Journal of Advances in Medicine and Medical Research

32(14): 22-38, 2020; Article no.JAMMR.60307
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Assessment of Pathological Features and Molecular Profiling of Triple-Negative Breast Cancer: A Retrospective Study at King Abdulaziz University Hospital, Jeddah, Saudi Arabia

Fatma Khinaifis Al-thoubaity[1*]

[1]Department of Surgery, Faculty of Medicine, King Abdulaziz University, King Abdulaziz University Hospital, P.O. Box 80215, Jeddah 21589, Kingdom of Saudi Arabia.

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i1430561
Editor(s):
(1) Syed Faisal Zaidi, King Saud Bin Abdulaziz University-HS, Saudi Arabia.
(2) Dr. Evangelos Marinos, University of Athens, Greece.
Reviewers:
(1) Razan Zohairee, Damascus University, Syria.
(2) Firoj Allauddin Tamboli, Bharati Vidyapeeth College of Pharmacy, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/60307

Original Research Article

Received 15 June 2020
Accepted 19 August 2020
Published 27 August 2020

ABSTRACT

Background: Triple-negative breast cancer (TNBC) is a hostile sub-type consisting of nearly 10-20 % of breast cancer patients. TNBC has been known to have a poor prognosis and overall survival (OS) compared to many other breast cancer tumors categories. These tumors are highly aggressive and have a higher risk of early recurrence. Nevertheless, no evidence exists to date and this is also the situation in Saudi Arabia. Recently, it was found to be a heterogeneous disease.

Objective: To subtype breast cancer (BC) following the recent advance molecular classification, and to ascertain the correlation of those sub-types with pathological parameters and to study triple-negative breast cancer and its correlation with other subtypes and its association with recurrence and poor prognosis.

Methods: The study was performed on 740 breast cancer patients at the Department of Pathology, King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia diagnosed between 2005 to 2018. The parameters like Estrogen receptor (ER), Progesterone

**Corresponding author: E-mail: fthoubaity@kau.edu.sa, fatmaalthoubaity@yahoo.com;*

receptor (PR), and human epidermal growth factor receptor immunostaining were analyzed semi-quantitatively to establish the HER-2, triple-negative, molecular subtypes of luminal A and B in paraffin-embedded sections of BC. We review the histopathology report, tumor invasion, grade, margin, type of surgery, recurrence, metastases, and survival rate.

Results: The most common sub-types were luminal B (19.7%), followed by triple-negative breast cancer (10.9%) and HER2-positive (9.5%), whereas luminal A was the least common subtype (8.1 %). In luminal A majority of their age less than or equal to 50 years, most of these subtypes have tumor invasion, 59.2% of triple-negative breast cancer had positive axillary lymph node involvement. 63.4 % of triple-negative breast cancer had grade 3 tumors most of the recurrence in luminal B.

Conclusion: The biological behaviors of each molecular subtype is likely to be with characteristic pathological features. In addition to molecular sub-typing and further prognostic indicators, might be useful in investigating the prognosis and management of BC patients. The early diagnosis and screening of BC are recommended in our population.

Keywords: Breast cancer; pathological features; diagnosis; prognosis.

ABBREVIATIONS

AC : Adjuvant chemotherapy;
BC : Breast cancer;
BRCA1 : Breast Cancer gene-1;
ER : Estrogen receptor;
HER2 : Human epidermal growth factor receptor-2;
LN : Lymph node;
MRM : Modified radical mastectomy;
PR : Progesterone receptor;
TN : Triple negative;
TNBC : Triple-negative breast cancer.

1. INTRODUCTION

1.1 Background

Breast cancer (BC) is considered the second leading cancer amongst women throughout the world, which accounts for approximately 10.40% of all types of cancers [1-3]. It is the major cause of mortality in women of the age group 45 to 55 [4-5]. Triple-negative breast cancer (TNBC) is a type of breast cancer which are considered negative for progesterone receptors (PR), estrogen receptors (ER), and human epidermal growth factor receptor-2 (HER2) [4-5]. The diagnosis of breast cancers is commonly carried out by immunohistochemistry (IHC) staining analysis of three biological markers like estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor2 (HER2). There are different aspects in the diagnosis of various types of BC and TNBC among different patients. Several factors like various risk factors, race, age, including pathological and molecular properties of the patient play an important role in the diagnosis of different types of breast cancer [4,6-7]. TNBC has an aggressive nature in comparison with other breast cancer types and hence routine hormonal treatments are ineffective [8-9]. The immunohistochemical substitutes of TN tumors and the lack of ER, PR and HER-2 are the main specific markers of breast cancer which has been generally used for the identification of TNBC [10-13]. This is an effective approach, it is having a sensitivity of 76% and a specificity of 100 % [14], Moreover, TNBC are linked with younger patient age, poor prognosis [15], poor relapse, [16-18] the high prevalence of recurrence and metastasis [19-21], poor overall survival and outcome in comparison with other breast cancer types [22-25]. It has been estimated that approximately 10-20% of BC are diagnosed as triple-negative breast cancers. Recently, TNBC has become a center of attention in therapeutic and counseling cancer centers in many countries [26]. TNBC is of great interest in research because of the multiple factors. It has no effective treatment as it does not respond to hormonal therapy. It has a very poor prognosis as compared with other breast cancer, which leads to a low level of survival. Further, TNBC is basal-like cancer which tends to be more aggressive and more likely to spread and recur. Moreover, it is more likely to be a higher grade in comparison with other breast cancer types. And, it is also reported that approximately, 70 % of patients who inherited BRCA1 mutation are diagnosed with triple-negative breast cancer. Finally, African-American women and Hispanic women are more commonly diagnosed with Triple-negative breast cancer, while Asian women and non-Hispanic white women are comparatively less likely to be diagnosed with this type of cancer. The

excessive mitosis, high-grade ductal histology, and cell proliferation are characteristic features of TNBC [27].

TNBC has special characteristics showing aggressive behavior, unique molecular profile, and distinct metastatic patterns. It is usually started at a younger age having high-grade tumors and tumor size. The metastasis of TNBC is more likely to occur in the brain, and lungs, while less likely metastasis to bones as compared with other subtypes [28]. Moreover, TNBC has shown a low survival rate but, high relapse rate after diagnosis [27]. TNBC patients have an exceptionally poor prognosis and deterioration with a high mortality rate. It has no targeted therapies. In TNBC, there is an absence of hormone receptors and HER2 expression, therefore, no response to hormone therapy and Transtuzumab [27]. TNBC is normally treated with a combination of chemotherapy, radiation therapy, and surgery [29]. The current study was carried out to estimate the demographic characteristics and histopathological features of TNBC in Jeddah and to compare it with non-TNBC. 740 patients of breast cancer in the KAU hospital were studied and data has been collected for the patient to classify the breast cancer type based on the receptors status diagnoses and review the demographic characteristics of the patients with breast cancer. Also, this report represents the correlation of the tumor grade, margin, axillary Lymph node, and tumor invasion with the breast cancer type, especially the Triple-negative type.

Therefore, this report will contain two main sections; the first section is descriptive statistics for the sample and the breast cancer characteristics among the sample, while the second section will examine the correlation and statistical significance between the demographic characteristics of the patients and breast cancer type and overall survival.

2. MATERIALS AND METHODS

The present study reports the analysis of 740 breast cancer patients at the Department of Pathology, King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia diagnosed between the year 2005 to 2018. The analysis of immunohistochemically stained slides from paraffin-embedded sections of tissues from BC patients was performed. 52 % of our sample had ER and PR immunohistochemistry staining and 49% had immunohistochemistry staining for ER, PR and (Her2/neu), So the molecular classification of 42 % of the sample into 4 subtypes The immunostaining studies of Estrogen receptor (ER), Progesterone receptor (PR), and human epidermal growth factor receptor were carried out to describe the molecular subtypes of luminal-A , luminal-B, HER2 and triple negative breast cancer among breast cancer patients.

2.1 Statistical Analysis

All statistical analysis of the data was carried out with the help of SPSS for windows version 12 (Chigago, IL, USA). The data were expressed as mean ± SD.

3. RESULTS

Seven hundred and forty patients who diagnosed with breast cancer in the duration between 2005 to 2018 were evaluated in this study. The results of the different studied characteristics like gender, age, cancer invasion, axillary lymph node status, margin, tumor size, tumor grade, survival status and molecular subtypes of breast cancer are summarized in the Table 1.

Fig. 1 represents sample distribution by gender. Results show that 98.8 % of the patients are females and 1.2 % are males.

Fig. 2 shows patient's distribution as per their age group. The distribution of sample of patients by age group shows that most of the sample aged lesser than or/equal 50 years old and 45.8 % of the sample aged older than 50 years.

Fig. 3 shows Sample distribution by Cancer Invasion. Results showed that 96.6 %of cases in the sample had a positive result to Tumor Invasion compared to 3.4 % had a negative result.

Fig. 4 shows Sample distribution by axillary Lymph Node status. Chi square test for the association between breast cancer type and axillary lymph node is statistically significant. Results show that 62.5% of the patient had a positive axillary Lymph node compared to 37.5% had a negative axillary lymph node.

Fig. 5 shows Sample distribution by Margin. Results showed that 84.1% of the sample had a negative margin while 15.9 % of the patients had a positive margin and need a second surgery.

Table 1. Summary of the different characteristics studied

Personal Data		No.	%
Gender	Female	721	98.8
	Male	9	1.2
Age in years	=<50	391	53.6
	>50	339	46.4
Cancer Invasion	Negative	22	3.4
	Positive	630	96.6
Axillary Lymph Node status	Negative	224	37.5
	Positive	373	62.5
Margin	Negative	518	84.1
	Positive	98	15.9
Tumor size	0 - 3	235	39.1
	3 – 6	286	47.6
	> 7	80	13.3
Tumor grade	grade1	106	17.6
	grade 2	305	50.6
	grade 3	192	31.8
Survival status	Dead	77	37.7
	alive	127	62.3
Molecular subtypes of breast cancer	Luminal A	60	8.1
	Luminal B	146	19.7
	HER2 – Positive	70	9.5
	Triple Negative (TN)	81	10.9

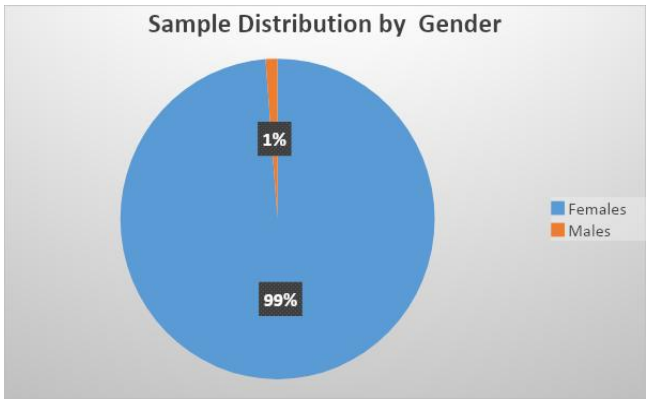

Fig. 1. Sample distribution by Gender

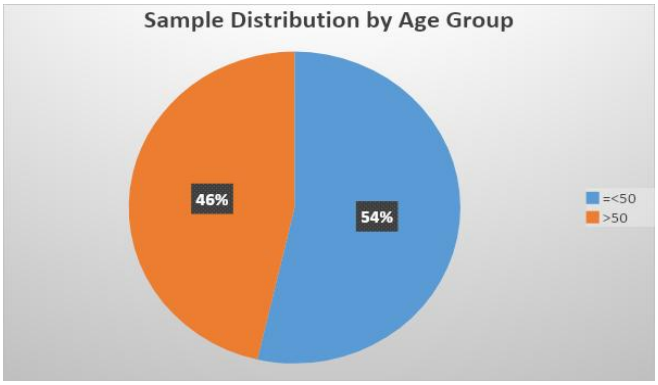

Fig. 2. Sample distribution by Age Group

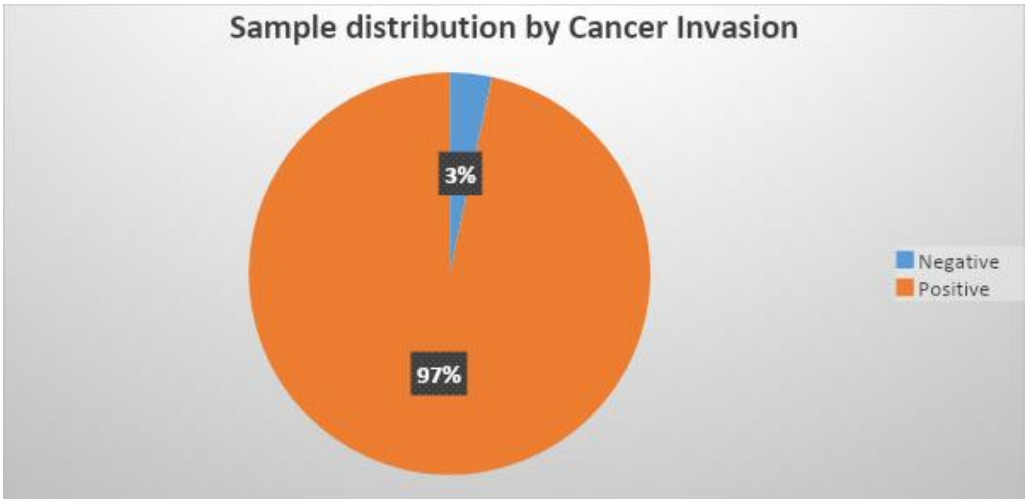

Fig. 3. Sample distribution by Cancer Invasion

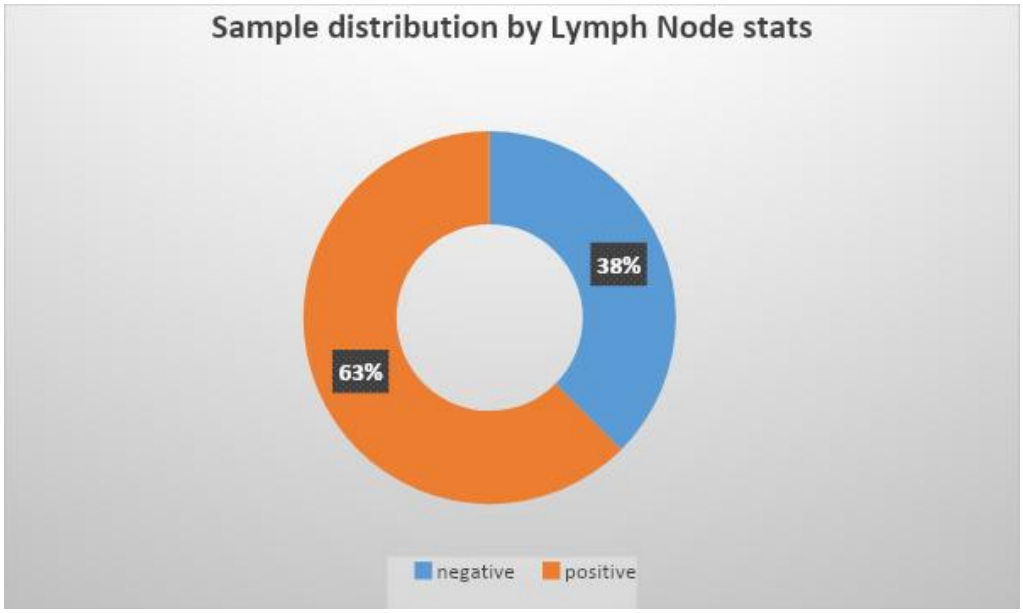

Fig. 4. Sample distribution by axillary Lymph node involvement

Chi square test for association between breast cancer type and tumor size showing a significant relation at 95% significant level between breast cancer type and tumor size. Results show that the tumor size for 39.1 % of the patient was from 0 to 3, and 47.6 % of the patient in the sample the tumor size is from 3 to 6 and 13.3 % the tumor size is more than 7 cm.

Fig. 6 shows sample distribution by tumor grade. Chi square test result shows a highly significant association between tumor grade and breast cancer type. The result showed that 17.6 % of the patient in the study their tumor classified as grade 1, while 50.6 % classified as grade 2 and 31.8 % classified as grade 3.

Fig. 7 shows results among 740 patient survival status data has been collected for 204 of them, and among those patients which their survival status data was collected 62.3 % of them are alive compared to 37.7 % is dead. Chi square test for association between breast cancer type and survival status is significant with a significant level 95%.

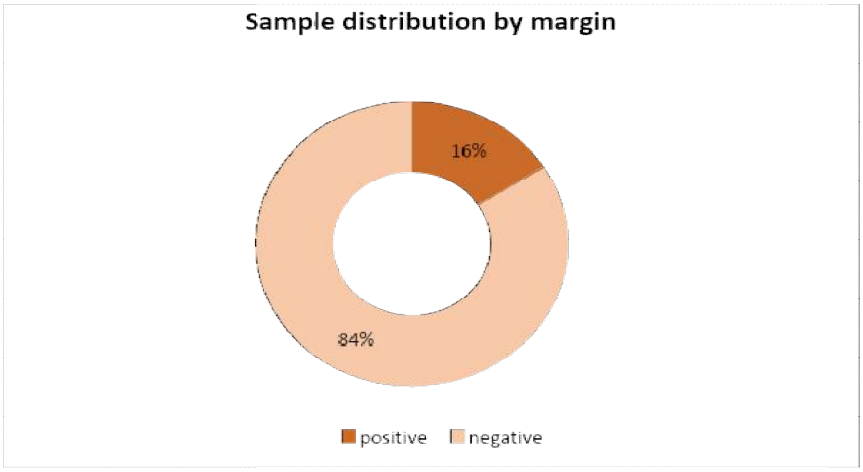

Fig. 5. Sample distribution by Margin

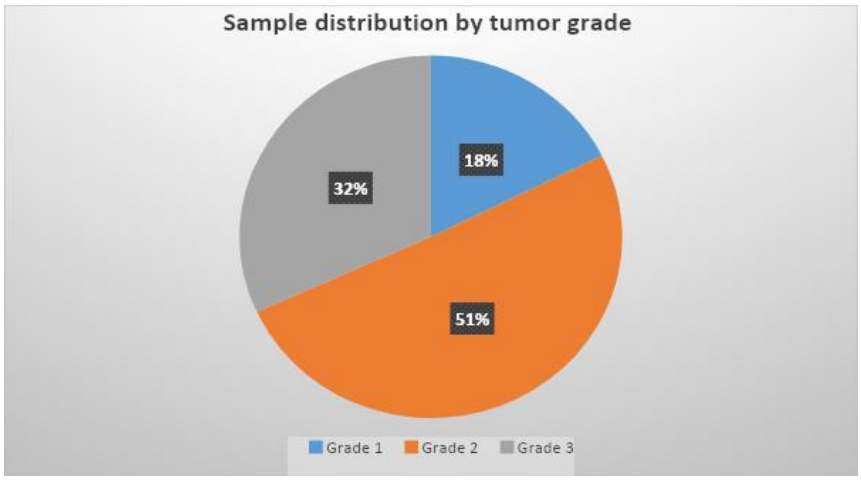

Fig. 6. Sample distribution by tumor grade

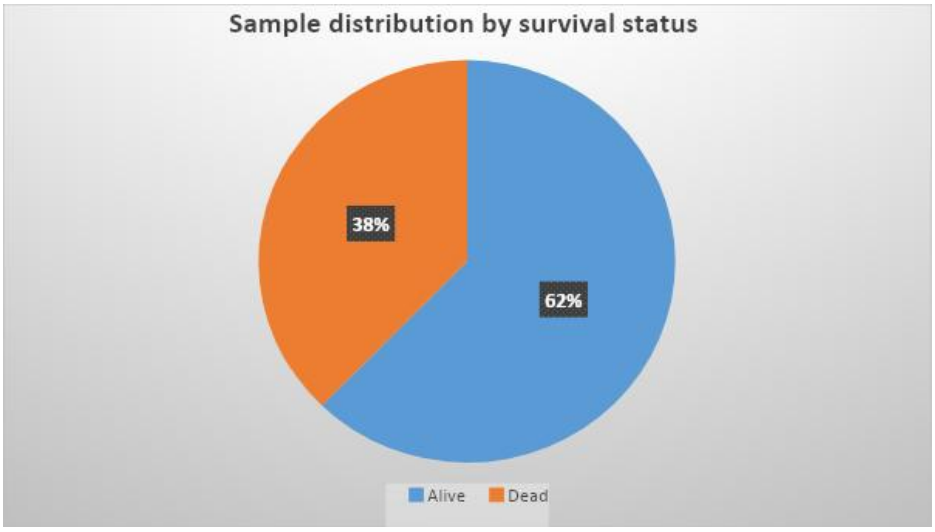

Fig. 7. Sample distribution by survival status

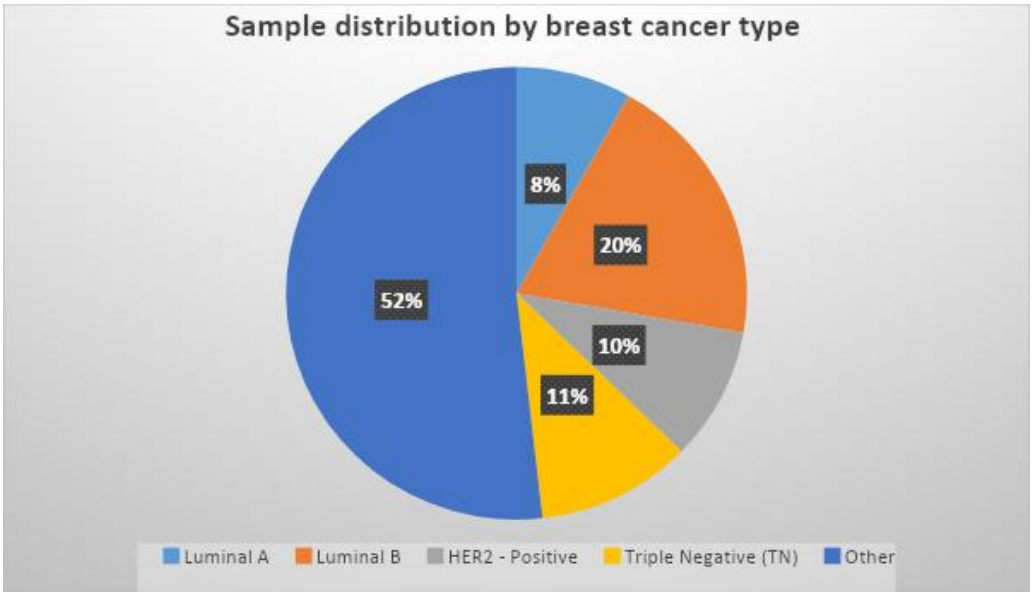

Fig. 8. Sample distribution by breast cancer type

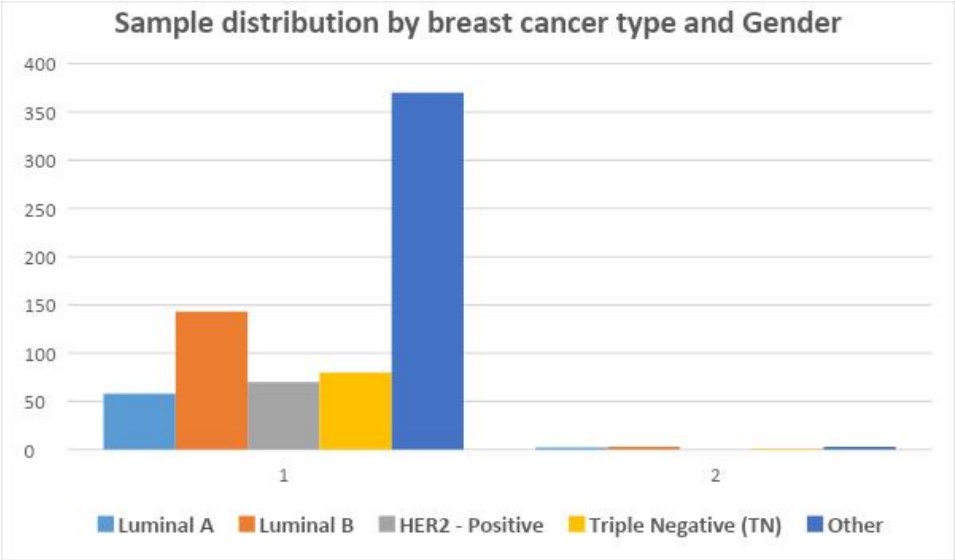

Fig. 9. Sample distribution by breast cancer type and gender

Fig. 8 shows Sample distribution by molecular subtypes of breast cancer. Molecular subtypes of breast cancer have been classified using ER, PR and HER2 receptors result into four main categories; Luminal A, Luminal B, HER2 positive and triple negative (TN), and results show that 19.7 % of the sample had the Luminal B breast cancer while 8.1 % had the luminal A breast cancer; on the other hand, 10.9 % of the sample had the TN (triple negative) breast cancer and 9.5 % had the HER2 positive breast cancer.

3.1 Cross-tabulations for Different Characteristics

Fig. 9 shows sample distribution by molecular subtypes of breast cancer and gender. Results show that the majority of the patients with all molecular subtypes where females and this because of that the majority are females and 1.2% are males.

Fig. 10 shows sample distribution by molecular subtypes of breast cancer and age group. Results show that among the patients with molecular subtype TN there was no difference between the two age groups, while for the patients classified with HER2-positive 61.4 % of them in the age group less than or equal 50 years and 38.6 % older than 50 years; and for the patients with Luminal B breast cancer, the majority of them in the age group older than 50 years, and the opposite among the patients with Luminal A breast cancer as the majority of them is the age group less than or equal 50 years.

Fig. 11 shows sample distribution by molecular breast cancer subtype and tumor invasion. Results show that the majority of the sample for all molecular breast cancer subtypes have a positive T invasion.

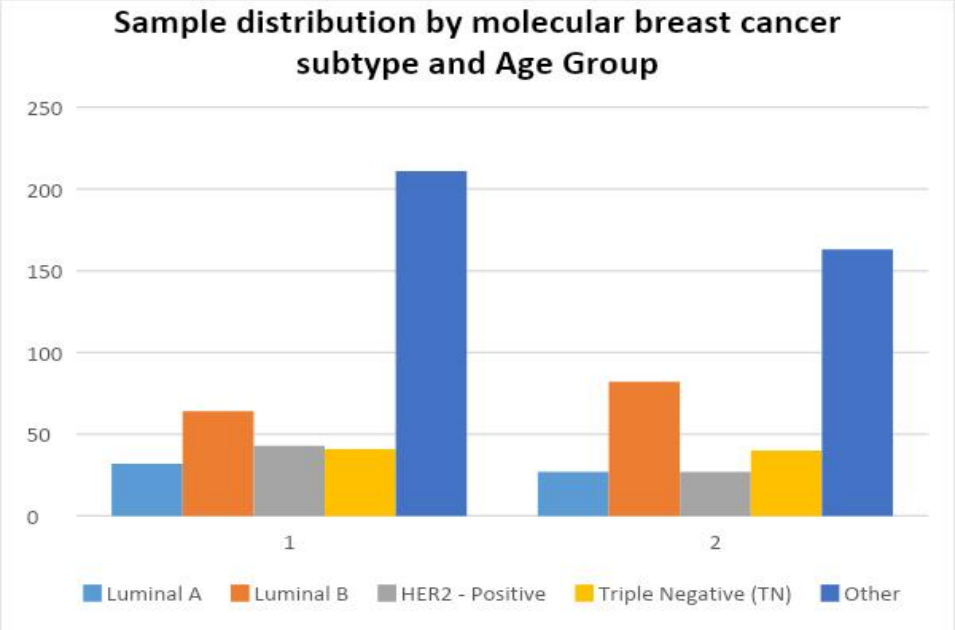

Fig. 10. Sample distribution by molecular breast cancer subtype and age group

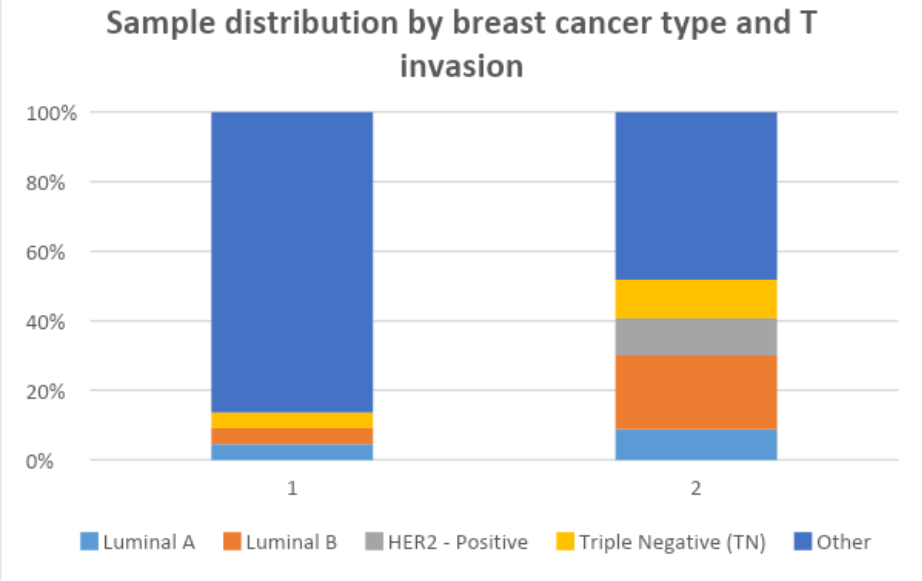

Fig. 11. Sample distribution by molecular breast cancer subtype and tumor invasion

Fig. 12 shows sample distribution by molecular breast cancer subtype and axillary lymph node (LN). Results show that the majority of the patients with TN breast cancer type had positive LN status represents 59.2 % of TN breast cancer type patients, and the majority of the patients with HER2- positive breast cancer also have a positive LN represents 79.6 % of the HER2-positive patients.

Fig. 13 shows sample distribution by molecular breast cancer subtype and margin. Results show that the majority of the patients with all types of breast cancer have a negative margin with ratios exceeded 83 % and reached 90.7 % for the TN breast cancer patients.

Fig. 14 shows sample distribution by breast cancer type and tumor size. Results show that the majority of Luminal A breast cancer patients their tumor size is from 0 to 3 represents 48 % of Luminal A breast cancer patients; on the other hand, patients with Luminal B, HER2-positive and TN breast cancer tends to have tumor size from 3 to 6 with ratios between 42% to 52%.

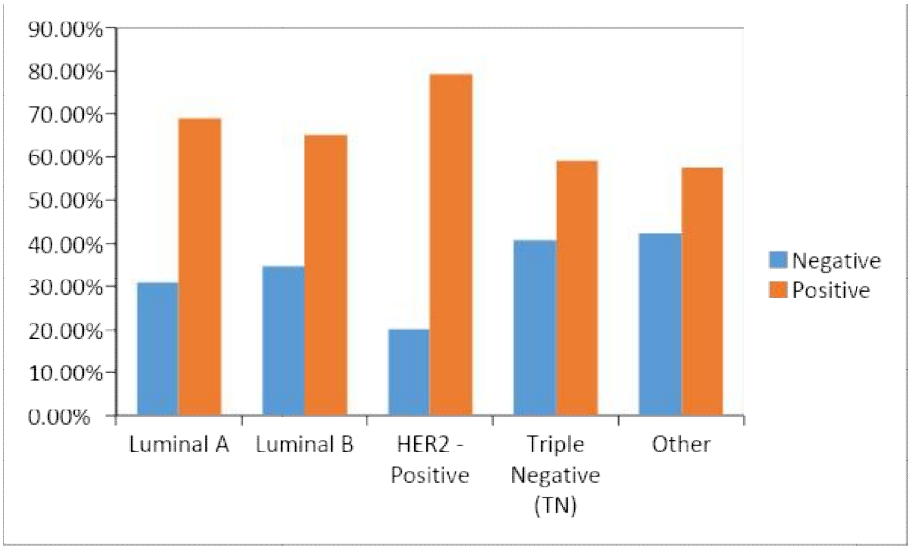

Fig. 12. Sample distribution by molecular breast cancer subtype and axillary LN

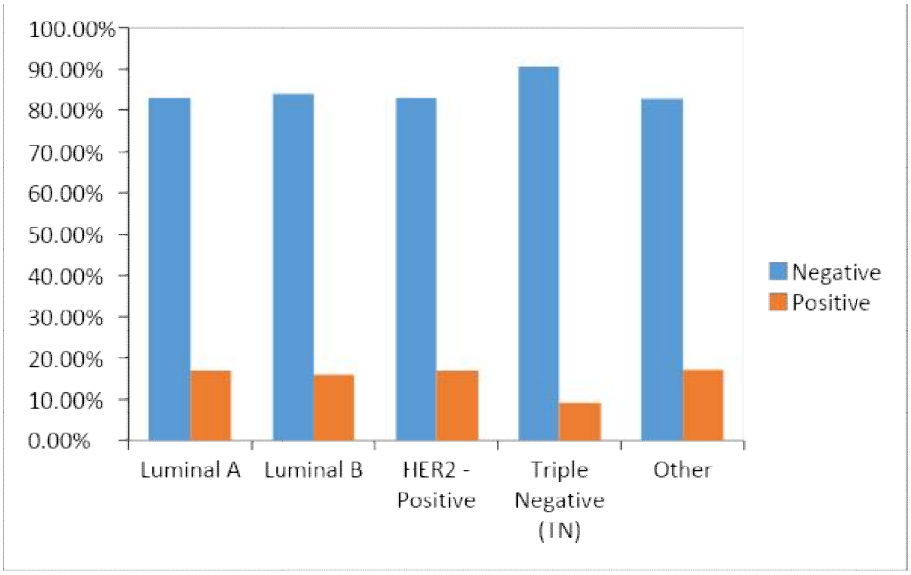

Fig. 13. Sample distribution by molecular breast cancer subtype and Margin

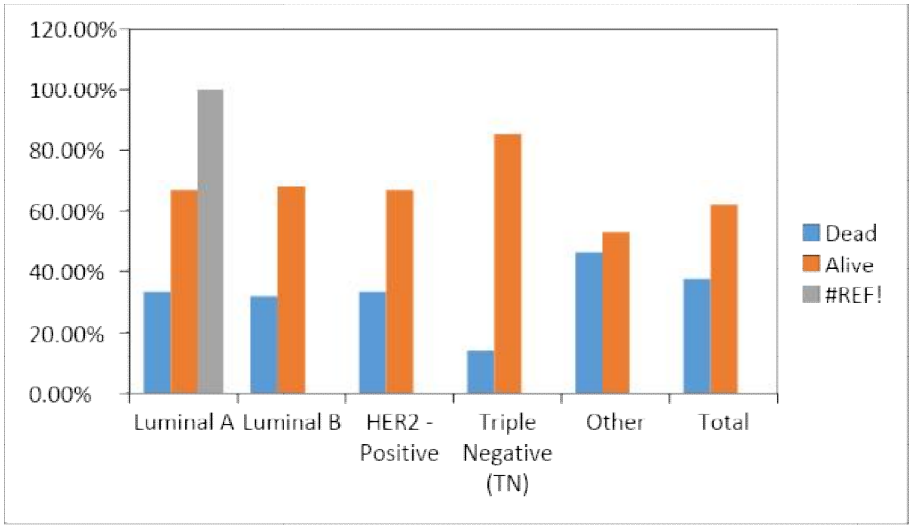

Fig. 14. Sample distribution by breast cancer type and tumor size

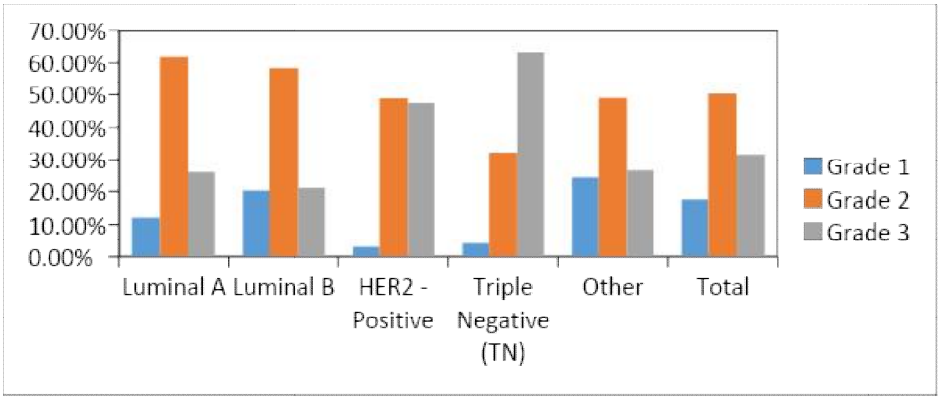

Fig. 15. Sample distribution by molecular breast cancer subtype and tumor grade

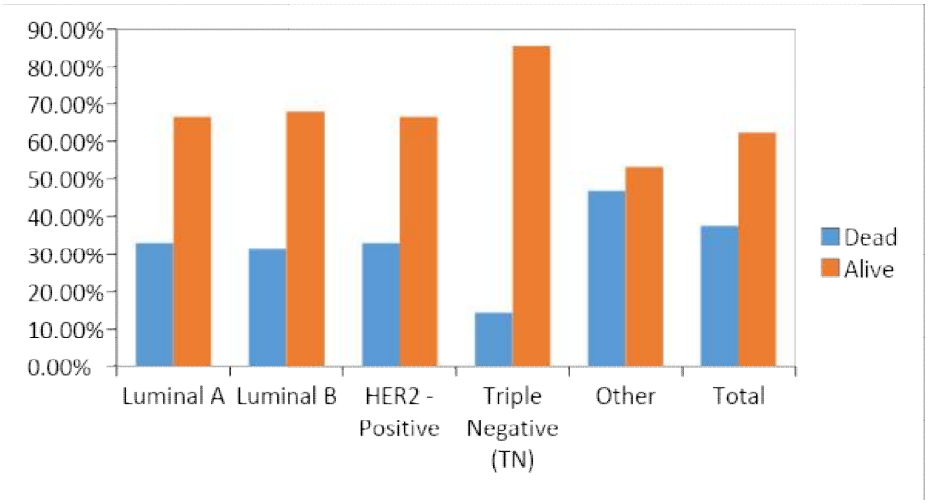

Fig. 16. Sample distribution by molecular breast cancer subtype and Survival Status

Fig. 15 shows sample distribution by molecular breast cancer subtype and tumor grade. Results show that unlike the other breast cancer types, 63.4 % of the TN breast cancer patients had a grade 3 tumor, while the majority of the rest of the breast cancer types patients had a grade 2 tumor.

Fig. 16 shows sample distribution by molecular breast cancer subtype and survival status. Results show that the majority of patients with different types of breast cancer are alive.

3.2 Results of Additional Requested Analysis

3.2.1 Histopathology type and staging of breast cancer

Fig. 17, results show that 89.4 % of the patients had invasive ductal carcinoma while 10.6 % were other type.

Results show that 77.9 % of the patients in the sample in the early stage compared to 22.1 % in the late stage (Fig. 18).

Results for breast cancer stage and breast cancer type shows that 28.3 % of the patients in the early stage have the Luminal B breast cancer, while 11.3 % of the patient in the early stage had the Triple Negative breast cancer. On the other hand, 40 % of the patient in the late stage had HER2 positive breast cancer and none of them had the TN breast cancer (Fig. 19).

3.2.2 Surgical treatment

Results show that 62.6 % of the patients had MRM+AC (modified radical mastectomy and adjuvant chemotherapy) compared to 37.4 % had a lumpectomy(breast conserving therapy) .So high rate of patient had modified radical mastectomy (Fig. 20).

3.2.3 Correlation with molecular breast cancer types like TN triple negative breast cancer associated with high rate of mastectomy

Results show insignificant relation between breast cancer type and surgical treatment (Fig. 21).

3.2.4 Recurrence rate and in which sub-types

Results show that 71.6 % of the patients in the sample has no recurrence compared to 27.8 % had recurrence and only 0.6 % had a metastasis at diagnosis (Fig. 22).

Results show that the majority of patient that had a recurrence were in the breast cancer type "Luminal B" compared to 7.4 % of the patient with recurrence had the TN breast cancer (Fig. 23).

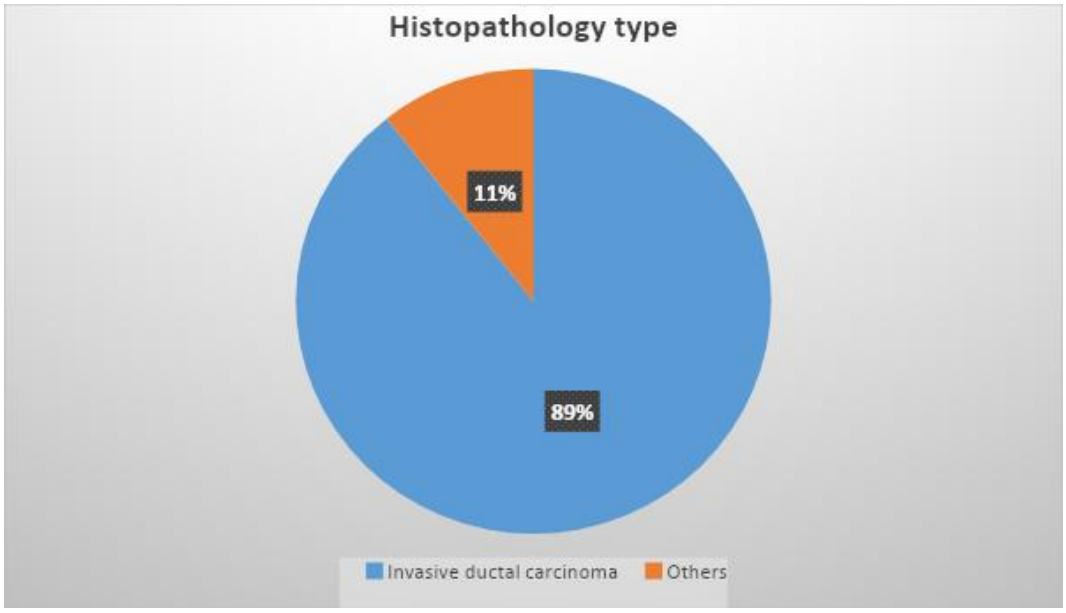

Fig. 17. Histopathology type

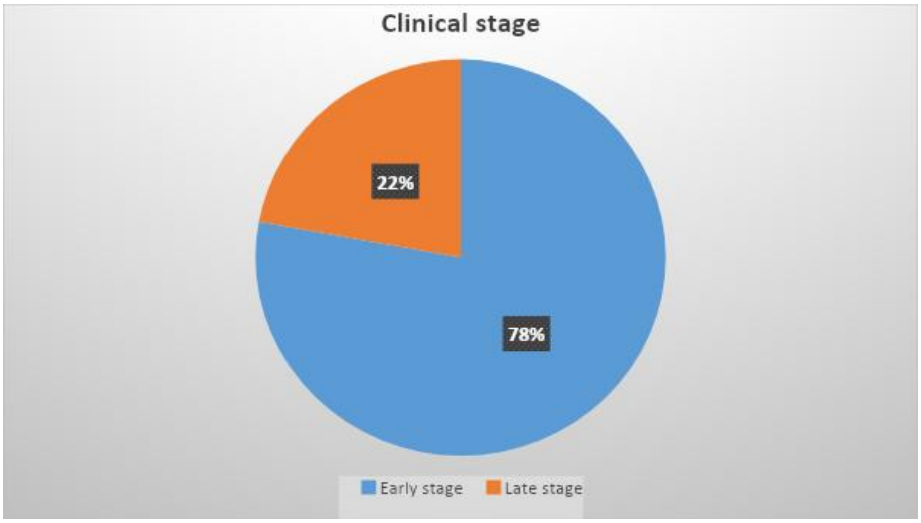

Fig. 18. Clinical stage

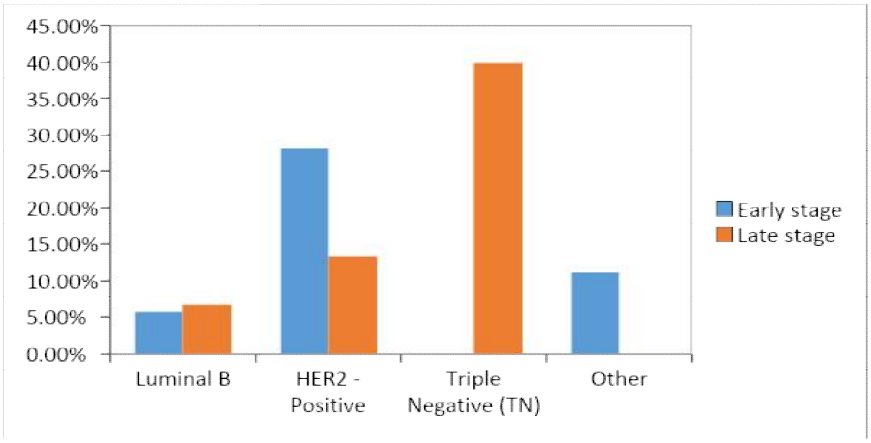

Fig. 19. Relation between breast cancer stage and breast cancer type

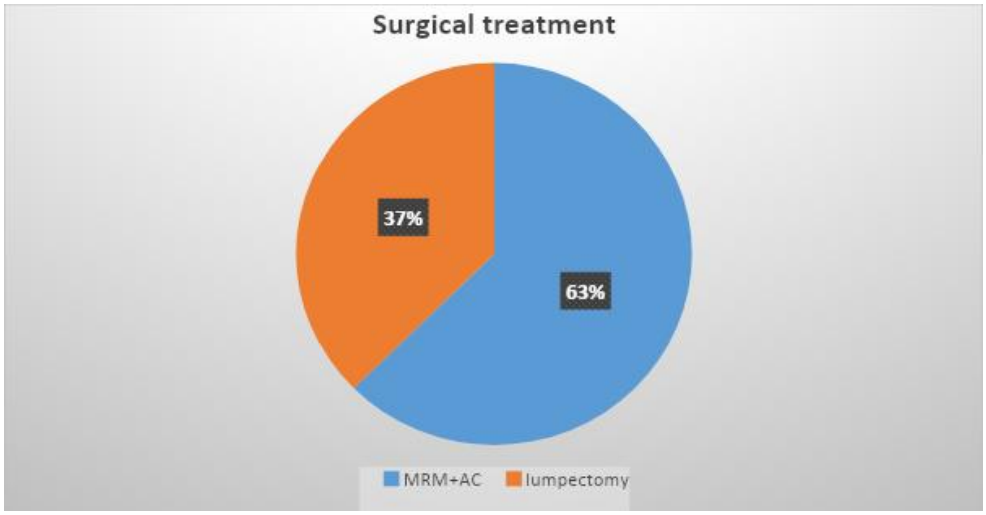

Fig. 20. Surgical treatment

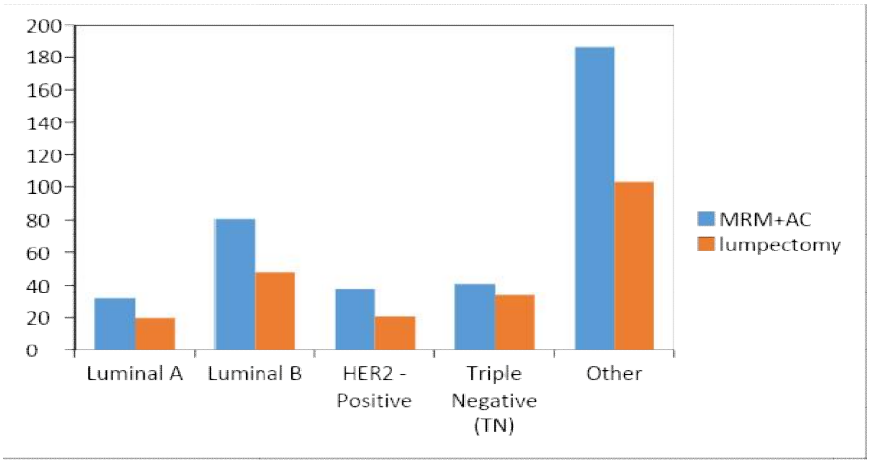

Fig. 21. Relation between breast cancer type and surgical treatment

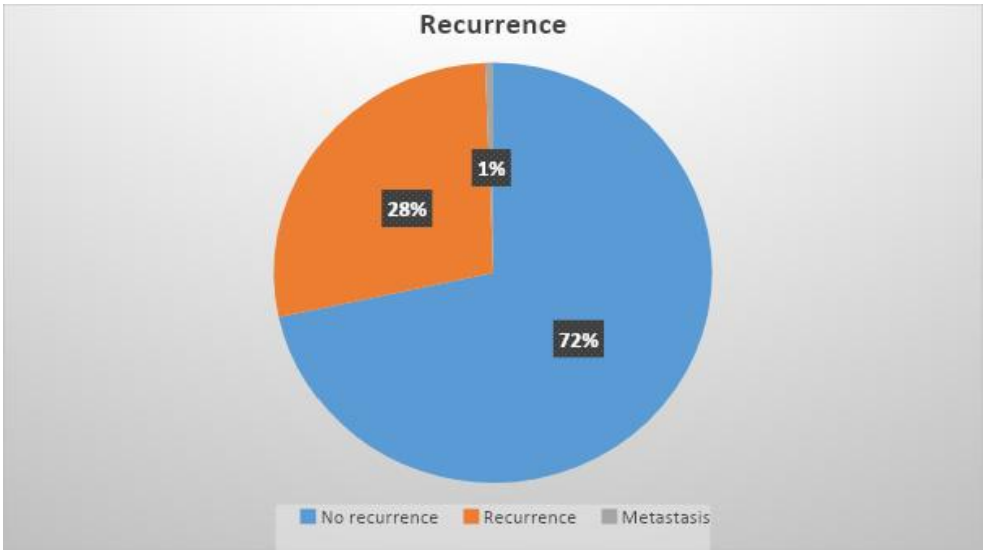

Fig. 22. Recurrence

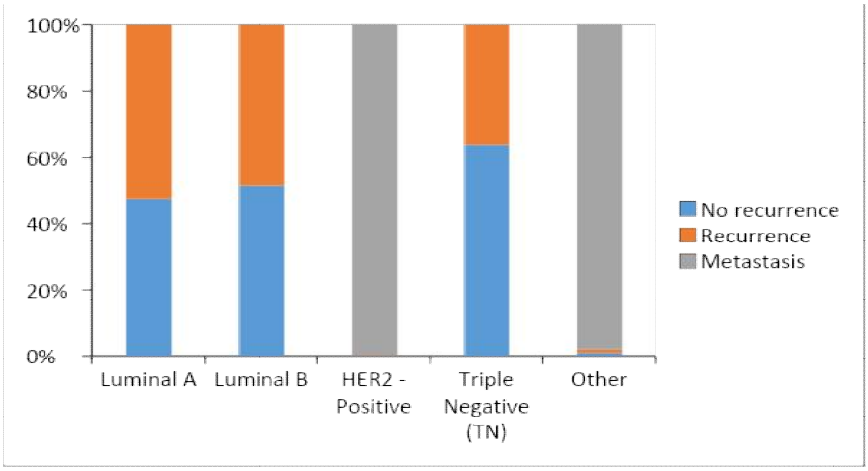

Fig. 23. Relation between breast cancer type and recurrence

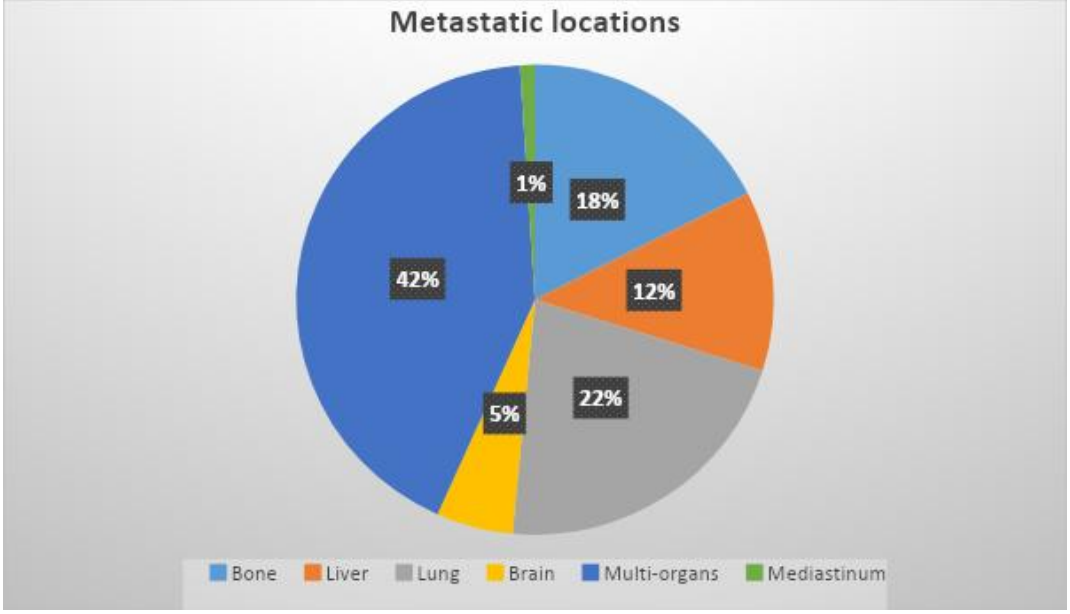

Fig. 24. Metastatic locations

3.2.5 Site of metastasis

Results show that the majority of the patient that have a metastasis was in the multi-organs with 42.3 % (Fig. 24).

4. DISCUSSION

Breast cancer is the most common cancer in women and accounts for 14.7 % of cancer-related deaths among females worldwide. The present study was carried out to subtype breast cancer (BC) according to the recent molecular classification and to correlate these subtypes with pathological parameters and to study triple negative breast cancer and its correlation with other subtypes and its association with recurrence and poor prognosis.

740 patients with breast cancers were classified into (49%) 4 molecular subtypes, using immunohistochemistry: luminal A (estrogen receptor [ER], or progesterone receptor [PR] positiveand human epidermal growth factor receptor 2 [HER2] negative)(8,1%), luminal B (ER and/or PR positive and HER2 positive)(19,7%), HER2-positive (ER and PR negative and HER2 positive)(9,5%), and triple negative (ER, PR, and HER2 negative)(10,9%), others (52%) in which ER and PR performed only and no HER2.

In the present study, the average age of diagnosis was approximately 50 years as reported by a study performed in King Khalid University Hospital in the year 2001-2010 and by the Saudi Arabian Cancer Incidence Report (Saudi Cancer Registry), Cancer Incidence Report, Saudi Arabia 2010[30-31].It was found that in our study majority of them were females (98.8 %) as reported earlier by a study conducted in Oman [32]. 96.6 % of the patients were positive for cancer invasion, 62.5 % for Axillary Lymph Node status and 15.9 % for margin. 39.1 % of the patients showed a tumor size of 0-3, 47.6% with a tumor size of 3-6 and 13.3 % of the patients showed a tumor size of >7 [Table-1]. Earlier studies conducted in United States and Poland where only 33.15 % of people showed a tumor size <2 cm and 58.4 % and 51.9 % of people showed a tumor size ≤2 cm [33-34]. This suggests late diagnosis in Saudi Arabian population which might be due to several reasons such as inadequate information pertaining to breast cancer.

Regarding the tumor grade, 17.6 % of patients showed grade 1, 50.6 % grade 2 and 31.8 % showed grade 3. As far as molecular subtypes of breast cancer are concerned, in our study, 8.1 % were luminal A, 19.7 % were luminal B, 9.5 % were HER2 – Positive and 10.9 % were Triple Negative (TN). Unlike the present findings, nearly 52.8 %/half the patients were triple negative in a study conducted by Tamimi et al. 2010 [35], and luminal tumors consisting of 28.5 %. Even though the incidence of molecular subtypes

varies from one population to other, majority of them have a similar order of distribution with triple negative carcinomas being the second most prevalent subtype.

Classification of breast cancer revealed that luminal B tumors were the most common subtype, followed by triple negative tumors. Breast cancer subtypes exhibited particular characteristics. No association between molecular breast cancer subtype and gender whereas association between molecular breast cancer subtype and age group was marginally significant. Association between breast cancer type and tumor invasion and breast cancer type and axillary lymph node status was statistically significant while between breast cancer type and Margin was insignificant. Association between breast cancer type and tumor size showed significant relation between breast cancer type and tumor size. High significant association was found between tumor grade and breast cancer type and breast cancer type and survival status.

In the present study, majority of the patients had invasive ductal carcinoma and majority of the patients were in the early stage. Relation between breast cancer stage and breast cancer type showed that less than half of the patients in the early stage had the Luminal B breast cancer, while very few of them in the early stage had Triple Negative breast cancer. 40 % of the patients in the late stage had HER2 positive breast cancer and none of them had the TN breast cancer. More than half of the patients had modified radical mastectomy and adjuvant chemotherapy compared to 37.4 % who had breast conserving therapy . No relation was observed between breast cancer type and surgical treatment. 71.6% of the patients has no recurrence compared to 27.8 % had recurrence and only 0.6% had a metastasis at diagnosis. Majority of patients that had a recurrence were in the Luminal B breast cancer type compared to 7.4 % of the patients with recurrence had the TN breast cancer. Majority of the patients who had metastasis was in the multi-organs with 42.3 %.

5. CONCLUSION

The behavior of each molecular subtype could be predicted on the basis of its characteristic pathological features. Molecular subtyping would be great help in predicting prognosis and management of breast cancer patients, in addition with other prognostic indicators. Early screening and early diagnosis of breast cancer would play a beneficial role.

FUNDING

The work in this manuscript is self-funded and no funding agency supported or funded this work. However, the author acknowledges the facilities of King Abdulaziz University Hospital (KAUH), King Abdulaziz University (KAU), Jeddah, Kingdom of Saudi Arabia.

THE DATA AVAILABILITY

All the data of the undertaken study have been included within the manuscript. The personal data of the patients are not publicly available due to protecting individual's privacy. However, additional information of the current study may be obtained from the corresponding author upon request (fthoubaity@kau.edu.sa).

CONSENT AND ETHICS APPROVAL

The current manuscript is an outcome of a retrospective study, hence there is no or least ethical issues. The author of this manuscript "Dr. Fatma Al-thoubaity" was individually involve to collecting, review and analyzed data from file of patients diagnosed with breast cancer. The identity and confidentiality of the patient were maintained by allocating a specific serial number to each patient. Furthermore, only the principal investigator along with research assisting team had gone through the patients' records. Informed and written consent from the participants have been collected and preserved. This study was approved by the Institutional Review Board, Department of Surgery and Faculty of Medicine, King Abdulaziz University (Approval number: 6/D/39/10851)on 25-9-2017.

ACKNOWLEDGEMENTS

The author is thankful to the medical staff at the King Fahad Research Center for their valuable in the collection of data. I would like offer my sincere gratitude to Professor Adnan Merdad, who allow to collect the data from his patients.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney

cancer. Nature Reviews Urology. 2010;7(5):245.

2. King SC, Pollack LA, Li J, King JB, Master VA. Continued increase in incidence of renal cell carcinoma, especially in young patients and high grade disease: United States 2001 to 2010. The Journal of Urology. 2014;191(6):1665-70.
3. Low G, Huang G, Fu W, Moloo Z, Girgis S. Review of renal cell carcinoma and its common subtypes in radiology. World Journal of Radiology. 2016;8(5):484.
4. Abdollahi A, Etemadi M. Pathological Characteristics of Triple-Negative Breast Cancer at Main Referral Teaching Hospital, April 2014 to April 2015, Tehran, Iran. International journal of hematology-oncology and stem cell research Int J Hematol Oncol Stem Cell Res. 2016;10(4):200-205.
5. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, Gore JL, Sun M, Wood C, Russo P. Epidemiology of Renal Cell Carcinoma. European Urology. 2019;75(1):74-84.
6. Bharthuar A. Metastatic renal cell carcinoma: Current scenario and future trends. South Asian Journal of Cancer. 2012;1(1):30-5.
7. Sameh WM, Hashad MM, Eid AA, Abou Yousif TA, Atta MA. Recurrence pattern in patients with locally advanced renal cell carcinoma: The implications of clinicopathological variables. Arabian Journal of Urolology. 2012;10(2):131-7.
8. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes and survival in the Carolina Breast Cancer Study. JAMA. 2006;295:249-502.
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer Journal for Clinicians. 2019;69(1):7-34.
10. Tischkowitz M, Brunet JS, Begin LR, Begin LR, Huntsman DG, Cheang MC, Akslen LA, Neilsen TO, Foulkes WD. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC Cancer. 2007;7:134.
11. Cheang MC, Voduc D, Bajdik C, Leung S, McKinney S, Chia SK, Perou CM, Neilsom TO. Basallike breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res. 2008;14:1368-76.
12. Chae BJ, Bae JS, Lee AW, Park WC, Seo YJ, Song BJ, Kim JS, Jung SS. p53 as a specific prognostic factor in triple-negative breast cancer. Jpn J of Clin Oncol. 2009;39:217-224.
13. Al-Thoubaity FK. Molecular classification of breast cancer: A retrospective cohort study. Annals of Medicine and Surgery. 2020;49:44-48.
14. Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, Hu Z, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin Cancer Res. 2004;10:5367-74.
15. Han W, Kin SK, Park IA, Kang D, Kin SW, Youn YK, et al. Young age: an independent risk factor for disease-free survival in women with operable breast cancer. BMC Cancer. 2004;4:82.
16. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor classes with clinical implication. Proc Natl Acad Sci USA. 2001;98:10869-74.
17. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. 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;109:1721-8.
18. Cleator S, Heller W, Coombes RC. Triple-negative breast cancer: therapeutic options. Lancet Oncol. 2007;8:235-44.
19. Rodriguez-Pinilla SM, Sarrio D, Honrado E, Hardisson D, Calero F, Benitez J, Palacios J. Prognostic significance of basal-like phenotype and fascin expression in node-negative invasive breast carcinomas. Clin Cancer Res. 2006;12:1533-39.
20. Carey LA, Ewend MG, Metzger R, Sawyer L, Dees EC, Sartor CI, Moore DT, Graham ML. Central nervous system metastases in women after multimodality therapy for high risk breast cancer. Breast Cancer Res Treat. 2004;88:273-80.
21. Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, Weidhaas J, Harris L, Hait W, Toppmeyer D. Locoregional relapse and distant metastasis in conservatively managed triple negative earlystage breast cancer. J Clin Oncol. 2006;24:5652-7.

22. Livasy CA, Karaca G, Nanda R, Tretiakova MS, Olopade OI, Moore DT, Perou CM. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol. 2006;19:264-71.
23. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res. 2007;13:2329-34.
24. Kang SP, Martel M, Harris LN. Triple negative breast cancer: current understanding of biology and treatment options. CurrOpinObstet Gynecol. 2008;20:40-46.
25. Dawood S, Broglio K, Esteva FJ, Yang W, Kau SW, Islam R, et al. Survival among women with triple receptor-negative breast cancer and brain metastases. Ann Oncol. 2009;20:621-7.
26. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer Journal for Clinicians. 2019;69(1):7-34.
27. Siva S, Kothari G, Muacevic A, Louie AV, Slotman BJ, Teh BS, Lo SS. Radiotherapy for renal cell carcinoma: renaissance of an overlooked approach. Nature Reviews Urology. 2017;14(9):549.
28. Kapoor AK, Hotte SJ. Current status of cytokine therapy in management of patients with metastatic renal cell carcinoma. Canadian Urological Association Journal. 2007;1(2):S28.
29. Morais C. Sunitinib resistance in renal cell carcinoma. Journal of Kidney Cancer and VHL. 2014;1(1):1.
30. Saudi Cancer Registry. Cancer Incidence Report, Saudi Arabia 2010. Riyadh (KSA): Saudi Cancer Registry; 2014;36.
31. Al-Rikabi A, Husain S. Increasing prevalence of breast cancer among Saudi patients attending a tertiary referral hospital: a retrospective epidemiologic study. Croat Med J. 2012;53(3):239-43.
32. Mehdi I, Monem AA, Al Bahrani B, Ramadhan FA. Breast cancer molecular subtypes in oman: correlation with age, histology, and stage distribution-analysis of 542 cases. Gulf J Oncolog. 2014;1:38–48.
33. Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, Peplonska B, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomarkers Prev. 2007;16:439-443.
34. Kurian AW, Fish K, Shema SJ, Clarke CA. Lifetime risks of specific breast cancer subtypes among women in four racial/ethnic groups. Breast Cancer Res. 2010;12:R99.
35. Tamimi DMA, Shawarby MA, Ahmed A, Hassan AK, AlOdaini AA. Protein expression profile and prevalence pattern of the molecular classes of breast cancer - a Saudi population based study. BMC Cancer. 2010;10:223.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/60307