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Study of Outcome of Early Breast Cancer Patients Treated with Different Chemotherapy Protocols

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ABSTRACT

Background: If detected and treated early, breast cancer has a chance of being cured. Therapy has progressed utilizing multiple chemotherapeutic regimens with great efficacy and minimal toxicity.

Objective: To improve the outcome of patients with early breast cancer by clarifying the most effective adjuvant therapy regimen.

Subjects and methods: In a clinicopathological retrospective study, we included 854 patients with non-metastatic breast cancer patients treated at Medical Oncology Department, Maadi Armed Forces Medical Complex and Medical Oncology Department, Zagazig University; from January 2015 to December 2018.

Results: Most of our study population 505 patients (59.1%) received adjuvant chemotherapy protocol of (4 AC (Adriamycin and Cytoxan) + 4 taxanes), while the 2nd most common used protocol was 6FAC (Fluorouracil, Adriamycin, and Cytoxan), which was received by 17.7% of patients, on the other hand some patients received 4AC, 3AC+3 taxanes and 4TC protocols. Percentage of our patients who were still alive after 4 years of diagnosis were 86.5% (739 patients). Disease recurrence or metastasis occurred in 317 patients (37.1%) during follow up period ranged from 13-84 months, while 537 patients (62.9%) didn't experience either recurrence or metastasis to time of study.

Conclusion: Early breast cancer is considered potentially curable disease. Disease recurrence or metastasis occurred in 37.1% of our patients. Survival rate after 4 years of diagnosis was 86.5%. The FAC protocol has been used in just 17.7% of our patients, but DFS rate of those patients who received FAC was the highest (73.5%), even superior to AC+Taxanes.

Keywords: Chemotherapy, Breast cancer, Chemotherapy protocols.

INTRODUCTION

With an estimated 1.9 million new cases in 2017, breast cancer (BC) is the most frequent cancer in women and the fifth greatest cause of death in women worldwide. In the same year, breast cancer accounted for 601,000 deaths among women **(1).**

Breast cancer is the most frequent type of cancer in women in Egypt. It's the third most common form of cancer among females **(2).**

Epidemiologic studies have established a number of risk factors for breast cancer, some of which are unavoidable (such as race and ethnicity) and others that are modifiable (such as increased alcohol use, physical inactivity, exogenous hormones, and specific female reproductive variables). Potential long-term impacts on sex hormone levels or other biological mechanisms link an earlier age at menarche, higher parity, and later age at first full-term pregnancy to an increased risk of breast cancer **(3).**

If detected and treated early, breast cancer has a chance of being cured. Over the past few years, significant strides have been made in the field of cancer treatment, with a corresponding decrease in the severity of therapy for both locoregional and systemic therapy **(4).** Patient age and menopausal status, hormone receptor status, HER2/neu overexpression, and the presence of lymph node involvement; all are factors into the decision to use adjuvant systemic therapy. Systemic chemotherapy, endocrine therapy, and radiation are the standard treatments for node-positive breast cancer (for hormone receptor-positive cancer), both HER2/neu overexpressing cancers and trastuzumab. Chemotherapeutic regimens comprising anthracyclines and taxanes are effective against breast cancer **(4).**

Numerous adjuvant chemotherapy regimens are detailed in the National Comprehensive Cancer Network (NCCN) recommendations for the treatment of breast cancer, involving; concurrent anthracycline-cyclophosphamide and taxane (ACT); sequential anthracycline-cyclophosphamide and taxane (AC-T), cyclophosphamide, methotrexate, and fluorouracil (CMF); anthracycline-cyclophosphamide without taxane (AC); as well as docetaxel and cyclophosphamide (TC)**(5)**.

To provide more effective treatment with reduced side effects, it is vital to tailor medicines to each individual patient and their tumor's unique molecular and clinical profile **(6).**

This study aim was to estimate disease outcome in each chemotherapy regimen and also to correlate this outcome with clinical and pathological characteristics.

SUBJECTS AND METHODS

This clinicopathological and immunohistochemical retrospective study included 854 patients with non-metastatic breast cancer patients treated at Medical Oncology Department, Maadi Armed Forces Medical Complex and Medical Oncology Department, Zagazig University from January 2015 to December 2018.

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Inclusion criteria:

Female patients who aged more than 18 years old, with histologically proven diagnosis of early breast cancer, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 neu (HER2 neu) were done to all patients on the pathological specimens, and who underwent curative surgery then received adjuvant treatment.

Exclusion criteria:

If the patient had other malignancy, or carcinoma in situ, had locally advanced, recurrent and metastatic breast cancer, and patients who didn't receive adjuvant chemotherapy were all excluded from the study.

Methods:

All patients in the sample underwent careful history taking, and full clinical examination, imaging studies including: Breast ultrasound, Diagnostic mammography and/or MRI Breast, Plain X-ray chest or CT chest if needed, as well as Bone scan.

Macroscopic analysis of mastectomy specimens revealed tumour size, quantity, and location.

Examining hematoxylin and eosin-stained tissue slices allowed us to determine the histological subtype, stage, grade, lymphovascular invasion, and lymph node involvement.

We used the TNM staging approach [where T indicates the tumour size, N describes nodular involvement, and M describes distant metastases] and the Nottingham modification of the Scarff Bloom and Richardson's (SBR) grading system to categorize and stage tumours. According to the guidelines established by the Nottingham Prognostic Index (NPI), the tumours were graded.

We followed the classification that has been described previously by **Blows *et al.*** [7] to classify the tumours into subtypes on the basis of their protein expression profile (Fig. 1). Luminal tumours were those with positive staining for ER or PR.

Specimens were then subdivided into luminal 1 (HER2-negative) and luminal 2 (HER2-positive) groups based on HER2 status. Luminal 1 is roughly identical to the luminal A tumours identified by gene expression. Each of the luminal 1 tumours was further classified as either CK5/6 positive or EGFR positive, or CK5/6 negative and EGFR negative.

Tumors that lacked ER and/or PR expression were classified as non-luminal. According to the presence or absence of HER2 expression, these tumours were classified as either HER2-like or triple-negative phenotype (TNP). Tumors with the triple-negative phenotype (TNP) were further classified into those with a core-basal phenotype (CBP) (CK5/6 or EGFR positivity) and those with a 5-negative phenotype (5NP) (CK5/6 negativity and EGFR negativity).

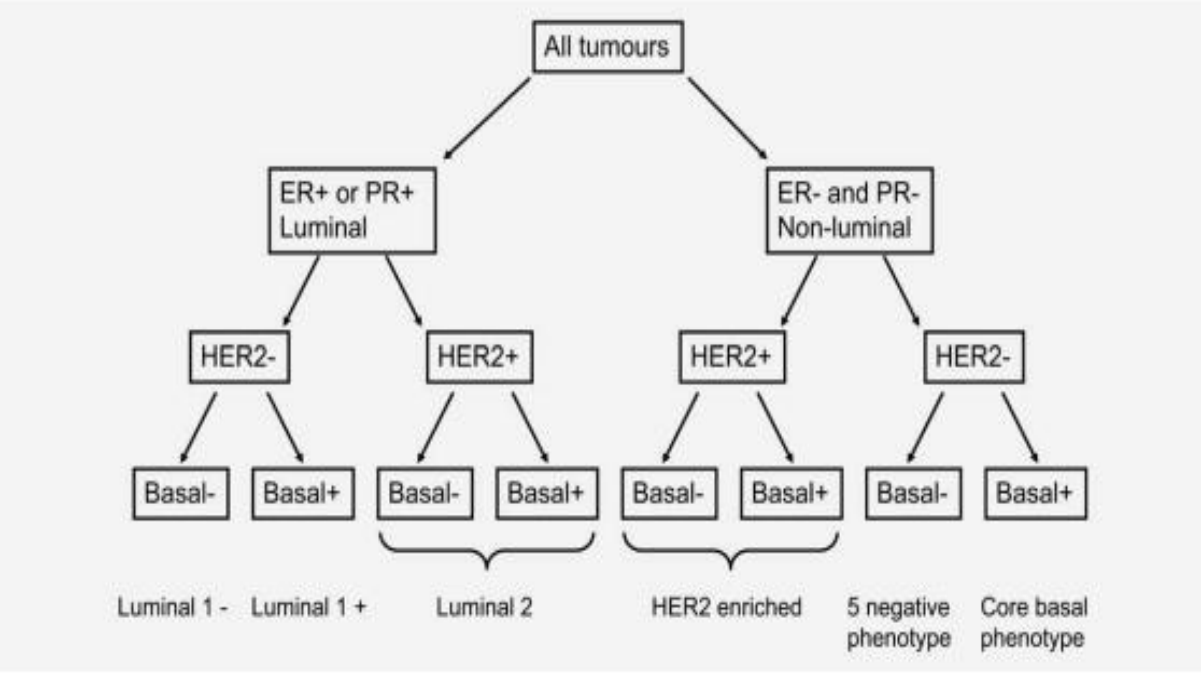

Figure (1): Classification of breast cancer sub-types according to IHC marker profile [7].

Treatment

1- **Curative surgery**
Modified radical mastectomy or breast conserving surgery with axillary dissection was the surgical procedure of choice for these patients.

2- **Chemotherapy (Sequential anthracycline-cyclophosphamide and taxane (AC-T) (Table 1)**

Taxane (docetaxel or paclitaxel) chemotherapy administered before an anthracycline-based chemotherapy, intravenous docetaxel once weekly, every 14 days, or every 21 days for three to four cycles, intravenous administration of paclitaxel once weekly for 12 cycles, every 14 days, or every 21 days, for a total of three or four cycles.

Comparator

Treatment with anthracycline-based chemotherapy (doxorubicin, epirubicin) prior to taxane treatment. Drugs were given in the same order as the intervention group, but in a different order. Dose-dependent intravenous doxorubicin administration every 21 days for three to four cycles. Every 21 days for three or four cycles, intravenously administered epirubicin at any dose.

Cyclophosphamide, methotrexate, and fluorouracil (CMF)

The first treatment plan was a twist on the standard CMF protocol, with cyclophosphamide 600 mg/m^2 given intravenously on days 1 and 8 of a 28-day cycle instead of 100 mg/m^2 taken orally on days 1-14. Doses of 5-fluorouracil (5-FU) administered through infusion were derived from those seen in prior breast cancer research, either alone or in tandem with epirubicin and cisplatin.

Docetaxel and cyclophosphamide (TC)

Premedication

Infusions of ondansetron and dexamethasone before to chemotherapy, then 8 mg of dexamethasone orally twice day for three days, beginning one day before each docetaxel infusion.

Recommended Take Home Medication

8 mg ondansetron orally. Twice a day for two- or three-days dexamethasone dose orally (premedication as above). Metoclopramide 10 mg, every 12 hours as needed.

Table (1): Drug administration schedule [7].

Day	Drug	Dose	Route	Diluent & Rate
0-2	Dexamethasone	8mg BD*	Oral	For three days, starting one day prior to docetaxel
1	Sodium Chloride 0.9%	250/500ml	Infusion	Fast Running
1	Dexamethasone	8mg	Intravenous	Over at least 2 minutes
1	Ondansetron	8mg	Oral /Slow bolus/15 min infusion	
1	**Docetaxel**	**75mg/m^2**	**Intravenous**	**250ml Sodium Chloride 0.9% over 60 minutes**
1	**Cyclophosphamide**	**600mg/m^2**	**Intravenous**	**Via fast running Sodium Chloride 0.9% Drip**

Assessment of outcomes were assessed among all cases.

Ethical approval:

This experiment was ethically approved by the Zagazig University's Ethics Committee. After being fully informed, all participants provided written consent. The study was conducted in line with the Helsinki Declaration.

Statistical analysis

IBM SPSS was used, version 22.0. The range of values, from minimum to maximum, as well as the mean and standard deviation were employed to describe numerical information. Categorical data were presented as frequency and percentage. The acquired results were deemed statistically significant at the 5% level.

RESULTS

The age of patients ranged from 29 to 80 years, 338 patient (40%) aged 50-59 years, 269 patient (31%) aged 60-69 years, 177 patient (21%) aged 40-49 years, while the other age groups were little sum as in **Figure 2.**

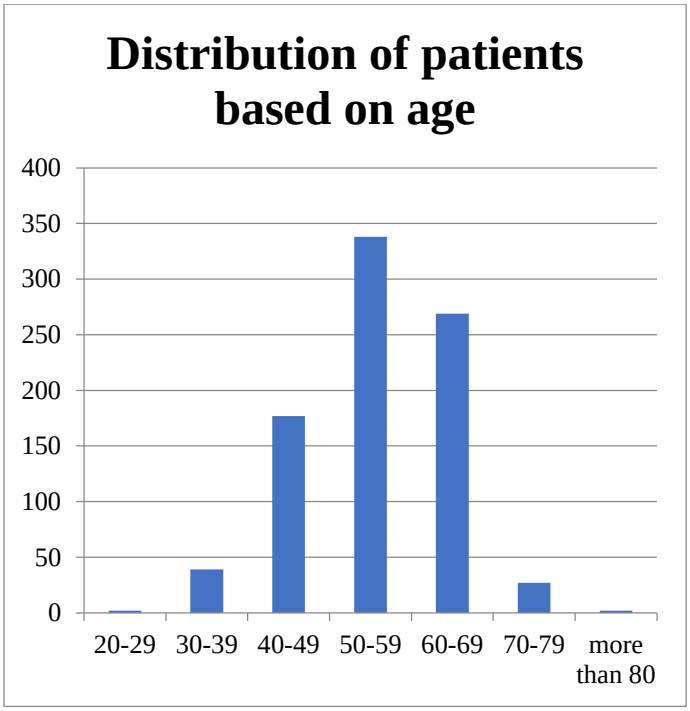

Figure (2): distribution of patients based on age grouping.

All patients with HER2neu positive tumors (224 patients) received their anti-HER2neu therapy.

99% of patients received post-operative radiotherapy while 8 patients didn't receive adjuvant radiotherapy. 704 patients were receiving adjuvant endocrine therapy, while 150 patients didn't receive any endocrine treatment. Most of our study population 505 patients (59.1%) were receiving adjuvant chemotherapy protocol of (4 Ac + 4 taxanes), while the 2nd most common used protocol was 6FAC, which was received by 17.7% of patients, on the other hand there were some patients who received 4AC, 3AC+3 taxanes and 4TC protocols (Fig. 3).

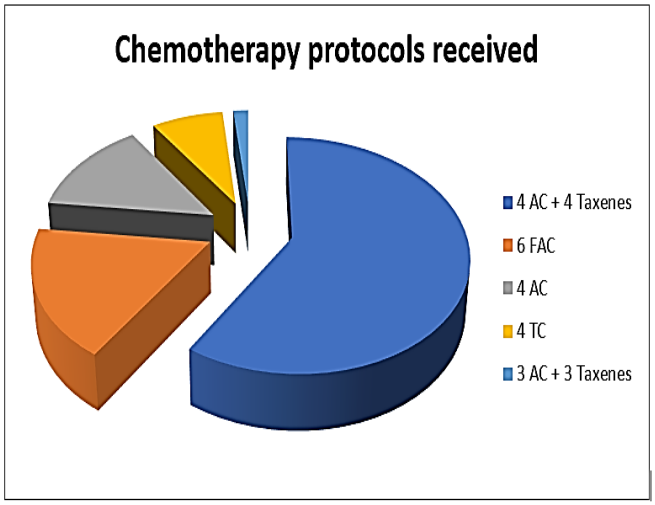

Figure (3): Chart of chemotherapy protocols have been used

Clinicodemographic data of the studied population are shown in table 2. Most of the patients were post-menopausal at diagnosis, without positive family history, had offsprings, and used to live in urban areas. Most of patient were ECOG performance status PS 1 at time of presentation, were estrogen receptor (ER) +ve, were PR +ve, and were HER2neu -ve. There were 53.5% of patients (457) diagnosed as right sided breast cancer. 384 patients were pathological N0, which compromise 45% of all patients. 75% of our study population were T2.

Patients underwent therapeutic surgical mastectomy and the results were 95% of our patients were R0 resection or negative surgical margins. Histopathological studies for collected specimens revealed lymphovascular invasion in 97 patients while the others were free **(Table 2)**.

Table (2): Clinicodemographic data of the studied population (N= 854)

Parameter		Total (N=854)
		N (%)
Age, Mean ±SD		55.5±8.8
Menopausal status	Premenopausal	180 (21.1%)
	Postmenopausal	674 (78.9%)
Family history	Negative	723 (84.7%)
	Positive	131 (15.3%)
Offsprings	No	41 (4.8%)
	Yes	813 (95.2%)
ECOG	PS 0	36 (4.2%)
	PS 1	762 (89.2%)
	PS 2	55 (6.4%)
	PS 3	1 (0.1%)
Residence	Urban	639 (74.8%)
	Rural	215 (25.2%)
ER	Negative	157 (18.4%)
	Positive	697 (81.6%)
PR	Negative	301 (35.2%)
	Positive	553 (64.8%)
HER2neu	Negative	630 (73.8%)
	Positive	224 (26.2%)
KI 67%		22.2±5.6
Tumor sidedness	***Rt***	***457 (53.5%)***
	Lt	397 (46.5%)
Lymph node status	N 0	384 (45.0%)
	N 1	309 (36.2%)
	N 2	111 (13.0%)
	N 3	50 (5.9%)
Tumor size	T1	59 (6.9%)
	T2	645 (75.5%)
	T3	150 (17.6%)
Surgical margins	Free (R0)	815 (95.4%)
	Involved (R1)	39 (4.6%)
Lymphovascular invasion	Negative	757 (88.6%)
	Positive	97 (11.4%)
Anti-HER2neu therapy	No	630 (73.4%)
	Yes	224 (26.6%)
Radical radiotherapy	No	8 (0.9%)
	Yes	846 (99.0%)
Endocrine therapy	No	150 (17.6%)
	Yes	704 (82.4%)
Chemotherapy regimens	4 AC + 4 Taxanes	505 (59.1%)
	6 FAC	151 (17.7%)
	4 AC	117 (13.7%)
	4 TC	67 (7.8%)
	3 AC + 3 Taxanes	14 (1.6%)

In our study, most of the patients received adjuvant 4 AC + 4 Taxanes. DFS was 73.5% in 6FAC protocol. 4-year survival rate was 91% in 4 TC protocol **(Table 3 and figure 4).**

Table (3): Comparison of disease recurrence or metastasis data based on the chemotherapy regimens

Parameter		***Chemotherapy regimens***				
		4 AC + 4 Taxanes N=505	6 FAC N=151	4 AC N=117	4 TC N=67	3 AC + 3 Taxanes N=14
		N (%)	N (%)	N (%)	N (%)	N (%)
Dis. recurrence or Metastasis	No	298 (59.0%)	111 (73.5%)	77 (65.8%)	44 (65.7%)	7 (50.0%)
	Yes	207 (41.0%)	40 (26.5%)	40 (34.2%)	23 (34.3%)	7 (50.0%)
4 year survival rate	Passed away	78 (15.5%)	15 (9.5%)	12 (10.5%)	6 (9%)	4 (28.5%)
	Alive	427 (84.5%)	136 (90.5%)	105 (89.5%)	61 (91%)	10 (71.5%)

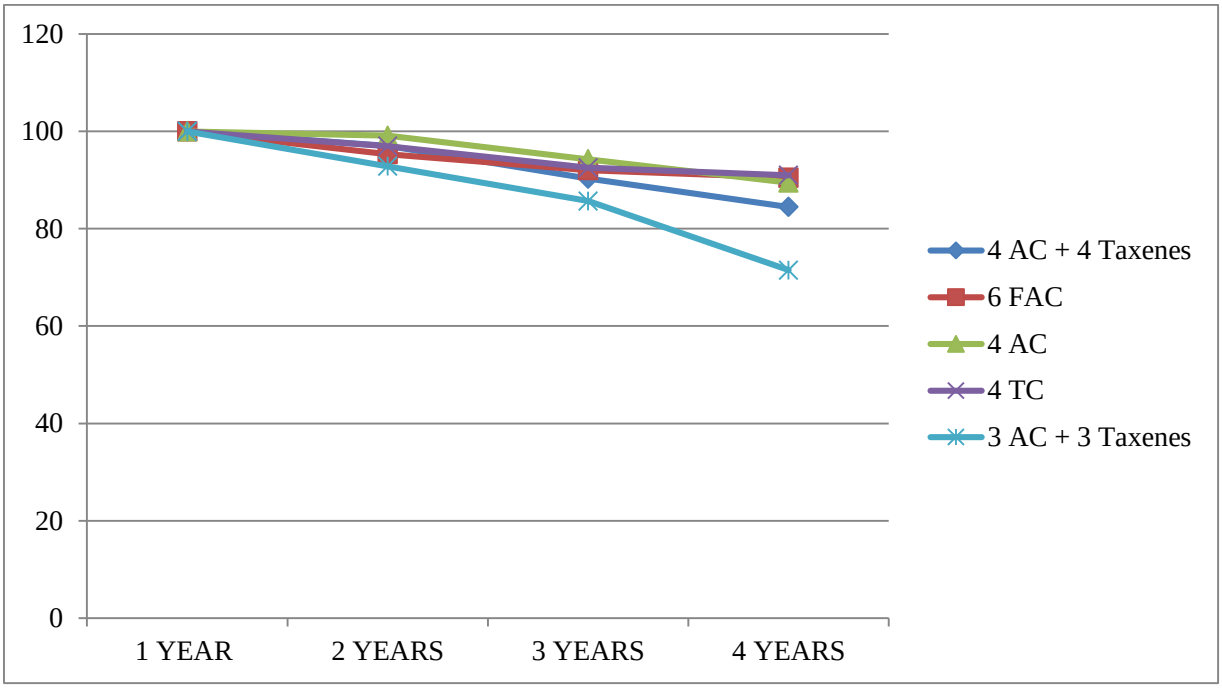

Figure (4): Survival rate curve of each chemotherapy protocol

All variable with P-value <0.05 in univariate analysis were entered in multivariate regression model. Multivariant cox-regression analysis for relapse free survival revealed that progesterone receptor (PR) positivity, lymph node excised N0, N1, using FAC chemotherapy protocol and endocrinal treatment were significant prophylactic variants to decrease disease recurrence and metastasis in our population. As regard our study multivariant Cox-regression analysis revealed that using FAC protocol has a good indicator in decreasing disease recurrence and metastasis. Also using endocrinal treatment has a good indicator in decreasing disease recurrence and metastasis. While KI67% was significant risk variant that increased disease recurrence and metastasis in our population.

Table (4): Multivariate Cox-regression analysis for relapse-free survival

	Multivariate		
	Sig.	HR	95.0% CI for HR
Menopausal status Pre Vs Post	0.863		
ECOG 0 ref			
ECOG 1	0.08		
ECOG 2	0.979		
ECOG 3	0.095		
Comorbidities (Yes Vs No)			
Diabetes mellites (Yes Vs No)	0.209		
ER (+ vs -)	0.142		
PR (+ vs -)	0.004	0.612	0.438-0.853
HER2neu (+ vs -)	0.826		
KI 67%	0.001	1.018	1.008-1.029
Lymph nodes N3	Ref		
Lymph nodes N0	<0.001	0.441	0.295-0.660
Lymph nodes N1	<0.001	0.472	0.312-0.716
Lymph nodes N2	0.243		
Chemotherapy regimens(4AC+4Taxanes) ref			
Chemotherapy regimens (6 FAC)	0.029	0.678	0.478-0.962
Chemotherapy regimens (4 AC)	0.964	1.008	0.712-1.428
Chemotherapy regimens (4 TC)	0.563	1.140	0.732-1.775
Chemotherapy regimens (3 AC + 3 Taxanes)	0.118	0.522	0.231-1.179
anti HER2neu therapy (Yes Vs No)	0.832		
Endocrine therapy (Yes Vs No)	<0.001	0.266	0.159-0.447

HR: hazard ratio; 95%CI: 95% confidence interval**.**

DISCUSSION

Breast cancer is the most frequent cancer among women around the world. Breast cancer is the second leading cause of cancer-specific mortality in women, behind lung cancer, accounting for 29% of new cases and 14% of fatalities. Male breast cancer accounts for about 1% of all cases, with 90% of them being ER-positive **[(8)].**

In our study, the mean age of the studied patients at diagnosis was 55.5±8.8 (SD). The age of patients ranged from 29 to 80 years; the commonest age group were aged 50-59 years. with 338 patients (40%), followed by 269 patients (31%) aged 60-69 years, 177 patients (21%) aged 40-49.

The average age of diagnosis was 46.0 ± 12.0 (SD) years, which is older than the study by **Vostakolaei *et al.* [(9)]** as 14.6 percent of patients were under the age of 35, 49.6 percent were between the ages of 35 and 49, 27.7 percent were between the ages of 50 and 64, and 8.3 percent were 65 and older.

In our study positive family history had been recorded in 15.3% of our patients (131/854) compared with 84.7% of patients (723/854) were with negative family history. Although **Feng *et al.* [(10)]** found that only about 15% of breast cancer patients have a first-degree relative with the disease, the risk is increased for those who do have such a relative. Our data recorded that 52% of patients were right sided while 48 % of patients were left sided. Our study revealed that most of our patients were post-menopausal at time of diagnosis (674 patients or 78.9%). According to the findings of **Surakasula *et al.* [(11)],** who studied the same group, 52% were post-menopausal at the time of diagnosis, whereas 48% were in the pre-menopausal stage.

In our study, there were 550 patients received adjuvant 4 AC + 4 Taxanes, 151 patients received 6 FAC protocol, 117 patients received 4 AC, 67 patients received 4 TC and just 14 patients received 3 AC + 3 Taxanes. DFS was 73.5% in 6 FAC protocol, 59% in 4 AC +4 Taxanes protocol, 65% in 4 AC protocol and 4 TC protocol and 50% in case of 3 AC+ 3 Taxanes protocol. 4 years survival rate was 90.5% in case of 6 FAC protocol, 84.5% in 4 AC +4 Taxanes protocol, 89.5% in 4 AC protocol, 91% in 4 TC protocol and 71.5% in 3 AC + 3Taxanes protocol.

While in multivariate Cox-regression analysis the type of adjuvant chemotherapy protocol didn't have a significant impact on DFS or OS. So, difference between results may be due to different patient characteristics and sample size.

The absolute benefit for irradiated women was 15.7% (p 0.0001), according to a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) that pooled data from 17 randomised studies comparing postoperative radiotherapy vs. none and found that WBI (whole breast irradiation) reduced the 10-year recurrence rate (local or distant) from 35 to 19.3%. In addition, the death rate from breast cancer after 15 years was reduced by WBI from 25.2% to

21.4%, a 3.8 percentage point improvement. [12]. Univariate Cox-regression analysis, similar to our study, found the benefit of post-operative adjuvant radiation, although the P value was not statistically significant (P value 0.477).

Patients with HER2-positive breast tumours who were given trastuzumab-based chemotherapy in the pivotal adjuvant trials were the focus of a meta-analysis that looked at their outcomes. Patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer at any stage had significantly better outcomes when treated with trastuzumab-based chemotherapy, according to the study's findings. At 8 years, the risk of disease recurrence was reduced by 9.4 percent (P .0001) and the rate of death was reduced by 8.8 percent (P .0001) when trastuzumab was added to chemotherapy [13]**.** Consistent with our findings, patients who received anti Her2neu therapy fared significantly better than those who did not. The HR for this group was 1.557 (95% CI: 1.233-1.964), and the corresponding P value was 0.001.

Increases in both DFS and OS have been documented for breast cancer patients thanks, in large part, to adjuvant systemic medication and screening. Gains in overall survival already account for the possibility that a patient may perish as a result of toxicities caused by their treatment. However, the effect on health-related quality of life is not fully captured by this metric alone. In order to determine which patients are at the most risk, it is necessary to investigate the frequency with which therapy-related toxicities occur, as well as their short- and long-term effects. Expected therapy advantages (relative and absolute percentage improvements in disease-free survival or overall survival) must be weighed against known possible risks in order to reach a final choice [14]**.**

Comparatively, in our data we found that neutropenia was recorded in 81 patients (16%) in 4T+4AC protocol, 16 patients (10.5%) in FAC protocol, 13 patients (11.1%) in 4AC protocol, 8 patients (11.8%) in 4TC protocol and 2 patients (14%) in 3T+3AC protocol. While GIT disturbance in form of vomiting was recorded in 45% of patients with 4T+4AC protocol, 23% of patients with 6FAC protocol, 12.8% of patients with 4AC protocol, 23.9% of patients with 4TC protocol and 28.6% of patients with 3T+3AC protocol.

Also, our study revealed that positive indicators in decreasing disease recurrence or metastasis include adherence to endocrinal treatment, progesterone receptor (PR) positivity and lymph node excised N0, N1. While the more the Ki- 67 percentage value, the poorer was the prognosis.

Adherence problems with adjuvant endocrine medication for breast cancer patients, be it tamoxifen or AI, are associated with an increased risk of death. Reduced survival was seen in those with adherence rates of 80% (hazard ratio= 1.20; 95% confidence interval= 1.03-1.40, P = 0.019) [4]**.** Our results suggest that a patient's willingness to comply with their endocrine therapy is a strong predictor of a reduced risk of disease recurrence and metastasis (0.266% Hazard ratio, 0.159-0.447 Confidence Interval, and P0.001).

As regard our population, multivariate Cox-regression analysis revealed that tumor with N1 positive lymph node has the least disease recurrence and metastasis compared to N2 and N3 tumors.

In breast cancer, Ki-67 may serve as a useful biomarker. Patients whose Ki-67 levels were below 15% fared better than those whose Ki-67 levels were above 15% (P 0.01). Patients with a Ki-67 percentage more than 15% had a significantly higher risk of developing metastases and experiencing a recurrence of their cancer (P 0.0001) [15]**.**

Regarding our investigation, Ki-67 was a major risk variation that was associated with an increased chance of illness recurrence and metastasis (Hazard Ratio = 1.018; Confidence Interval = 1.008–1.029; P 0.001).

CONCLUSION

Early breast cancer is considered potentially curable disease. Disease recurrence or metastasis occurred in 37.1% of our patients. Survival rate after 4 years of diagnosis was 86.5%.

The FAC protocol has been used in just 17.7% of our patients, but DFS rate of those patients received FAC was the highest (73.5%), even superior to AC+Taxanes.

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Competing interests: Nil.

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