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Clinico-pathological study and treatment results of 1009 operable breast cancer cases: Experience of NCI Cairo University

Magda El Mongy, MD[1], Hesham El Hossieny, MD[1], Farouk Haggag, MD[2], Rania Fathy, MSc[1]

(1) Department of Radiation Oncology, National Cancer Institute, Cairo University
(2) Department of Clinical Oncology, Kasr El-Aini Centre, Cairo University

✉ *Corresponding Author: Dr Hesham El Hosseiny, MD*
Department of Radiation Oncology, National Cancer Institute, Cairo University
E-mail: hishamelhossieny@yahoo.com

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Abstract

Aim of study: This retrospective study was designed to evaluate clinico-pathological data including stage, results of treatment, and prognostic factors which affect the overall survival & disease free survival.

Patients and methods: This is a retrospective study carried out at the radiotherapy department, National Cancer Institute, Cairo University on 1009 patients treated for primary breast cancer between1999 – 2003.

Results: The median follow-up was 68 months. Loco regional relapse occurred in 23 patients (2.3%) and distant relapse occurred in 203 patients (20.1%). Both loco regional and distant relapse were reported in 32 patients (3.2%). The DFS at 3 and 5 years were 87% and 78% respectively , while OAS at 3 and 5 years were 96.4% and 91.4% respectively. Multivariate analysis of different prognostic factors showed that the independent bad prognostic factors in the study for disease relapse are positive lymph nodes (more than 10) , tumor size T3, T4 with significance of 0.0001 for each. and pathologic grade with significance of 0.003.

Adjuvant chemotherapy showed no significant improvement in the survival for node negative patients as a whole, but for T3 andT4 lymph nodes negative patients, significant improvement in the median survival in favor of the use of adjuvant chemotherapy was reported. (P value = 0.03).

As regard timing of radiotherapy the 3 and 5 year disease free survival was significantly higher in patients who started radiotherapy within three months after date of surgery (93% and 85% respectively) (p value = 0.0001) , while the delay in starting chemotherapy didn't affect the prognosis significantly in the studied group as a whole.

Conclusions & Recommendations: The most important independent bad prognostic factors for relapse are positive LNs more than 10 , tumor size T3,T4 and pathologic grade. The timing of radiotherapy affects the disease free survival significantly. It is recommended to analyze the group of patients with LNs negative using well designed randomized trials .

Introduction

Breast cancer is the most frequently diagnosed cancer in women, and it accounts for 32% of all female cancers. It is estimated that there will be 212,920 new cases of invasive breast cancer and 61,980 new cases of in situ breast cancers among women in the United States in 2006 (1).

In Egypt, data from Gharbia population based cancer registry indicated that breast cancer is the most common (37.6%) and ranked first among females cancer (2) .At National Cancer Institute, Breast cancer constitute 33% of all female cancers, the median age is 46 years, one decade younger than the corresponding age in western countries (3).

Breast cancer in Egypt has been reported to be biologically more aggressive disease than that in Western countries with predominance of premenopausal patients with late presentation in advanced stages (3).

Many prognostic factors have been studied. Tumor size and nodal status are clearly among the strongest predictors of overall survival and metastasis (4,5,6). Margin status is a strong predictor of relapse in the conservatively treated breast, but is not strongly correlated with distant metastasis (7,8,9,10). Young age is also a very strong predictor of local relapse after breast-conserving therapy, and although it has been shown to be predictive of systemic metastasis, the effect of young age on distant metastasis as an independent factor is clearly not as significant as it is for local relapse in the conservatively managed patient (11)

Patients and Methods

This is a retrospective study on female patients with operable non metastatic primary breast cancer who were treated at the radiotherapy department of the National Cancer Institute of Cairo between 1999 and 2003. The medical records of 1009 patients were reviewed and the data collected for each patient included age, clinical stage at diagnosis, pathologic grade, hormone receptor status, treatment outcome and last follow up date. Patients were diagnosed as below.

Fine needle aspiration was done for 62% of cases, excision biopsy for 29% of cases, true cut biopsy for 7% of cases while frozen section was done to 2% of cases.

Treatment methods

Surgery

Modified radical mastectomy (MRM) was the commonest treatment modality and was carried out in 871 patients (86.3%). Conservative surgery in the form of wide local excision of the tumor and axillary dissection followed by radiotherapy was carried out in 138 patients (13.7%) mostly with T1 & T2 lesions.

Table 1 shows the treatment methods for these patients.

Table 1: Treatment methods for 1009 breast cancer patients

Treatment	Number	Percent
Surgery		
MRM	871	86.3%
Conservative	138	13.7%
Radiotherapy	930	92%
PORT	792	78.4%
Radical	138	13.6%
Adjuvant CT	811	80.3%
FAC	522	51.7%
FEC	196	19.4%
CMF	93	9.2%
Tamoxifen	654	65%

Radiotherapy

Post operative radiotherapy (PORT) was given to the patients with tumor size 4 cm or more and patients with positive axillary lymph nodes (792 patients, 78%). Radical radiotherapy was given for patients treated by Conservative surgery (138 patients). All patients were treated in the supine position with the arm abducted using breast tilt board with arm rests. The treatment volume include the entire chest wall ± the supraclavicular lymph node in patients with positive axillary lymph node. Irradiation of chest wall was delivered using standard 2 tangential fields with cobalt 60 machine, the upper border is at inferior aspect of sternoclavicular head, the medial border at the midline, the lateral border is usually near the mid axillary line and the inferior border lies 2cm below the contralateral inframammary fold. Supraclavicular lymph nodes were irradiated by direct anterior field, the upper border at thyrocricoid groove, the inferior border is matched to the tangential field usually just below the clavicular head, the medial border is 1cm across the midline and the lateral border was extended laterally to the surgical neck of humerous with shielding to the head of humerous. Patients received tumor dose of 45 Gy in 20 fractions over 4 weeks. In patients treated with conservative surgery, (continue from next line)whole breast radiotherapy was delivered to a dose of 50 Gy in 25 fractions over 5 weeks using standard tangential fields followed by boost dose of 16 Gy in 8 fractions to tumor bed using electron beam.

Adjuvant systemic treatment

The patients were divided into 3 groups according to the type of systemic treatment adopted:

1. No systemic treatment, 55 patients (5.4%).
2. Systemic chemotherapy with or without hormonal treatment for 811 patients (80.4%).
3. Hormonal treatment only for 143 patients (14.2%).

As regard Adjuvant chemotherapy, the majority of patients (522) received adjuvant FAC regimen (51.7%).Adjuvant FEC was given to 196 patients (19.4%) while adjuvant CMF was given to 93 patients (9.2%).

The chemotherapy was given within 1-8 weeks after surgery. All three agents were administrated as single IV shot on day 1, every 21 days for 6 cycles.

The FAC regimen was as follows:

Cyclophosphamide	500mg/m²	IV day 1
Doxorubicin	50mg/m²	IV day 1
5-Fluorouracil	500 mg/m²	IV day 1

The FEC regimen was as follows:

Cyclophosphamide	500mg/m²	IV day 1
Epirubicin	75-100mg/m²	IV day 1
5-Fluorouracil	500 mg/m²	IV day 1

The CMF regimen was as follows:

Cyclophosphamide	600mg/m²	IV day 1
Methotrexate	40mg/m²	IV day 1
5-Fluorouracil	600 mg/m²	IV day 1

Adjuvant hormonal therapy was given to 654 patients (65%) with ER, PR positive in the form of Tamoxifen 10 mg bid. The duration of treatment was 5 years in 526 patients, less than 5 years in 126 patients and more than 5 years in 2 patients. Only 2 patients developed endometrial hyperplasia from Tamoxifen so shifted to Aromatase inhibitor.

Statistical methods

The data was summarized by descriptive statistics [i. e., mean, standard deviation (SD), frequencies]. Mean values and standard deviation were compared using simple t test (2 variables). Percentages are compared using Chi-square test or Fisher's exact test. Logistic regression was used whenever the dependant factor is binary in nature (e.g. yes or no) during multivariate analysis. Kaplan-Meier test was used for predictive survival rates. P value less than 0.05 is considered to be statistically significant.

For all patients, relapse free survival was calculated starting from date of mastectomy to the date of relapse, whether locoregional or distant and correlated with different prognostic factors.

The overall survival was calculated starting from date of diagnosis to the date of last follow up and correlated with different prognostic factors.

Results

The study included 1009 patients, the median follow up was 68 months.

The age of the patients ranged between 24 and 84 years, the mean age was 47.14±9.7 years with the peak incidence in the fifth decade then the fourth decade of life (44.9%, 22.8% respectively) constituting about two thirds of the patients. Those below 35 years constituted about 20.6% of patients.

Premenopausal patients constitutes about one half of our patients while postmenopausal patients constituted 36.6% of cases. Perimenopausal patients are those around the age of menopause and had irregular menses at time of discovery of the disease constituted 15.5% of cases.

The pathology was revised and classified according to AJCC classification (12) and the commonest pathological type was invasive duct carcinoma (89%) while invasive lobular carcinoma was found in 5.8% of the cases.

Reviewing the tumor grade showed that only 18 patients (1.8%) had grade I tumors, while grade II and III tumors were 87% and 11.2% respectively .There were 11 patients in whom grade was not documented and the majority of them

were invasive lobular carcinoma, a type which is not graded by many pathologists. Five hundred and fourteen patients (51%) had pathological T2 lesion followed by T3 in 333 patients ((33%) and only 70 patients (7%) had T1 tumor. T4 tumor constituted 9 % of the studied group.

The average number of dissected axillary lymph node was 15.8 with maximum number of 44 nodes. Negative axillary lymph node were reported in 282 patients (27.9%) while 727 (72.1%) had positive axillary lymph node. About 27.3% of patients had less than 4 positive lymph nodes, 31.2% had 4-10 positive lymph nodes and only 13.6% (137 patients) had more than 10 positive lymph nodes .The patients and tumor characteristics are summarized in Table 2.

Table 2: Patient's characteristics

Percent	Number	
20.6% 79.4%	208 801	Age <35 >35
47.9% 15.5% 36.6%	484 156 369	Menopausal status Premenopausal Perimenopausal Postmenopausal
89% 5.8% 5.2%	898 59 52	Pathology Invasive duct Invasive lobular Others
1.8% 87% 11.2%	18 878 113	Grade I II III
60.3% 32.3% 7.4% 59.7% 32.9% 7.4%	608 326 75 602 332 75	Hormonal Status Estrogen receptor status Positive Negative Unknown Progesterone receptor status Positive Negative Unknown
7% 51% 33% 9%	70 514 533 92	Tumor size T1 T2 T3 T4
27.9% 27.3% 31.2% 13.6%	282 275 315 137	Nodal status Negative < 4 positive 4-10 positive > 10 positive

The study included 1009 patients; relapse was recorded for 258 (25.6%) patients while 751 (74.4%) were relapse free till time of reporting.

Loco regional relapse occurred in 23 (2.3%) patients, while 32 (3.2%) had both loco regional and distant relapse while only distant relapse was seen in 203 (20.1%) patients.

The 3 and 5 year over all survival for the whole studied group was 96.4% and 91.4% respectively. (Fig 1)

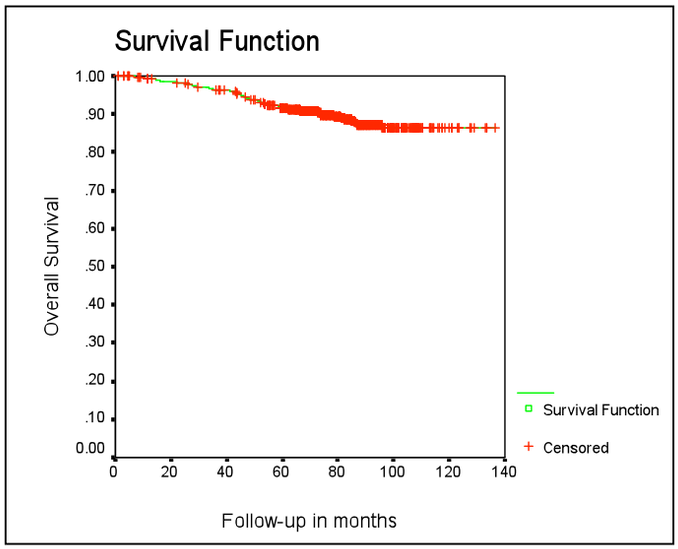

Fig 1: OS for 1009 breast cancer patients

Table 3 shows the correlation of 3 and 5 year OS with different prognostic factors.

Table 3: The correlation of 3 and 5 year OS with different prognostic factors

P value	5-year OS	3-year OS	
	91.4%	96.4%	All patients
0.0001	92% 93% 91% 74%	96% 97% 95% 88%	Nodal Status LN=0 LN +ve 1-3 LN +ve 4-10 LN> 10 +ve
0.012	90% 90% 88% 88%	95% 95% 93% 90%	Tumor size T1 T2 T3 T4
0.03	100% 92% 82%	100% 97% 92%	Tumor Grade GI GII GIII
0.8	91% 88%	97% 92%	Age > 35 <35

Univariant analysis showed that lymph node status was strongly a significant factor affecting overall survival with P value = 0.0001, this was followed by pathologic grade with P value = 0.03.

The 3 and 5 year relapse free survival was 87% and 78% respectively as shown in Figure 2.

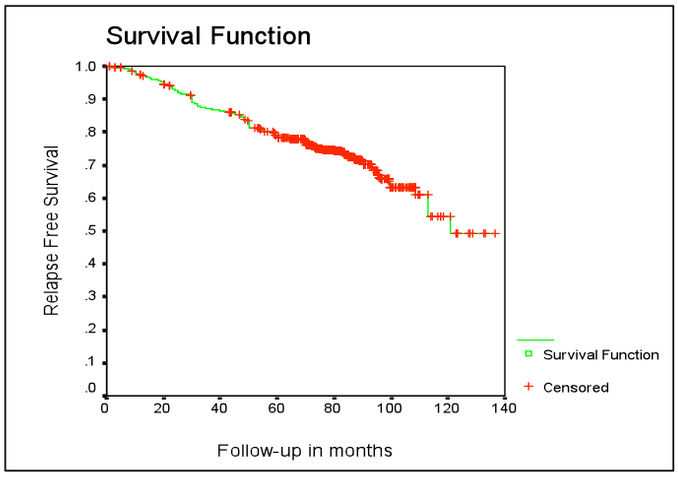

Fig 2: RFS for 1009 breast cancer patients

Table 4 shows the correlation of the 3 and 5 year RFS with different prognostic factors. Univariant analysis showed that all factors significantly affected the relapse free survival.

Table 4: The correlation of 3 and 5 year RFS with different prognostic factors

P value	5- year RFS	3-year RFS	
	91.4%	96.4%	All patients
0.0001	85% 91% 72% 46%	90% 95% 85% 62%	Nodal Status LN=0 LN +ve 1-3 LN +ve 4-10 LN> 10 +ve
0.02	88% 83.3% 56.5% 53%	93% 91% 72.4% 67%	Tumor size T1 T2 T3 T4
0.008	80% 66%	87% 82%	Tumor Grade GI&II GIII
0.02	69% 80%	81% 88%	Age > 35 <35

The 3 and 5 year relapse free survival for patients with 1-3 positive axillary nodes was 95% and 91% respectively in comparison to 85% and72% for patients with 4-10 positive axillary nodes and 62% and 46% for patients with more than 10 positive axillary nodes. For node negative patients the 3 and 5 year relapse free survival was 90% and 85% respectively (Fig 3). This difference proved to be statistically significant (p = 0.0001).

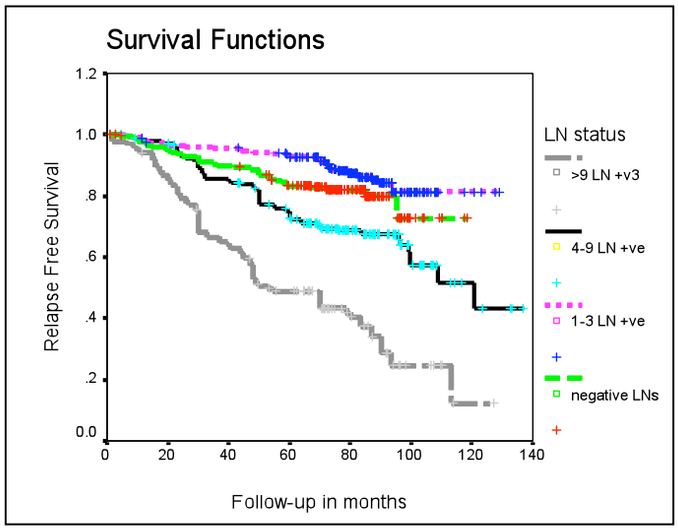

Fig 3: RFS in relation to LN status

The 3 and 5 year RFS for T1 tumors was 93% and 88% respectively and it decreased with the increase in the tumor size reaching 91% and 83 % for T2 tumors with further drop to 72% and 56% for T3 tumors reaching their lowest levels for T4 tumors 67% and53% respectively (figure 4).

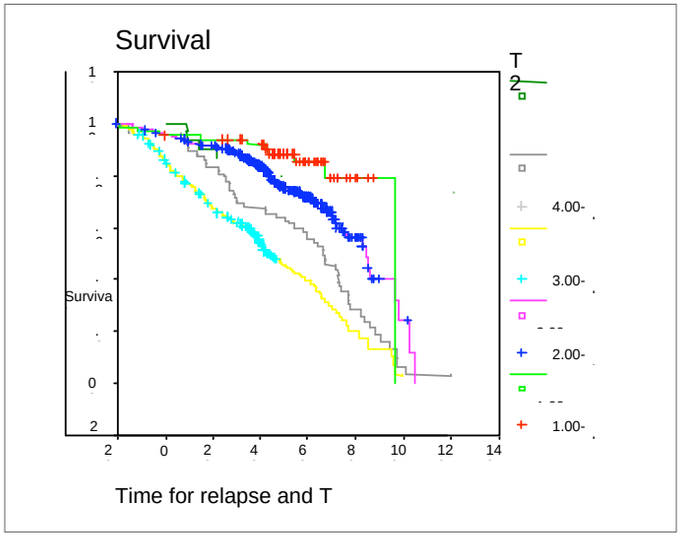

Fig 4: RFS in relation to tumor size

Patients with grade I and grade II have the 3 and 5 year relapse free survival rate of 87% and 80% in comparison to 82% and 66% for grade III patients (p = 0.008)(figure 5).

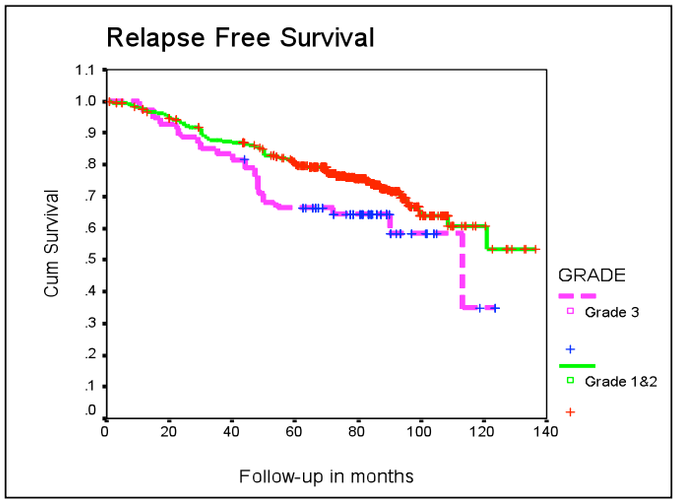

Fig 5: RFS in relation to tumor grade

The 3 and 5 year relapse free survival for patients younger than 35 years was 81% and 69% respectively which is significantly lower than 88% and 80% reported for patients above 35 years(p=0.02). (figure 6).

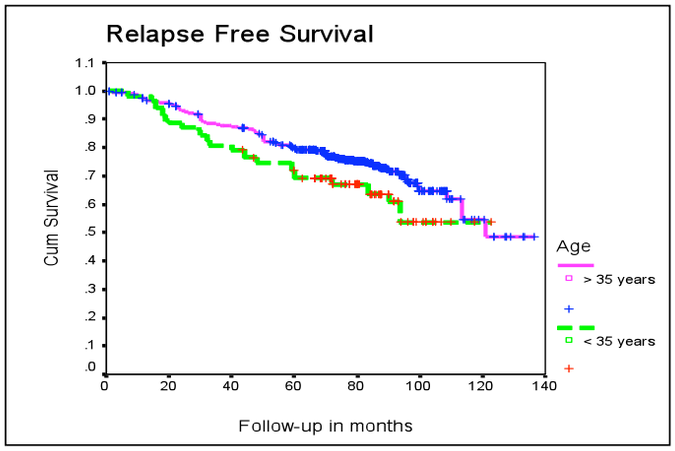

Fig 6: RFS in relation to age

Multivariate analysis of age, nodal status, tumor size, grade and systemic treatment received showed that the group of patients with more than 10 positive axillary lymph node, tumor size and grade are independent prognostic factors for relapse (p value 0.001, 0.001 and 0.003 respectively).

The study included 282 patients with lymph node negative with available data regarding adjuvant chemotherapy, hormonal treatment and follow up , adjuvant treatment showed no significant improvement in the relapse free survival in node negative patients as a whole, but for patients with T3andT4 lesions, a significant improvement in the median survival was observed in patients who received adjuvant chemotherapy treatment (P = 0.03) (Figure 7).

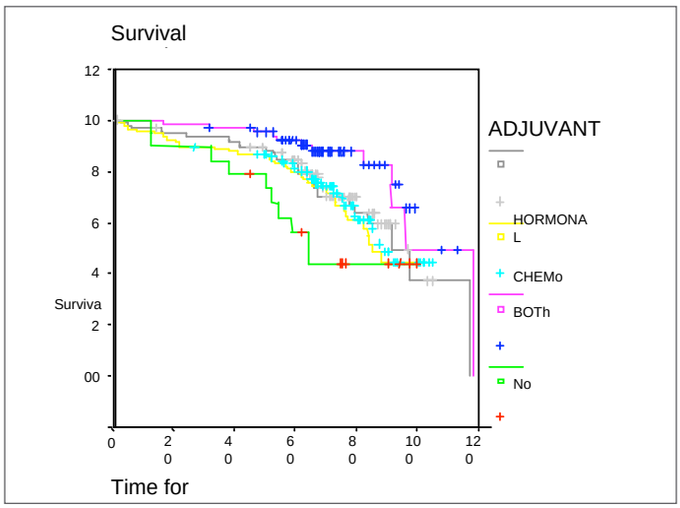

Fig 7: Adjuvant treatment in282 node negative patients

The time interval between surgery and the start of chemotherapy vary from one week to 8 weeks. We divided the patients into 2 groups in whom CT was started within 3 weeks (group 1) and where CT was started after 3 weeks (group 2) .The 3 and 5 year relapse free survival was 84% and 75% in group 1 respectively versus 84% and 74% in group 2 , the difference was not statistically significant (p value is 0.83).

As regard timing of radiotherapy, 518 patients started within the first 3 months after date of surgery and 313 started between 3- 6 months and the rest were delayed for more than 6 months. The 3 and 5 year disease free survival was significantly higher in patients who started radiotherapy within three months after date of surgery (93% and 85% respectively) versus 76% and 63% for those who started radiotherapy within six months after date of surgery (p = 0.0001) as shown in figure 8 .

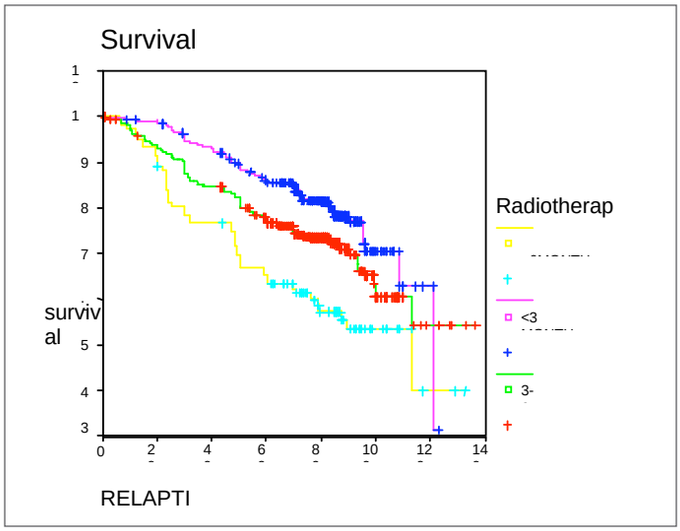

Fig 8: DFS in relation to timing of radiotherapy

Discussion

This is a retrospective study on 1009 female patients with operable non metastatic primary breast cancer treated at the radiotherapy department of the National Cancer Institute of Cairo between 1999 to 2003 with a median follow up duration of about 68 months.

The age of the patients in the present study ranged between 24 and 84 years with the peak incidence in the fifth decade (44.9%).The median age was 47 years and premenopausal women constituted 47.9% of the studied group. The results are similar to other Egyptian studies *(3,13)* **.**The median age of the studied group is relatively younger than the 50 years of age reported in western series, while the postmenopausal group in the present study was 36% as compared to 67% in western series *(14)*.

The frequency of T1 in the present series was (7%). T2 was 51%, T3was 33% while T4 tumor constituted 9% of the studied group. These data are similar to that reported by El Gantiry *(13)* ,who revised 1208 premenopausal women treated between 1980 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 *(15)*.

The frequency of N0, N1, N2and N3 in the present series were 27.9%, 27.3%, 31.2% and13.6%. The incidence of negative lymph nodes in the present study is higher than the 13% reported by ***Elgantiry et al*** *(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%) *(16)***.** 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.

Regarding histological grade, a western series studied 1831 patients and showed a very strong correlation with prognosis, patients with grade I and II tumors have a significantly better survival than those with grade III tumors (p=0.0001) *(17)*, this was in concordance with the results obtained in the present study that showed 5 year RFS for grade I-II 80% compared to 66% for grade III patients (p= 0.008).

The 3 and 5 year over all survival for the whole studied group was 96.4% and 91.4% while the 3 and 5 year relapse free survival was 87% and 78% respectively. In the present study, only 23 patients of 1009 developed loco regional relapse (2.3%) which was in concordance to the reported results by ***Nazmy et al*** *(18)* who reported 3.3% rate of loco regional relapse . ***Fisher et al*** *(19)* 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 et al*** *(20)***,** comparing breast-conserving surgery without radiation to breast-conserving surgery with radiation confirms an approximate threefold reduction in local relapse with radiation therapy and an 8.6% improvement in mortality. In the present study 751 (74.4%) patients were relapse free till time of reporting , this marked improvement in the loco regional free survival rates can be contributed to, first the improvement of the quality of radiotherapy given to the patients and the use of computer system planning and the more effort given for the quality assurance, second the wide use of systemic adjuvant treatment in indicated patients as 94% of the studied patients received adjuvant systemic treatment.

In our study the 3 and 5 year relapse free survival were high for patients with 1-3 positive axillary group (95% and 91%) and for node negative (90% and 85%) and decreased with the increase in number of positive axillary lymph nodes reaching 85% and 72% with 4-10 positive axillary nodes with further drop to 62% and 46% with more than 10 positive axillary lymph nodes .The difference in survival was statistically significant (P=0.0001). The 3 and 5 year RFS for patients with negative lymph nodes in the present study is higher than reported by ***Nazmy et al*** *(18)***,** this may be explained by the fact that 80.3% of the patients received chemotherapy treatment in the present study, similar 3 and 5 year RFS were obtained by ***Nazmy et al*** *(18)* for patients with more than 10 positive lymph nodes . Lower survival rates obtained from *NSABP trials* treated primarily with locoregional therapy alone revealed 5-year 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 *(21)***,** 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 93% and 88% respectively, and they decreased to 91% and 83.3% for T2 tumors with further drop to 72.4% and 56.5% for T3 tumors reaching their lowest levels for T4 tumors (67% and53%) respectively , (P=0.002). This was similar to the results of ***Clarke et al*** *(22)***,** 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 *(23)***.**

The 3 and 5 year relapse free survival rate for grade I and grade II tumors was 87% and 80% in comparison to 82% and 66% for grade III tumors , this difference was statistically significant P=0.008. These results are similar to that reported by ***Ellis et al****(24)***,** 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).

In the present study,patients younger than 35 years showed significantly lower disease free survival at 3 and 5 years than older patients (81% vs 88% and 69% vs 80%) respectively and the p value was (0.02).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 *(25)* .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 *(25)*.

Conclusions & 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 this group of patients are in need of more aggressive treatment.

Further analysis using well designed randomized trials for the group of patients with LNs 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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