

## Post-Surgical Loco Regional Recurrence Of Breast Carcinoma In Iraq

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### Summary

*J Fac Med Baghdad*  
2007; Vol. 49, No.2  
Received June 2006  
Accepted Oct. 2006

**Background :** From the standpoint of mortality & morbidity, cancer is by far the most important clinical problem that concerns the breast today .The age adjusted incidence of new cases has been increasing steadily with increase in the incidence among the Iraqi women during the last few years .

**Materials & method :** A prospective study was arranged to assess the occurrence of post-surgical loco-regional recurrence of breast carcinoma in the Iraqi female patients , a total number of 91 female patients were assessed during period from Dec.2000 to Dec.2002, the median period of follow up was two years .

**Result :** Loco-regional recurrence developed in 20 patients (22%). Chest wall and axilla were the main sites of loco-regional recurrence seen in 12 (60%) and 6 (30%) patients respectively. Significant association were found regarding the duration between first complaint and surgical management (latency period), the size of primary tumour , the number of lymph nodes involved , staging , histopathology & grading of primary tumour .

While the association between the rate of loco-regional recurrence and age ,education level ,socioeconomic status ,contraception history, marital state , lactation state , family history , parity , type of adjuvant therapy, type of surgery were in-significant .

**Conclusion:** Carcinoma of the breast affecting Iraqi females at younger ages in a high & increasing rate than other studies with a higher Loco-regional recurrence rate. Significant association were found regarding latency period, staging, histopathology & grading of primary tumour .

#### **Aims Of Study:**

1. To assess the incidence of post operative loco regional recurrence of breast carcinoma in Iraqi female patients.
2. To determine the significance of certain variables that may affect the loco regional recurrence rate .

**Keywords :** breast cancer , locoregional , recurrence

### Introduction:

Breast cancer account for 32% of all female cancer and is responsible for 19% of cancer related death in women . Approximately 400,000 women in the world die of breast cancer each year , in the U.S. it is the leading cause of cancer related mortality among women responsible for about 43,000 deaths annually. It is the leading cause of death from cancer for female age 40-44 year <sup>(1)</sup>.

Breast cancer has remained the commonest tumour in Iraqi female patients over the last three years with 14.3% incidence among other tumour . Among females it accounts for more than 30% of registered female cancer with sharp increase in the rate of this tumour in the younger age groups . Patients under 30 years of age form about 5% and 75% of cases occur in women older than 40 years. The highest number of cases is between 40-50 years of age groups <sup>(2)</sup> .

Metastasis presumably occurs within any period of neoplastic growth after the first few doubling . This reflects to the importance of early detection of cancer especially with new techniques , like nuclear morphometry using polyvar microscope that use three parameters

(nuclear area, maximum diameter ,circular diameter ) <sup>(3)</sup>. And the MRI spectroscopy for early detection of malignant breast disease <sup>(4)</sup>.

Surgery is one of the cardinal therapeutic option for this clinical problem. There has been transition to more conservative surgery, nevertheless still MRM commonly practiced all over the world<sup>(5)</sup>. Especially if the tumour is large in relation to size of breast ,central in location , involve the nipple, or multifocal <sup>(6)</sup>. Breast conservative surgery for invasive breast cancer was introduced in Sweden in the late 1970s, during 1980s the technique became the treatment of choice for early breast cancer <sup>(7,8,9)</sup>.

Loco-regional recurrence is defined as recurrence not preceded or followed by distant metastasis within 6 weeks <sup>(10)</sup>. After conventional surgical treatment with or without radiation therapy for primary operable breast cancer .The incidence of loco-regional recurrence range from 4.6 - 27%

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according to various statistical reports (11,12,13,14,15,16,17). Local and distant metastasis occur most frequently within the first three years (18).

Approximately 80% of local recurrence appear by 5 years after mastectomy and nearly all occur by 10 years. LRR after conservative surgery and radiotherapy appears to have a better prognosis than local recurrence after classical mastectomy. The majority of breast recurrence are operable and the majority of patients are alive 5 years (19).

Patients with axially recurrence had a poor prognosis except when complete eradication was achieved and axillary lymph nodes were negative at the time of diagnosis of primary tumour (6).

The main initial parameter predicting both loco-regional recurrence free & metastasis free interval are presented by statistical analysis in the following order of importance ; number of invaded lymph nodes in the axilla , tumour size , histopathological type, grade. loco-regional recurrence predict the imminence of distant nmetastasis (20).

Total excision of loco-regional recurrence gave better rate of local ultimate control and survival than other kinds of treatment ,with or without adjuvant local or systemic therapy (10).LRR may signals the presence of wide spread disease but is not always a sign of imminent generalized disease (18) Five years survival after loco-regional recurrence is 26.2% , where if only true isolated loco-regional recurrence are considered, the survival is 37% (10).

### Patients And Methods:

A prospective study involving 91 Iraqi female patients who underwent surgery by different surgeons who are eligible to do such operations from different hospitals & parts of Iraq for early breast cancer (stage 1 & stage 2 ) were selected from Hospital of Radiation & Nuclear medicine in Baghdad during 2 years period, from Dec.2000-Dec.2002 .Patients were assessed by history taking & physical examination & investigations were requested namely ultrasound of the abdomen , chest X-ray & skeletal survey to exclude distant metastasis before patients being incorporated in our study, they received different modalities of adjuvant therapy according to the staging, grade of the tumour & really the availability of the adjuvant therapy. Data had been collected and analysed regarding the risk factors for breast cancer and it's recurrence. The patients had been followed for 2 years and the LRR were detected by history, clinical examination & histopathological confirmation.

### Results:

Table 1, show the description of the study sample, the highest peak of incidence of breast carcinoma involve the young age group patients

(30-39) years then the incidence will decrease in the gradual rate in the older age groups, while the LRR rate was seen to be equal in both young (20-39) years & the (50-69) years old patients . Association between age and LRR rate was in-significant .Females with low education level ( less than 6 years of formal education ) constituted 61.5% of cases, they have significant increasesd risk of LLR rate than ladies with higher educational level.

Female with low socio-economic status constituted two-third of cases & had a significantly higher LRR rate than other patients.

Nulliparus female constituted 60.5% of the cases, while 39.5% of cases with different grades of parity. Multiparus patients had a higher LRR rate than nulliparus patients . Unmarried patients were more than the married females, constituting 57.2% & 42.8% respectively .Un-married patients had a higher LRR rate than other patients but the association between marital state & LRR was statistically in-significant .

The incidence of cancer was more in the non-lactating women 60.5% of the cases, while Lactating patients had a higher LRR rate. The highest proportion of cases had negative history of contraception 78.1% and had a higher LRR rate than other patients .

Positive family history had been seen in 53.8% of cases . Patients with family history ( first degree from mother side ) concerning breast cancer had a higher LRR rate.

Table 2 ,show that intra-ductal carcinoma of the breast was the most frequently diagnosed tumour , being reported in 86.8% of cases, while lobular carcinoma constituted 6.6% . Patients with lobular carcinoma had a higher LRR rate than other patients . The association between histopathological types & LRR rate was statistically significant .Well differentiated tumour was 11% , while moderately differentiated tumour was 58% & poorly differentiated tumour constituted 31% . Patients with poorly differentiated tumour had a higher LRR rate than other patients . The association between grade of the tumour & LRR rate was significant .

More than two-third of cases had their tumour size ranging between 2-5 cm and had a higher LRR rate than patients with tumour size less than 2 cm. The association between tumour size & LRR rate was significant .

Thirty three of patients had no lymph nodes involvement by the tumour in the histopathological reports , while 67% of the cases had positive lymph nodes . Patients with more than 4 lymph nodes involvement had a higher LRR rate than other patients . This indicate that more than two-third of cases collected had stage II disease and associated with a higher LRR rate than patients with stage 1 .The association between stage of the tumour & LRR rate was significant .

Primary tumour was laterally located in 74.%, with a higher LRR rate than medially or centrally located tumour, the main site of loco-regional recurrence was seen in the chest wall 60%, then the axilla was 30% & then supra-clavicular region was 10%.

The latency between first complaint and surgical management was less than 1 month in only 11.1%, while 44% of cases had a delayed surgical intervention of less than 6 months & 28.9% of cases had a delayed surgical intervention of less than 12 months & 16% of cases had a delayed surgical intervention of more than 12 months.

Longer latency period had a significantly higher LRR rate than other patients. Table 3

Table 4, show that the highest proportion of cases (96.7%) subjected to modified radical mastectomy, while simple mastectomy constituted

3.3% of cases. Patients treated with simple mastectomy had a higher rate of LRR rate than those patients treated with MRR. Chemotherapy was the method of adjuvant therapy most frequently employed, being used as a single treatment in 37.3% of cases & in combination with radiotherapy in 41.7% of cases. Tamoxifen was used alone in 5.5% of cases & in combination with chemotherapy in 8.8% of cases. Radiotherapy was used with other treatment (tamoxifen & chemotherapy) in 6.6% of cases. The study shows that patients received a combination therapy developing higher rate of loco-regional recurrence in comparison to those groups received single adjuvant therapy.

Table 5, show that the earlier time of LRR occurred 10 months after treatment, and increasing to reach 22% after 2 years.

**Table (1) Relationship between Independent variants and recurrence:**

variant	NO.	Recurrence		Relative Risk	P. value	
Age	20-29	5	1	20%	0.9	p>0.05
	30-39	40	10	25%	1.3	
	40-49	18	3	16.7%	0.7	
	50-59	16	4	25%	1.2	
	>60	12	2	16.7%	0.7	
Education	Low	56	15	27%	1.9	P<0.05
	high	35	5	14%	0.5	
Socioeconomic state	Low	58	16	28%	2.3	P<0.05
	high	33	4	12%	0.4	
parity	Positive	36	8	22%	1	p>0.05
	Negative	55	12	22%	1	
Marital	Married	39	8	20%	0.87	p>0.05
	Non-married	52	12	23%	1.15	
Lactation	Lactate	36	8	22%	1	p>0.05
	Non-lactate	55	12	22%	1	
Contraception history	Positive	20	3	15%	0.6	p>0.05
	Negative	71	17	24%	1.6	
Family history	Positive	49	12	24%	1.3	p>0.05
	Negative	42	8	19%	0.8	

**Table( 2)Relationship between the histopathology, grade & stage of tumour with recurrence rate:**

Variant		No.	Recurrence		Relative Risk	p.value
Histopathology	Ductal	79	17	21.5%	0.4	p<0.05
	Lobular	6	3	50%	2.1	
	Paget	1	0	0%	0	
	Medullary	3	3	0%	0	
	Tubular	1	0	0%	0	
	Papillary	1	0	0%	0	
Grade	Well	10	1	10%	0.4	P<0.05
	Moderate	53	10	19%	0.7	
	Poor	28	9	32%	1.9	
Tumor size	<2 cm	30	3	10%	0.36	P<0.05
	2-5 cm	61	17	28%	2.8	
Lymph node	none	30	3	10%	0.36	P<0.05
	1-3	35	6	17%	0.68	
	>4	26	11	42%	3	
Stage	1	30	3	10%	0.36	P<0.05
	2	61	17	28%	2.8	

**Table (3) Relation between latency (months) and recurrence:**

variant	No.	Recurrence		Relative Risk	p.value	
latency	< 1month	10	0	0%	0	P<0.05
	1-5	40	3	8%	0.24	
	6-12	26	7	27%	1.35	
	>12	15	10	66%	5	

**Table( 4) Relation between treatment and recurrence**

variant		No.	Recurrence		Relative Risk	p.value
surgery	Simple mastectomy	3	1	33%	1.5	P>0.05
	MRM	88	19	22%	0.66	
	RM	0	0	0%	0	
Adjuvant therapy	CT	34	6	18%	0.7	p>0.05
	CT+RT	38	9	24%	1.14	
	Tamoxifen	5	1	20%	0.9	
	CT+ Tamoxifen	8	2	25%	1.13	
	CT+Tamoxifen+RT	6	2	33%	1.6	

**Table (5) Association between latency period and loco-regional recurrence:**

Time in months	recurrence	Recurrence rate	Recurrence free
0-4	0	0	100
4-8	0	0	100
8-12	2	2.22	97.78
12-16	7	9.9	90.8
16-20	6	16.5	83.48
20-24	5	22	78

**Discussion:**

This study shows that the commonest age groups affected (44%) was the young age patients at 30-39 years, which give an earlier age incidence than the Iraqi cancer registry at the years 1997 – 1999 that found the fifth decade is the commoner age groups affected by breast cancer in Iraqi females<sup>(4)</sup>. This finding is in contrary to the usual age incidence of the breast cancer of the U.S. women that increased sharply after the age of forty-five and another sharp increment after the age of sixty-five<sup>(2)</sup>.

This finding reflect the high and serious stressful condition (both environmental and psychological factors) that the Iraqi peoples including females subjected to during the recent years which seems to be increasing and accumulative in nature.

The interval between mastectomy & LRR is the most reliable indicator of the time to subsequent distant failure and over all survival<sup>(21)</sup>. The rate of loco-regional recurrence was found to be 22% after a follow up of 2 years and this rate is much high in comparison to Guy Andry et al . in Belgium , who found a LRR rate (14%) after a follow up of 5 years<sup>(12)</sup> & I .Fredreiksson et al . in Sweden , who found a lower rate of LRR (9.2% and 21.1%) at 5 and 10 years respectively<sup>(9)</sup> .

This can be explained on the basis of late presentation of our patients with breast cancer and may be to the aggressive nature and behavior of the breast cancer in our people and to the ineffective post-operative adjuvant therapy that was available to our patients during this period of time .

In our study less significant association had been seen between the LRR and the age of our patients (table 1) , and this correlates with study by Maureen Chung et al 1996<sup>(24)</sup> .

Patients with low socio-economic & educational level had statistically significant higher LRR rate than patients with high socio-economic & educational level , probably because the former groups were less able to gain benefit from health

education program and usually presented late in their disease .

The size of the primary tumour had significantly affected the rate of LRR (table 2) and this fact corresponds to Guy Andry et al who stated that tumour larger than 2 cm significantly increase the risk of loco regional recurrence<sup>(12)</sup> ,and correlated with Nottingham prognostic index analysis by G .D.Eredita et al<sup>(23)</sup> , so it is important to intensify screening programs to discover tumour at smaller size < 1 cm (pre-clinical state)<sup>(1)</sup> .

the absolute number of lymph nodes involved with metastatic neoplasm represent the single most significant predictive factor of 10-20 years survival<sup>(1)</sup> , risk of loco-regional recurrence in the studied patients with histopathological reports showing more than 4 lymph nodes involved by tumour was significantly higher than that for patients with no lymph nodes involved , Risk of LRR in our study was significantly higher with poorly differentiated carcinoma which indicates more aggressive nature and should receive more attention in the post-operative adjuvant therapy and follow up .This correlates with G .D.Eredita et al study<sup>(23)</sup> .

laterally located tumour had a higher rate of LRR than medially or centrally located tomour . This can be explained by that medially located tumour received additional radiotherapy to the parasternal and supra-clavicular area .This correlates with result obtained by Fisher et al study 1991<sup>(20)</sup> .

The study show that the group of patients who received a combination of adjuvant therapies developing higher rate of LRR rate than those who received single adjuvant therapy .This can be explained on the basis that the patients received combined therapies being at higher risk groups i.e advancing stage (lymph nodes involved more than 3 ,tumour size 3 – 4.9 cm ) , it has been found in different therapeutic trial the dose response curve for cytotoxic drugs used in the treatment of breast cancer is relatively steep in nature , that is small

reduction in the administration dose will lead to disproportion large decrease in the efficiency<sup>(25)</sup>, this fact will explain the high LLR of the studied sample who are receiving inadequate & irregular (at most of times) doses of adjuvant therapy in the old and only available oncology center in Iraq .

In our study the LRR occurred at earlier time (table 5 ) and this finding reflects the poor prognosis in our patients and corresponds to what is mentioned by Guy Andry et al who confirmed that the five years survival after loco-regional recurrence is 26.2% , where if only true isolated loco-regional recurrence are considered, the survival is 37%<sup>(12)</sup>. Because it predicts the imminence of distant metastasis once loco-regional recurrence had occurred<sup>(22)</sup>

The sites of LRR in our patients were differ from Guy Andry et al 1989<sup>(12)</sup> who showed that the LRR at the chest wall was 65% , the supra-clavicular fossa was 16% and the axilla was 6% , the remaining 13% occurred in two sites while in our study the axilla represented the second site for LRR 30% which might indicates the need for post-operative radiotherapy to the axilla as a routine therapy .

### Conclusion

1. Carcinoma of the breast affecting Iraqi females at younger ages in a high & increasing rate than other studies with a higher Loco-regional recurrence rate, a problem that need a real attention.
2. Significant association were found regarding the duration between first complaint and surgical management (latency period), the size of primary tumour , the number of lymph nodes involved ( staging ), histopathology & grading of primary tumour and the education level and socioeconomic status . While the association between the rate of loco-regional recurrence and age , type of adjuvant therapy , marital state , lactation state , family history , parity , type of surgery were less significant .

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