

Clinico-Pathological Study of Prognostic Factors in HER-2 Positive Patients with Breast Cancer

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Abstract

Background: Recurrence of disease is one of the major problems in patients with breast cancer during the first 2 years after diagnosis. Now, considering advanced laboratory techniques and complementary therapies, the rate of breast cancer recurrence has decreased.

Aim of Study: The rationale of this study is to discuss the clinico-pathological prognostic factors in HER2/neu positive breast cancer.

Patients and Methods: This current study was conducted on 50 patients diagnosed with breast cancer. Patients in this study were underwent either Modified radical mastectomy (MRM) or Breast conserving therapy (BCT) with axillary lymph nodes dissection. The follow-up period varied between 12 months to 24 months.

Results: No mortality related to surgery was reported. Outcome of surgery was flap necrosis in 2 patients (4%), seroma in 3 patients (6%) but infection only in one patient (2%). Recurrence was observed in ten patients (20%). Three patients (6%) died during their follow-up due to distant metastasis. All recurrent patients having grade N3 >9 positive lymph nodes; *p*-value; 0.0001.

Conclusion: Prognostic factors in HER-2 positive patients with breast cancer play important roles and it is considered an indicator of recurrence and the predictor of overall survival. The most significant prognostic is axillary lymph nodes involvement.

Key Words: Breast cancer – HER2 incidence – Prognostic factors – Outcomes.

Introduction

BREAST cancer is the most common cancer and the second most common cause of death from cancer in women. Because of the high frequency of the disease and the esthetic and symbolic value invested in the breast, breast cancer has always

been a source of severe distress to patients and their families. For the same reasons, breast cancer research has increased dramatically during the last 2 decades, resulting in extraordinary progress in our understanding of the disease and in new, more efficient and less toxic treatments. Furthermore, the diffusion of knowledge, the medical advancements, and the increased public awareness have led to earlier diagnosis at stages usually amenable to complete resection and potential cure of the disease [1].

Over the past few decades, breast cancer management has undergone significant changes characterized by less aggressive approaches to diagnosis and treatment. Mammogram and ultrasound or stereotactic biopsies have supplanted clinical diagnosis and surgical biopsy for the diagnosis; breast-conserving surgery (BCS) and sentinel lymph node biopsy (SLNB) have successfully replaced the more aggressive radical mastectomy (RM) and axillary lymph node dissection (ALND) [2].

Modern trials comparing different forms of loco-regional control for patients at the same stage of disease show that variations in local treatment do not result in differences in long-term survival, validating the first premise of these models regarding the inadequacy of local approaches to control the disease in the absence of systemic therapy. In addition, screening mammography results in early detection of breast cancer (average size 1.4cm vs 2.2cm for tumors clinically detected) and is associated with a 25% decrease in the mortality rate for breast cancer, thus lending credibility to the spectrum model. This model stresses the importance of both local and systemic treatment [3].

Lymph node status is a significant prognostic factor. Axillary lymph node involvement and the

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number of lymph nodes involved remain the most important prognostic factors for invasive breast cancer [4].

Hereditary breast cancers have been thought to represent a small proportion (5-10%) of all breast cancers. However, based on new data derived from the comparison of identical and non identical twins, up to 27% of breast cancers may be attributed to inherited factors. The mutated genes BRCA 1 & 2 are responsible for approximately 30-40% of inherited breast cancers [5].

Estrogens, by their proliferation-promoting effect on the breast epithelium later, increase the chance of DNA replication errors leading to carcinogenic mutations. Indeed, the common denominator to many of these risk factors is their effect on the level and duration of exposure to endogenous estrogenic stimulation [6].

The epidermal growth factor (EGF) receptor family plays a critical role in mammary tumor genesis. Other than the EGF receptor itself, 3 other members of this family have been described, including c-erb-B2 (HER2, HER2/neu), c-erb-B3, and c-erb-B4; the latter is called a kinase-dead receptor because it does not carry a kinase function on the cytoplasmic domain of the receptor, which is in contrast to the other members of the family [7].

The discovery of the role of HER2 in breast cancer was one of the landmarks in breast cancer research in the last 2 decades. HER2 is over expressed in 20-30% of breast cancers. Tumor cells over expressing HER2/neu may have up to 2 million copies of the receptor on their surface compared with 20,000-50,000 copies in normal breast epithelial cells. Because of this abundance of HER2/neu, many heterodimers contain HER2/neu, resulting in potent intracellular signaling and malignant growth [8].

Despite persistent controversy regarding certain aspects of its biology, prognostic value, and methods of evaluation, HER2 overexpression or amplification is generally accepted to be correlated with a high histologic grade, the absence of hormone receptor expression, aneuploidy, a high proliferation index, tumor size, and a poor clinical outcome. Its role as a predictor of response to chemotherapy and hormonal therapy (HT) is not clearly defined [9].

Patients and Methods

This current study was conducted on 50 patients diagnosed with breast cancer in the Department of

Surgery at Benha University and department of surgical oncology in 6th October Hospital, Health Insurance Organization.

After local ethical committee of Benha University and 6th October Insurance Hospitals approval and obtaining written fully informed patients consent, Patients with breast cancer were enrolled at these 2 clinical centers; From January 2015 till February 2019; So the enrollment period was 24 months and the patient follow-up period varied between 12 months to 24 months.

Patients included in this study were female patients fit for general anesthesia with Histopathologically proved breast cancer, Any T and Any N. But patients excluded from this study were male patients, patients with distant metastasis, patients unfit for general anesthesia; ASAIV and All deaths that occurred during this study due to non surgical cause i.e. pulmonary embolism, myocardial infarction, stroke, ... etc.

All patients in this study were underwent proper History taking, General and local clinical examination, Laboratory examination in the form of CBC, Liver functions, kidney functions, RBS, PT and PC. 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 50 years and Pathological diagnosis by True cut or excisional biopsy.

Operative procedure:

Patients in this study were underwent either Modified radical mastectomy (MRM) or Breast conserving therapy (BCT) with axillary lymph nodes dissection. Anaesthesia was of general type.

I- Modified radical mastectomy:

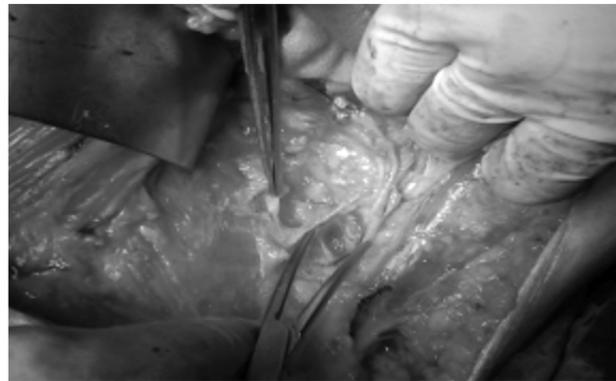
A modified radical mastectomy removes all breast tissue, the nipple-areola complex, necessary skin, and the level I, II and III axillary lymph nodes. Upon positioning of the patient and applying betadine antiseptic solution; Skin incision was done. Then Skin flaps were developed with consistent thickness to avoid creation of devascularized subcutaneous tissues, which can contribute to wound seroma, skin necrosis, and flap retraction; using cautery or scalpel and extend to the boundaries of dissection for the modified radical mastectomy, which are (a) The anterior margin of the latissimus dorsi muscle laterally, (b) The midline of the sternum medially, (c) The subclavius muscle superiorly, and (d) The caudal extension of the breast, which is 3 to 4cm inferior to the inframammary fold, till the rectus sheath; Once the skin

flaps were developed, the breast parenchyma and pectoralis major fascia were elevated from the underlying pectoralis major muscle in a plane parallel with the muscle bundles as they course from their medial origin (ribs 2 to 6) to their lateral insertion on the humerus. Perforating vessels from the lateral thoracic or anterior intercostal arteries, which are end arteries, were individually secured. Elevation of the breast parenchyma and pectoralis major fascia was continued laterally until the lateral edge of the pectoralis major muscle and the underlying pectoralis minor muscle were exposed. Once elevation of the breast parenchyma and pectoralis major muscle fascia from the underlying pectoralis major muscle was completed, an incision axillary lymph node dissection was performed. The pectoralis minor muscle was defined, and lymph nodes, which may lie between the pectoralis mus-

cles (Rotter nodes), were cleared. As the axillary lymph node dissection proceeded, the loose areolar tissue of the lateral axillary space is elevated with identification of the lateral extent of the axillary vein in its course anterior and caudal to the brachial plexus and axillary artery. (The axillary contents was removed in a medial to lateral direction). The investing layer of the axillary vein was dissected sharply, with allowing complete visualization of the anterior and ventral surfaces of the vein. Ligation and division of intervening venous tributaries is performed. Dissection continued till complete axillary clearance (level I,II,III) was done with preservation of nerve to serratus anterior & nerve to latissimus dorsi muscle. After assuring hemostasis, Skin flaps were closed over medially placed drain. Fig. (1).



A- Skin incision "Oblique".



B- Preservation of nerve to latissimus dorsi & nerve to serratus anterior muscle.



C- Closure of the skin.



D- Skin closed over Sc drain.

Fig. (1A-D): Steps of modified radical mastectomy; case (1); Lt breast.

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 two separate incision 1st 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.

Outcome items:

All specimens was sent for Histo-pathological study and Immuno-histochemistry for ER, PR and HER2 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:

The collected data were tabulated and analyzed using SPSS version 16 soft ware (SpssInc, Chicago, ILL Company. Categorical data were presented as number and percentages using Fisher's exact test (FET) for their analysis. While quantitative data were expressed as mean ± standard deviation and range. They were tested for normality using Shapiro-Wilks test, assuming normality at $p > 0.05$. Student "t" test was used to analyze normally distributed variables among 2 independent groups. While non parametric variables were analyzed using Man Whitney U test. Difference among 3 independent means was analyzed using ANOVA for parametric variables or Kruskal Wallis test (KW) for non parametric ones. The accepted level of significance in this work was stated at 0.05 ($p < 0.05$ was considered significant).

Results

No mortality related to surgery was reported; Age range was 29-84 years old with Mean ± SD was 51.6 ± 10.9 ; All patients were fit for general anesthesia depending on American Society of Anesthesiologists; ASAI and ASAII. Site of the tumor was common in UOQ; 43 patients (86%). The range of tumor size was (0.2-16.0cm) with Mean ± SD; 5.8 ± 3.5 . Table (1), Fig. (2).

Table (1): Socio-demographic data of the studied patients.

Variable	No. (N=50)	(100%)
<i>Age (years):</i>		
Mean ± SD (Range)	51.6 ± 10.9 (29-84)	
<i>Site:</i>		
UOQ	43	86.0
LOQ	3	6.0
LIQ	3	6.0
UIQ	1	2.0
<i>Size (cm):</i>		
Mean ± SD (Range)	5.8 ± 3.5 (0.2-16.0)	

UOQ = Upper Outer Quadrant.
 LOQ = Lower Outer Quadrant.
 LIQ = Lower Inner Quadrant.
 UIQ = Upper Inner Quadrant.

- Data are presented as numbers & mean ± SD; percentages & ranges are in parenthesis.

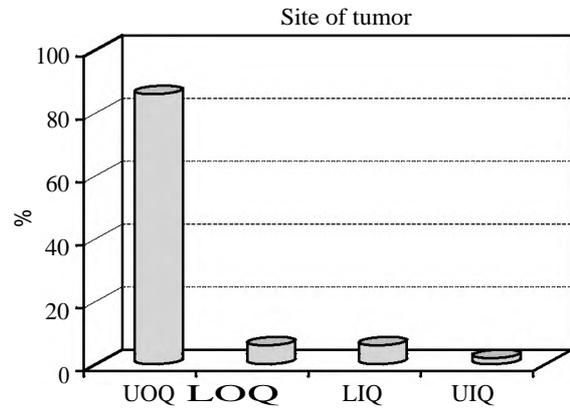


Fig. (2): Site of the tumor of the studied patients.

In tumor pathology; most of tumors were invasive in 47 patients (94%); of Ductal carcinoma type in 41 patients (82%). Table (2), Fig. (3).

Table (2): Histopathology and type of the tumor.

Variable	No. (N=50)	(100%)
<i>Histopathology:</i>		
In situ	3	6.0
Invasive	47	94.0
<i>Type:</i>		
Ductal carcinoma	41	82.0
Ductal carcinoma insitu	3	6.0
Lobular carcinoma	4	8.0
Mucinous carcinoma	1	2.0
Undifferentiated carcinoma	1	2.0

Data are presented as numbers & percentages are in parenthesis.

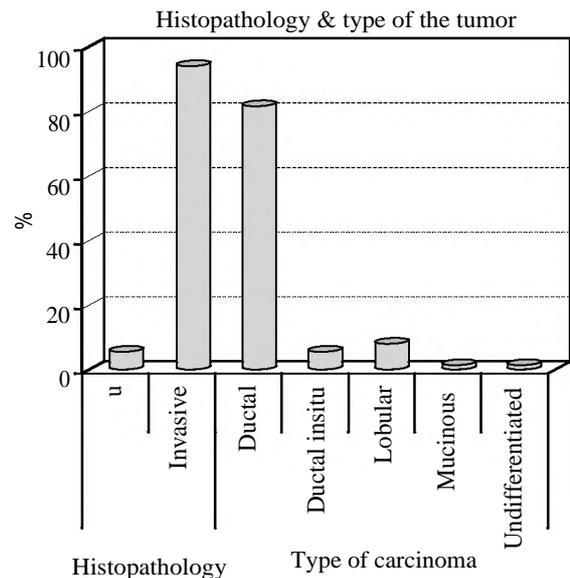


Fig. (3): Histopathology and type of the tumor.

As regard to lymph nodes and hormonal status; positive lymph nodes were equally distributed. But hormonal status; patients with positive ER & PR receptors were more; 37 & 32 patients (74.0% & 64.0%) respectively. Table (3), Fig. (4).

Table (3): Distribution of lymph nodes and hormonal status.

Variable	No. (N=50)	(100%)
LN's:		
N ₀ =0 LN's	12	24.0
N ₁ =1-3 LN's	16	32.0
N ₂ =4-9 LN's	12	24.0
N ₃ >9 LN's	10	20.0
ER receptors:		
Negative	13	26.0
Positive	37	74.0
PR receptors:		
Negative	18	36.0
Positive	32	64.0

LN's = Lymph nodes. ER = Estrogen. PR = Progesterone. Data are presented as numbers & percentages are in parenthesis.

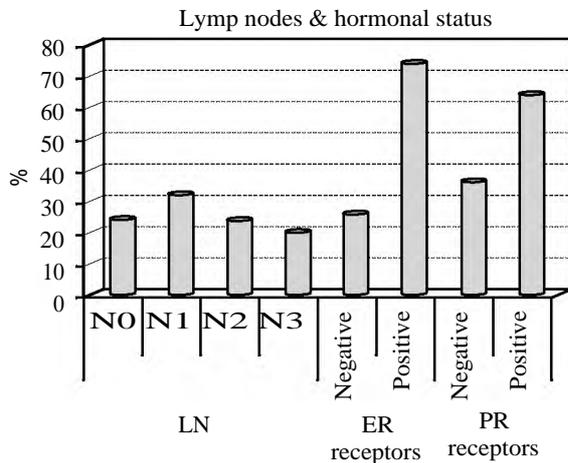


Fig. (4): Lymph nodes and hormonal status.

There were two types of surgery used depending on indications; MRM in 23 patients (46%) when there were contraindications of CBS or patients preferred radical surgery and CBS in 27 patients (54%) when indicated. Outcome of surgery; flap necrosis was reported in 2 patients (4%), seroma in 3 patients (6%) but infection only in one patient (2%). Recurrence was observed in ten patients (20%). Three patients (6%) died during their follow up due to distant metastasis. Table (4), Fig. (5).

Table (4): Types and outcome of surgery & prognosis of patients.

Variable	No. (N=50)	(100%)
Type of surgery:		
MRM	23	46.0
CBS	27	54.0
Outcome of surgery:		
Flap necrosis	2	4.0
Seroma	3	6.0
Wound infection	1	2.0
Prognosis of patients:		
Recurrence	10	20
Overall survival	47	94

MRM = Modified Radical Mastectomy. CBS = Conservative Breast Surgery. Data are presented as numbers & percentages are in parenthesis.

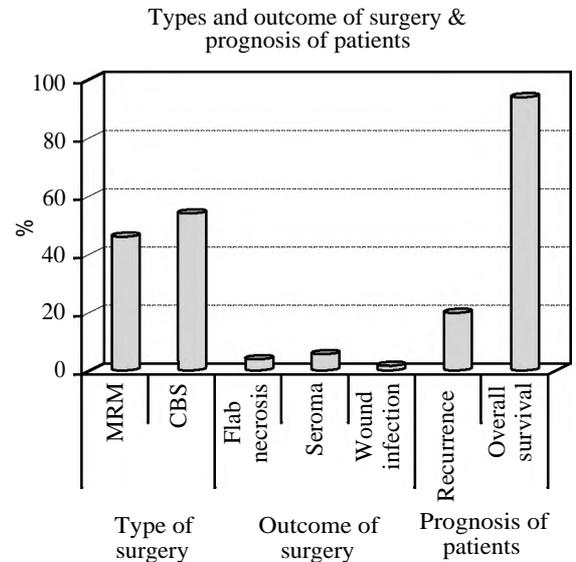


Fig. (5): Types and outcome of surgery.

Aggressive Lymph nodes involvement; N₃; was observed in younger patients; 46.6 ± 11.8 . The size of N₃ was 8.6 ± 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. Table (5), Fig. (6).

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

Variable	Age (years)		ANOVA	<i>p</i>
	Mean ± SD	Range		
Nodal status:				
N ₀ =12	47.6±8.74	38-65	2.66	0.059 (NS)
N ₁ =16	53.3±9.56	38-73		
N ₂ =12	57.2±11.8	44-84		
N ₃ =10	46.6±11.8	29-63		
Size (cm)				
KW test <i>p</i>				
Nodal status:				
N ₀ =12	4.51±3.55	0.16-12	8.08	0.044 (S)
N ₁ =16	5.20±2.53	1.8-10.5		
N ₂ =12	5.43±3.53	2.1-15.4		
N ₃ =10	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.

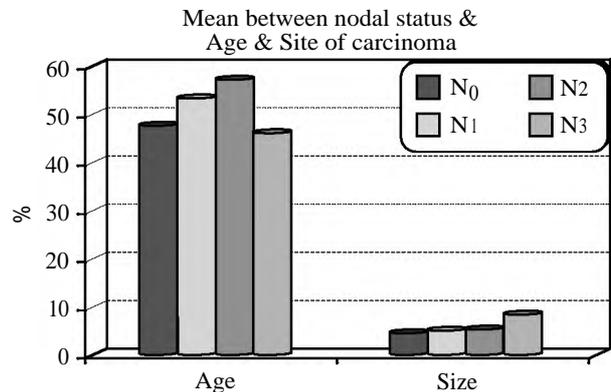


Fig. (6): Correlation between nodal status and Age and Size of the tumor.

Most of patients with positive progesterone receptors; 30/50 patients (93.8%); had carcinoma in upper outer quadrant and there was statistical significance in correlation between PR receptors and Site of the tumor; FET & *p*; 7.05 & 0.041 (S) respectively. Table (6), Fig. (7).

Table (6): Correlation between PR receptors and site of carcinoma.

Variable	PR receptors				Total N (%)	FET & P
	Negative (N=18)		Positive (N=32)			
	N	%	N	%		
<i>Site of carcinoma:</i>						
UOQ	13	72.2	30	93.8	43 (86%)	7.05 & 0.041 (S)
LOQ	2	11.1	1	3.1	3 (6%)	
LIQ	3	16.7	0	00	3 (6%)	
UIQ	0	00	1	3.1	1 (2%)	
Total	18	100	32	100	50 (100%)	

- Data are presented as numbers; percentages & ranges are in parenthesis using FET & *p*-value.

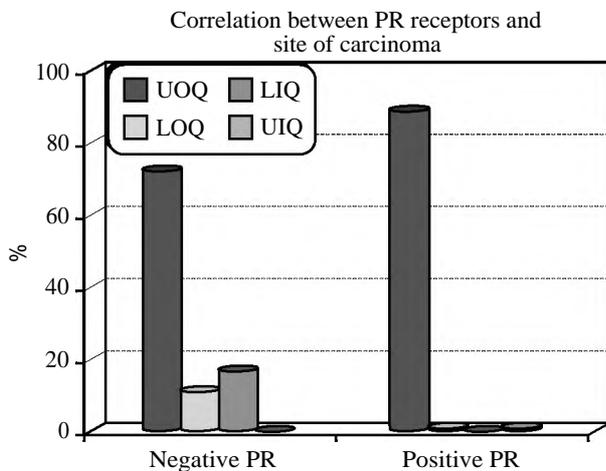


Fig. (7): Correlation between PR receptors and site of carcinoma.

Discussion

Breast cancer (BC) is the most common health problem in women that its incidence is increasing rapidly. It is the fifth cause of death and third burden of disease among women malignant disease [10].

There were few preceding literature and research work that addressed the tumor expression and the clinical stage. This study was designed to those females with HER2 positive patients with breast cancer to study relationship between HER2 and prognostic factors of 50 cases of breast cancer during four years. Female patients with metastasis were excluded to avoid the effect of metastatic tumor load on the gene expression [11-13].

The rationale of this study was to discuss the clinico-pathological prognostic factors in HER2/neu positive breast cancer for selection of adjuvant regimen based on the clinico-pathological stage only. So, cost-effectively, patient could be saved enormous amount of budget needed for assessment of gene expression.

In the current study, the demographic features of the studied group showed the following; Age range was 29-84 years old with Mean ± SD was 51.6±10.9; All patients were fit for general anesthesia depending on American Society of Anesthesiologists; ASA I and ASA II. Site of the tumor was common in UOQ; 43 patients (86%). The range of tumor size was (0.2-16.0cm) with Mean ± SD; 5.8±3.5. These demographic features were comparable to "Amirifard et al." who mentioned in his study; The mean age for the patients at diagnosis was 46.02±8.04 years, 100% female and The most frequency tumor location was belonging to upper outer of breast and the less frequency was belonging to inner and axillary tail of breast [14]. Also were line with "Abdollahi et al." who reported in his study; the mean age of the patients was 54.8 ± 11.4 years [15].

In tumor histopathology; most of tumors were invasive in 47 patients (94%) and others were insitu. Recorded types were ductal carcinoma in 41 patients (82%) and others were lobular carcinoma, ductal carcinoma insitu, mucinous carcinoma and undifferentiated carcinoma. Distribution of these types was less than observed by "Chuangsuwanich et al."; Of 100 BC cases, 89 cases had invasive ductal carcinomas, 4 cases had invasive lobular carcinomas and 7 had other types [16]. But this distribution was slightly more than mentioned by "Amirifard et al."; Of 130 cases, 104 had invasive ductal carcinomas, 16 had invasive lobular carcinomas and 10 had other types [14].

As regard to lymph nodes and hormonal status; positive lymph nodes were nearly equally distributed. It should be noted that lymph node metastases are the most significant prognostic factors in breast carcinoma [17]; these lymph nodes involvement were comparable to "Amirifard et al." who noticed in his study; N0 in 45 patients (34.6%) N1 in 51 patients (39.2%) N2 in 25 patients (19.2%) N3 in 9 patients (6.9%) [11]. But hormonal status; patients with positive ER & PR receptors were 37 & 32 patients (74.0% & 64.0%) respectively. This result was near similar to "Abdollahi et al." who mentioned in his study; Estrogen and progesterone receptor were positive in (70.6% & 66.6%) of patients respectively [15]. But this result was more

than reported by "Amirifard et al."; ER & PR receptors were positive in 13, 15 patients (19.6%, 22.7%) respectively [14].

By reviewing types of surgery used; There were two types depending on indications; MRM in 23 patients (46%) when there were contraindications of CBS or patients preferred radical surgery and CBS in 27 patients (54%) when indicated. This was comparable to "Abdollahi et al." who reported in his study; type of surgery used was Mastectomy in (66%) and Quadrectomy in (34%) of his patients [15].

Current study showed that 1-year to 2-years rate of survival in studied patients was 47 patients (94%). This result was near similar to "Abdollahi et al." who reported in his study; According to results of Kaplan-Meier test, 1-, 3-, 5- and 7-year rates of survival without recurrence were 96.4%, 78.4%, 66.3%, and 54.8%, respectively [15,18].

Recurrence of disease is one of the major problems in patients with breast cancer during the first 2 years after diagnosis. Now, considering advanced surgical techniques and complementary therapies, the rate of breast cancer recurrence has decreased. Recurrence rate was observed in ten patients (20%). Three patients (6%) died during their follow-up due to distant metastasis; patient with anaplastic carcinoma died after 4 months follow-up, patient with lobular carcinoma died after 14 months follow-up and last patient with ductal carcinoma died after 22 months follow-up. Reported outcome of surgery in the current study was; flap necrosis in 2 patients (4%), seroma in 3 patients (6%) but infection only in one patient (2%). The present study recurrence rate was near similar to "Abdollahi et al." report; recurrence either local or distant was (22.9%) of his patients [15,19].

Kheradmand et al., [20] showed no significant correlation between age, tumor site and 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, ER receptors and other prognostic factors. However, in contrast to their results we found a significant correlation between nodal status, histopathology, site and tumor size, type of carcinoma and size of the tumor and PR receptors and site of carcinoma. Also there was no statistical significance in correlation between outcome and type of surgery. The differences between these two studies may be explained by difference in sample volume.

Conclusion: Prognostic factors in HER-2 positive patients with breast cancer play important roles and it is considered an indicator of recurrence and the predictor of overall survival. The most significant prognostic is axillary lymph nodes involvement.

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مستقبلات الهرمونات هير-٢ الايجابية

الهدف من الدراسة: الأساس المنطقي لهذه الدراسة هو مناقشة العوامل النذير المرضية السريرية في HER2 / neu سرطان الثدي الإيجابي.

المرضى والطرق: أجريت هذه الدراسة الحالية على ٥٠ مريضاً تم تشخيصهم بسرطان الثدي. خضع المرضى في هذه الدراسة إما استئصال الثدي تعديل جذري (MRM) أو العلاج الحفظ على الثدي (BCT) مع تشريح الغدد الليمفاوية الإبطية. كانت فترة المتابعة ٢٤ شهراً.

النتائج: لم يتم الإبلاغ عن أي وفيات المتعلقة بالجراحة. وكانت نتيجة الجراحة تاكل الجرح في ٢ المرضى (٤٪)، الأمصال في ٣ مرضى (٦٪) ولكن العدوى في مريض واحد فقط (٢٪). وقد لوحظ تكرار في عشرة مرضى (٢٠٪) توفى ثلاثة مرضى (٦٪) أثناء متابعتهم بسبب ورم خبيث بعيد. جميع المرضى المتكررة بعد الصف $N3 > 9$ الغدد الليمفاوية الإيجابية p القيمة ; 0.0001.

الخلاصة: تلعب العوامل النذير لدى مرضى HER-2 المصابين بسرطان الثدي أدواراً مهمة ويعتبر مؤشراً على التكرار ومؤشراً على البقاء على قيد الحياة بشكل عام. أهم النذير هو تورط الغدد الليمفاوية الإبطية.