

## Risk Factors of Local–Regional Recurrence of Invasive Breast Cancer

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### Summary

Loco-regional recurrence of invasive breast cancer is fairly uncommon, however, it has significant adverse impact on the patients. Recurrence within the first 5 years of initial diagnosis associated with poor prognosis. Several contributed risk factors have been reported in previous studies; nonetheless, data about these risk factors are somewhat scarce in our country. Therefore, we aimed to assess the risk factors that increase the incidence of local regional recurrence of breast cancer among Iraqi patients. Therefore, we conducted a cross sectional study included 100 Iraqi women who had proved diagnosed invasive breast cancer, half of them develop local or regional recurrence within the first 4 years after diagnosis. Multiple patients and clinical factors were evaluated as predictor risk factors. Findings of our study revealed that 80% of patients diagnosed at age above 40 years. The significant , ( $P$  value < 0.05), risk factors associated with higher recurrence rates were obesity (100%), tumor size  $\geq 5$  cm with a recurrence rate of (91.7 %) , family history (87.5%), closed surgical margin (83.3%), hormonal receptor negative and Her 2-neu positive breast cancer (81 %) , involvement of axillary lymph nodes especially N2 and high grading (recurrence rate 74.2 % , 73.1 %) respectively. No significant association ( $P > 0.05$ ) was reported with other variables. Furthermore, delay in the initiation of adjuvant chemotherapy was significantly associated with high recurrence rate ( $P = 0.02$ ). In conclusion, the main risk factors of local-regional recurrence of breast cancer were obesity, larger tumor size, positive family history, closed surgical margin triple negative receptor status, high grade cancer, positive lymph node and delay in initiation of adjuvant chemotherapy.

**Keywords:** Breast cancer, Pathophysiology, Recurrence, Local-regional, risk factors

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## 1. INTRODUCTION

Breast cancer is a major public health problem for women throughout the world. Worldwide, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths, although there is a fivefold variation in incidence between high-incidence areas such as the United States and Western Europe, and low incidence areas such as Africa and Asia . The adult female breast lies between the second and sixth ribs, and between the sternal edge and the midaxillary line. The breast is composed of skin, subcutaneous tissue, and breast tissue, with the breast tissue including both epithelial and stromal elements. Epithelial elements make up 10% to 15% of the breast mass, with the remainder being stroma. Each breast consists of 15 to 20 lobes of glandular tissue supported by fibrous connective tissue the blood supply of the breast is derived from the internal mammary and lateral thoracic arteries. The breast lymphatic drainage occurs through a superficial and deep lymphatic plexus, > 95% of the lymphatic drainage of the breast is through the axillary lymph nodes, with the remainder via the internal mammary nodes (1) . The most common histologic type of breast cancer is invasive (infiltrating) ductal carcinoma, comprising (70 %) to (80 %) of cases. Breast cancer histologic classifications recommended by the AJCC Staging Manual include NOS; ductal; inflammatory; medullary, NOS; medullary with lymphoid stroma; mucinous; papillary (predominantly micro papillary pattern); tubular; lobular; Paget disease with infiltration; undifferentiated; squamous cell; adenoid cystic; secretory; and cribriform. (2). Local Recurrence after primary therapy for breast cancer includes in-breast recurrence after Breast Conservative Surgery, chest wall recurrence after mastectomy, while Regional recurrence refer to regional nodal recurrence(3). At the time of local regional recurrence, the chest wall is the most common site, representing about two-third of recurrence while the remaining one third is related to the supraclavicular / Infraclavicular region followed by axillary recurrence(4) . There are multiple factors associated with breast cancer local-regional recurrence including:

Obesity which is associated with both an increased risk of breast cancer development in postmenopausal women and increased breast cancer mortality due to the effects of obesity on the increased production of estrogen and insulin activation of tyrosine kinase growth

receptor pathway. Obesity may impact the rate of local- regional recurrence in breast cancer patients and the higher BMI predicted worse distant recurrence-free interval and overall survival (5). Tumor size, play a significant role in the recurrence rate, the larger tumor size associated with higher recurrence rates (7). Family history of breast and/or ovarian cancer, particularly if onset occurred at younger than age 50, is associated with a higher risk of breast cancer, particularly in first degree relatives (8) . Marginal status; margin width is the distance from the cancer to the ink painted on the surface of the excision specimen. Margins are checked after surgical biopsy, lumpectomy and mastectomy. Type of surgical margin based on the pathological report either clear (also called negative or clean) where no cancer cells seen at the edge of the removed tissue. Positive; cancer cells seen at the edge of the removed tissue. Close; cancer cells are close to the edge of the tissue, but not at the edge (9). Furthermore, high risk of recurrence reported when the cancer cells are triple negative, i.e. no receptors for estrogen or progesterone and don't have extra HER2 gene copies or cancer cells are HER2 positive. High grade tumor , spread to lymph or blood vessels in the breast tissue, cancer spread to  $\geq 4$  lymph nodes, muscles, chest or skin and inflammatory breast cancer are reported to increase the recurrence rates of breast cancer <https://cancer.ca/en/cancer-information/cancer-types/breast/treatment/risk-of-breast-cancer-recurrence-and-adjuvant-therapy>

## **2. PATIENTS and METHODS**

This was a retrospective comparative study conducted at Oncology teaching hospital at the Medical city in Baghdad during the period from 1st of November / 2017 to 1st of December / 2018. Including 100 patients diagnosed with breast cancer through a proper histopathological evaluation at the hospital Half of these patients develop local or regional recurrence within the first 4 years after diagnosis .All cases had been attended oncology teaching hospital were considered eligible according to the following inclusion and exclusion criteria

### **Inclusion criteria:**

1. Iraqi patients proved diagnosed with breast cancer of any histological type
2. Patient who did mastectomy or breast conservative surgery.

3. Patients with positive, closed and negative margin.
4. Patients with any tumor grade.
5. Patient with any hormonal receptor and Her 2-neu status.

**Exclusion Criteria:**

1. T4 tumors .
2. Inflammatory breast cancer.
3. N2 who had been received neo-adjuvant treatment.
4. Tumor metastasized to N3 levels of lymph nodes .
5. Sentinel lymph nodes evaluation surgery .
6. Metastatic breast cancer (M1).
7. Carcinoma in situ (Tis) .
8. Occult breast mass with positive axillary lymph nodes.
9. Distant breast cancer recurrence.
10. Patients aged 80 years or older .

Exclusion done through full history, examination , investigations and through surgical evaluation. all patient where investigate by chest and abdominal Contrast Tomography – scan and all surgical specimen (including both the breast tissue and lymph nodes) had been evaluated through a proper histopathological review .

**Data Collection:**

Data was collected through clinical evaluation (history and physical examination), radiological evaluation, histopathological review including Immunohistochemistry and surgical notes of the breast cancer patients . This Data including general demographic informations: name ,age at the time of diagnosis , height , weight ,body mass index (measured for all patients according to equation  $BMI = \text{weight} / \text{height}^2$  ). Data also include assessment of tumor size /cm, histopathological type , tumor grade ,number of lymph node involvement ,marginal status (all assess through histopathological review), surgical type (assess by evaluation of surgical. notes), family history of malignancies (assess through taking full patient’s family history) ,hormonal and Her2-neu receptor status (evaluated by using immunohistochemically reports) and recurrence status (evaluated through fine needle aspiration cytological reports ) .

**Statistical analyses** carried out by using SPSS version 23. Number, percentage used to represent the categorical data and Mean, standard deviation for scale variables. Independent student t test, Chi-square test and logistic regression used to confirm significance at a level of two-tailed P. value of  $\leq 0.05$  considered as significant.

### 3. RESULTS

The mean age of patients at diagnosis was  $48.1 \pm 10.2$ , 54 of patients (54%) diagnosed with an age between 40-60 years old , 40 of them (40%) with normal body mass index and only 16 of them (16%) had positive family history of the disease (Table 1).

The results revealed that 20 of patients (20 %) had tumor size of T1 , 68 (68 %) had T2 and 12 (12%) had T3 tumor size. The histological examination showed ductal type of tumor in 77 patients (77 %), lobular type in 21(21 %) and other types were reported in only 2 patients. Lymph node involvement revealed that 65 patients (65 %) had N1, 31 (31 %) had N2 and 4 of cases (4 %) N0. About half of the patients (52%) reached grade 3 of tumor, while 45 (45%) with grade 2 and only 3 cases (3%) had tumor of grade one. Seventy six of patients (76%) with tumor of negative marginal status, while 24 (24%) had tumor of closed margin while none of patients had tumor of positive marginal status. The ER, PR + ve , Her 2- neu - ve expressed in 46 patients (46 %) followed by triple negative tumors in 20 of them (20%), triple positive tumors in 18 of cases (18%) and ER, PR - ve , Her2 - neu + ve in 16 patients (16%). Recurrence status was reported in (50%) of cases, 8 of the recurrent status (8%) occur in regional (axillary) area while 42 (42%) recur locally, all these findings are shown in (Table 2). The findings showed that the recurrence of tumor was significantly associated with :

obesity; obese patients had the highest recurrence rate of (100 %) ( P= 0.001 ), Tumor size more than 5 cm, with recurrence rate (91.7 %) , (P=0.007). Positive family history with a recurrence rate reach up to 87.5 % (P value 0.001) . Closed surgical margin 83.3 % ( P value 0.001). Hormonal negative and Her2neu positive receptor status, where the recurrence rate reach up to 81.3 % ( P= 0.001 ). Four or more axillary lymph nodes involvement with a recurrence rate of 74.2 % (P= 0.001), and high grade tumor (grade 3) where the recurrence rate was 73.1% (P= 0.001).No significant association was reported with other parameters including age of the patients at diagnosis , types of surgical intervention and

histopathological subtypes, in all comparison ( $P > 0.05$ ), (Table 3).

Regression analysis for the predictors of recurrence revealed that BMI, tumor size, family history , LN involvement, hormonal receptors expression status, tumor grade and marginal status are significant predictors of recurrence with an odds ratio (OR) and (95% confidence interval for OR) for each factor as followed:

For obesity, [OR= 1.9(1.4-2.4), for tumor size of more than 5 cm [OR= 1.4(1.1-1.9)], for family history [OR= 3.4(1.0-3.6) ], for 4-9 LN involvement [OR= 2.8(0.7-2.4], for hormonal status (ER,PR -ve ,Her-neu-2 +ve) [OR= 2.2(1.4-3.5) ], for tumor grade (Grade 3) [OR= 7.7(3.1-18.7) ] and for marginal status [OR= 2.2(0.4-2.4) ], in all these factors , P. value was significant  $< 0.05$ , (Table 4)

Table 1. Descriptive characteristics of studied group

Variable		No.	%
Age at diagnosis / years	20- 40	20	20.0
	40-60	54	54.0
	60-80	26	26.0
Body mass index	Normal	40	40.0
	Overweight	50	50.0
	Obese	10	10.0
Family history	Positive	16	16.0
	Negative	84	84.0

**Table 2.** Clinical characteristics of the studied group (N=100)

		No.	%	
Tumor size at diagnosis/cm	T1	20	20.0	
	T2	68	68.0	
	T3	12	12.0	
Histopathological type	Ductal	77	77.0	
	Lobular	21	21.0	
	Other	2	2.0	
Lymph node/s involvement	N0	4	4.0	
	N1	65	65.0	
	N2	31	31.0	
Tumor grade	Grade 1	3	3.0	
	Grade 2	45	45.0	
	Grade 3	52	52.0	
Marginal status	Positive	0	0.0	
	closed margin	24	24.0	
	Negative	76	76.0	
Hormonal status	ER,PR,Her-2 neu+ve	18	18.0	
	ER,PR +ve,Her-neu-2 -ve	46	46.0	
	ER,PR -ve,Her-neu-2 +ve	16	16.0	
	ER,PR,Her-neu-2 -ve	20	20.0	
Type of surgical intervention	Mastectomy	66	66.0	
	Breast conservative surgery	34	34.0	
Recurrence	Yes	Local	42	42.0
		regional	8	8.0
	No	50	50.0	

Table 3. Association of recurrence status and studied parameters

Variable		Recurrence status				P - Value
		Yes		No		
		No.	%	No	%	
BMI	Normal	4	10.0	36	90.0	0.001
	Overweight	36	72.0	14	28.0	
	Obese	10	100.0	0	0.0	
Tumor size at diagnosis/cm	T1 ≤ 2cm	10	50.0	10	50.0	0.007
	T2 (2-5cm)	29	42.6	39	57.4	
	T3 > 5 cm	11	91.7	1	8.3	
Family history	Positive	14	87.5	2	12.5	0.001
	Negative	36	42.9	48	57.1	
Marginal status	Closed	20	83.3	4	16.7	0.001
	Negative	30	39.5	46	60.5	
Hormonal & Her2-neu receptor status	ER ,PR +ve, Her2-neu +ve	8	44.4	10	55.6	0.001
	ER ,PR +ve, Her2-neu -ve	13	28.3	33	71.7	
	ER , PR -ve, Her2-neu +ve	13	81.3	3	18.8	
	ER , PR -ve, Her2-neu -ve	16	80.0	4	20.0	
Axillary lymph node/s status	NO	2	50.0	2	50.0	0.001
	N1	23	35.4	42	64.6	
	N2	23	74.2	8	25.8	
Tumor grade	Grade 1	0	0.0	3	100.0	0.001
	Grade 2	12	26.7	33	73.3	
	Grade 3	38	73.1	14	26.9	
Histopathological type	Ductal	42	54.5	35	45.5	0.100
	Lobular	8	38.1	13	61.9	
	Other	0	0.0	2	100.0	
Type of surgical intervention	Mastectomy	36	54.5	30	45.5	0.200
	Breast conservative surgery	14	41.2	20	58.8	
Age at diagnosis (year)	20-40	12	60.0	8	40.0	0.600
	40-60	50	92.0	4	8.0	
	60-80	20	76.0	6	24.0	



Table 4. Results of logistic regression analysis for the predictors of recurrence of local-regional Breast cancer

Variable	Odd's ratio (OR)	95% CI of OR	P. Value
BMI (obese)	1.90	1.4-2.4	0.010
Tumor size (>5cm)	1.40	1.1-1.9	0.020
Marginal status (closed margin )	2.20	0.4-2.4	0.010
ER , PR –VE Her2-neu +ve	2.20	1.4-3.5	0.010
Lymph nodes (4-9 LN)	2.80	0.7-2.4	0.003
Tumor grade ( Grade 3)	7.70	3.1-18.7	0.001
Histopathological type	0.40	0.1-1.1	0.060
Type of surgery	0.50	0.2-1.3	0.200
Age at diagnosis	0.90	0.8-1.1	0.200
Positive family history	3.40	1.9-3.6	0.010

#### 4. DISCUSSION

This study included 100 women diagnosed with invasive breast cancer , half of them develop local or regional recurrence , firstly we noticed that elevated body mass index is associated with increase incidence of LRR especially in obese patient ( reach up to 100 %) with ( P-value=0.001) table.3.3.a similar results was noticed In a study of 878 women with early stage invasive breast cancer who underwent breast –conservation therapy (BCS) by Laura E. G. Warren . et al. (2016) . In a multivariable analysis, BMI was positively associated with local-regional recurrence but only in premenopausal women(15) . This result was compatible to our result since median age of our patients is 48 years old. This study also noticed that the increment in tumor size especially those with more than 5 cm (T3) is associated with high LRR reach up to 91.7 % (P value 0.007) , this result was more similar to a study done by Hai . Ping .Xia .et .al. in China published in July /2017 where 102 breast cancer patients who underwent breast surgery . the study concluded that

recurrence of breast cancer is more with tumor volume more than 5 cm, with cutting edge invasion, HER-2 and estrogen receptor-positive, patients with lymph node metastasis, and stage III disease(16) . In patient with positive family history of malignancy ( including breast and/or ovary) that affecting first degree relative, we noticed that there is an association with increment of LR up to 87.5 % of cases with positive history (P=0.001) this fact is completely different from another study done by Brekelmans CT .et. al published in April/1999 to determine the impact of a family history of breast cancer on the LR risk after breast conserving therapy (BCT) .The study concluded that the sole presence of a positive family history of breast cancer does not appear to be a risk factor for local recurrence after BCT(17).

We noticed that closed surgical margin is more associated with increment in LRR that reach up to 83.3 % (P=0.001). This result was more similar to another study done by Charles Kunos et. al. published at January /2006,. After a median follow-up of 56 months from the completion of breast conservation surgery, the study concluded that cosmetically acceptable tumor-free ( $\geq 2$  mm) surgical margins significantly reduce local in-breast and regional lymph node recurrence (18). We found that patient with triple negative and those with ER ,PR -ve and Her-2-neu +ve were associated with highest LRR reaching up to (80%, 81.3 % ) respectively ( P= 0.001 ) , this was highly agreed with a study done by K. David Voduc . et .al .(2009) which determined the association between breast cancer local-regional metastasis and molecular subtypes in a large cohort study .the study concluded that the luminal A tumors (ER or PR positive, HER2 negative, Ki-67 14%) had the best prognosis and the lowest rate of local or regional relapse while patients with HER2-enriched and basal subtypes demonstrated an increased risk of regional recurrence (19). We also reported that axillary lymph nodes involvement is associated with high local –regional recurrence reaching up to 74.2 % for those with more than 4 lymph nodes involvement .(P-value 0.001 ) . This result is comparable with other study done by Samuel W. Beenken et .al. who assessed the significance of axillary lymph node status for predicting LRR and overall survival after mastectomy for breast cancer . After median follow-up of 15 years, the study concluded that neither type of surgery nor chemotherapy was shown to affect local- regional disease-free or overall survival. Local – regional rates were higher and overall survival rates were lower in patients with nodal involvement (20). In the current study, high grade tumor

(grade III) was significantly associated with increased risk of LRR reaching up to 73.1 (P-value 0.001) that result is similar to another one done by Pauline T. Troung .et .al. for 5,688 women . The study concluded that Patients with N+ and Grade III disease have high LRR risks approximating 15% to 20% despite surgery, RT and systemic therapy(21). In a thorough literature review, we couldn't find any study that determined the tumor grade as a sole factor and its correlation with breast cancer local regional recurrence. Another finding in our study that there was no significant association between histopathological type of tumor and LRR. table. 3 .which is the same result with another study done by Stuart J. et. al. that first published in 15 / July/1989 to determine the influence of infiltrating lobular histology on local tumor control. Results were compared with those in 561 cases of infiltrating ductal carcinoma similarly treated during the same period. The 5-year actuarial risk of local recurrence was similar for patients with infiltrating lobular or ductal carcinoma when the latter was evaluated as a single group (12% versus 11%) (22) . We found that the mean age at diagnosis was 48 years and the increment in age is not consider as a significant risk factor for LRR ( $P>0.05$ ),in contrast to another study done by Marc A Bollet .et . al. (2007) where the age was the only prognostic factor for LRR and the relative risk of LRR increased by 7% for every decreasing year of age (23). This study found no significant association between LRR and the type of surgical intervention which is close to the finding of E. Botteri et al. in 2009 who concluded that LRR was not affected by the type of surgery (24). Another study performed by Noufel Sh. Mutlak et al. to assess the rate of recurrence for early breast cancer in Iraqi female patients, in relation to certain risk factors concluded that the rate of recurrence after modified radical mastectomy is relatively high and an important risk factors are related to the stage, grade and delay of treatment(25) . Moreover, Ali M. Al-saiegh found a significant association with the duration between first complaint and surgical management (latency period), the size of primary tumor , the number of lymph nodes involved (staging ), histopathology & grading of primary tumor and the education level and socioeconomic status . While the association between the rate of LRR and age , type of adjuvant therapy , marital state , lactation state , family history , parity , type of surgery were less significant(26) .

## **5. CONCLUSIONS**

We concluded that local –regional recurrence in breast cancer patients was significantly associated with obesity, increasing in tumor size, positive family history, closed surgical margin, triple negative and Her2-neu positive receptor status, positive axillary lymph nodes and high grade tumors. We didn't find any correlation between local-regional recurrence and the age of the patients, histopathological type and the type of surgery. Hence, we recommend that Surgical margin to be carefully determined during surgery. And further multicenter studies should be performed with larger sample size for further evaluation. Additionally, public education and motivation of screening program are still important protective factors.

**Ethical Clearance:** Ethical clearance and approval of the study are ascertained by the authors. All ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 for ethical principles for medical research involving human subjects, informed consent obtained from all patients. Data and privacy of patients were kept confidentially.

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