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Predictors for locoregional recurrent breast cancer in Egyptian females

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ABSTRACT

Introduction: Locoregional recurrence (LRR) after proper therapy for breast cancer is not uncommon; it represents around 13%. LRR is classified into true recurrence (TR) or new primary (NP) breast cancer. In true recurrence (TR), some cells may survive and multiply to be detected after mastectomy or breast conservative surgery (BCS). However, in new primary (NP) breast cancer, de novo cancer cells arising from preserved breast tissue after BCS in spite of proper treatment to eliminate all cancer cells.

Aim: The aim of the study was to assess and identify the predictors for locoregional recurrent breast cancer in Egyptian females as there is a lack of studying these factors among them.

Patients and methods: The study was conducted retrospectively on 60 female patients with locoregional recurrent breast cancer presented to Alexandria Main University Hospital, Surgical Oncology Unit with exclusion criteria of bilateral breast cancer and male breast cancer.

Results: 30 cases had a recurrence after BCS while the other 30 cases had a recurrence after modified radical mastectomy (MRM), the mean age of the patients was 36.67 years. 40 cases harvested less than ten lymph nodes with 42 cases have ≥ 4 lymph nodes affected. Regarding the 30 cases that had undergone BCS; 16 cases had negative margin in the frozen section, 12 cases had close margin, and 2 cases were negative in frozen section while positive in paraffin. Pathologically, 34 cases were grade II, 38 cases had a lymphovascular invasion, 24 cases had an extracapsular extension, 28 cases were ER-positive, and 54 cases were negative for Her 2neo.

Conclusion: Predictive factors of significance for local failure are young age, positive resection margins, lymphovascular invasion, and heavy affection of axillary lymph nodes, extracapsular extension, extensive intraductal component, and high histologic grade. Some of these predictive factors proved to be significant in this study.

Key words: *Breast cancer, recurrent breast cancer, predictors of cancer recurrence*

Introduction

After the concept of Bernard Fisher; breast cancer is a systemic disease, recurrent breast cancer is that cancer which recurs after initial treatment with complete response to therapy [1].

Although treatment aimed to eliminate all cancer cells, some cells after resection may survive and multiply to grow and called true recurrence (TR) after mastectomy or breast conservative surgery (BCS) [2].

There are three main types of recurrent breast can-

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cer: local, regional and metastatic. Local recurrence may occur after conservative breast surgery in the preserved breast tissue and is called ipsilateral breast tumor recurrence (IBTR). It may also occur after modified radical mastectomy (MRM) or skin-sparing mastectomy (SSM) in the skin along scar of the previous operation, in the subcutaneous tissue or in the musculature of the chest wall or in the reconstructed breast. Regional recurrent breast cancer is found in the regional lymph nodes as ipsilateral axillary, infraclavicular or supraclavicular lymph nodes or in ipsilateral internal mammary lymph nodes. Metastatic recurrent breast cancer is that occurring in the lung, bone, liver, brain or soft tissues other than breast [3].

Locoregional recurrence (LRR) after proper therapy for operable breast cancer is not uncommon; the 10-year incidence is about 12% after breast conservation therapy and around 13% following mastectomy [3].

Many factors have been studied in the international literatures as prognostic factors for LRR such as the age of patients at time of diagnosis, size of the tumor, site of the tumor, axillary lymph node status, safety margin status specially after BCS, presence or absence of lymphovascular or perineural invasion, the histological grading of the primary tumor, hormonal receptor status for Estrogen receptor (ER), Progesterone receptor (PR) and Her2 neo receptor of the primary tumor, patient compliance for adjuvant therapy and its duration including chemotherapy, hormonal therapy, target therapy and postoperative radiotherapy. There is a lack of studying these factors among Egyptian females. [4, 5] The aim of this study is to assess and identify the predictors for locoregional recurrent breast cancer among Egyptian females.

Patients and Methods

This retrospective study was conducted on 60 female patients with locoregional recurrent breast cancer admitted to Alexandria Main University Hospital, Surgical Oncology Unit. 30 cases of them had a recurrence after breast conservation therapy (BCT) while the other 30 cases had a recurrence after modified radical mastectomy (MRM) with exclusion criteria of bilateral breast cancer and male breast cancer.

All patients were subjected to the classical triple assessment which includes thorough history taking and physical examination, radiological imaging (mammogram with ultrasound), metastatic workup and biopsy (FNAC or core biopsy or excisional biopsy).

After collection of the data from the patient, we correlated between the recurrence and the original tumor with regard to:

The site of the tumor and its relation to the previous one (in the same quadrant or in another quadrant if BCS was performed), the type of surgery and operative data (adequacy of the safety margin if BCS was performed) or use of myocutaneous flaps for reconstruction.

The pathological report of the original tumor in terms of

a) The size of the original tumor.

b) The number of involved lymph nodes

c) The histopathological grading

d) Lymphovascular invasion

e) ER and PR status and HER2neu

The type, timing and the number of cycles of adjuvant or neoadjuvant therapy

The history and timing of radiotherapy to the chest wall, breast or axilla in relation to surgery.

History and type of hormonal therapy

Results

The mean age of the patients was 36.67 years ±11.16 years in all the studied cases. This is lower than the mean age of breast cancer patients being admitted to Alexandria Main University Hospital which is 48.2±6.7.

Regarding the size of the primary tumor in time of diagnosis; in our study, it was found that 10 cases were T1 tumors, 36 cases were T2 tumors, 6 cases were T3, and 8 cases were locally advanced tumors T4. (Table 1)

Regarding the status of axillary lymph nodes of the primary surgery; in our study, it was found that 40 cases harvested less than 10 lymph nodes which mean inadequate axillary clearance, while 20 cases harvested ≥ 10 lymph nodes. All the cases have affected lymph nodes either macroscopically or microscopically where 18 cases have 1-3 affected lymph nodes while 42 cases have ≥ 4 lymph nodes affected and 24 out of 60 cases have extranodal extension. (Table 2).

Regarding the safety margin status for the 30 cases undergone BCT; 16 cases had a negative margin >1 mm in the frozen section; 6 cases were negative from

Table 1. Classification of cases according to tumor size and surgical management.

Tumor size category	Total number of cases	Management (no. of cases)
T1	10	BCT (10)
T2	36 (4of them multicentric) (2 of them multifocal)	• BCT (18) • MRM (12) • SSM (6) "4 TRAM & 2 LD for reconstruction"
T3	6 (2 of them multifocal)	BCT (2) "received pre-operative chemotherapy to decrease the size of tumor" "quadrantectomy & LD for coverage MRM (4)
T4 Locally advanced (Without distant metastasis.)	8	MRM (8) "6 of them received pre-operative chemotherapy"
Total	60	

Table 2. Number and pattern of affection of axillary lymph nodes.

	Number of lymph nodes>10 harvested	Number of lymph nodes<10 harvested	Total
Number of lymph nodes>4affected	12	30	42
Number of lymph nodes<4affected	8	10	18
Total	20	40	60

Table 3. Statistics of same and different sites of tumor (before and after recurrence).

Site of Primary Tumor	Same Site	Different Site	Percent Same	Percent Different
Retroareolar	6	2	33.33	16.67
LOQ	2	2	11.11	16.67
UOQ	8	2	44.44	16.67
LIQ	0	4	0.00	33.33
UIQ	2	2	11.11	16.67
Sum	18	12	100.00	100.00
(P-value >0.05 in all sites)				

the first time while 10 cases were negative after re-excision. 12 cases had close margin <1 mm in the frozen section; all of them were scheduled for booster dose radiotherapy and did not undergo re-excision. 2 cases were negative in the frozen section while in the paraffin section were positive with no safety margin. Also, 12 cases out of the 30 cases that have undergone BCS had extensive intraductal component (EIC).

It can be observed that tumors that occur in the retroareolar and the upper outer quadrant (UOQ) are very likely to occur in the same site after recurrence. On the other hand, tumors occurring in the lower outer quadrant (LOQ), lower inner quadrant (LIQ), and upper inner quadrant (UIQ) have a higher likelihood of occurring on a different site. (Table 3)

Table 4 shows the contingency table for the site of the tumor, before and after recurrence. It is found that there exists a strong correlation between the site of the tumor, before and after recurrence (x2=20, contingency coefficient (C)=0.76, and Cramer's V coefficient=0.67).

Regarding the histological characters of the primary tumor; in our study, it was found that 8 of the cases were grade I, 34 were grade II, 18 cases were grade III, and 38 cases had lymphovascular invasion while 22 cases with no lymphovascular invasion.

Regarding the status of the hormonal receptors of the primary tumor, in our study; it was observed that 28 cases out of the 60 studied cases were ER-positive and 54 cases were negative for Her 2neo.

Regarding adjuvant therapy (hormonal therapy, radiotherapy, and chemotherapy), in our study; all cases

Table 4. Contingency table for site of tumor.

Before/After	Retroareolar	LOQ	UIQ	UOQ	LOQ	Total
Retroareolar	6	0	0	2	0	8
LOQ	0	2	0	2	0	4
UIQ	2	0	2	0	0	4
UOQ	2	0	0	8	0	10
LOQ	0	0	0	4	0	4
Total	10	2	2	16	0	30

(x^2=20, contingency coefficient (C)=0.76, and Cramer's V coefficient=0.67).

Table 5. Adjuvant therapy among studied cases.

	Chemotherapy	Hormonal therapy
Patients received	48 (80 %)	14 (50 %)
Patients did not receive	12 (20 %)	14 (50 %)

Table 6. Descriptive statistics of the two continuous predictors in the study.

Statistic/Predictor	Age (Years)	Disease Free Interval (DFI) (Months)
Median	33.50	27.50
Mean	36.67	26.10
Standard deviation	11.16	12.55

that have undergone MRM with ≥4 lymph nodes were scheduled for radiotherapy. Furthermore, all BCS were scheduled for radiotherapy. It was found that 48 cases received adjuvant chemotherapy (all of them FAC regimen); 28 of them completed their six cycles. Also, it was found that 14 cases out of the 28 cases who are ER-positive received adjuvant hormonal therapy in the form of tamoxifen. 8 cases of them received it less than 1 year, 4 cases received it >1 year but <3 years. Only 2 cases received it > 3 years but < 5 years. (Table 5, Figures 1 and 2)

It can be seen that there is a direct relationship between age of the patient and disease-free survival (DFI). (Table 6, Figure 3)

Discussion

Regarding to the age, this study showed that the risk of LRR is increased in younger female patients regardless of age cut-point. Jobsen et al.[6] showed that; in patients less than 40 years old presented with early breast cancer T1 tumors with negative axilla and managed by BCT; the age is considered the only significant risk factor for LRR. Harrold et al. [7] suggested that when the age is less than 40, there is an increased rate of local recurrence a correlation with young age and LRR by using 40 years as a cut point of age.

Regarding the size of the primary tumor, Touboul E et al. [8], Jacobson JA et al.[9] have found that there is no significant difference in the risk of ipsilateral breast tumor recurrence (IBTR) between T1 and T2 that are eligible for BCT. The most debatable tumor size category is T3. In our study 6 cases were T3 and had received neoadjuvant chemotherapy then BCS was done, and there was no available data about the effect of the neoadjuvant chemotherapy on tumor size in these cases. Khanna et al. [10] also found that after the follow up of median 46 months only 3 cases (8%) out of 36 cases with T3 tumors and managed by BCT showed IBTR. In national surgical adjuvant breast and bowel project (NSABP) B-18, in patients presented with T3 tumors and randomized divided into 2 groups for pre or postoperative chemotherapy, there was increased rate of IBTR (14% vs 7%) in the group of preoperative chemotherapy in which tumors were decreased in size, in comparison to those tumors of upfront breast conservation [10].

Regarding the status of axillary nodes of the primary tumor; Iyer et al. [11] found that the risk of LRR is increased in the presence of fewer positive lymph nodes examined, this is due to under staging of the axilla. This fact is also proved by Recht et al., [12] the rate of LRR is decreased when the number of examined lymph nodes is increased from 2 to 5 lymph nodes or 6 to 10 lymph nodes. Kuske et al. [13] found that in patients with 1 to 3 positive nodes the presence of extracapsular extension is associated with the 17% increased risk of

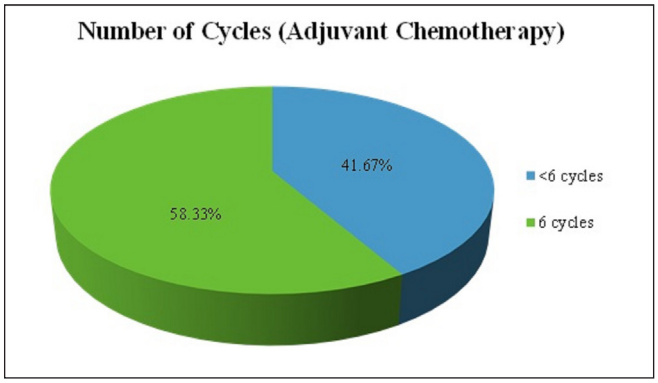

Figure 1. Distribution of number of adjuvant chemotherapy cycles among studded cases.

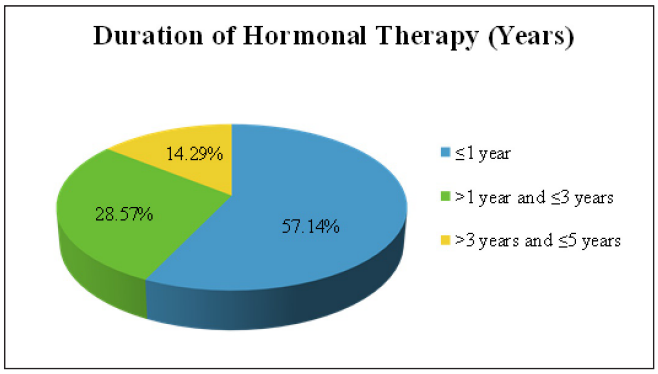

Figure 2. Duration of hormonal therapy among studded cases.

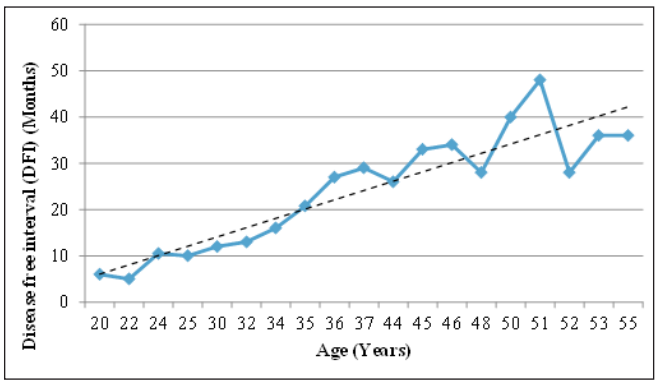

Figure 3. Relationship between age and DFI.

LRR compared to 7% in patients without extracapsular extension.

Regarding the safety margin status after BCT, the risk of IBTR is increased 2 to 3 times in the presence of positive margins compared to those of negative margins following BCT. [14, 15] Park et al. [16] found that there is no difference of IBTR. (7%) between close margin (< 1mm) or negative margin after 8 years follow up. However, Recht et al. [17] in the prospective trial found that close margin is considered a significant risk factor for IBTR.

In the presence of an EIC, wider margins should be obtained even after several attempts of resections, and so mastectomy decision should be postponed till failure to reach to negative margins is recognized [18].

In their study of 500 female patients with breast cancer stage I or II, Vicini et al.[19] reported that smaller volumes of resection were associated with high rate of IBTR and thus larger volumes of resection were needed in resection of EIC. In the same study they found that for patients with EIC-positive tumors, the larger resections were associated with lower risks for recurrence when compared with the smaller volume resections.

Many studies found that the most common type of LRR after BCS, happen within the same site of the previously excised tumor due to incomplete excision present in 57% to 88% of patients. The second type, happen within the same quadrant away from the site of the original tumor which represents 22% to 28% of LRRs; it is mostly due to the evolution of hidden multifocal DCIS since initial surgery. The third type of recurrence is de novo or true recurrence which happens in the different quadrant and represents 10% to 12% of patients. The fourth type of LRR is the rare due to postoperative and happen within the radiated tissue. The fifth type of LRR is less than 5%, and it is an inflammatory relapse [20,21].

Regarding to disease-free interval (DFI), we found that the mean DFI was 26.1 months with standard deviation 12.55 months and there was a direct relationship between age of the patient and DFI. This implies that, for younger ages, the DFI is reduced, and vice-versa. Schuck A et al. [22] states that the early incidence of LRR is an indicator of aggressive tumor behavior, while this relationship is not proved by Janni W et al. [23].

After reviewing of literatures; the predictive factors of significance for locoregional recurrence are young age, positive resection margins after BCS, lymphovascular invasion, the heavy affection of axillary lymph nodes, extracapsular extension, and extensive intraductal component, high histologic grade, the absence of radiation after BCS, incompliance of adjuvant hormonal therapy and chemotherapy. Some of these predictive factors proved to be significant in this study with no clear statistics due to retrospective nature of the study.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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