

# Functional Analysis of Axillary Lymph Nodes Dissection As A Prognostic factor in Breast cancer-Positive HER<sub>2</sub>

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## **Abstract:**

**Background:** Recurrence of cancer breast is a major problem during the first 2 years after diagnosis in addition to selection of adjuvant regimen is based mainly on the axillary lymph nodes stage. So, cost-effectively, patient will save much amount of budget needed for detection of gene expression. This study evaluates axillary lymph nodes dissection in prognosis of HER<sub>2</sub>-positive breast cancer.

**Patients and methods:** The current study analyzed 100 patients complained breast cancer. There were two types of surgery performed; MRM in 46 cases (46%) when there were contraindications of BCT or patients preferred radical surgery and BCT in 54 cases (54%) when indicated. Follow-up was for 2 years.

**Results:** All cases passed operation without mortality. Recurrence was reported in ten patients (10%). Six patients (6%) died during their follow up due to distant metastasis. All recurrent patients having grade N<sub>3</sub> >9 positive lymph nodes; P-value; 0.0001. There was statistical significance between nodal status and tumor size; KW test & P; 8.08 & 0.044 (S) respectively and between Histopathology and Nodal status; FET & P; 5.96 & 0.031 (S) respectively.

**Conclusion:** Positive or negative axillary lymph nodes are considered the most important predicting factor for recurrence and overall survival



of HER<sub>2</sub>-positive patients complained breast cancer. Moreover worsening prognosis is closely related to which group positive and the number of affected lymph nodes.

**Keywords:** Axillary lymph nodes, Breast cancer -Positive HER<sub>2</sub>, Prognosis.

## **Introduction:**

Breast cancer (BC) has rapid increase of its incidence and this disease is considered the most common annoying problem in females. It is the 5<sup>th</sup> etiology of mortality and 3<sup>rd</sup> common disease among female malignancy. There were few preceding literature and research work that addressed the tumor expression and the clinical stage. <sup>(1-3)</sup>

Breast cancer is always severely distressing of not only diseased patients but also their relatives. So, researching in this field has gained dramatic interest in the past 20 years, so there is so much progress in knowledge about this disease and so less toxic and more beneficial management. Advancements and improved awareness of peoples enable early diagnosis that allow complete resection of this cancer. <sup>(4,5)</sup>

Over the past few decades, easy interventions have been made depending on soft tissue mammography and stereotactic biopsies; More conserving breast therapy (CBT) and sentinel lymph node biopsy (SLNB) have been done in success than annoying modified radical mastectomy(MRM) and axillary lymph node dissection (ALND). <sup>(6,7)</sup>

Screening mammography allows early detection of breast cancer and this could be related to 25% reduction of death rate for these



cases. This early diagnosis can explain both local and systemic therapy how important. <sup>(7, 8)</sup>

Dissected axillary lymph nodes are the most important predicting factor for recurrence and survival; not only diseased lymph nodes but also their positive numbers are still the most significant prognostic factors for breast malignancy invasiveness. <sup>(9, 10)</sup>

Inherited factors may be responsible for 27% of breast malignancies. BRCA<sub>1&2</sub> gene mutations are the cause of about 30-40% of cases. The role of HER<sub>2</sub> in breast cancer was studied well in this field in the past 20 years. HER<sub>2</sub> is over expressed in 20-30% of breast malignancies. About 2 million copies of receptor are present in cells expressing HER<sub>2</sub> but only 20,000-50,000 copies are present in normal cells. So HER<sub>2</sub> expression is closely related to potent intracellular signaling and malignant growth. <sup>(11-13)</sup>

HER<sub>2</sub> amplification is generally correlated with a high proliferation index, aggressive histology, aneuploidy, no expression of hormone receptor, size of the tumor and bad outcomes. But this amplification as a predictor of postoperative therapy response is still unclear. <sup>(14, 15)</sup>

The rationale of this study is to evaluate axillary lymph nodes dissection in prognosis of HER<sub>2</sub>-positive breast cancer and detection of its role in selection of adjuvant regimen. So, cost-effectively, patient will save much amount of budget needed for detection of gene expression.

## **Patients and Methods:**

This current study included 100 cases with breast cancer in the



department of surgery at Benha University. After local ethical committee of Benha university and obtaining written fully informed patients consent, Patients with breast cancer were enrolled; From June 2017 till January 2020; Follow-up period was 2 years. All procedures in this study were done according to the Declaration of Helsinki and its updates.

Patients involved in this study were female patients with Histopathologically proved breast cancer-Positive HER<sub>2</sub>, fit for general anaesthesia, Any T and Any N. But patients excluded from this study were male patients, patients with distant metastasis, patients unfit for general anaesthesia; ASA<sub>IV</sub> and All deaths that occurred during this study due to non surgical cause.

All patients in this study were underwent proper history and clinical examination, Laboratory investigations for fitness. Radiological examination in the form of Chest X-ray, Abdominal U/S, Bilateral breast mammography with complementary breast U/S, Bone scan. ECG for patients above 40 years and Pathological diagnosis by True cut or excisional biopsy.

### **Operative procedure:**

Supine position with head tilted to the opposite side & the arm on the same side is abducted 90°. General anaesthesia was performed then either modified radical mastectomy (MRM) or Breast conserving therapy (BCT) with dissection of all levels of axillary lymph nodes has been performed.

### **I-Modified radical mastectomy:**

Elliptical (transverse or oblique) incision 5cm from the mass



including the nipple & areola starting from the parasternal line to anterior axillary fold. Mobilization of the skin flaps; They are dissected as following; superiorly to the clavicle and subclavius muscle, inferiorly to the rectus sheath, medially to the sternum & laterally to the anterior border of latissimus dorsi.

Dissection of pectoral fascia from the pectoralis major muscle under traction by Kocher's forceps & counter traction of the muscle starting from up downwards. Exposure of axilla; by dissection of the clavi-pectoral fascia & pectoralis minor is either divided or retracted at it's insertion.

Axillary clearance; axillary vein is exposed 1<sup>st</sup> then all levels of axillary L.Ns are cleared by blunt dissection; level I: lateral to pectoralis minor, level II: deep to pectoralis minor and level III: medial to pectoralis minor. So structures that should be removed: Ellipse including nipple & areola, Whole breast tissue, Interpectoral group of L.Ns (L.Ns of Rooter) and All fat, fascia & L.Ns in the axilla. But structures to be preserved; Axillary vessels & Nerves, Cephalic vein, Nerve to latissimus dorsi; (most posterior & known by Mercedes Benz sign) and Nerve to serratus anterior; along mid-axillary line. Structures to be sacrificed; Medial & Lateral pectoral nerves and Inter-costobrachial nerve (divided twice; near the chest & near the arm).

During dissection; adequate hemostasis especially 2nd, 3rd & 4th perforators of internal mammary artery should be ligated and divided. Finally; Ensure hemostasis & closure over Subcutaneous drain that come out from the medial side of the lower flap. **Figure (1)**

**II-Breast conserving therapy:**



Tumor control é acceptable appearance of the breast that included lumpectomy (safety margin 1cm) with axillary clearance up level III in addition to post-operative radiotherapy. This was done by one incision or two separate incisions 1<sup>st</sup> around the mass (its edges were marked for proper safety margins) and the other incision was done at the anterior axillary fold between latissimus dorsi and pectoralis major muscle. **Figure (2)**

### **Outcome items:**

All specimens was sent for Histo-pathological study and Immuno-histochemistry for ER, PR and HER<sub>2</sub> receptors. Postoperative outcome items included incidence of recurrence (local and distant), overall survival and complications; duration & amounts of seroma, removal of the drain, hematomas, wound infection, skin loss...etc.

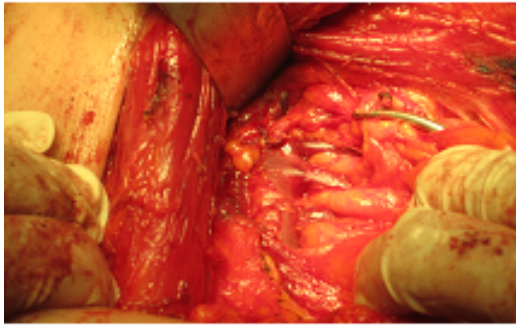
### **Statistical analysis:**

Analysis of this study data were done using SPSS version 16 software (SpssInc, Chicago, ILL Company. Quantitative data were expressed as mean ± standard deviation and range using Student "t" test. While categorical data were presented as number and percentages using Fisher's exact test (FET). ANOVA test was used for parametric variables if there was difference among 3 independent means or Kruskal Wallis test (KW) for non parametric ones. (P <0.05 was considered significant),.

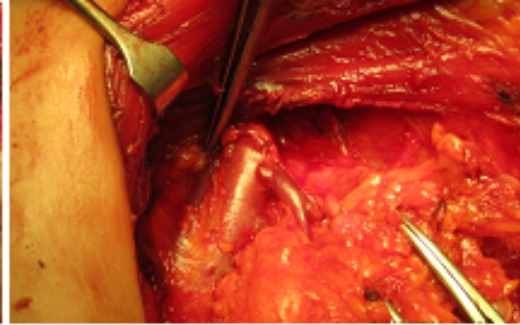
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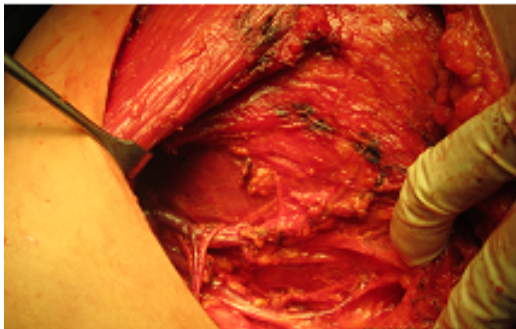




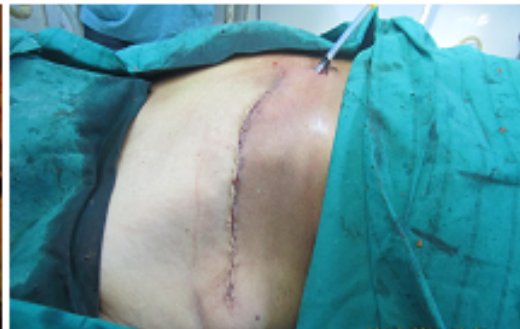
**A-Apical lymph nodes dissection.**



**B-Other groups of LNs dissection.**



**C-Complete LNs dissection.**

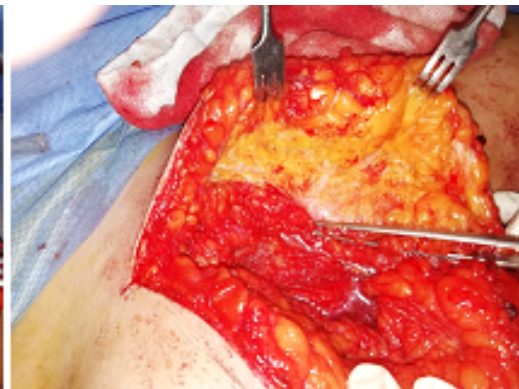


**D-Postoperative skin incision.**

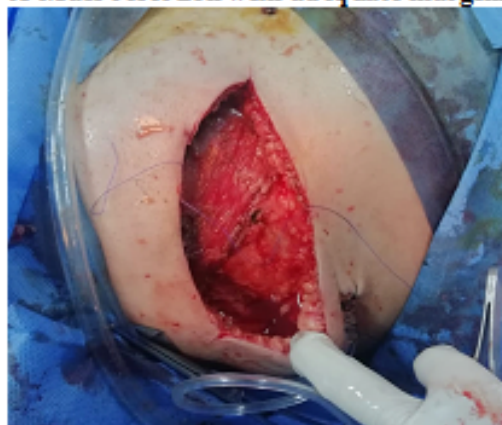
**Figure (1A-D): Steps of modified radical mastectomy; Rt breast.**



**A-Mass resection with adequate margin.**



**B-Axillary clearance.**



**C-Complete axillary LNs dissection.**



**D-Postoperative skin incision.**

**Figure (2A-D): Steps of Breast conserving therapy; Lt breast.**

**Results:**



Age range of patients of this study was 31-79 years old with Mean  $\pm$ SD was 46.9 $\pm$ 9.3; All patients were fit for general anesthesia depending on American Society of Anesthesiologists; ASA<sub>I</sub> and ASA<sub>II</sub>. Site of the tumor was common in UOQ; 86 patients (86%). The range of tumor size was (1.6-9.4cm) with Mean  $\pm$ SD; 7.1 $\pm$ 2.3. The most common presenting symptoms of the study cases were painless breast mass in 86 cases (86%). There were two types of surgery performed; MRM in 46 cases (46%) when there were contraindications of BCT or patients preferred radical surgery and BCT in 54 cases (54%) when indicated. Tab. (1).

**Table (1): Demographic data of the cases:**

Variable		No. (N=100)	% (100%)
<b>Age (years)</b>	<i>Mean <math>\pm</math>SD (Range)</i>	46.9 $\pm$ 9.3 (31-79)	
<b>Site</b>	<i>UOQ</i>	86	86.0
	<i>LOQ</i>	6	6.0
	<i>LIQ</i>	6	6.0
	<i>UIQ</i>	2	2.0
<b>Size (cm)</b>	<i>Mean <math>\pm</math>SD (Range)</i>	7.1 $\pm$ 2.3 (1.6-9.4)	
<b>Presenting symptoms</b>	<b>Mass</b>	86	86%
	<b>Pain</b>	18	18%
	<b>Axillary mass</b>	14	14%
	<b>Peau d orange</b>	11	11%
	<b>Ulceration</b>	6	6%
<b>Type of surgery</b>	<i>MRM</i>	46	46.0
	<i>BCT</i>	54	54.0
<i>UOQ =Upper Outer Quadrant, LOQ =Lower Outer Quadrant, LIQ =Lower Inner Quadrant and UIQ =Upper Inner Quadrant.</i>			

Data are presented as numbers & mean  $\pm$  SD; percentages & ranges are in parenthesis.





No mortality related to surgery was reported. Outcome of surgery; wound dehiscence was reported in 4 patients (4%), seroma in 6 patients (6%) but infection only in two patient (2%). Recurrence was reported in ten patients (10%). Six patients (6%) died due to distant metastasis. Tab. (2).

**Table (2): Outcome of surgery and prognosis of cases:**

Variable		No. (N=100)	(100%)
Outcome of surgery	<i>Wound dehiscence</i>	4	4.0
	<i>Seroma</i>	6	6.0
	<i>Infection</i>	2	2.0
	<i>Bleeding</i>	1	1.0
Prognosis of patients	<i>Recurrence</i>	10	10
	<i>Overall survival</i>	94	94

Data are presented as numbers & percentages are in parenthesis.

In tumor pathology; most of tumors were invasive in 94 patients (94%); of Ductal carcinoma type in 78 patients (78%). Tab. (3).

**Table (3): Histopathology and type of the tumor:**

Variable		No. (N=100)	(100%)
Histopathology	<i>Insitu</i>	6.0	6.0
	<i>Invasive</i>	94.0	94.0
Type	<i>Ductal</i>	78.0	78.0
	<i>Ductal Insitu</i>	6.0	6.0



	<i>Lobular</i>	8.0	8.0
	<i>Comedo</i>	4.0	4.0
	<i>Mucinous</i>	2.0	2.0
	<i>Undifferentiated</i>	2.0	2.0

Data are presented as numbers & percentages are in parenthesis.

As regard to lymph nodes; positive lymph nodes were equally distributed. Tab. (4).

**Table (4): Distribution of lymph nodes:**

Variable		No. (N=100)	% (100%)
LN <sub>s</sub>	$N_0 = 0$ LN <sub>s</sub>	24	24.0
	$N_1 = 1-3$ LN <sub>s</sub>	32	32.0
	$N_2 = 4-9$ LN <sub>s</sub>	24	24.0
	$N_3 > 9$ LN <sub>s</sub>	20	20.0

LN<sub>s</sub> =Lymph nodes.

Data are presented as numbers & percentages are in parenthesis.

Aggressive Lymph nodes involvement;  $N_3$ ; was observed in younger patients;  $46.6 \pm 11.8$ . the size of  $N_3$  was  $8.6 \pm 3.83$ . There was statistical significance in correlation between nodal status and Size of the tumor; KW test & P; 8.08 & 0.044 (S) respectively. Tab. (5).

**Table (5): Correlation between nodal status and Age and Size of the tumor:**

Variable		Age (years)		ANOVA	P
		Mean $\pm$ SD	Range		
nodal	$N_0 = 24$	47.6 $\pm$ 8.74	38-65	2.66	0.059
					(NS)



<b>status</b>	$N_1 = 32$	53.3±9.56	38-73		
	$N_2 = 24$	57.2±11.8	44-84		
	$N_3 = 20$	46.6±11.8	29-63		
<b>Size (cm)</b>				<b>KW test</b>	<b>P</b>
<b>nodal status</b>	$N_0 = 24$	4.51±3.55	0.16-12	8.08	0.044 (S)
	$N_1 = 32$	5.20±2.53	1.8-10.5		
	$N_2 = 24$	5.43±3.53	2.1-15.4		
	$N_3 = 20$	8.6±3.83	3.8-16.0		

Data are presented as numbers & mean ± SD; percentages & ranges are in parenthesis using ANOVA & KW test & P value.

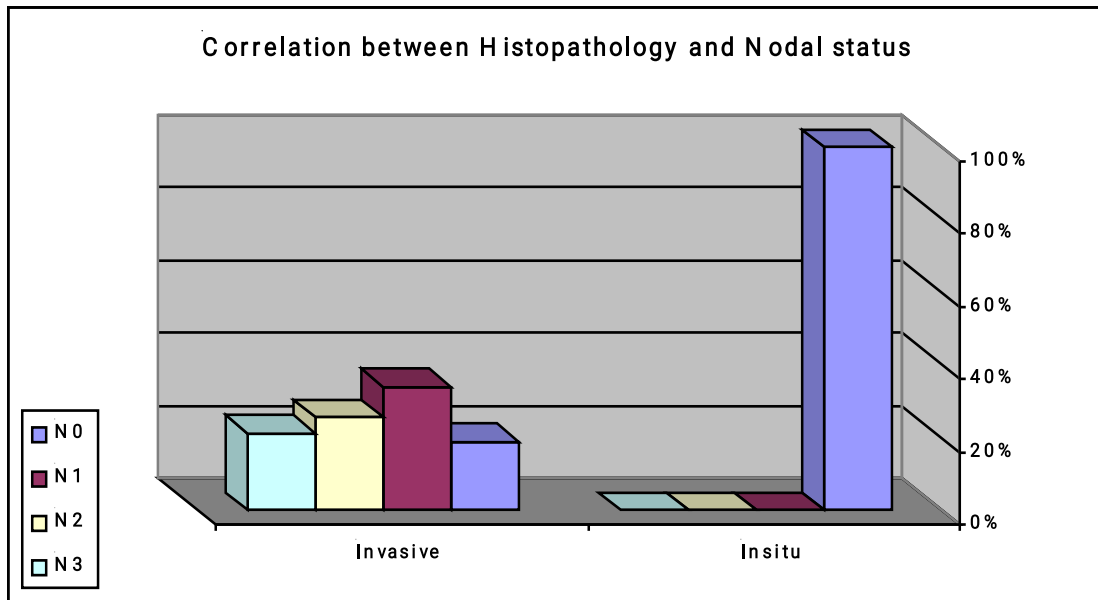
Lymph nodes involvement were reported only in invasive carcinoma. There was statistical significance in correlation between Histopathology and Nodal status; FET & P; 5.96 & 0.031 (S) respectively. Tab. (6), Graph. (1).

**Table (6): Correlation between Histopathology and Nodal status:**

Variable		Histopathology		Total	FET & P
		<i>Insitu (N =6)</i>	<i>Invasive (N =94)</i>		
		N (%)	N (%)	N (%)	5.96 & 0.031 (S)
<b>Site</b>	$N_0 = 24$	6 (100%)	18 (19.1%)	24 (24%)	
	$N_1 = 32$	0 (00%)	32 (34%)	32 (32%)	
	$N_2 = 24$	0 (00%)	24 (25.6%)	24 (24%)	
	$N_3 = 20$	0 (00%)	20 (21.3%)	20 (20%)	
<b>Total</b>		6 (100%)	94 (100%)	100 (100%)	

Data are presented as numbers; percentages & ranges are in parenthesis using FET & P value.





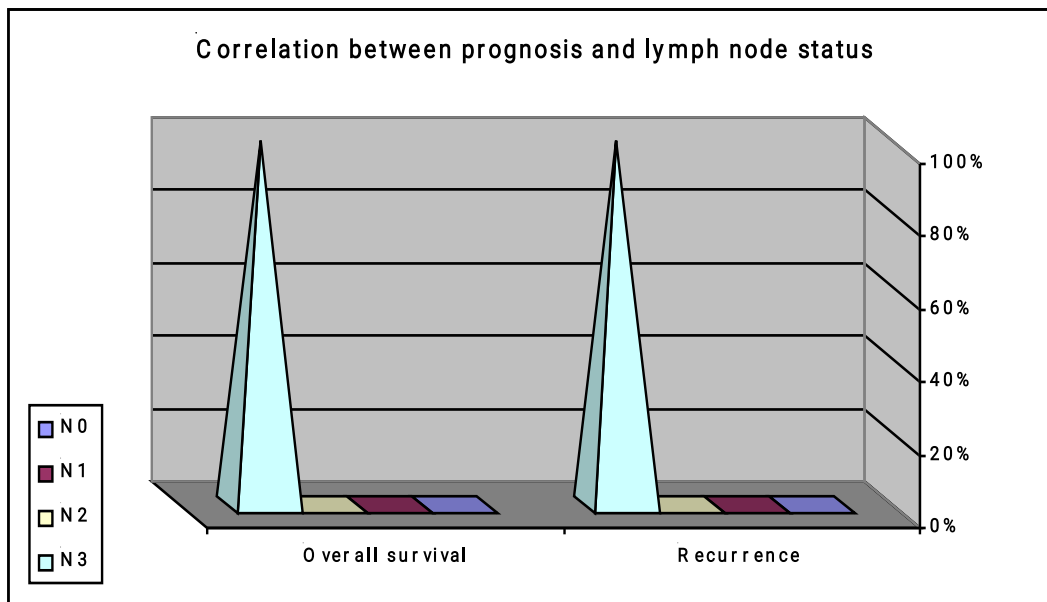
Graph. (1): Correlation between Histopathology and Nodal status.

By reviewing prognosis and lymph node status; recurrence was reported in ten patients; all of them grade  $N_3$  >9 positive lymph nodes; P-value; 0.0001. Tab. (7), Graph. (2).

Table (7): Correlation between prognosis and lymph node status:

Variable		Prognosis			
		<i>Recurrence (N =10)</i>		<i>Overall survival (N =94)</i>	
		N	%	N	%
Type of carcinoma	$N_0 =24$	0	00%	0	00%
	$N_1 =32$	0	00%	0	00%
	$N_2 =24$	0	00%	0	00%
	$N_3 =20$	10	100%	6	100%
<b>Total</b>		10	100%	6	100%
<b>P-value</b>		0.0001 (HS)		0.0001 (HS)	

Data are presented as numbers; percentages & ranges are in parenthesis using P value.



**Graph. (2): Correlation between prognosis and lymph node status.**

As regard to correlation between outcome and lymph node status; complications were observed in thirteen patients; most of them; 9 (69.2%) were grade N<sub>3</sub> >9 positive lymph nodes i.e. complications were directly related to aggressiveness of lymph nodes but there were no complications observed in grade N<sub>0</sub> lymph nodes.

### **Discussion:**

Cancer of the breast is a frequent tumor and is considered the leading reason for mortality among women all over the world. Incidence of breast cancer is 32.04% in Egypt. As regard to statistics of WHO (World Health Organization), 30% of woman are diseased and death rate is increasing in younger patients, so the main rationale is the early diagnosis and screening and to provide efficient treatment protocols. <sup>(16-18)</sup>

Accurate assessment and detection of this cancer especially in the early stages are the goals of different imaging modes to supply effective therapy, reduce the incidence of both local recurrence and

systemic metastases and provide better prognosis. <sup>(19)</sup>

In the current study, the demographic features of the studied cases were comparable to "Amirifard et al" who reported; The mean age was  $46.02 \pm 8.04$  years, 100% women and The main site was upper outer quadrant and the less frequent site was inner quadrant and axillary tail. <sup>(20)</sup> Also were line with "Abdollahi et al" who observed; the mean age was  $54.8 \pm 11.4$  years. <sup>(21)</sup>

By reviewing types of surgery used; There were two types; MRM in 46 patients (%46%) when there were contraindications of CBS or patients preferred radical surgery and BCT in 54 patients (54%) when indicated. This was comparable to "Abdollahi et al"; type of surgery used was Mastectomy in (66%) and Quadrectomy in (34%) of his patients. <sup>(21)</sup>

The 2-year rate of survival in studied cases was near similar to "Abdollahi et al." who reported in his study; depending on Kaplan-Meier test, 1-, 3-, 5- and 7-year rates of no recurrence were 96.4%, 78.4%, 66.3%, and 54.8%, respectively. <sup>(20, 23)</sup>

Recurrence of disease is one of the major problems in patients with this tumor during the first 2 years after detection. Now, considering advanced surgical techniques and complementary therapies, the rate of breast cancer recurrence has decreased. Recurrence rate was observed in ten patients (10%). Six patients (6%) died during their follow up due to distant metastasis; two patients with anaplastic carcinoma died after 4 months follow up, three patients with lobular carcinoma died after 14 months follow up and last patient with ductal carcinoma died after 22 months follow up. This recurrence rate was near similar to "Abdollahi et al" report; recurrence either local





or distant was (22.9%) of his patients. <sup>(21, 24)</sup>

In tumor histopathology; Distribution of these types was less than reported by "Chuangsuwanich et al"; in one hundred cases, 89 had invasive ductal carcinomas, 4 had invasive lobular carcinomas and 7 had other types. <sup>(22)</sup> But this distribution was slightly more than observed by "Amirifard et al"; Of 130 cases, 104 patients had invasive ductal carcinomas, 16 patients had invasive lobular carcinomas and 10 patients had other types. <sup>(20)</sup>

As regard to lymph nodes; positive lymph nodes were nearly equally distributed. The affected lymph node are the most significant prognostic factors in this cancer. <sup>(9)</sup>; these lymph nodes involvement were comparable to "Amirifard et al" who noticed; N<sub>0</sub> in 45 patients (34.6%) N<sub>1</sub> in 51 patients (39.2%) N<sub>2</sub> in 25 patients (19.2%) N<sub>3</sub> in 9 patients (6.9%). <sup>(20)</sup>

Kheradmand et al., <sup>(25)</sup> showed no significant correlation between age, tumor size, nodal status, type and histology of tumor in 114 patients with breast cancer underwent mastectomy. In agreement with Kheradmand et al., we found no significant correlation between age and nodal status. However, in contrast to their results we found a significant correlation between nodal status, histopathology and tumor size.

Prognosis is any measurement available at time of surgery that correlates with disease-free (no recurrence) or overall survival. <sup>(20)</sup>

Through reviewing the literature, the most significant prognostic indicator is the presence or absence of axillary lymph nodes. In the current study like other studies; "Amirifard et al" and "Fathi et al" <sup>(20, 26)</sup>,



there was a direct significant relationship between involved axillary lymph nodes and the risk for recurrence; recurrence was observed in ten patients; all of them grade N3 >9 positive lymph nodes; ; P-value; 0.0001. But this result was dissimilar to; "Kheradmand et al." <sup>(25)</sup> who found no significant correlation between positive lymph nodes and locoregional recurrence and survival.

Analysis and evaluation of LNs as a prognostic factors plays very important role in the good choice of beneficial tumor-specific regimens and to exclude inadequate treatment protocols with toxic effects. <sup>(15,27)</sup>

**Conclusion:** Positive or negative axillary lymph nodes are considered the most important predicting factor for recurrence and overall survival of HER<sub>2</sub>-positive patients complained breast cancer. Moreover worsening prognosis is closely related to which group positive and the number of affected lymph nodes.

## Figure legends

Figure (1<sub>A-D</sub>): Steps of modified radical mastectomy; Rt breast.

Figure (2<sub>A-D</sub>): Steps of Breast conserving therapy; Lt breast.

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