Abstract

Background:
Incidence of breast cancer in patients <40 years old accounts for 20% of the total breast cancer patients in Egypt which is quite higher than the incidence reported worldwide. This study was conducted to evaluate the differences in survival between age groups below and above the age of 40.

Method:
170 patients <40 years and 500 patients ≥40 years were evaluated retrospectively to assess the differences in disease free survival (DFS) and overall survival (OS) between age groups after adjustment of other risk factors like stage, lymph node status, tumor size, and hormonal positivity.

Results:
After median follow up of 49 months, there was no significant difference between the 2 age groups with regards to DFS p= 0.6 and OS P=0.7 and there was no significant difference between the 2 groups when we stratified the patients according to stages, hormonal status and number of metastatic lymph nodes. However, we found significant increase in local recurrence after breast conserving surgery in patients <40 years compared to patients ≥40 years.

Conclusion:
Patients <40 years exhibited more often at advanced stage and large tumors size compared to patients ≥ 40 years; However, there was no significant difference in DFS and OS when we adjusted other risk factors. Furthermore, our analysis revealed that age <40 years can be considered as an adverse prognostic factor for the locoregional failure after breast conserving surgery.

Keywords:
breast cancer, young age, <40 years old, locoregional failure, DFS

Introduction
Breast cancer is the leading cause of cancer-related deaths among all women worldwide and approximately 45% of the annual 300,000 deaths occurring in developing countries (1). In Egypt, similar to many other countries in the world, breast cancer is the most common cancer and accounts for approximately 38% of the total reported malignancies among Egyptian women where about 20% of them occur in women aged <40 years(2). Diagnosis of breast carcinoma in young patients usually impacts these patients, their families and society very badly. Therefore, there was a great concern that young age at the time of diagnosis is a reflection of poor prognostic factor (3). Based on that, many studies have been conducted in young patients with breast cancer to evaluate the effect of age on survival (4-6). In early 1990, Swanson, et al, reported that mortality due to breast cancer is greater in young women (7). Another study on invasive non-metastatic breast cancer in premenopausal women documented that young age at diagnosis had an adverse effect on cancer specific survival and relapse free interval (3). Moreover, other studies showed that breast cancer patients ≤40 years tend to have more triple-negative and fewer luminal
A and B breast cancers\(^8\), high grade tumor, more extensive intraductal component, more lymphovascular invasion, more likely to have estrogen receptor (ER) negative tumors\(^9\), and more often BRCA-1 or -2 germline mutations \(^{10-11}\). On the other hand, younger age has been shown in several studies to be an independent predictor of adverse outcome \(^{12}\).

Several current consensus guidelines have included age \(\leq 35\) years as an absolute indication for adjuvant systemic chemotherapy irrespective of other tumor characteristics \(^{13-14}\). However, in 2011 a study was done by Anders CK et al., suggesting that there are few age-specific differences in breast tumor biology. They concluded that age alone does not appear to provide an additional layer of biologic complexity above breast cancer subtype and grade; therefore, when considering treatment programs, decisions should be driven by biological subtype and performance status, and much less influenced by age \(^{15}\).

Concerning the type of surgery, some studies have indicated higher local relapse rate in young women with breast cancer treated with breast-conserving therapy which emphasizes the role of type of treatment received as another factor to be studied when evaluating the effects of age on prognosis \(^{16}\).

Our study was conducted to evaluate differences in survival between age groups in our patients while adjusting for the confounding factors available in the dataset like stage, lymph node status, tumor size or hormonal positivity, tumor grade and prescribed oncological treatment.

**Material and methods**

**Study design and population**

Medical information has been retrieved from patients’ files who were diagnosed at South Egypt Cancer Institute (SECI) between 2004-2010. However, only 670 files from 1400 files have been included in the study as they contain complete pathology reports describing the tumor size and lymph node status. Patients had been stratified according to their age into 2 groups, group no. 1 included 170 patients with age \(<40\) years old at the time of diagnosis and group no. 2 included 500 patients \(\geq 40\) years old at the time of diagnosis. The study was conducted after obtaining the approval from the Local Institutional Review Board Committee and in accordance with the Declaration of Helsinki, the Good Clinical Practices, and local ethical and legal requirements. The study was conducted retrospectively on newly diagnosed patients with breast cancer who were treated at South Egypt Cancer Institute, Assiut University, Egypt.

**Study procedures**

In each group, we analyzed patients’ characteristics according to tumor size, lymph node status, disease stage, hormonal positivity and types of surgery. The disease was staged according to TNM Stage Grouping for Breast Cancer (AJCC) system 2009 \(^{17}\). Surgical treatment includes breast conserving surgery or mastectomy with curative intent. Breast conserving surgery (BCS) consisted of wide local excision or lumpectomy and axillary dissection. Oncoplastic breast surgery and skin sparing mastectomy were performed in selected cases. After modified radical mastectomy, selected patients’ breast reconstruction with TRAM-flap or latissimus dorsi-flap, was performed.

Adjuvant chemotherapy used were 6 cycles anthracycline based chemotherapy like Fluorouracil, Doxorubicin, Cyclophosphamide (FAC), Fluorouracil, Epirubicin, Cyclophosphamide (FEC), or with adding Taxane “4Doxorubicin, Cyclophosphamide (AC 4-Paclitaxel)”. The decision of selecting the type of adjuvant therapy is usually taken based on stage, age and hormonal status.

Radiotherapy dose used in the remaining breast parenchyma is in the form a total dose of 50–54 Gy (Gray) as standard treatment after breast conserving surgery. Radiotherapy to the axilla with a dose of 46–54 Gy was given to women with involved axillary nodes (to all with \(>4\) involved nodes and to a majority with 1–3 involved nodes). After performing mastectomy, a total dose of 50–54 Gy will be given to the chest wall if the tumor primarily invaded the pectoral
muscle, if there is extensive multi-focality, and if tumor size is >50 mm or smaller in involved axillary nodes.

**Study endpoints**

The overall survival (OS) rate, disease-free survival (DFS) rate, and local recurrence rate, were the primary endpoints in this study. These rates were calculated from the date of the diagnosis. Overall survival was defined as the time interval between the date of diagnosis and the date of death. Disease-free survival was defined as the time interval between the date of diagnosis and the date of disease progression or death, the local recurrence rate was defined as the time between surgery to locoregional relapse.

**Statistical Analysis**

Variables were summarized using descriptive statistics, and $\chi^2$ test was used to determine the differences in clinical and pathological factors between two groups. The local recurrence, DFS, and OS rates were estimated by the Kaplan-Meier method (18). The effects of clinical variables on the local recurrence and OS were assessed by the univariate analysis (The log-rank test). Follow-up duration was calculated from the date of diagnosis until the date of death or last contact. P value =0.05 were considered significant; all P values are two-sided. The statistical software adopted in this study was SPSS16 software (SPSS Inc., Chicago, USA).

**Results**

Between January 2004 and December 2010, 670 patient’s files were reviewed retrospectively. The patients and tumors characteristics are shown in (Table 1), which demonstrates that the 2 groups almost have similar distribution regarding the percentage of hormonal receptors status. On the other hand, we can see that there is significant difference between 2 groups regarding tumor size and number of lymph nodes metastases and stages as young patients tend to present in more advanced stage.

With regards to adjuvant chemotherapy, the percentage of patients who received FEC chemotherapy were slightly higher in patients ≥ 40 years than those who were < 40 years. On the contrary, the number of patients who received FAC chemotherapy is slightly higher in the younger group than the older group, but the parentage of patients who received Taxane based chemotherapy were almost identical.

**Locoreginal failure**

Regarding the types of surgery, a total of 93 patients (32 in group 1, 61 in group 2) underwent breast conserving surgery (BCS). Both groups have similar distribution of variables such as hormonal receptors status, grade and small difference in distribution of stages (Table 2).

Nine patients (29%) in group 1 have local recurrence after median follow up of 13 months, while 6 patients (9.8%) in group 2 have local recurrence after median follow up of 25 months which is significantly lower than the younger group with (p =0.03) (Table.2), (Figure.1).

On the other hand, there was no significant difference between the 2 groups in patients who underwent breast conserving surgery with regards to distance metastases (p =0.7), also there were no significant difference between those patients who underwent breast conserving surgery and those who had modified radical mastectomy in each group with regards to distance metastases.

**Survival**

Median follow up of all patients was 49 months, and there was no significant difference between 2 groups with regards to disease free survival (p= 0.6) and overall survival (p =0.7),

![Fig. 1: Locoregional failure free survival after breast conserving therapy, group (1) <40 tend to have more and rapid local failure than patients who ≥40 years old](image)
<table>
<thead>
<tr>
<th>characteristics</th>
<th>$P$ value</th>
<th>&gt;40 N=500</th>
<th>%</th>
<th>≤40 N=170</th>
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<td>235</td>
<td>265</td>
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<td>157</td>
<td>7.6) 34.7)</td>
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<td>T1</td>
<td></td>
<td>(35.4) 21.6)</td>
<td>177</td>
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<td>T2</td>
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<td>105</td>
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<td>33.1) 27.6)</td>
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<td>N0</td>
<td>0.000</td>
<td>(28.2) 26.6)</td>
<td>124</td>
<td>117</td>
<td>18.4) 20.8)</td>
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<tr>
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<td>63) 36)</td>
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<td>111</td>
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<td>(38.1) 26.9)</td>
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<td>27</td>
<td>(16) 8)</td>
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Table 1: Patients and tumor characteristics

Table 2: Patients’ characteristics by group who received BCT

Acronyms: BCT; Breast conserving therapy, AC; Doxorubicin, Cyclophosphamide, ¶; ER or PR receptor positive

Fig.2: (A) Disease free survival (DFS) difference between 2 groups in patients with positive hormonal receptors expression (B) DFS between 2 groups in patients with negative hormonal receptors expression
females with breast cancer had a better survival than older females (5). Also a population-based study from Switzerland showed no effect of young age on survival and their prognosis is not worse than their older counterparts (22).

Many studies have been undertaken to unlock some of the mystery behind health disparities affecting young African American women with breast cancer (23). Carey et al (24) have demonstrated that at least some of the differences in outcome are likely to be related to different incidence of breast cancer subtype by race/ethnicity as a function of age. The study also found premenopausal African American women having more than twice the likelihood of developing basal-like breast cancer compared with both white women and older African American women and a substantially lower likelihood of having the most favorable breast cancer subtype, luminal A. Anders CK et al. (2011) concluded from their study that when considering treatment programs, decisions should be driven by biological subtype and performance status, and much less influenced by age (15).

The objective of this study was to identify the prognostic value of age in younger premenopausal patients under age of 40 years old. Our results did not indicate any significant differences between two patients age groups and the impression of bad outcome usually affected by late presentation as young women usually present with more advanced stage than

![Fig. 3: Disease Free Survival difference between 2 groups according to different stages in non-metastatic patients at presentation. (A) stage I; (B) stage II; (C) stage III](image)

Discussion

Young age at diagnosis of breast cancer has been reported in many studies as a bad prognostic factor (19). However, this issue remains controversial (20). Few reports from developing countries such as Saudi Arabia found that young age does not have any adverse effect on survival of breast cancer patients (21). Chia et al, demonstrated in a retrospective study of breast cancer patients from Singapore that young and when we stratified the patients according to stages, hormonal positivity and numbers of metastatic lymph nodes, there was no statistical difference between the 2 groups regarding the hormonal status (Figure.2) and the three stages of the disease (Figure.3).
older counterparts and when these factors are adjusted, we found that age alone is not a poor prognostic factor. The same findings has been reported in a study made by van de Vijver et al (25) which demonstrated that whereas gene-expression profile was a powerful predictor of disease outcome in younger women with breast cancer, age was not an independent prognostic factor. Younger premenopausal women are also reported to have more frequently presented with breast cancer marked by poor prognostic features such as higher T stage, positive lymph nodes, endocrine non-responsiveness, high grade, extensive PVI and high proliferating fraction than older premenopausal women (26-27).

In addition, our data showed that young age at presentation doesn’t have any significant negative impact on disease free survival or overall survival when compared with older group and these results are matched with the results of previous mentioned studies. Conversely we found that age alone has a negative prognostic factor for the locoregional control after breast conserving therapy. The same finding has been reported by many studies (26-30) that raised the question about the optimal surgical approach of this patient group.

On the other hand, when we analyzed the disease free survival regarding distance metastases and overall survival, no significant difference was detected between BCS or mastectomy in patients <40 (P = 0.7). This observation is matched by a recently published large population-based analysis consisting of early breast cancer patients ≤40 years that showed the 10-years overall survival was not impaired after BCS as compared to mastectomy(31).

At the end of this study, we concluded that patients <40 years usually present themselves with advanced stages and larger tumor size compared with patients ≥40 years. After adjusting the risk factors, we found that age alone is not a bad prognostic factor apart from increased locoregional failure-free survival of breast cancer patients receiving breast conserving surgery in comparison with patients ≥40. A further study with a large number of patients is recommended to validate these initial findings.

References


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