Clinicopathological features and five-year survival of invasive non-metastatic breast cancer patients surgically treated in a single breast unit in Jordan in 2013

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ABSTRACT

Background: Breast cancer is still the most common cancer in females worldwide. In 2013, the number of female breast cancer cases in Jordan was 1040 (36.5% of all female cancers)[1]. Studying survival and clinico-pathological features will provide an objective assessment about tumour biology in our region and specific treatment outcomes.

Objective: to assess the five-year survival of breast cancer patients who were treated at our breast unit, to evaluate clinicopathlogical features and correlate them with molecular subtypes.

Materials and Methods: A retrospective study that revised the histopathology reports of 129 breast cancer patients surgically treated at Al-Hussein Hospital from January 2013 until January 2014. The patients were followed up till 2019 to assess their 5 year survival, clinicopathological features and molecular subtypes.

Results: The most common age group was 40–60 years (51.16%). Eighty six (66.67%) patients had axillary LN involvement. Most of the tumours were reported to be between 2 and 5 cm (T2) in 82 (63.57%) patients. One hundred and fifteen (89.15%) patients had invasive ductal carcinoma (IDC) nonspecific type. Grade 3 tumours were reported in 64 (49.61%) patients. The tumours in 105 (81.40%) patients were ER positive, those in 94 (72.87%) patients were PR positive and those in 96 (74.42%) patients were Her2 receptor negative. Luminal A subtype was observed in 86 (66.6%) patients, followed by Luminal B subtype in 21 (16.28%) then Her2 enriched subtype in 12 (9.30%) and least in Triple Negative subtype in 10 (7.75%) patients. There were nine (6.98%) patients who had stage 1, 58(44.96%) patients had stage 2 and 62 (46.06%) patients who had stage 3. The five year survival according to stage was 100%, 87.93%, 69.35% for stages 1, 2 and 3 respectively.

Conclusion: Approximately half of the patients presented in the middle age group with relatively large tumour sizes and involved lymph nodes. However, the majority of patients had a favourable molecular subtype (Luminal A) accounting for why the 5-year survival for stage 3 was around 70%, which is relatively good and is comparable to worldwide results. There was also a significant relationship (P = 0.022) between molecular subtypes and age groups used in the study warranting larger scale studies.

Keywords: Breast cancer, prognostic factors**,** axillary metastasis, histological grade, histological type, tumour size, receptor status, lymph node involvement, 5-year survival

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Introduction

Breast cancer remains the most common cancer in females worldwide and is the leading cause of death in females between the ages of 20 to 60[1]. In 2010, breast cancer accounted for 19.6% of total cancer cases

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in both genders in Jordan[2]. In 2013, there were 1040 female breast cancer cases in Jordan (36.5% of all female cancers)[3]. The aetiology for breast cancer involves many factors such as genetic, environmental and hormonal but most cases are attributed to DNA mutations that are acquired rather than inherited.

The most important hormones that affect breast cancer are oestrogen and progesterone. When these hormones attach to their receptors on cancer cells they invoke a cascade that increases cell growth and multiplication, therefore one of the main arms of treatment of patients with positive receptor status is anti-hormonal drugs. Some studies even reported higher risk of mortality with different ER/PR status combinations[20]. Moreover, molecular subtyping divided breast cancers into five main categories; Luminal A, Luminal B, Her2 enriched, Triple negative, and normal breast-like tumours[4] depending mainly on receptor status. Luminal A tumours are mainly ER+ and have a favourable prognosis, due to their responsiveness to anti-hormonal treatment[9,18]. On the other hand, triple negative tumours (basal) have the worst prognosis due to the fact that they lack all three receptors[4]. This also resulted in treatment options being tailored according to the submolecular type and this was adopted in 2015 at the 14th St Gallen international breast cancer conference for some subtypes such as Her2 positive disease with node negative cancers up to 1 cm[17]. So, the results of investigating the survival of breast cancer tumours classified by submolecular types and studying their relationship with clinico-pathological features will provide an objective assessment about tumour biology in our region and our treatment outcomes.

Materials and Methods

This retrospective study revised the histopathology reports of all female patients who underwent surgery for breast cancer in the period from January 2013 until January 2014. After a 5-year period, the data concerning their survival was analysed along with their clinicopathological features. Inclusion criteria were female patients who had invasive non-metastatic breast cancer and were surgically operated on within the same period. Exclusion criteria included prior surgery on the same breast for malignancy, being given neoadjuvant chemotherapy, previously having had a contralateral breast cancer or having another malignancy diagnosed within five years of diagnosis of her breast cancer. Patients who lost follow up after surgery and could not be contacted were also dropped from the study. The total number of patients that were accounted before exclusion was 161 patients, and the number of excluded patients were 32 patients. Our sample represents 80.1% of the total number of patients treated. Approval of the study was granted by the Institutional Review Board. The clinicopathological data included age of patients at diagnosis, tumour type, tumour size, tumour grade, lymph nodes (LN) involved and receptor status; Oestrogen receptor (ER), Progesterone receptor (PR) and Human epidermal growth factor 2 receptor (Her2).

The age of patients at diagnosis was divided into three categories; less than 40, 40–60 and over 60 years. The invasive breast cancer histopathological type used World Health Organization (WHO) 2012 classification [13,14](Table I). The grading system used was the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system (Table II). Immunohistochemical (IHC) staining assays were used for reporting ER, PR and Her2 status. In cases where HER2 staining was borderline (+2), fluorescence in situ hybridization analysis was performed. For Staging, the American Joint Committee on Cancer (7th ED) (AJCC) classification[15] was used which relied on size of tumour, number of lymph nodes and if distant metastasis was found (Table III). A table was then constructed studying the patient criteria. (Table IV), then another table was formulated to study the relationship between both clinical and tumour pathological characteristics with tumour molecular subtypes. (Table V). Data was analysed using SPSS v21. Chi-square tests were used to find associations and $P < 0.05$ was considered significant.

Table I: WHO Classification of Breast Tumours 2012

Invasive carcinoma of no special type (NST) 8500/3
Pleomorphic carcinoma 8522/3
Carcinoma with osteoclast-like stromal giant cells / Carcinoma with choriocarcinomatous features / Carcinoma with melanotic features 8035/3
Invasive lobular carcinoma 8520/3
Classic lobular carcinoma
Solid lobular carcinoma
Alveolar lobular carcinoma
Pleomorhic lobular carcinoma
Tubulolobular carcinoma
Mixed lobular carcinoma
Tubular carcinoma 8211/3
Cribriform carcinoma 8201/3
Mucinous carcinoma 8480/3
Carcinoma with medullary features
Medullary carcinoma 8510/3
Atypical medullary carcinoma 8513/3
Invasive carcinoma NST with medullary features 8500/3
Carcinoma with apocrine differentiation / Carcinoma with signet-ring-cell differentiation / Invasive micropapillary carcinoma 8507/3
Metaplastic carcinoma of no special type 8575/3
Low-grade adenosquamous carcinoma 8570/3
Fibromatosis-like metaplastic carcinoma 8572/3
Squamous cell carcinoma 8070/3
Spindle cell carcinoma 8032/3
Metaplastic carcinoma with mesenchymal differentiation Chondroid differentiation 8571/3 Osseous differentiation 8571/3
Other types of mesenchymal differentiation 8575/3
Mixed metaplastic carcinoma 8575/3
Myoepithelial carcinoma 8982/3
Epithelial-myoepithelial tumors / Adenomyoepithelioma with carcinoma 8983/3
Adenoid cystic carcinoma 8200/3
Rare types
Carcinoma with neuroendocrine features
Neuroendocrine tumor, well-differentiated 8246/3
Neuroendocrine carcinoma poorly differentiated (small cell carcinoma) 8041/3
Carcinoma with neuroendocrine differentiation 8574/3
Secretory carcinoma 8502/3
Invasive papillary carcinoma 8503/3
Acinic cell carcinoma 8550/3
Mucoepidermoid carcinoma 8430/3
Polymorphous carcinoma 8525/3
Oncocytic carcinoma 8290/3
Lipid-rich carcinoma 8314/3
Glycogen-rich clear cell carcinoma 8315/3
Sebaceous carcinoma 8410/3

.

Precursor lesions:

Ductal carcinoma in situ 8500/2
Lobular neoplasia
Lobular carcinoma in situ (LCIS)
Classic lobular carcinoma in situ 8520/2
Pleomorphic LCIS (Atypical lobular hyperplasia) 8519/2*
Intraductal proliferative lesions
Usual ductal hyperplasia
Columnar cell lesions including flat epithelial atypia
Atypical ductal hyperplasia
Papillary lesions
Intraductal papilloma 8503/0
Intraductal papilloma with atypical hyperplasia 8503/0
Intraductal papilloma with ductal carcinoma in situ 8503/2*
Intraductal papilloma with lobular carcinoma in situ 8520/2
Intraductal papillary carcinoma 8503/2
Encapsulated papillary carcinoma 8504/2
Encapsulated papillary carcinoma with invasion 8504/3
Solid papillary carcinoma In situ 8509/2 Invasive 8509/3

.

Table II: Elston-Ellis Score

Grade	1	**2**	**3**
Tubule Formation	Majority of tumour >75%	Moderate degree 10-75%	Little or none <10%
Mitotic Count	0–9 mitosis/ 10 HPF	10–19 mitosis/ 10 HPF	20 or > mitosis/ 10 HPF
Nuclear Pleomorphism	Small regular uniform cells	Moderate nuclear size and variation	Marked nuclear variation

Combined Histologic Grade (Addition of score for each category)	
Low grade (I)	3–5
Intermediate grade (II)	6–7
High grade (III)	8–9

Table III: AJCC Breast cancer TNM classification

		Stage	T	N	M
T - Tumour		0	Tis	N0	M0
T1	Tumour <=2cm	I	T1	N0	M0
T2	Tumour > 2 cm and <=5cm)		T0	N1	M0
T3	Tumour > 5 cm		T1	N1	M0
T4	Any size with direct extension to chest wall or skin	IIA	T2	N0	M0
N - Lymph node		IIB	T2	N1	M0
N0			T3	N0	M0
N1	1-3 Lymph nodes involved	IIIA	T0	N2	M0
N2	4-9 Lymph nodes involved		T1	N2	M0
N3	>9 Lymph nodes involved		T2	N2	M0
M – Metastasis			T3	N1/N2	M0
M0	No distant metastasis	IIIB	T4	Any N	M0
M1	Distant metastasis	IIIC	Any T	N3	M0
		IV	Any T	Any N	M1

Table IV: Patient Criteria

Age (years)	No (%)
< 40	18 (13.95%)
40–60	66 (51.17%)
> 60	45 (34.88%)
Tumour Size (CM)	
T1 (<=2cm)	19 (14.73%)
T2 (> 2 cm and <=5cm)	82 (63.57%)
T3 (> 5 cm)	28 (21.70%)
Tumour grade	
Grade 1	11 (8.53%)
Grade 2	54 (41.86%)
Grade 3	64 (49.61%)
Lymph node Involved	
N0 (No LN)	43 (33.33%)
LN involved (N1,N2,N3)	86 (66.67%)
N1 (1–3LN)	29 (22.48%)
N2 (4–9 LN)	35 (27.13%)
N3 (> 9 LN)	22 (17.05%)

Table V : Relationship between molecular subtypes and other variables

	Luminal A 86(66.67%)	Luminal B 21(16.28%)	Her2 enriched 12(9.30%)	Triple Negative 10(7.75%)	P Value
Age (years)					
< 40	7(5.43%)	8(6.20%)	2(1.55%)	1(0.78%)	
40–60	45(34.88%)	8(6.20%)	8(6.20%)	5(3.88%)	0.022
> 60	34(26.36%)	5(3.88%)	2(1.55%)	4(3.10%)	
Tumour Size (Cm)					
T1 (<=2cm)	13(10.08%)	3(2.33%)	2(1.55%)	1(0.78%)	
T2 (> 2 cm & <=5cm)	57(44.19%)	11(8.53%)	8(6.20%)	6(4.65%)	0.82
T3 (> 5 cm)	16(12.40%)	7(5.43%)	2(1.55%)	3(2.33%)	
Tumour grade					
Grade 1	8(6.20%)	1(0.78%)	1(0.78%)	1(0.78%)	
Grade 2	42(32.56%)	7(5.42%)	1(0.78%)	4(3.10%)	0.15
Grade 3	36(27.91%)	13(10.08%)	10(7.75%)	5(3.88%)	
Lymph node involvement					
Negative	27(20.93%)	9(6.98%)	5(3.88%)	2(1.55%)	0.54
Positive	59(45.74%)	12(9.30%)	7(5.43%)	8(6.20%)	

Luminal A; ER+ and/or pR+, Her2- , Luminal B; ER+ and or pR+, Her2+, Her2 Enriched; ER-, pR -, Her2+, Triple negative: ER, pR-, Her2-

RESULTS

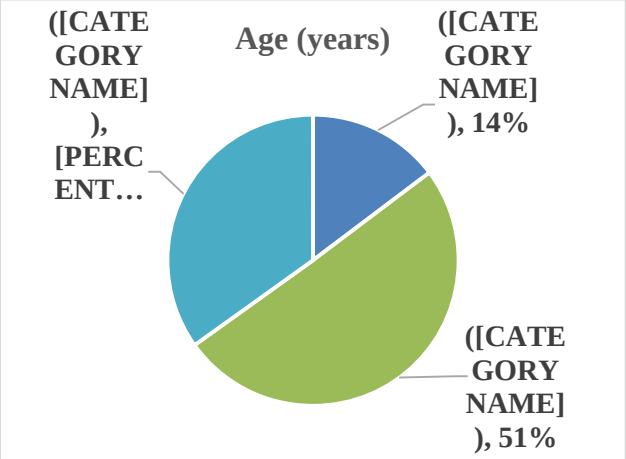
Out of the 129 cases of breast cancer reviewed, the most common age group was (40–60) years in 66 (51.16%) patients followed by 45 (34.88%) patients in the 'over 60' age group, and only 18(13.95%) patients were less than 40 years old.

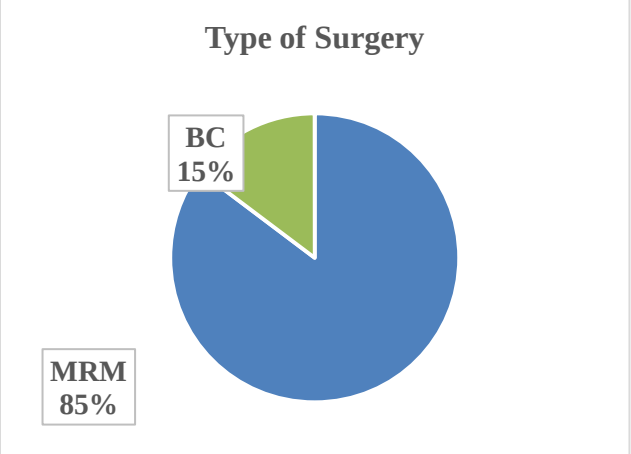
There was a statistically significant relationship between molecular subtype and age groups used in the study (P = 0.022). For the type of surgery that was done for these patients, 110 (85.27%) underwent Modified Radical Mastectomy (MRM) and only 19 (14.73%) had breast conserving surgery (BCS).

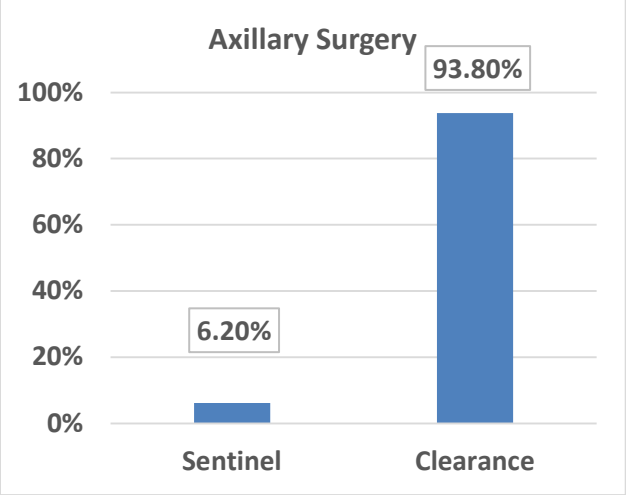
Axillary dissection was done for 121 (93.80%) patients and Sentinel LN in only 8 (6.20%) patients.

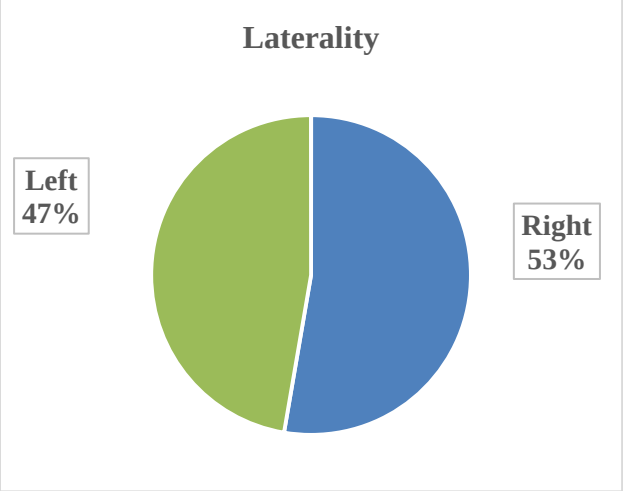
Right-sided breast tumours were observed more often in 68 (52.71%) patients. Regarding LN involvement, 86 (66.67%) patients had axillary LN involvement whereas only 43 (33.33%) patients had no LN involved. The range of LNs was from 0–48 LN with an average of 4.4. Twenty nine (22.48%) patients had (1–3 LN) involved, whereas 35 (27.13%) patients had (4–9) LN involved and only 22 (17.1%) patients had more than (9 LN) involved. The average tumour size was 3.91 cm (range 0.2–12cm). Nineteen (14.72%) patients had tumours below 2 cm (T1) while 82 (63.57%) patients had tumour sizes between 2 and 5 cm (T2) and only 28 (21.70%) patients had a tumour size over 5 cm. One hundred and fifteen (89.15%) patients had invasive ductal carcinoma (IDC) nonspecific type (which was the most common tumour) followed by invasive lobular carcinoma (ILC) in nine cases (6.98%). There were four (3.10%) patients with Special type of IDC tumours and one (0.78%) with an invasive neuroendocrine tumour. The histopathological grade was mostly grade 3 in 64 (49.61%) patients, grade 2 in 54 (41.86%) patients and the least was grade 1 in 11 (8.53%) patients. As for receptor status: 105 (81.40%) patients were ER positive, 94 (72.87%) patients were PR positive and 96 (74.42%) were HER2

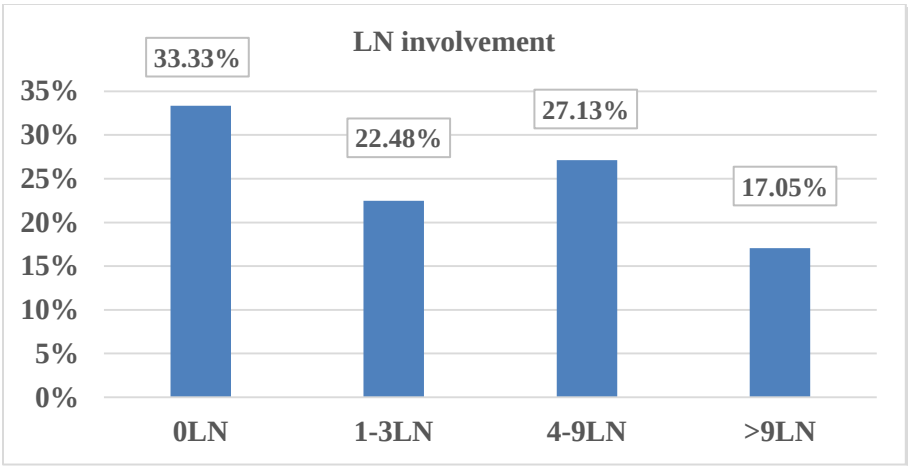
negative. The Luminal A subtype was observed in 86 (66.6%) patients, the Luminal B subtype was observed in 21 (16.28%) patients, the Her2-enriched subtype occurred in 12 (9.30%) patients and the Triple Negative subtype was only observed in 10 (7.75%) patients. When the patients were divided according to stage, there were nine (6.98%) patients with stage 1, 58 (44.96%) patients with stage 2 and 62 (46.06%) patients who had stage 3. The five-year survival according to stage was 100% in stage 1, 87.93% in stage 2 and 69.35% in stage 3.

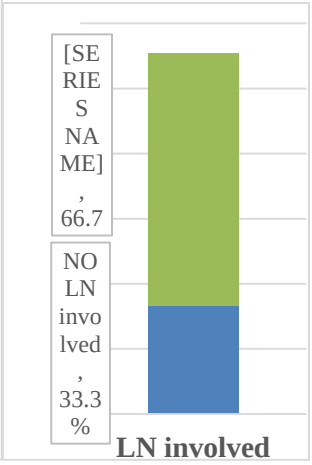


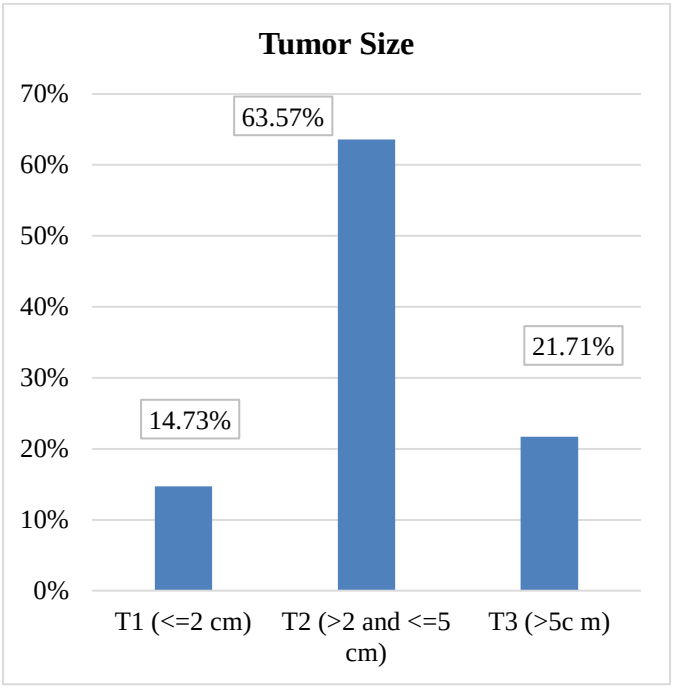


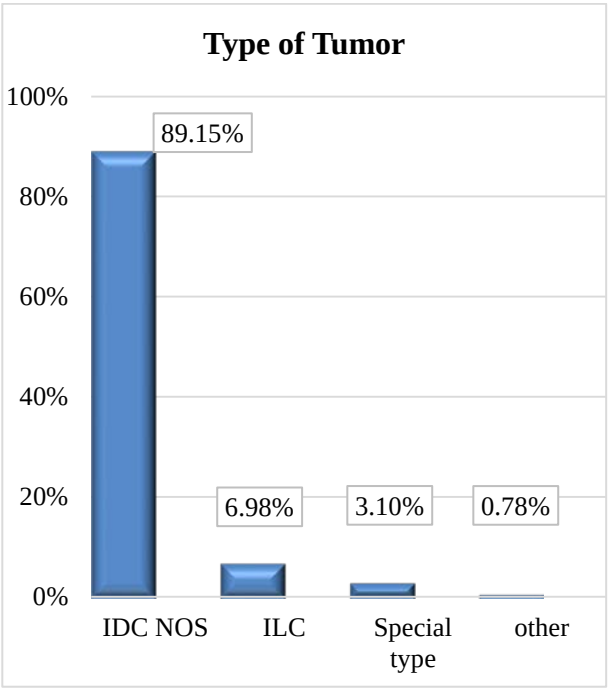


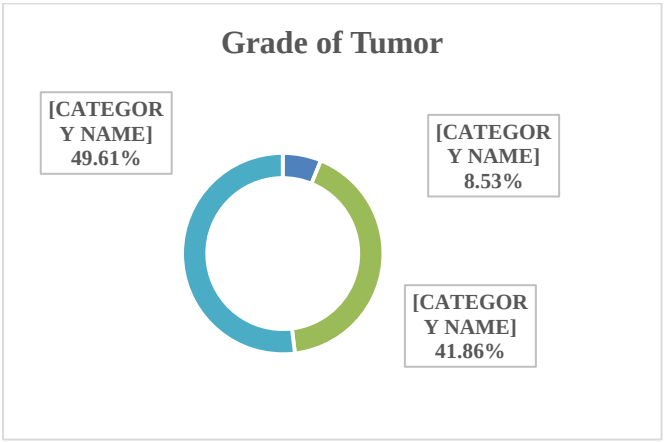


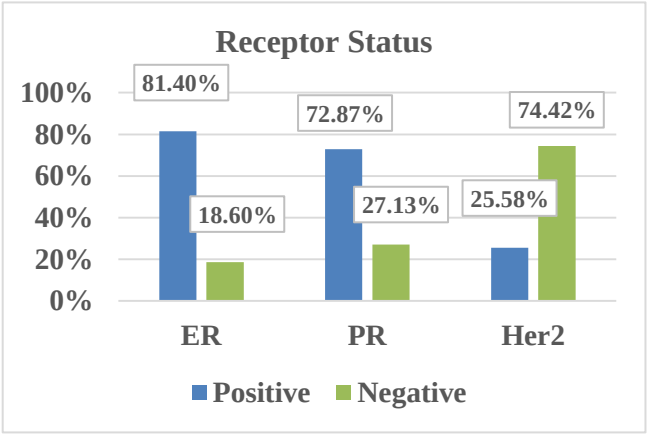

LN involvement
33.33%
22.48%
27.13%
17.05%
35%
30%
25%
20%
15%
10%
5%
0%
0LN
1-3LN
4-9LN
>9LN

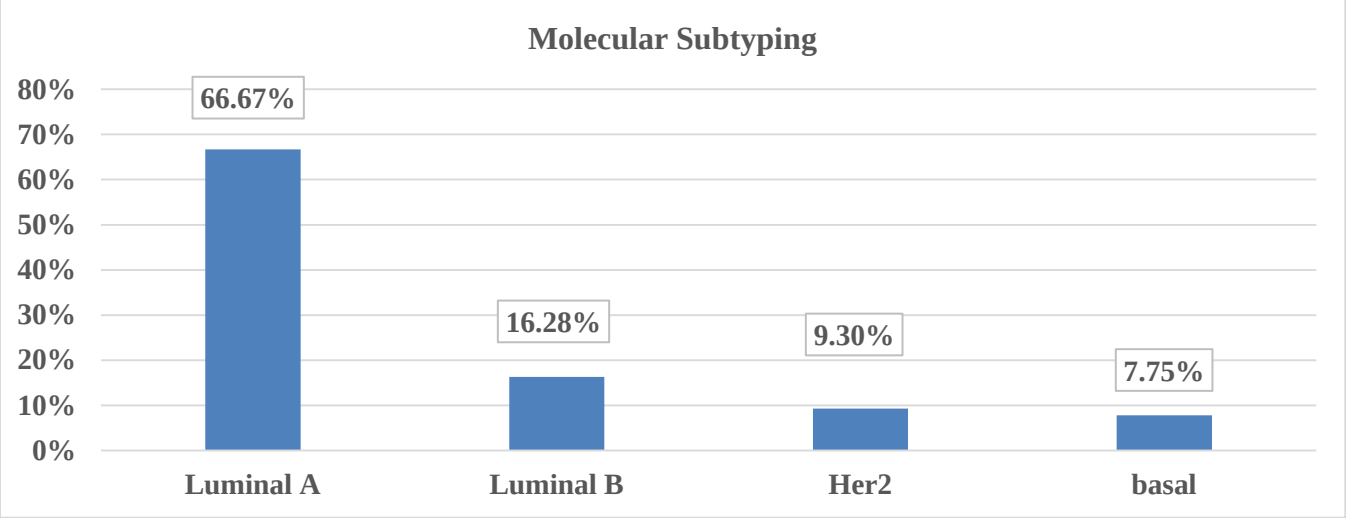

[SERIES NAME], 66.7
NO LN involved, 33.3 %
LN involved

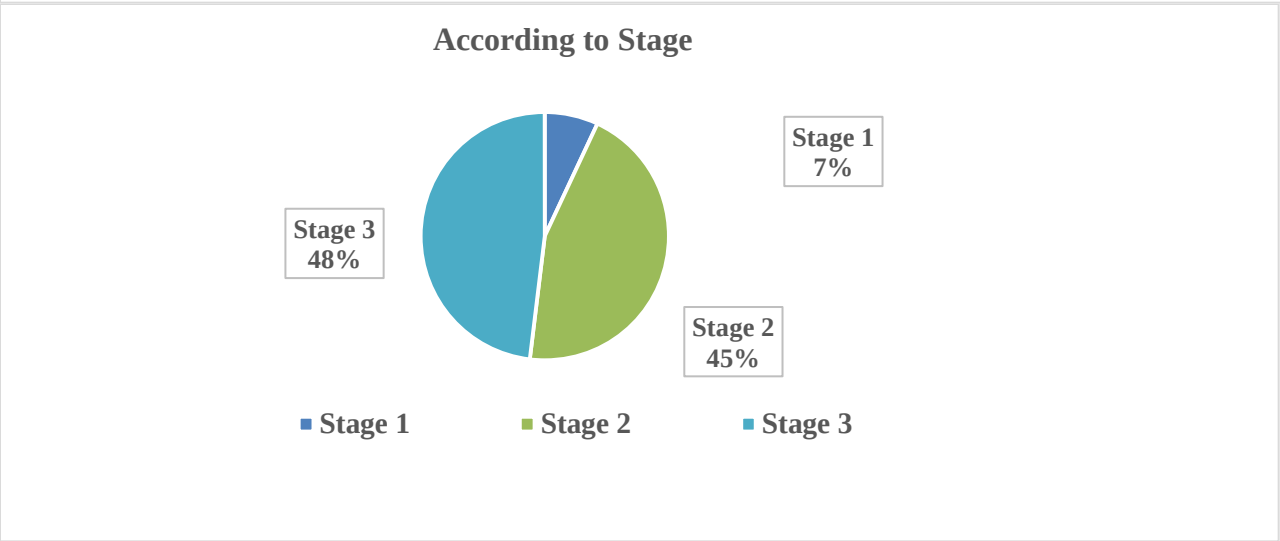

Tumor Size
70%
60%
50%
40%
30%
20%
10%
0%
63.57%
21.71%
14.73%
T1 (<=2 cm)
T2 (>2 and <=5 cm)
T3 (>5c m)

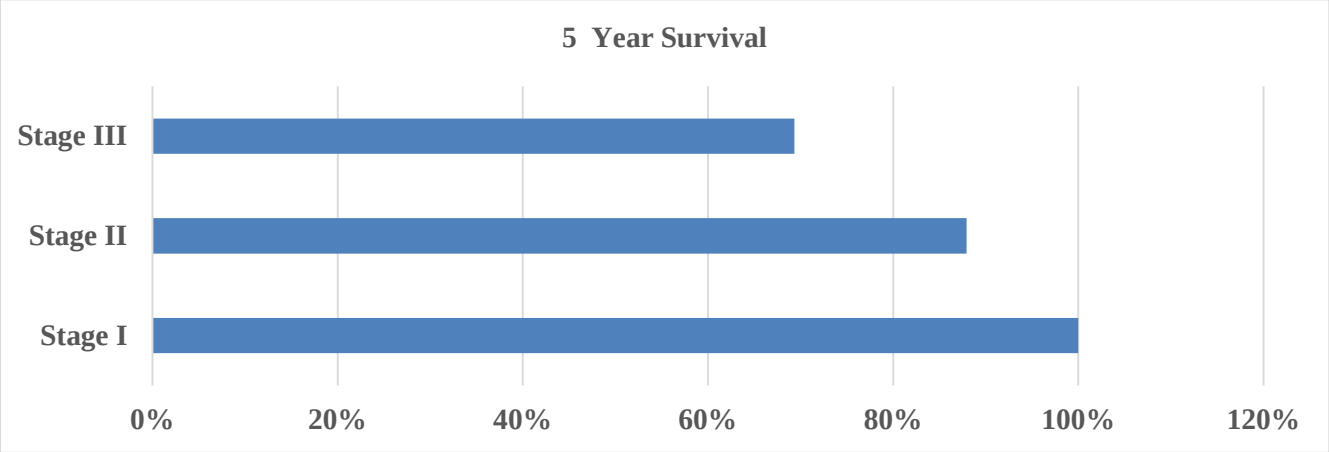

Type of Tumor
100%
80%
60%
40%
20%
0%
89.15%
6.98%
3.10%
0.78%
IDC NOS
ILC
Special type
other


Grade of Tumor
[CATEGORY NAME] 49.61%
[CATEGORY NAME] 8.53%
[CATEGORY NAME] 41.86%


Receptor Status
100%
80%
60%
40%
20%
0%
81.40%
18.60%
72.87%
27.13%
74.42%
25.58%
ER
PR
Her2
Positive
Negative


Molecular Subtyping
80%
70%
60%
50%
40%
30%
20%
10%
0%
66.67%
16.28%
9.30%
7.75%
Luminal A
Luminal B
Her2
basal


According to Stage
Stage 1
7%
Stage 2
45%
Stage 3
48%
Stage 1
Stage 2
Stage 3


5 Year Survival
Stage III
Stage II
Stage I
0%
20%
40%
60%
80%
100%
120%

DISCUSSION

The majority of patients in our study had Luminal A (66.6%) (ER+ and/or PR+ and Her2-) molecular subtype, which is consistent with a study conducted in Jordan by Shomaf et al[11] which found it to be around 60%. Similar studies also concluded that luminal cancers were the most common breast cancer subtypes (70–80%) [5] and that luminal A is the most commonly diagnosed subtype[6]. Most of the breast cancer patients in our study fell into the 40–60 year age group, which is younger than the most common age groups occurring in various other western countries. McGuire reported in a multicentre study[5] that the most frequent age group was over 60 years (54%). However, we noticed a significant P value between the age groups we used and the molecular subtype in our region.

The type of surgery performed was the Modified Radical Mastectomy (MRM) in more than 80% of cases due to many factors such as a relatively large tumour to breast ratio, central tumours, multifocal tumours and the preference among patients. Furthermore, the fact that most of the patients had ipsilateral metastatic axillary LN (proven by Fine Needle Aspiration) prior to surgery warranted axillary dissection at the time of surgery whereas only one third of patients had negative LN involvement and hence some of them underwent sentinel LN biopsy. Regarding the laterality of tumours, right sided breast tumours were observed in a higher percentage of patients than left sided with no clear cause; most studies reported a similar percentage between right and left breast cancers.[4]

Many studies have shown that the best prognosis is for patients with Luminal A tumours and negative LN involvement[6,9,12]. In our study, this category was only reported in one fifth of patients. Noticeably, the most frequent tumour size was between 2 and 5 cm in around 64% of patients. This percentage may be explained by a lack of screening awareness, or shame of being clinically examined due to social or religious attitudes in our country.

The most common histological type of tumour is invasive ductal carcinoma (IDC) nonspecific type reported in 89% of patients. A similar result was observed in a large prospective cohort study conducted in Germany to assess prognosis by Hennigs where the percentage of IDC was 85%[7].

Surprisingly, the most common histopathological grade was 3 in approximately 50% of patients, which might explain why two thirds of patients had positive LN involvement. However, this is different from previous results reported in a German cohort study in which the majority of tumours were grade 2 (50% of patients) and the more aggressive grade 3 tumours were observed in only 26% of patients[7].

The receptor status in the majority of patients was ER, PR positive and Her2 negative in approximately 80%, 73% and 74% patients, respectively. The Luminal A subtype was seen in two thirds of patients, followed by Luminal B subtype in 16.28%, both of which carry a good prognosis due to the fact that they respond to anti-hormonal treatment in pre and postmenopausal women. When dividing the patients according to the AJCC TNM classification for stages; 44% were stage 1, approximately 7% were stage 2 and the rest were stage 3.

The five-year survival according to stage was 100%, 87.93% and 69.35% for stages 1, 2 and 3, respectively. The results are far superior to the results of a five year survival study conducted in Jordan in 2002 by Tarawneh et al, which showed a five year survival of 82.7%, 72.2% and 58.7% for stages 1, 2, and 3 respectively[19], but again, during the period from 2002 till 2013, many advances in screening, surgical and medical treatments for breast cancer evolved and this may explain the vast difference. Similar results obtained to our study was reported in The Saudi Cancer Registry in 2015, where the five-year survival for breast cancer patients there was

100%, 86% and 57.2% for stages 1, 2 and 3, respectively[10]. However, the survival statistics obtained from the American cancer Society[8] in 2019 are still higher especially for locally advanced tumours necessitating further investigation for possible causes.

When studying the relationship of age, tumour size, tumour grade and LN involvement with molecular subtype there was no significant relationship except in the age group category (P value = 0.022). This finding was also noted in a study conducted in Algeria by Cherbel et al, where they concluded that there was a significant difference in the distribution of age at diagnosis among the four cancer subtypes (P = 0.004)[16]. But in study done in a university hospital in Jordan by Obeidat et al[4] did not find a significant relationship with the above variables but the age group that was used in their study was different than ours.

CONCLUSIONS

Approximately 50% of patients were aged 40–60 years, presented with stage 3 breast cancer, with a tumour size T2 (2–5 cm), and on presentation had LN involvement. On the other hand, the most frequent subtype was Luminal A, which has a good prognostic outcome. And although the majority of characteristics favoured a relatively advanced tumour, the five-year survival for stage 3 was nearly 70%. There was a significant relationship between molecular subtype and the age groups used in our study warranting additional larger studies. Follow up of breast cancer patients is very important to objectively assess the treatment protocols that were used and to evaluate the survival in these patients and to plan strategies in order to screen such patients earlier. A larger scale study is required to understand why patients are being diagnosed rather late in terms of stage in Jordan and to assert the findings of our study.

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