Abdelazim, H.: Cancer pathology registry 2000-2011; chapter 2, pp. 8-31,2016.
8. Ghosn M, Hajj C, Kattan J, et al. Triple-negative breast cancer in Lebanon a case series. Oncologist. 2011; 16:1552-6.
9. Heitz F, Harter P, Traut A, et al. Cerebral metastases (CM) in breast cancer (BC) with focus on triple negative tumors. J clinOncol. 2008; 26 (15 suppl) (abstract 1010).
10. Line NU, vanderplas A, Hughes ME, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network, Cancer. 2012 (PMC Free article) (Pub Med).
11. 11-Liedke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J clinOncol. 2008; 26:1275-8.
12. Rais G, Raissouni S, Aitelhaj M, et al; Triple – negative breast cancer in women: clinicopathologic and therapeutic study at the National Institute of Oncology BMC Women's Health. 2012, 12:35.
13. Abulkair O, Moghraby J, Badri M, et al, Clinicopathologic features and prognosis of triple negative breast cancer in patients 40 years of age and younger in Saudi Arabia. Hematol Oncol Stem Cell Ther. 2012; 5(2);101-6.
14. Hamm C, El-Masri M, Poliquin G, et al. A single – center chart review exploring the adjusted association between breast cancer phenotype and prognosis. Curroncol. 2011; 18:191-6.
15. Kaplan HG, Malmgren JA. Impact of triple negative phenotype on breast cancer prognosis. Breast J. 2008; 14:456-63.
16. Lee JA, Kim KI, Bae JM, et al. Korean Breast Cancer Society. Triple negative breast cancer in Korea-distinct biology with different impact of prognostic factors on survival. Breast Cancer Res Treat. 2010;123:177-87.
17. Mandal R, Achoryya S, Mollah A, et al: Analysis of Patterns of Recurrence & Survival in Triple Negative Breast cancer patients in A Rural Based Medical College Hospital of west Bengal, India:

A Retrospective Study 2017. IOSR Journal of Denal and Medical Sciences (IOSR – JDMS) pp 36-41.
18. Hashmi A, Edhi M, Naqvi H, et al: Clinicopathologic features of triple negative breast cancers: an experience from Pakistan (2014). Diagnostic Pathology 9:43.
19. Cheng HT, Huang T, Wang W, et al: clinico pathological Features of breast cancer with different molecular subtypes in Chinese women. J Huazhong Univ, Sci Technolog Med Sci. 2013, 33(1); 117-121.10. 1007/s 11596-013 – 1082 – 2.
20. Carey LA, Perou CM, Livasyc A, et al: Race, breast cancer subtypes, and survival in the Carolina breast cancer study. JAMA. 2006, 295(21):2492-2502.10.1001/Jama. 295. 21.2492.
21. Souad H, Zahia F, Abdelhak L, et al (2018): Descriptive Study of triple negative breast cancer in Eastern Algeria. Pan African Medical Journal, 29:45 doi:10. 11604.
22. Tan GH, Taib NA, choowy, et al. Clinical characteristics of Triple negative Breast Cancer: Experience in an Asian Developing Country Asian Pacific J Cancer Prev, 2009,10, 395 – 398.
23. Bauer KR, Brown M, Cress RD, et al: Descriptive analysis of estrogen receptor (ER) – negative, progesterone receptor (PR) – negative, and HER2 negative invasive breast cancer, the so-called triple – negative phenotype: a population-based study from the California cancer Registry. Cancer 2007. 109(9):1721-1728.
24. Giles GG, English DR: The Melbourne collaborative cohort study. IARC Sci Publ. 2002, 156: 69-70.
25. SAJID, M.T., Ahmed M., Azhar M., et al: Age-related frequency of triple negative breast cancer in women. J. collphysicians Surg. Pak, 24(6): 400-3, 2014.
26. Zakaria A, El-Kinaai N, Loay I, et al: Triple Negative Breast Cancer, Clinicopathologic Study of Egyptian patients, NCI Experience (2018) Med. J. Cairo Univ. Vol.86, No.5, September:2747-2753.
27. Aksoy S, Dizdar O, Harputluoglu H, Altundag K. Demographic, clinical, and pathological characteristics of Turkish triple- negative breast cancer patients: single center experience. Ann Oncol 2007; 18 (November 11)): 1904-6.
28. Gado N, Ibrahim D, Atef D, et al.: clinical characteristics of triple negative breast cancer in Egyptian women: a hospital – based experience (2016): International Journal of cancer therapy and Oncology 4(2): 426.
29. Sub AZ.: Triple-negative breast cancer risk in women is defined by the defect of estrogen signaling. Preventive and therapeutic implications: Oncotargets and therapy, 7:147-64,2014.
30. Fakhoury W. prognostic Factor in Breast Cancer; Correlation with other Factors, Estrogen and Progesterone Receptors, MIB and Histoprognostic Grade. Thesis, Saint. Joseph University, Beirut, Lebanon, 1996-1997:1-50.
31. Kwan ML, Kushi LH, Weltzien E, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. Breast cancer res. 2009; 11(3): R31.
32. Fayaz MS, El-Sherify MS, El-Basmy A et al. Clinicopathological Features and prognosis of triple negative breast cancer in Kuwait: A comparative / perspective analysis. Reports of practical oncology and radiotherapy. 2014; 19;173-81.
33. Phipps AI, Chlebowski RT, Prentice R, et al. Body size, physical activity, and risk of triple-negative and estrogen receptor – positive breast cancer. Cancer Epidemiol Biomarkers Prev. 2011; 20 (3):454-63.
34. Pistelli M., Pagliacci A., Battelli N., Santinelli A., Biscottit., Ballatore Z., et al: Prognostic factors in early – stage triple – negative breast cancer: lessons and limits from clinical practice. Anti cancer research, 33 (6): 2737 – 42, 2014.
35. Ajay A and Radhakrishnan (2017): Clinical pathological and epidemiological study of triple negative breast cancer. International Journal of Reasearch in Medical sciences 5(6):2657-2661.
36. Mohammed S. Fayuaz, Mustafa S. El – Sherify, Amany El-Basmy: (2013). Clinicopathological features and prognosis of triple negative breast cancer in Kuwait: A comparative / perspective analysis Reports of practical oncology and Radiotherapy 19 (2014) 173-181.
37. Ishikaway, Horiguchi J, Toya H, et al. Triple – negative breast cancer histological subtypes and immunohistochemical and clinicopathologicalfeatures. Cancer Sci. 2011; 102 (3): 656-62.
38. Montagna E, Maisonneuve P, Rotmensz N, et al. Heterogeneity of triple negative breast cancer: histologic subtyping to inform the outcome, Clin Breast cancer:2013, 13(1):31-9.
39. Monhollen L, Morrison C, Ademuyiwa FO, et al. Pleomorphic lobular carcinoma: a distinctive clinical and molecular breast cancer type. Histopathology. 2012; 61(3);365-77.