International Surgery Journal
*Elfol HA et al. Int Surg J. 2019 Jan;6(1):287-292*
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20185489

**Original Research Article**

# Assessment of predictors and prognostic factors for locoregional recurrent breast cancer

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**Received:** 28 September 2018
**Revised:** 21 November 2018
**Accepted:** 29 November 2018

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## ABSTRACT

**Background:** Assessment of predictors and prognostic factors of locoregional recurrent breast cancer will help in management of those patients. The aim of this study was to assess and identify the predictors and prognostic factors for locoregional current breast cancer.
**Methods:** This prospective study will be carried out on 50 female patients with history of breast cancer underwent surgical procedures either modified radical mastectomy (MRM) or conservative breast surgery (CBS) and adjuvant therapy (chemotherapy, radiotherapy, hormonal therapy).
**Results:** Significant relationship between recurrence of breast cancer and Oral contraceptive pills of the studied female patients with history of breast cancer underwent surgery.
**Conclusions:** Number of positive lymph nodes, lympho-vascular invasion, positive safety margin and presence of extensive intra-ductal component all these factors increase risk of recurrent breast cancer.

**Keywords:** Conservative breast therapy, Locoregional recurrent breast cancer, Modified radical mastectomy

## INTRODUCTION

Breast cancer is the most common type of cancer in females in developed and developing countries. Since 2004, a French national screening program of breast cancer has been established for females between 50-74years old.[1]

Although there is an increase in breast cancer incidence, breast cancer mortality is decreasing in the last decade. This decrease in mortality is mainly caused by both the introduction of breast cancer screening and the improvement and more extensive use of adjuvant systemic therapy. Currently, approximately 2/3 of the patients who are diagnosed with breast cancer do not have nodal involvement at diagnosis and about 2/3 of the patients are 55 years of age or older at diagnosis.[2]

Presence of a LR and/or RR can be defined as loco-regional recurrence (LRR). The majority of LRRs are diagnosed within five years of the primary tumor. LRR rates vary between 3% for patients with stage T1N0 who underwent mastectomy to 13% for patients with nodal involvement and breast-conserving surgery. SP breast cancer (diagnosed at least three months from the primary tumor diagnosis and with different primary location and morphology) occurs in 2-6% of the patients.[3]

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different primary location and morphology) occurs in 2-6% of the patients.[4]

Clinical studies dealing with bilateral breast cancer as a prognostic factor either arrive at contradictory results or show a wide range of variation in the reported incidence rates, varying from 1 to 20%. Authors, therefore, believe that studies performed to date may have been inaccurate in estimating the rate of bilateral breast cancer, since standard diagnostic tools do not seem to enable a firm distinction between a de novo and a metastatic growth in the contralateral breast.[5]

The most commonly used classification of invasive breast cancers divides them into ductal and lobular types, there are three main types of recurrent breast cancer: local, regional and metastatic. Local recurrent breast cancer may be after BCT in the preserved breast tissue or after MRM in the skin along the scar of the previous operation or in the subcutaneous or in the soft tissues on the chest wall. Regional recurrent breast cancer is recurrence that occurred in the regional lymph nodes as ipsilateral axillary lymph nodes, supraclavicular lymph nodes, infraclavicular lymph nodes and internal mammary lymph nodes. Metastatic recurrent breast cancer is that occurring in distant organs like bone, lung, liver, brain and soft tissues other than breast.[6]

## METHODS

The current studies had been done after obtaining a written consent from each patient and an approval by Ethical Committee, Faculty of Medicine, Menoufia University. It was designed to include fifty patients with history of breast cancer at the Department of General Surgery, Faculty of Medicine, Menoufia University in the period between 2017 to 2018.

### *Inclusion criteria*

Female patient with history of breast cancer underwent surgical procedures either modified radical mastectomy (MRM) or conservative breast surgery (CBS) and adjuvant therapy (chemotherapy, radiotherapy, hormonal therapy). All patients were subjected to:

### *Full history taking*

- Breast lump: onset, course, duration.
- Pain.
- Axillary swelling.
- Skin, subcutaneous or chest wall swelling.
- Nipple discharge: bloody, serous, milky.
- History of neoadjuvant or adjuvant therapy.
- History of post-operative radiation after BCS.
- History of primary breast cancer with detailed pathological, radiological, clinical and operative data.
- History of hormonal therapy.

### *Clinical examination*

*Inspection*

- Obvious swelling.
- Scar of previous operation.
- Areola and nipple.
- Skin manifestations: dimpling, nipple retraction, skin fungation, ulceration, peau d'orange.

*Palpation*

- Four breast quadrants.
- Areola and nipple.
- Axillary lymph nodes: hard, non-tender and fixed.
- Breast lump: hard, non-tender and fixed.
- Subcutaneous nodules along scar of previous operation.

### *Investigations*

*Laboratory investigation*

CBC, coagulation profile, liver function test, kidney function test, serum calcium and alkaline phosphatase.

*Radiological investigation*

Mammogram with complementary ultrasound, Chest x-ray, CT chest for detection of chest wall invasion (if indicated).

*Biopsy:* FNAC, true cut needle (if indicated).

Immunohistochemical studies (if indicated):

- ER.
- PR.
- HER 2 / neu.
- Ki 67.

After collection of the data from the patients we correlated between the recurrence and the original tumor as regard to:

1. Site of the tumor and its relation to the previous one (in the same quadrant or in another quadrant if BCS was performed.
2. The type of surgery and operative data (adequacy of safety margin) if BCS was performed or use of myocutaneous flaps for reconstruction.
3. The pathological report of the original tumor in terms of:

- The size of the original tumor.
- The histopathological picture.
- The number of involved lymph nodes.
- The histopathological grading.
- Lymphovascular invasion.

- Peritumoral and perineural invasion.
- ER and PR status.
- Ki 67 and HER2/neu.

4. The type, timing and the number of cycles of adjuvant or neoadjuvant therapy.
5. The history and timing of radiotherapy to chest wall, breast or axilla in relation to surgery.
6. History and type of hormonal therapy.

***Statistical methods***

The collected data were organized, tabulated and statistically analyzed using SPSS software (Statistical Package for the Social Sciences, version 19, SPSS Inc. Chicago, IL, USA). For quantitative data, the range, mean, standard deviation and median were calculated.

For qualitative data, which describe a categorical set of data by frequency, percentage or proportion of each category, comparison between two groups and more was done using chi-square test ($\chi^2$ test). For comparison between more than two means of parametric data, F value of ANOVA test was calculated.

To predict the recurrence of breast cancer (locoregional recurrence) and its prognostic factors among females with history of breast cancer and underwent surgical procedures, binary logistic regression was done to estimate B coefficient (Logistic Regression Coefficient) for prediction and Odds ratios (EXP (B)) for risk factors and prognostic factors of locoregional recurrence of breast cancer. Significance was adopted at $p<0.05$ for interpretation of results of tests of significance.

## RESULTS

Postoperative type of recurrence of breast cancer among the studied cases. 35 cases show local recurrence, 8 cases show regional recurrence while 7 cases show both local and regional which called locoregional recurrence. Table 2 show relationship between recurrence of breast cancer and data of the studied cases which show that there is significant relationship between recurrence of breast cancer and oral contraceptive pills.

Table 3 show there is significant relationship between recurrence of breast cancer and mean numbers of detected positive axillary lymph nodes. Significant relationship between recurrence of breast cancer and mean numbers of detected positive axillary lymph nodes among the studied female patients with history of breast cancer underwent surgical procedures (n=50).

**Table 1: Postoperative type of recurrence of breast cancer among the studied female patients with history of breast cancer underwent surgical procedures (n=50).**

| Variables | n | % |
|---|---|---|
| **Recurrence of cancer** | | |
| Locoregional recurrence | 7 | 14.0 |
| Regional recurrence | 8 | 16.0 |
| Local recurrence | 35 | 70.0 |

**Table 2: Correlation between recurrence of breast cancer and data of the studied female patients with history of breast cancer underwent surgical procedures (n=50).**

| Variables | Recurrence of breast cancer among the studied female patients with history of breast cancer (n=50) | | | | | | $\chi^2$ P |
|---|---|---|---|---|---|---|---|
| | Locoregional (n=7) | | Regional (n=8) | | Local (n=35) | | |
| **Age years** | | | | | | | |
| Range | 29.00-57.00 | | 30.00-55.00 | | 28.00-65.00 | | |
| Mean±SD | 40.43±11.13 | | 38.62±7.19 | | 43.48±11.87 | | |
| F-value, P | 0.724, 0.490 | | | | | | |
| | **n** | **%** | **n** | **%** | **n** | **%** | |
| **Menstrual history** | | | | | | | |
| Postmenopausal | 2 | 14.3 | 1 | 7.1 | 11 | 78.6 | 1.159 |
| Premenopausal | 5 | 13.9 | 7 | 19.4 | 24 | 66.7 | 0.560 |
| **Parity** | | | | | | | |
| Multipara | 6 | 15.4 | 6 | 15.4 | 27 | 69.2 | 0.300 |
| Nullipara | 1 | 9.1 | 2 | 18.2 | 8 | 72.7 | 0.861 |
| **Ocp** | | | | | | | |
| Negative | 3 | 7.9 | 5 | 13.2 | 30 | 78.9 | 6.826 |
| Positive | 4 | 33.3 | 3 | 25.0 | 5 | 41.7 | 0.033* |
| **Family history of breast cancer** | | | | | | | |
| Negative | 3 | 9.7 | 5 | 16.1 | 23 | 74.2 | 1.295 |
| Positive | 4 | 21.1 | 3 | 15.8 | 12 | 63.2 | 0.523 |

**Table 3: Relationship between recurrence of breast cancer and detection of axillary lymph nodes among the studied female patients with history of breast cancer underwent surgical procedures (n=50).**

| Variables | Recurrence of breast cancer among the studied female patients with history of breast cancer (n=50) | | | F-value P |
|---|---|---|---|---|
| | Locoregional (n=7) | Regional (n=8) | Local (n=35) | |
| **Detected axillary lymph nodes** | | | | |
| Range | 10.00-25.00 | 10.00-20.00 | 9.00-21.00 | 1.348, 0.270 |
| Mean±SD | 17.00±4.79 | 15.00±3.16 | 14.00±3.46 | |
| **Positive lymph nodes** | | | | |
| Range | 4.00-23.00 | 2.00-10.00 | 0.00-3.00 | 59.739, 0.0001* |
| Mean±SD | 11.00±5.93 | 4.00±2.51 | 1.00±0.78 | |
| **% of positive lymph nodes out of detected lymph nodes** | | | | |
| Range | 40.00%-92.00% | 17.00%-56.00% | 0.00%-20.00% | 165.313, 0.0001* |
| Range | 63.90%±16.67 | 29.70%±11.47 | 2.78%±4.78 | |

*Significant (P <0.05)

**Table 4: Relationship between recurrent breast cancer and lympho-vascular invasion and safety margin among the studied female patients with history of breast cancer underwent surgical procedures (n=50).**

| Variables | Recurrence of breast cancer among the studied female patients with history of breast cancer (n=50) | | | | | | $\chi^2$, P |
|---|---|---|---|---|---|---|---|
| | Locoregional (n=7) | | Regional (n=8) | | Local (n=35) | | |
| | n | % | n | % | n | % | |
| **Lympho-vascular invasion** | | | | | | | |
| Negative | 0 | 0 | 2 | 25.0 | 26 | 74.3 | 16.779, 0.0001* |
| Positive | 7 | 100 | 6 | 75.0 | 9 | 25.7 | |
| **Safety margin** | | | | | | | |
| Negative | 3 | 42.9 | 5 | 62.5 | 31 | 88.6 | 8.437, 0.015* |
| Positive | 4 | 57.1 | 3 | 37.5 | 4 | 11.4 | |

**Table 5: Relationship between recurrence of breast cancer and presence of extensive intra-ductal component (EIC) and among the studied female patients with history of breast cancer underwent surgical procedures (n=50).**

| Variables | Recurrence of breast cancer among the studied female patients with history of breast cancer (n=50) | | | | | | $\chi^2$, P |
|---|---|---|---|---|---|---|---|
| | Locoregional (n=7) | | Regional (n=8) | | Local (n=35) | | |
| | n | % | n | % | n | % | |
| **Presence of extensive intra-ductal component (EIC)** | | | | | | | |
| Negative | 5 | 71.4 | 7 | 87.5 | 29 | 82.9 | |
| Positive | 2 | 28.6 | 1 | 12.5 | 6 | 17.1 | |
| 5% | 1 | 14.3 | 0 | 0 | 2 | 5.7 | 5.116, 0.745 |
| 10% | 1 | 14.6 | 0 | 0 | 1 | 2.9 | |
| 15% | 0 | 0 | 0 | 0 | 1 | 2.9 | |
| 20% | 0 | 0 | 1 | 12.5 | 2 | 2.7 | |

Significant relationship between recurrence of breast cancer and mean percent (%) of detected positive axillary lymph nodes from all detected nodes among the studied female patients with history of breast cancer underwent surgical procedures.

Table 4 show there was significant relationship between recurrent breast cancer and presence of lympho-vascular invasion. Table 4 show there was significant relationship between recurrent breast cancer and presence of positive safety margin.

Significant relationship between recurrence of breast cancer and oral contraceptive pills of the studied female patients with history of breast cancer underwent surgical procedures (n=50) (Table 2). Significant relationship between recurrence of breast cancer and mean numbers of detected positive axillary lymph nodes among the studied female patients with history of breast cancer

underwent surgical procedures (n=50) (Table 3). Significant relationship between recurrence of breast cancer and mean percent (%) of detected positive axillary lymph nodes from all detected nodes among the studied female patients with history of breast cancer underwent surgical procedures (Table 3).

**Table 6: Multiple logistic regression analysis denoting prognostic factors of locoregional recurrence of breast cancer among the studied female patients with history of breast cancer underwent surgical procedures (n=50).**

| Variables | B | SE | Sig. (P value) | EX (B) | Confidence interval (CI) | |
|---|---|---|---|---|---|---|
| | | | | | Lower limit | Upper limit |
| Detected axillary lymph nodes | 0.166 | 0.108 | 0.123 | 1.181 | 0.956 | 1.459 |
| positive lymph nodes | 0.689 | 0.221 | 0.002* | 1.992 | 1.291 | 3.074 |
| % of positive lymph nodes out of detected lymph nodes | 0.165 | 0.065 | 0.011 | 1.180 | 1.038 | 1.341 |
| Histopathology | 19.088 | 24.303 | 0.999 | 0.000 | 0.000 | |
| Lympho-vascular invasion | 2.318 | 0.137 | 0.0001* | 1.825 | 1.102 | 3.402 |
| Safety margin | 1.925 | 0.868 | 0.027* | 0.146 | 0.027 | 0.800 |
| Presence of extensive intra-ductal component (EIC) | 1.978 | 0.161 | 0.0001* | 0.894 | 0.780 | 2.027 |

*Significant (P < 0.05); B=Logistic Regression Coefficient; SE=Standard Error of B; P=Significance level; Exp (B) =Estimated Odds Ratio

Significant relationship between recurrent breast cancer and lympho-vascular invasion among the studied female patients with history of breast cancer underwent surgical procedures (Table 4).

Significant relationship between recurrence of breast cancer and safety margin among the studied female patients with history of breast cancer underwent surgical procedures (Table 4).

Significant relationship between recurrence of breast cancer and presence of extensive intra-ductal component (EIC) and among the studied female patients with history of breast cancer underwent surgical procedures (Table 5).

## DISCUSSION

The purpose of this study was to assess and identify the predictors and prognostic factors for locoregional current breast cancer and the management policy for those patients and the rule of surgery in the treatment which include Salvage mastectomy if the LRR was after BCT and wide local excision whenever possible for chest wall recurrence after MRM.

This study was conducted mainly prospectively on 50 female patients presented with LRR after MRM or BCT and certain factors were studied and compared with the primary tumor as independent predictors for LRR. These factors include the age at time of diagnosis of the primary tumor, site of primary tumor, lymph node status after primary surgery, size of primary tumor, lymphovascular invasion of the primary tumor, safety margin status specially after BCS, histopathological subtype and grading of the primary tumor, presence of extensive intraductal component (EIC) at the primary tumor, the ER, PR, Her2 status of the primary tumor. And according to the available data; the management policy for the studied cases was included.

Regarding to the age, this study showed that the younger the patient, the higher the risk for LRR regardless of age cut-point. The influence of young age on the risk for LRR is striking.

Jobsen et al, reported that age <40years was the only significant predictor of LRR for women treated with BCT with pathologic T1 tumors and negative lymph node status.[7]

Arvold et al, in this study, we found that, among 1,434 consecutive women with early-stage invasive BC who received BCT, increasing age was associated with decreased risk of LR independent of BC subtype approximation or other prognostic factors.[8]

Regarding to the size of the primary tumor, in our study it was found that 9 cases were T1 tumors, 26 cases were T2 tumors, and 4 cases were T3.

Regarding to the site of recurrence after BCT, in present study it was found that all the 30 cases undergone BCT have local recurrence in the form of ipsilateral breast tumor recurrence (IBTR) and it was noticed that the most common site for IBTR was in the same site of the primary tumor. This was seen in 6 cases with retroareolar location and 8 cases with upper outer quadrant location.

Regarding to lymph node status at time of primary surgery, in our study it was found that one case harvested

less than 10 lymph nodes while 49 cases harvested ≥ 10 lymph nodes, 26 cases have affected lymph nodes where 14 cases have 1-3 affected lymph nodes while 12 cases have ≥4 lymph nodes affected, 22 cases of them have extranodal invasion.

Derkx et al, found the rate of positive axillary lymph nodes among patients with local recurrence after breast surgery and negative SNB is too high to be ignored.[9]

Regarding to the safety margin status in BCT, in present study we had 30 cases undergone BCT and the following was found 24 cases had negative margin in the frozen section and 6 casas had positive margin. 5 cases had extensive intraductal component (EIC), since EIC within an invasive breast cancer generally indicates a larger subclinical tumor burden and an increased likelihood of microscopically positive margins.

Regarding to the safety margin after MRM, in our study we had 15 cases undergone MRM and 16 of them had negative margin in the paraffin section and 4 cases had positive margin.

The presence of positive resection margins is associated with a two to three times increased risk of developing IBTR (compared to negative margins) following breast-conserving surgery and radiation.[10]

## CONCLUSION

Number of positive lymph nodes, lympho-vascular invasion, positive safety margin and presence of extensive intra-ductal component all these factors increase risk of recurrent breast cancer.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Elfol H, Rageh TM, Hamed MA. Assessment of predictors and prognostic factors for locoregional recurrent breast cancer. Int Surg J 2019;6:287-92.