Clinico-Pathological Study of Breast Cancer; 5 Years Experience at Clinical Oncology Department Zagazig University

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Abstract: This study was done from record of 1650 with breast cancer cases from 5759 total cancer cases between Jan 2004 to December 2008 where data retrieved between may 2015 to November 2015, and data were analyzed at December 2015. Major clinico-pathological parameters were systematically investigated in this study. Invasive duct carcinoma is the most common type (82 %) followed by invasive lobular carcinoma (12 %. MRM done in (95.4%) and BCS in (4.6%). chemotherapy was given for 95 % of patients, Doxirubicin –containing regimen was used in (76 %) of patients. hormonal treatment was given1155 patients, 76.1 %were treated with tamoxifen, while radiotherapy for 88 % of cases, the radiotherapy treated volumes according to type of breast surgery). Univariate analysis show that menopausal status & Histological tgrade & T & N & hormone receptor status & HER2 oncogen were significant while Age & histological type not significant. In histological grade: Grade II: 3, 5, 7 Year over all survival (68.9 %, 63.7%, 58.5 %). Univariate Analysis show that adjuvant treatment & adjuvant hormonal treatment were significant Type of surgery and adjuvant chemotherapy & adjuvant radiotherapy were not significant in Adjuvant hormonal treatment +ve cases 3,5,7 over all survival (70.5%, 61.2%, 58.7%). Distant Metastasis Free Survival in 3, 5.7 years DFS (72%, 59.1%, 58.7%). Adjuvant hormonal treatment: +ve cases 3,5,7 years RFS (72%, 55.7%, 54.8%).
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1. Introduction:

Cancer of the breast represents 33% of all female cancers. The most common occurrence is between 40 and 60 years of age. It occurs commonly in the Western world, accounting for 3-5% of deaths, yet is a rare tumor in Japan. In developing countries, it accounts for 1-3% of deaths. Only 1% of patients with breast cancer are male[1]. A prognosis is how cancer will affect a patient. There are many prognostic factors associated with breast cancer: Staging, tumor size and location, grade, whether disease is systemic, recurrence of the disease, and age of patient[2]. Stage is the most important, as it takes into consideration size, local involvement, lymph node status and whether metastatic disease is present (Robb et al., 2007). Breast MRI may be used to distinguish between benign and malignant areas, reducing the number of breast biopsies done to evaluate a suspicious breast mass. Although MRI can detect tumors in dense breast tissue, it cannot detect tiny specks of calcium (known as micro calcifications), which account for half of the cancers detected by mammography[3], and hence using diffusion-weighted imaging (DWI) combined to MRI enhances such differentiation between malignant and benign breast lesions[4]. Magnetic resonance (MR) spectroscopy is providing biochemical information about the tissue under investigation[5]. Several studies over the past decade documented that Cho is specific to malignancy and can be used to differentiate cancerous from benign tissues[6]. Mastectomy is the usual surgical procedure carried out in many parts of the world, after the diagnosis of breast cancer has been established. For patients with operable breast cancer undergoing mastecotmy, radiation therapy to the chest wall and regional lymph nodes to a total dose of 5000-6000 cGy is usually employed [7]. Randomized trials suggest that postmastectomy patients with any number of positive nodes derive a disease free and overall survival benefit from radiotherapy. Radiation clearly showed reduction in the incidence of local recurrence in all and also improved survival in some.[8].

2. Patients and Method:

This study was done from record of 1650 with breast cancer cases from 5759 total cancer cases between Jan 2004 to December 2008 where data retrieved between may 2015 to November 2015, and data were analyzed at December 2015. Breast cancer cases consider 29% of all cancer cases. Data Collected Via histopathological reports and Metastatic work up including chest xray and Pelvi-Abd US and isotopic bone scan. Study Parameters and their definition: Major clinico-pathological parameters were systematically investigated in this study. Age of patient divided in two age group ($\leq$ 35 and more than >35). Menstrual status: all patient divided into 3 groups

(premenpausal -perimenopausal and post menopausal). Surgery divided into 3 groups. MRM–BCS- other surgical procedures. Histopathological classification according to (WHO) world health organization **(**Histopathological classification according to (WHO) world health organization [9]**.** Estrogen and progesterone receptor (ER, PR) and human epidermal growth factor receptor -2 expression (HER-2). TNM staging: for all patients according to American Joint committee on cancer / internation union against cancer (AJCC/UICC[10]**).**

Treatment modalities:
1st surgical procedures. Chemotheraptic agent. Hormonal treatment. Radiotherapy treatment.

Statistical Analysis:
All data were analyzed using SPSS 15.0 for windows (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for windows (MedCalc Software bvba). Continuous data are expressed as the mean ± SD & median (range), and the categorical data are expressed as a number (percentage). Overall Survival (OS) was calculated as the time from surgery to death or date last known alive (censored). Relapse Free Survival (RFS) was calculated from date of surgery to recurrence or metastasis, or date last known to be relapsing free (censored). Locoregional Recurrence Free Survival (LRFS) was calculated from date of surgery to recurrence (chest wall, regional lymph nodes & scar), or date last known to be recurrence free (censored). Distant Metastasis Free Survival (DMFS) was calculated from date of surgery to distant metastasis, or date last known to be distant metastasis free (censored). Stratification of OS, & RFS was done according to all possible prognostic factors. These time-to-event distributions were estimated using the method of Kaplan-Meier, and compared using two-sided exact stratified log-rank tests. The Cox proportional hazards regression model was used to identify the independent prognostic factors as well as to estimate their effects on OS, & RFS. For one tailed tests P < 0.05 was considered statistically significant, P < 0.05 was considered highly statistically significant,

and P > 0.05 was considered non statistically significant.

3. Results:
There was 1650 patients age distribution ranged from 20 year to 91years old with median age 51 years old divided into two groups: less than or equal 35 years old (165 cases 10. %) and more than 35 years old (1485 cases 90%). Premenopausal (577 cases 35 %), Perimenopausal (165 cases 10 %) and post menopausal (908 cases 55 %).

Tumor characteristics:
Invasive duct carcinoma is the most common type (82 %) followed by invasive lobular carcinoma (12 %) **Grade:** Grade II (74%) the most common lesion (table 1)**. TMN staging** T2 is the most common lesion (59 %) followed by T3(21%) N1 the most common lesion 40 % (table 1) **Hormonal receptor status** According to histochemical detection, ER +ve patients (71 %) and ER -ve patients (29%) -Her2 oncogene expression. Her2 over-expression was +ve in 37 % of cases (table 2)**.**

Treatment modalities:
Distribution of Surgical treatment procedures **MRM** done in (95.4%) and BCS in (4.6%) It was observed that MRM was more physical disfigurement and Psychological trauma **Chemotherapy:** 95 % treated with chemo therapy, Doxorubicin –containing regimen was used in (76 %) of patients (table 3) **Hormonal treatment:** 1155 patients treated with hormonal treatment, 76.1 %were treated with tamoxifen. Aromataze inhibitors in postmenopausal females 23 % (884 cases 76.5 %) treated for 5 years

Adjuvant radiotherapy:
88.2 % of cases were treated with radiotherapy, and most of them (1317 cases 90.7%) treated by cobalt machine the radiotherapy treated volumes were Chest wall + lymphatics in 83.7% .the majority of cases (1419 cases 97.7 %) had time gap > months after surgery . Radiotherapy doses was 50 Gy in (1214 cases 83.6%) (table 2). In histological Grade II: 3, 5, 7 Year over all survival 98.8 %, 82.5 % and 73 %) table (3).

Table (1): Patient's Characteristics

%	No.	Patient's Characteristics
Total =1650		
		Age (year)
51.31 ± 11.8		Mean ± SD
51 (20 – 91)		Median (Range)
10%	165	≤ 35 year
90%	1485	> 35 year
		Menopausal status
35%	577	Premenopausal
55%	908	Postmenopausal
10%	165	Perimenopausal

Table (2): Tumor Characteristics.

Total =1650			Total =1650		
%	No.	**Treatment**	%	No.	**Tumor Characteristics**
Type of surgery			**Histopathological type**		
95.4%	1574	MRM	82%	1353	Invasive duct carcinoma
4.6%	76	Conservative	12%	198	Invasive lobular carcinoma
Chemotherapy			3%	50	Mucinous carcinoma
5%	82	No	1.7%	28	Medullary carcinoma
95%	1568	Yes	0.9%	15	Sarcoma
Type of chemotherapy			0.4%	6	Other
77.6%	1217	FAC	**Grade**		
10.8%	170	FEC	2%	33	Grade I
10.4%	163	CMF	74%	1221	Grade II
1.1%	18	Other	24%	396	Grade III
Duration of chemotherapy					Surgical margin
53.3%	879	4 months	82%	1353	Negative
22.8%	376	5 months	18%	297	Positive
19%	313	More than 5 months	**T**		
Hormonal treatment			10%	165	T1
30%	495	No	59%	973	T2
70%	1155	Yes	21%	347	T3
Type of hormonal treatment N=1155			10%	165	T4
76%	878	Tamoxifen	**N**		
23%	266	AI	29%	479	N0
1%	11	Other	40%	660	N1
Duration of hormonal treatment N=1155			21%	346	N2
76.5%	884	5 years	10%	165	N3
23.2%	267	<5 years	**Hormonal receptors status**		
0.3%	4	>5 years	29%	479	Negative
Radiotherapy dose 1456 patients = 88.2%			71%	1171	Positive
4.4%	72	45 Gy	**HER2/neu**		
74.1%	1223	50 Gy	63%	1040	Negative
9.8%	161	Other	37%	610	Positive

Table (3): Correlation between Overall Survival & basic characteristics of patients

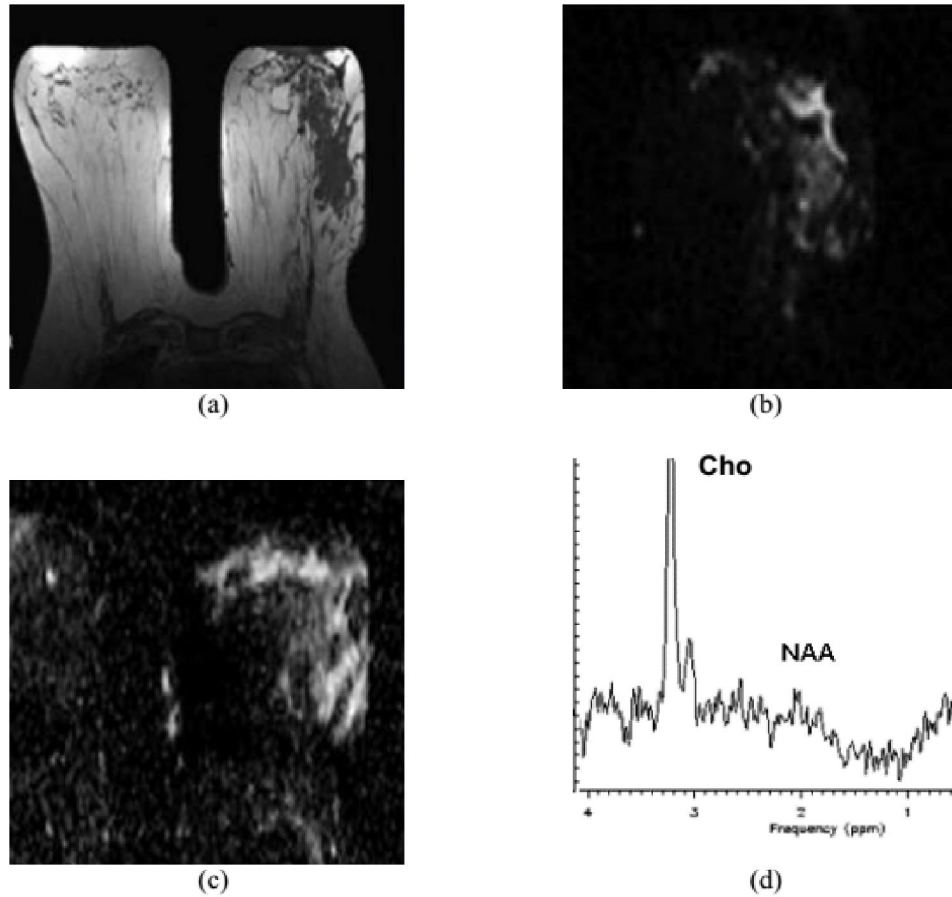| p-value§	HR (95%CI)	Overall Survival (%)			Basic characteristics of patients and tumors
		7 year	5 year	3 year	
		64.5%	79.5%	93.1%	**all patients Median S 100 month**
					Grade
P 0.01		73%	82.5%	98.8 %	Grade I,II
		38%	62%	75 %	Grade III
					T
		62.7%	62.7%	72%	T1
P 0.04		75%	83.8%	98.3%	T2
		50%	80%	92 %	T3
		35%	70%	87%	T4
					N
		90.7%	95%	98%	N0
P 0.009		70%	80%	96.9%	N1
		44 %	70%	86.4%	N2
		33%	53%	78%	N3

(a)

(b)

(c)

(d)

Fig. 1: A 61 year old female patient: (A) Axial T1WI shows right upper area, ill-defined hypointense breast mass with speculated margins. (B) DWI at b= 1000 shows bright signal of the mass denoting restriction. (C) Apparent ADC map reveals hypointense mass (the mean ADC value of the cystic lesion = 0.79 _ 10_3 mm2/s). (D) MRS of the lesion reveals tall choline peak. The lesion histopathologically proved as invasive lobular carcinoma

Table (4): Relationship between DFS and basic characteristics of patients and tumors.

p-value§	HR (95%CI)	Disease Free survival (%)			Basic characteristics of patients and tumors
		7 year	5 year	3 year	
		45	57	84.4	**Median DFS All patients 66 m**
					Grade
0.023		50 %	58.6%	90%	Grade I, II
		29.2%	50 %	66.6%	Grade III
					T
0.028		30%	30 %	70 %	T1
		68.8%	70.2 %	86.4 %	T2
		6%	40%	60%	T3
		2%	38 %	54 %	T4
					N
0.0013		87%	88%	98 %	N0
		47%	47 %	91 %	N1
		4%	40%	70 %	N2
		1%	38%	51.5%	N3
0.302		42.3%	42.3%	63.9%	< 35 y
		50.9%	52.1%	66.2%	>35 y

4. Discussion:

This is a retrospective study on 1650 female patients with breast cancer treated at the Clinical Oncology department, Zagazig University Hospitals between Jan 2004 to December 2012 with a median follow up duration of about 68 months. The age of the patients in the present study ranged between 20 and 91 years with the peak incidence in the fifth decade (44.9%). The median age was 51 years and premenopausal women constituted 35 % of the studied group. The results are similar to other Egyptian studies[11].

The median age of the studied group is relatively similar to the 50 years of age reported in western series while the postmenopausal group in the present study was 55% as compared to 67% in western series[12]. The frequency of T1 in the present series was (10%). T2 was 59 %, T3 was 21% while T4 tumor constituted 10% of the studied group. These data were similar to El-Mongy et al [1] who revised 1009 patients treated for primary breast cancer between 1999–2003 and reported that Five hundred and fourteen patients (51%) had pathological T2 lesion followed T3 in 333 patients (33%) and only 70 patients (7%) had T1 tumor. T4 tumor constituted 9 % of the studied group., were different to that reported by El-gantiry[13] who revised 1208 premenopausal women treated between 1 980 and 1989 and reported 4%, 45%, 38.5% and 15 % in T1, T2, T3 and T4 respectively. The frequency of T1 tumor is much lower and the frequency of T3and T4 tumor is higher in our series than reported in western series[14]. The frequency of N0, N1, N2 and N3 in the present series were 29%, 40%, 21% and 10%. The incidence of negative lymph nodes in the present study was similar to El-Mongy et al[1] (27.9%), was higher than the 13% reported by El-gantiry[13] and this may be explained by more awareness of doctors and early presentation of the patients. In Western countries the incidence of pathological negative lymph nodes is higher (50%)[15]. The low incidence of T1 tumors and lymph nodes negative in Egypt may be explained by the lack of screening and early detection, Health education and low socioeconomic levels leading to delay of seeking medical advice. In contrast, in Western countries programs of self examination and screening mammography are frequently carried out. Fisher et al[16] have clearly demonstrated a significant improvement in local control with the use of radiation therapy and systemic therapy compared with radiation therapy alone. A meta-analysis of randomized trials by Vinh-Hung and Verschraegen[17], comparing breast-conserving surgery without radiation to breast-conserving surgery with radiation confirms an approximate three folds reduction in local relapse with radiation therapy and an 8.6% improvement in

mortality. In the present study, 385 patients of 1650 developed loco regional relapse (23.3%) which was in different to the reported results by Nazmy [18] who reported 3.3% rate of loco regional relapse. In the present study, 822 (49.8 %) patients were relapse free, this can be contributed to, first the lack of computer system planning and the more effort given for the quality assurance and lack of LINAC in this time, second the wide use of systemic adjuvant treatment in indicated patients as 95% of the studied patients received adjuvant systemic treatment the era at which generic drugs was the almost always used, and finally possibly different environmental conditions.

In our study, the 3 and 5 year relapse free survival were high for patients with negative node (98% and 88%) and for patients with N1 (91% and 47%) and decreased with the increase for patients with N2 reaching 70% and 40% and for patients with N3 reaching 51.5% and 38%. The 3 and 5 year RFS for patients with negative lymph nodes in the present study is higher than reported by Nazmy (2000), this may be explained by the fact that 95.3 % of the patients received chemotherapy treatment in the present study, similar 3 and 5 year RFS were obtained by Nazmy (2000) for patients with more than 10 positive lymph nodes. Lower survival rates obtained from trials by Greene et al. (2002) treated primarily with locoregional therapy alone revealed 5 years survival rates of 82.8 % for node negative, 73 % for 1 to 3 positive nodes, 45.7 % for 4 to 12 positive nodes, and 28.4 % for > 13 positive nodes, these results may be explained by absence of chemotherapy treatment in this study. The 3 and 5 year relapse free survival for T1 tumors was 70% and 30% respectively, and they decreased to 86.4% and 70.2 % for T2 tumors with further drop to 60% and 40% for T3 tumors and for T4 tumors (84% and 57%) respectively, (P=0.0287). This was similar to the results of Clarke et al[19], who reported local recurrence at 5 years in breast cancer patients treated by conservative surgery and irradiation therapy were 6% in T1 and 14% in T2, the risk of recurrence increases linearly with tumor size for patients with fewer than four lymph nodes involved with metastases. Thereafter, the prognostic weight of lymph node metastases generally supersedes tumor size, the 20-year breast cancer-specific, disease-free survival for node-negative patients treated with mastectomy alone is about 92% for pT1 tumors and 75% to 80% for patients for pT2 tumors Carter et al[20].

In the present study The 3 and 5 year relapse free survival rate for grade I and grade II tumors was 90% and 58 % in comparison to 66.6 % and 50 % for grade III tumors, this difference was statistically significant P 0.023. These results are similar to that reported by Ellis and Elston[21], who assessed Histological grade in 1831

patients and showed a very strong correlation with prognosis as patients with grade I tumors have a significantly better survival than those with grade II and III tumors (p <.0001). Relapse free survival at 3 and 5 years in patient ≤35 yeas 63.9 % and 42.2% and in patient > 35 years old relapse free survival 3 and 5 years was 66.2 %, 52.1% p value = 0.302. These results are in agreement with the results reported in Western series in which younger patients have a higher rate of lumpectomy failure as well as a higher rate of chest wall failure after mastectomy than do older patients. It is possible that age serves as a surrogate for higher risk tumors as younger women are more likely to have extensive intraductal carcinoma (EIC), high nuclear grade, lymphatic space invasion, and tumor necrosis. It is likely that the recurrence patterns seen in these young women are related to a combination of these adverse histological features[22] **(Nixon et al., 1994).**

Conclusion and Recommendations:
Multivariate analysis for different prognostic factors including age, tumor size, grade, positive LN and type of chemotherapy showed that the most important independent bad prognostic factors for relapse are positive LNs more than 10, tumor size T3, T4 and higher pathologic grade. This indicates that these groups of patients are in need of more aggressive treatment. Further analysis using well designed randomized trials for the group of patients with L. Ns negative and those with 1-3 positive LNs is needed. More wide use of programs of self examination and screening mammography are recommended to detect disease early.

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