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Clinical Prognostic Factors in Breast Cancer

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Abstract

Background: Carcinoma of the breast is the commonest cancer in female and the second most cause of death in cancer related deaths.

Aim of Study: To overview the different prognostic factors in breast cancer in our patients with breast cancer.

Patients and Methods: This retrospective study was conducted on 100 patients undergoing mastectomy or breast conservative surgery at El-Demerdash University Hospital. Clinico-pathological features including age, weight, family history, axillary lymph node status, tumor size, pathology result will be reviewed.

Results: Axillary lymph node status shows a significant association between the grade of LN and the development of recurrence in group N3 patients compared with N, N1 and N2 groups. There is variability in disease-free survival among the ER/PR Her2 subtypes within the first 3 years following diagnosis after receiving the treatment. While probability of free from disease was best for the ER+, PR +or-/Her2-subtype followed by ER-PR-/Her2-(71%) and (50%) respectively. On the other hand all patients in subtypes ER+, PR +or-/Her2 + and ER-PR-/her2 + subtypes suffered from recurrence of disease.

Conclusion: We have found that the extent of nodal involvement and hormone receptor expression are very important prognostic and predictive factors in breast cancer management and recurrence.

Key Words: *Breast cancer – Tumor – Prognostic factors.*

Introduction

IT is estimated that there will be 276,480 new cases of invasive breast cancer and an estimated 42,170 patient will die of this disease in the United States in 2020 **[1].**

There are several independent but interrelated prognostic factors predictive of recurrence and survival in breast cancer. These include axillary nodal status, histopathology, steroid receptors, proliferative rate, DNA ploidy, and oncogene amplification. S-phase fraction can also be used to help define the high-risk patient. Axillary nodal status has been the traditional mainstay predictor for recurrence and survival in primary breast cancer. In addition, the presence of the estrogen and progesterone receptors has correlated with longer disease-free interval and overall survival in stage I and II breast cancer. Finally, tumors that amplify or over express the HER-2 gene may have a higher risk of relapse **[2].**

Screening and improved adjuvant therapy have led to reduced breast cancer mortality in the United States, highlighting the importance of appropriate detection and management of the disease. The U.S. Preventive Services task force recommends screening using mammography every two years in women between the ages of 50 and 74 **[3].**

Breast cancer is comprised of a number of complex and heterogeneous subtypes with differing clinical behavior and outcomes. Most clinical decisions are currently based on tumor expression of the Estrogen Receptor (ER), Progesterone Receptor (PR), and human epidermal growth factor receptor 2 (HER 2). These biomarkers have prognostic and predictive significance in breast cancer and have important implications for tumor growth and metastatic patterns **[4].**

Distant spread of breast cancer results in poor survival outcome and the site of the distance recurrence are also important to predict the clinical outcome **[5].**

It has been noted that there is a significant difference in survival among the molecular subtypes of breast cancer **[6].**

However data are limited concerning differences in distant recurrence sites between the breast cancer subtypes **[7].**

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A few studies have described different distant metastatic pattern according to molecular subtypes **[8]**.

The risk associated with a positive family history of breast cancer is strongly affected by the number of female first-degree relatives with and without cancer. As an example, in a pooled analysis using data from over 50,000 women with breast cancer and 100,000 controls, the risks of breast cancer were increased almost two folds if a woman had one affected first-degree relative and increased three folds if she had two affected first-degree relatives.

In addition to a family history of breast cancer, the age at diagnosis of the affected first-degree relative also influences the risk for breast cancer. Women have a threefold higher risk if the first degree relative was diagnosed before age 30, but only 1.5-fold increased if the affected relative was diagnosed after age 60 **[9]**.

Routine pathologic evaluation remains the most critical element in determining the prognosis of patients with breast cancer. Among the most potent prognostic factors available are lymph node status, tumor size and histologic grade, histologic tumor type, and lymphatic vascular invasion **[10]**.

Aim of the work:

Overview the different prognostic factors in breast cancer in our patients with breast cancer.

Patients and Methods

This study is a descriptive retrospective study at El-Demerdash University Hospital in which 100 patients underwent mastectomy or breast conservative surgery were recruited from 2013 to 2020. Clinico-pathological features including age, weight, family history, axillary lymph node status, tumor size, pathology result were reviewed.

Informed consent was taken from all patients who accept to participate in the study. Confidentiality is assured of the personal data and medical information of all patients.

Patients:

The study included patients with ages ≥ 18 years, with pathological diagnosis of breast cancer subjected to surgical management of the primary tumor via mastectomy or breast-conserving surgery.

Methods:

All patients were subjected to the following: Pre-operative clinical history including age, marital status, occupation, parity, contraception, menstrual history, age of menarche and menopause, special habits of medical importance particularly smoking. History of present illness: Mode of onset, duration of illness, any gynecological disease past history of medical diseases: Such as diabetes, infections, malignancy. Clinical examination: General examination: Body built. Umbilicus (Sister Josef) Upper limb & Lymphedema. (Brawny edema). Local examination: Inspection Symmetrical, overlying skin, pigmentation, dilated veins, scars. Swelling Nipple: Direction, Retraction, Displacement, Discoloration. Skin proper: - Dimpling - Pau de orange Palpation Warmth, tenderness, edge, surface, consistency, mobility, draining lymph nodes (axillary, supraclavicular) Investigations: Routine preoperative investigations are requested for all patients, including complete blood picture, coagulation profile, liver and kidney function tests, fasting blood sugar. Triple assessment was done for all patients include clinical examination, radiological imaging (mammography, ultrasonography) and pathology - Post-operative: Clinical assessment: Any post-operative complications were collected. Pathological assessment: All histopathology reports were collected.

Ethical and legal considerations:

- *Good clinical practice:* The procedures set out in the study protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the investigators abide by the principles of good clinical practice.
- *Delegation of researcher responsibility:* The researcher ensured that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The researcher maintained a list of sub-investigators and other appropriately qualified person to whom he or she has delegated significant trial-related duties.
- *Patient information and informed consent:* Before admission to the clinical study, patient consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them. An informed consent document, in Arabic language, contains all locally required elements and specifies who informed the patient. After reading the informed consent document, the participant signed the consent in writing. The participant's consent confirmed at the time of consent by the personally dated signature of the participant and by the personally dated signature of the person conduct-

ing the informed consent discussions. Participantsunable to read, oral presentation and explanation of the written informed consent form and information to be supplied to participants took place in the presence of an impartial witness. Consent confirmed at the time of consent verbally and by the personally dated signature of the participant or by a local legally recognized alternative (e.g., the patient's thumbprint or mark). The witness and the person conducting the informed consent discussions also signed and personally date the consent document. The original signed consent document retained by the researcher. The researcher did not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

Statistical methods:

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY) and MedCalc© version 18.2.1 (MedCalc© Software bvba, Ostend, Belgium). Categorical variables were presented as number and percentage and differences were compared using the Pearson chi-squared test or Fisher's exact test. Ordinal variables were compared using the linear-by-linear association. Multivariable binary logistic regression analysis was used to determine the independent predictors of 3-year overall survival or disease-free survival. Univariable time to event analysis was done using the Kaplan-Meier method. Cox proportional hazard regression analysis was used for multivariable time to event analysis. Two-sided *p*-values <0.05 were considered statistically significant.

Results

Basic characteristics of patients:

It was noticed that (9%), (61%), (16%) and (14%) according to tumor size with breast cancer had T1, T2, T3, and T4 respectively. It was noticed that the presence of distant metastasis majority (98%) of the group was M0 and two of them were M1. According to axillary lymph node status was noticed that (27%), (14%), (23%) and (36%) present in N0, N1, N2, and N3 patients respectively.

As regarding tumor stage in such patients, it was noticed that Stage III (59%) was the most frequent followed by Stage II (36%), Stage I (5%) and Stage IV (2%).

It was noticed that (91%), (58%) and (56%) patients had negative for local recurrence, distant metastasis, and overall recurrence on the incidence of recurrence respectively.

Table (1): Characteristics of the study population.

Variable	N	%
Age category:		
<50 years	48	48.0%
>_50 years	52	52.0%
Histological grade:		
Moderately differentiated	95	95.0%
Poorly differentiated	5	5.0%
T:		
T1	9	9.0%
T2	61	61.0%
T3	16	16.0%
T4	14	14.0%
M:		
M0	98	98.0%
M1	2	2.0%
N:		
N0	27	27.0%
N1	14	14.0%
N2	23	23.0%
N3	36	36.0%
Tumor stage:		
Stage I	5	5.0%
Stage II	34	34.0%
Stage III	59	59.0%
Stage IV	2	2.0%

Data are number (n) and percentage (%).

Table (2): The incidence of recurrence and mortality during the study period.

Variable	N	%
Local recurrence:		
–	91	91.0%
+	9	9.0%
Distant metastasis:		
–	58	58.0%
+	42	42.0%
Overall recurrence:		
–	56	56.0%
+	44	44.0%
Mortality:		
–	88	88.0%
+	12	12.0%

Data are number (n) and percentage (%).

Table (3): Main outcome measures.

Variable	N	%
3-Year disease -free survival:		
Recurrence within 3 years	35	35.0%
No recurrence within 3 years	65	65.0%
3-Year overall survival:		
Died within 3 years	6	6.0%
Survived for 3 years	94	94.0%

Data are number (n) and percentage (%).

Factors affecting main outcome measures:

Factors affecting 3-year disease-free survival shows in (Table 4), Figs. (1,2). It was found that statistically significant difference in tumor size, axillary lymph node status, ER, PR, Her2, ER/PR

Her2 classification and tumor stage between two events of 3-year disease-free survival either recurrence within 3 years or no recurrence within 3 years (p=0.014). (p=0.003), (p=0.047), (p=0.004), (p <0.001), (p=<0.001) and (p=0.010) respectively, however no statistically significant difference in age, histological grade, presence of distant metastasis and different lines of treatment.

Table (4): Factors affecting 3-year disease-free survival.

Variable	3-year disease-free survival: Recurrence within 3 years (n=35) N	Row %	No recurrence within 3 years (n=35) N	Row %	χ^2 (1)	p-value*
Age category:						
• <50 years	16	33.3%	32	66.7%	0.112	0.738§
• ≥50 years	19	36.5%	33	63.5%		
Histological grade:						
• Moderately differentiated	32	33.7%	63	66.3 %	1.431	0.232§
• Poorly differentiated	3	60.0%	2	40.0%		
T:						
• T1	4	44.4%	5	55.6%	6.017	0.014§
• T2	15	24.6%	46	75.4%		
• T3	6	37.5%	10	62.5%		
• T4	10	71.4%	4	28.6%		
M:						
• M0	33	33.7%	65	66.3 %	3.752	0.053 §
• M1	2	100.0%	0	0.0%		
N:						
• N0	5	18.5%	22	81.5%	8.713	0.003 §
• N1	3	21.4%	11	78.6%		
• N2	8	34.8%	15	65.2%		
• N3	19	52.8%	17	47.2%		
ER:						
• ER–	16	48.5%	17	51.5%	3.937	0.047
• ER+	19	28.4%	48	71.6%		
PR:						
• PR–	20	52.6%	18	47.4%	8.375	0.004
• PR+	15	24.2%	47	75.8%		
Her2:						
• Her2–	28	30.1%	65	69.9%	–	<0.001#
• Her2+	7	100.0%	0	0.0%		
ER/PR+ Her2+:						
• ER+ PR+/– Her2+	3	100.0%	0	0.0%	–	<0.001#
• ER+ PR+/PR– Her2–	18	25.4%	53	74.6%		
• ER– PR– Her2+	4	100.0%	0	0.0%		
• ER– PR– Her2–	10	45.5%	12	54.5%		
Tumor stage:						
• Stage I	2	40.0%	3	60.0%	6.726	0.010§
• Stage II	5	14.7%	29	85.3 %		
• Stage III	26	44.1 %	33	55.9%		
• Stage IV	2	100.0%	0	0.0%		
Surgery:						
• MRM	29	34.5%	55	65.5%	–	0.852#
• SM	6	40.0%	9	60.0%		
• BCS	0	0.0%	1	100.0%		
Chemotherapy:						
• –	2	40.0%	3	60.0%	–	1.000#
• +	33	34.7%	62	65.3 %		
Radiotherapy:						
• –	0	0.0%	0	0.0%	–	NA
• +	35	35.0%	65	65.0%		
Hormonal therapy:						
• –	13	50.0%	13	50.0%	3.475	0.062
• +	22	29.7%	52	70.3 %		

Data are number (n) and row percentage (%). NA: Test not applicable. *: Pearson Chi-squared test unless otherwise indicated. §: Chi-squared test for trend. #: Fisher's exact test.

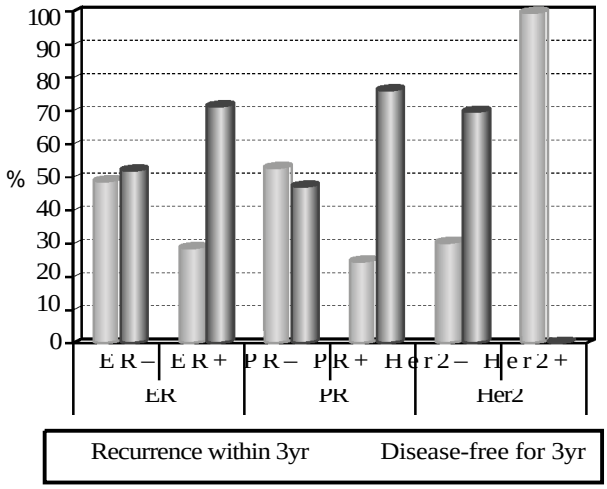

Fig. (1): A relation between ER, PR or Her2 type and three-year disease-free survival.

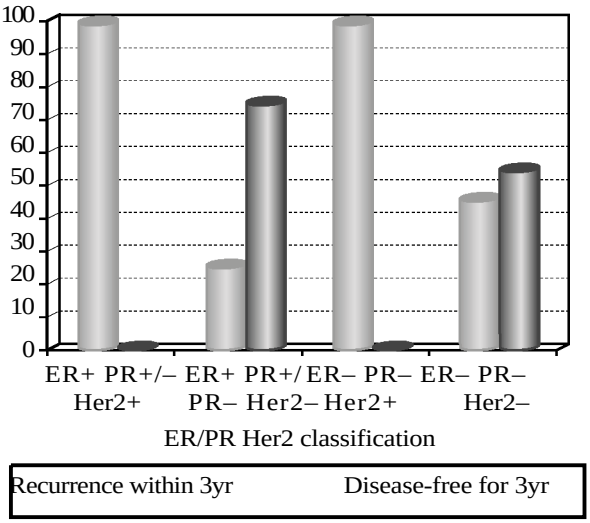

Fig. (2): Three-year disease-free survival in patients with ER+ PR+/– Her2+, ER+ PR+/PR– Her2–, ER– PR– Her2+ or ER– PR– Her2– tumor type.

Table (5), Figs. (3,4) show factors affecting 3-year overall survival. Unlike 3-year disease-free survival we found that PR, Her2, ER/PR Her2 classification were only statistically significant between two events of 3-year overall survival either died within 3 years or survived for 3 years (p= 0. 028), (p=0.004) and (p=0.001) respectively.

Table (6) shows that after adjustment for the effect of other covariates, there was an independent relation between 3-year disease-free survival and both the PR tumor type (odds ratio for PR+=4.625, 95% CI=1.393 to 15.356, p-value=0.012) and the tumor stage (odds ratio for stage III/IV=0.274, 95% CI=0.094 to 0.797, p-value=0.017).

Table (7) shows that after adjustment for the effect of other covariates, there was an independent relation between the Her2 tumor type and 3-year

overall survival (odds ratio for Her2+=0.038, 95% CI=0.003 to 0.483, *p*-value=0.012).

Table (5): Factors affecting 3-year overall survival.

Variable	3-year overall survival				χ^2 (1)	*p*-value*
	Died within 3 years (n=6)		Survived for 3 years (n=94)			
	N	Row %	N	Row %		
Age category:						
• <50 years	3	6.3%	45	93.8%	0.010	0.920§
• >-50 years	3	5.8%	49	94.2%		
Histological grade:						
• Moderately differentiated	6	6.3%	89	93.7%	0.333	0.564§
• Poorly differentiated	0	0.0%	5	100.0%		
T:						
• T1	0	0.0%	9	100.0%	0.003	0.960§
• T2	4	6.6%	57	93.4%		
• T3	2	12.5%	14	87.5%		
• T4	0	0.0%	14	100.0%		
M:						
• M0	6	6.1%	92	93.9%	0.130	0.718§
• M1	0	0.0%	2	100.0%		
N:						
• N0	1	3.7%	26	96.3%	1.013	0.314§
• N1	0	0.0%	14	100.0%		
• N2	2	8.7%	21	91.3%		
• N3	3	8.3%	33	91.7%		
ER:						
• ER–	4	12.1%	29	87.9%	–	0.090#
• ER+	2	3.0%	65	97.0%		
PR:						
• PR–	5	13.2%	33	86.8%	–	0.028#
• PR+	1	1.6%	61	98.4%		
Her2:						
• Her2-	3	3.2%	90	96.8%	–	0.004#
• Her2+	3	42.9%	4	57.1%		
ER/PR Her2 classification:						
• ER+ PR+/– Her2+	0	0.0%	3	100.0%	–	0.001#
• ER+ PR+/PR– Her2–	2	2.8%	69	97.2%		
• ER– PR– Her2+	3	75.0%	1	25.0%		
• ER– PR– Her2–	1	4.5%	21	95.5%		
Tumor stage:						
• Stage I	0	0.0%	5	100.0%	1.057	0.304§
• Stage II	1	2.9%	33	97.1%		
• Stage III	5	8.5%	54	91.5%		
• Stage IV	0	0.0%	2	100.0%		
Surgery:						
• MRM	4	4.8%	80	95.2%	–	0.271#
• SM	2	13.3%	13	86.7%		
• BCS	0	0.0%	1	100.0%		
Chemotherapy:						
• –	1	20.0%	4	80.0%	–	0.271#
• +	5	5.3%	90	94.7%		
Radiotherapy:						
• –	0	0.0%	0	0.0%	–	NA
• +	6	6.0%	94	94.0%		
Hormonal therapy:						
• –	2	7.7%	24	92.3%	–	0.649#
• +	4	5.4%	70	94.6%		

Data are number (n) and row percentage (%).
NA* : Test not applicable.
: Pearson Chi-squared test unless otherwise indicated.
§ : Chi-squared test for trend.
# : Fisher's exact test.

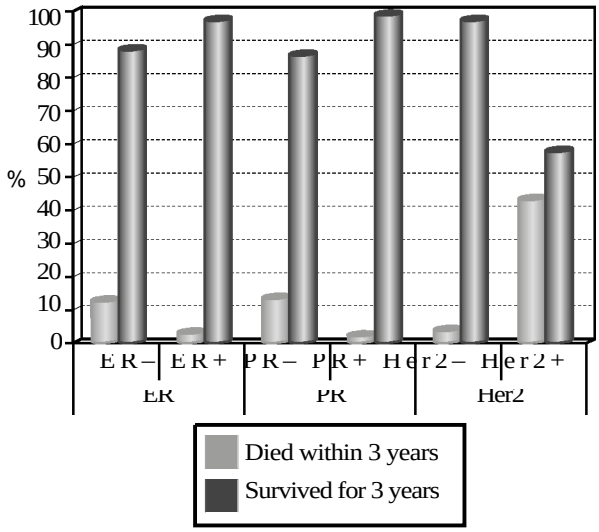

Fig. (3): A relation between ER, PR or Her2 type and three-year disease-free survival.

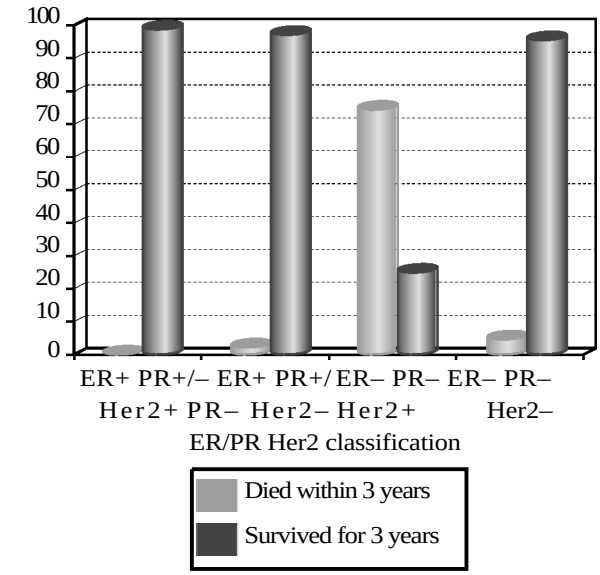

Fig. (4): Three-year overall survival in patients with ER+ PR+/– Her2+, ER+ PR+/PR– Her2–, ER– PR– Her2+ or ER– PR– Her2– tumor type.

Table (6): Multivariable binary logistic regression analysis for predictors of 3-year disease-free survival.

Variable	B	SE	Wald	*p*-value	Odds ratio	95% CI
• ER+	–0.435	0.646	0.455	0.500	0.647	0.183 to 2.293
• PR+	1.531	0.612	6.257	0.012	4.625	1.393 to 15.356
• Her2+	–22.294	8701.386	0.000	0.998	0.000	–
• Tumor stage III/IV	–1.296	0.545	5.651	0.017	0.274	0.094 to 0.797
• Constant	1.097	0.556	3.895	0.048		

B : Regression coefficient.
SE : Standard Error.
Wald : Wald chi-squared statistic.
95% CI : 95% confidence interval.

Table (7): Multivariable binary logistic regression analysis for predictors of 3-year overall survival.

Variable	B	SE	Wald	*p*-value	Odds ratio	95% CI
• ER+	–0.648	1.235	0.275	0.600	0.523	0.047 to 5.888
• PR+	2.439	1.342	3.303	0.069	11.462	0.826 to 159.085
• Her2+	–3.276	1.300	6.350	0.012	0.038	0.003 to 0.483
• Tumor stage III/IV	–0.323	1.252	0.066	0.797	0.724	0.062 to 8.417
• Constant	3.041	1.171	6.744	0.009		

B : Regression coefficient.
SE : Standard Error.
Wald : Wald chi-squared statistic.
95% CI : 95% confidence interval.

Survival analysis and life tables between different factors and main outcomes:
Disease -free survival:

Table (8): Disease free survival in patients with breast cancer according to ER tumour type.

Time	ER		*p*-value
	–ve (n=20) Estimate (%) ±	+ve (n=24) Estimate (%) ±	
Third year	45.5%±8.7	69.5%±5.7	0.016

(n): No of patients who had a recurrence of disease.

Table (9): Disease free survival in patients with breast cancer according to PR tumour type.

Time	PR		*p*-value
	–ve (n=38) Estimate (%) ±	+ve (n=62) Estimate (%) ±	
Third year	44.7%±8.1	71.6%±5.8	0.002

(n): No of patients who had a recurrence of disease.

Table (10): Disease free survival in patients with breast cancer according to Her2 tumour type.

Time	Her2		*p*-value
	–ve (n=93) Estimate (%) ±SE	+ve (n=7) Estimate (%) ±SE	
Third year	66.0%±5.0	Not reached	<0.001

(n): No of patients who had a recurrence of disease.

Table (11): Disease free survival in patients with breast cancer according to ER/PR Her2 tumour type.

Time	ER/PR Her2				*p*-value
	ER+, PR+ or –/Her2+ (n=3) Estimate (%) ±SE	ER+, PR+ or –/Her2– (n=71) Estimate (%) ±SE	ER–, PR–/Her2+ (n=4) Estimate (%) ±SE	ER–, PR–/Her2– (n=22) Estimate (%) ±SE	
• Third year	Not reached	71.0%±5.5	Not reached	50%±3.6	<0.001

(n): No of patients who had a recurrence of disease.

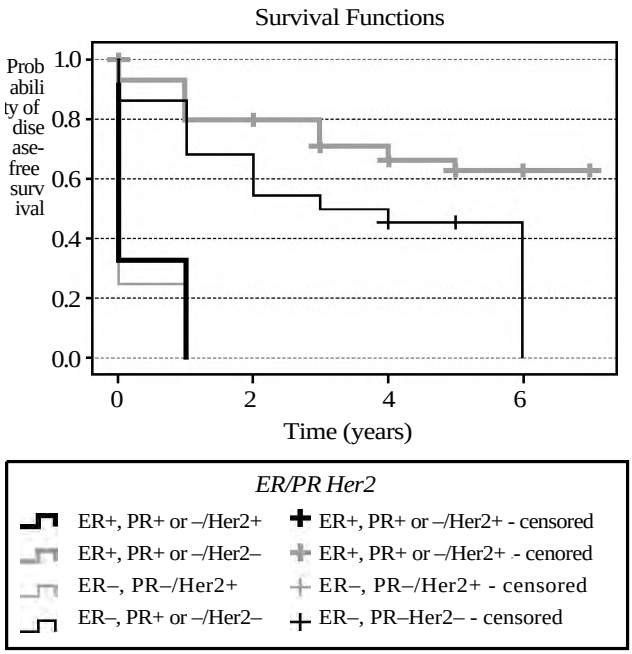

Fig. (5): Kaplan-Meier curves for disease-free survival in ER+ PR+/– Her2+, ER+ PR+/PR– Her2– ER– PR– Her2+, or ER– PR– Her2– patients. There is a statistically significant difference among the 4 curves (Log-rank test chi-squared=3 6.3 94, df=3, *p*-value <0. 001).

Table (12): Cox proportional hazard regression for determinants of the time to recurrence.

Covariate	b	SE	Wald	*p*-value	Cox PH	95% CI of Cox PH
ER+	0.393	0.048	0.827	1.090	0.504	to 2.357 0.086
PR+	0.362	4.904	0.027	0.449	0.221	to 0.912 –0.801

b : Regression coefficient.
SE : Standard Error.
Wald : Wald chi-squared statistic.
PH : Proportional hazard.
95% CI : 95% confidence interval.

After adjustment for the effect of other covariates, both the PR tumor type (Cox proportional hazard for PR+ type=0.449, 95% CI=0.221 to 0. 912, *p*-value=0.027) and the Her2 tumor type (Cox proportional hazard for Her2+ type=6.872, 95% CI=2.271 to 18.035, *p*-value=0.001) were independent determinants for the time to recurrence.

Overall survival:

Table (13): Overall survival in patients with breast Cancer according to ER tumour type.

Time	ER		*p*-value
	–ve (n=7) Estimate (%) ±SE	+ve (n=5) Estimate (%) ±SE	
Third year	81.1 %±7.0	93.9%±3.4	0.036

(n): No of patients who died.

Table (14): Overall survival in patients with breast Cancer according to PR tumour type.

Time	PR		*p*-value
	–ve (n=7) Estimate (%) ±	+ve (n=5) Estimate (%) ±	
Third year	80.6%±5.	95.1%±2.	0.075

(n): No of patients who died.

Table (15): Overall survival in patients with breast Cancer according to Her2 tumour type.

Time	Her2		*p*-value
	–ve (n=9) Estimate (%) ±SE	+ve (n=3) Estimate (%) ±SE	
Third year	92.2%±2.8	57.1%±18.7	0.003

(n): No of patients who died.

Table (16): Overall survival in patients with breast Cancer according to ER/PR Her2 tumour type.

Time	ER/PR Her2				*p*-value
	ER+, PR+ or –/Her2+ (n=0) Estimate (%) ±SE	ER+, PR+ or –/Her2– (n=6) Estimate (%) ±SE	ER–, PR–/ Her2+ (n=3) Estimate (%) ±SE	ER–, PR–/ Her2– (n=3) Estimate (%) ±SE	
• Third year	94.2%±2.8	25.0%±21.7	84.8%±8.1		0.001

(n): No of patients who died.

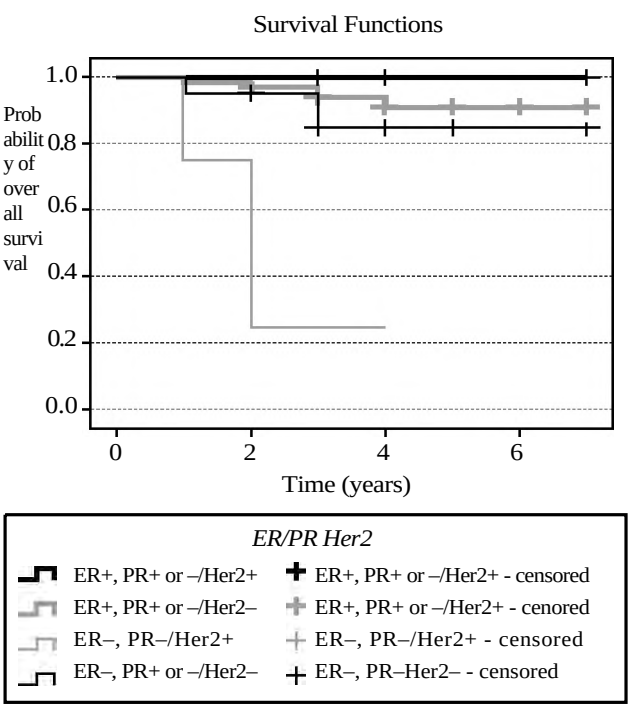

Fig. (6): Kaplan-Meier overall survival curves in ER+ PR+/– Her2+, ER+ PR+/PR– Her2–, ER– PR– Her2+, or ER– PR– Her2- patients. There is a statistically significant difference among the 4 curves (Log-rank test chi-squared=28.18, df=3, *p*-value=0.001).

Table (17): Cox proportional hazard regression for determinantsof the time to mortality.

Covariate	b	SE	Wald	*p*-value	Cox PH	95% CI of Cox PH
ER+	0.416	0.770	0.293	0.588	1.517	0.336 to 6.852
PR+	0.711	0.719	0.978	0.323	2.035	0.498 to 8.325
Her2+	–1.522	0.738	4.250	0.039	0.218	0.051 to 0.928

b : Regression coefficient.
SE : Standard Error.
Wald : Wald chi-squared statistic.
PH : Proportional hazard.
95% CI : 95% confidence interval.

After adjustment for the effect of other covariates, the Her2 tumor type (Cox proportional hazard for Her2 + type=0.218, 95% CI=0.051 to 0.928, *p*-value=0.039) was an independent determinant for the time to mortality.

Discussion

Breast cancer is a multifaceted disease whose variegate phenotype only partially recapitulates the underlying biological complexity. Treatment choices in routine management principally rely on the clinical and pathological characteristics of the disease, although molecular classification currently offers information alongside that provided by clinical and pathological examination **[11]**. Breast cancer phenotype continuously evolves during tumor progression and, while methodological issues might in part explain discrepancy in biomarker expression between primary tumor and metastasis, the contribution of innate and treatment-induced genomic instability is well demonstrated **[12]**.

Overall, more than 75% of breast carcinomas express the hormone receptors ER and/or PR. The percentage of cancer cells stained for those biomarkers has valuable prognostic and predictive information **[13]**.

The clinical significance of HER2 in breast cancer evolved from a marker of poor prognosis to a marker of response to treatment with therapies targeting the receptor, which normally regulates cell growth, differentiation and survival, is overexpressed in 15-20% of invasive breast cancers and correlates with more aggressive cancer features **[14]**.

A retrospective cohort study was started by 100 women diagnosed breast cancer according to clinical and other diagnosis parameters. All underwent closely follow-up until discharge or death and noted if recurrence or/and metastasis occurred or not.

The study in this thesis focused on the prognostic role of clinical factor: Age and pathologic factors: Primary tumor size; axillary lymph nodes

involvement; stage; histologic grade; hormone receptors; recurrence; metastasis and mortality in breast cancer with 3 years disease free survival and 3 years overall survival of their combination for the purpose of refined breast cancer stratification. Our data provides an additional perspective on the relationship between the ER, PR, HER-2, ER/PR Her2 and breast cancer survival.

Our study contains two age groups >50 years and <50 years. Our findings indicate that comparative analysis with 3-year disease-free survival shows no statistically significant difference between two groups according to disease recurrence or not. Likewise, 3-year overall survival univariate analysis shows no statistically significant difference between the two groups in terms of death within three years.

On the other hand in some studies, patients aged 35 years or younger at diagnosis have a worse absolute 5-year survival (74.7 vs. 83.8 to 88.3 percent for women aged 35 to 69 years), even after adjustment for histopathologic characteristics and given treatments, indicating an intrinsic aggressive biology **[15]**. Women >65 years diagnosed with breast cancer have an increased mortality mainly due to later stage at diagnosis **[16]**.

Majority of patients were moderately differentiated according to histological grade in our study. Not only age but also histological grade shows no statistically significant difference either 3-year disease-free survival or 3-year overall survival analysis.

Histological grade was not significantly associated with survival outcomes in this cohort **[17]**.

Patients were stratified according to primary tumor size into four groups, the majority of the T2. Associations between higher grade and poorer outcome according to 3-years survival analysis recurrence rate were noted in the T4 group. Alternatively, 3-year overall survival univariate analysis was showed no statistically significant difference with tumor size. According to axillary lymph node status, it shows a significant association between the grade of LN and the development of recurrence in group N3 patients compared with N, N1 and N2 groups. Conversely, no statistically significant difference with 3-year overall survival analysis. Our study shows a lack of significant association between the presence of distant metastasis and the development of recurrence or occurring of death within three years in patients. Tumor stage shows a significant association with the development of recurrence in stage IV compared with another staging, on the other hand, no association between staging and 3-year overall survival univariate analysis.

Many studies have had the same results for our study according to TNM classification **[17-19]**.

Regarding the different lines of treatment there was no significant differences between them either 3-year disease-free survival or 3-year overall survival analysis.

In our study ER+ and PR+ patients were noted that the incidence of disease recurrence was less than the ER–, PR– patients respectively and there was a statistically significant difference with 3-years disease-free survival. On the contrary, all patient of Her2+ was suffered from a recurrence of breast cancer compared with Her2 patients. As the recurrence of the disease in the four ER/PR/HER2 subtypes was quite variable, all patients ER+ PR+/– Her2+, ER– PR– Her2+ subtypes were noted to be suffered from a recurrence of breast cancer.

From multivariable binary logistic regression analysis for predictors of 3-year disease-free survival after adjustment for the effect of other covariates, there was an independent relation between 3-year disease-free survival and both the PR tumor type and the tumor stage.

In our study there is a 69.3% probability of free from disease up to the first 3 years following diagnosis after receiving the treatment in ER+ patients compared with 45.5% probability of ER– patients, the Kaplan-Meier curves showed a significant difference between the disease-free survival curves for the two ER subtype, it was clear from comparing the Kaplan-Meier curves for the two ER subtype that there was a better disease-free survival associated with the ER+ subtype.

Also, in our study PR tumor type determined that PR+ had 71.6% probability of free from disease up to the first 3 years in compared to PR– subtype by 44.7% probability. PR+ subtype had better disease-free survival in Kaplan-Meier curves analysis.

Alternatively, Her2 subtype analysis revealed that in all patients with Her2+, the disease was recurrent but Her2– patients showed 66.0% probability of free from disease up to the first 3 years. The Kaplan-Meier curves confirmed that by estimation, Her2– patients had better disease-free survival.

The present study further demonstrates that there is variability in disease-free survival among

the ER/PR Her2 subtypes within the first 3 years following diagnosis after receiving the treatment. While probability of free from disease was best for the ER+, PR + or –/Her2– subtype followed by ER– PR–/ Her2 - (71%) and (50%) respectively. On the other hand all patients in subtypes ER+, PR + or –/Her2 + and ER– PR–/Her2+ subtypes suffered from recurrence of disease.

In our study calculated cox proportional hazard regression for determinants of the time to recurrence indicates how each of the independent variables (ER+, PR+ and Her2+) is associated with the outcome (recurrence following treatment). There is a significant association between disease-free survival time, PR tumor type and Her2 tumor type adjusting for each other and for the potential confounder, ER+ tumor type.

Likewise, overall survival and Kaplan-Meier curves showed a significant difference with ER tumor type, there is a 93.9% probability of surviving up to the first 3 years following diagnosis after receiving the treatment in ER+ patients compared with 8 1. 1 % probability of ER– patients. Our data provide an additional perspective on the relationship between the estrogen receptor and breast cancer survival.

On the contrary, PR tumor subtypes had no statistically significant with overall survival, but still a difference between PR subtypes probability. PR+ had 95.1% probability of surviving up to the first 3 years in compared to PR– subtype by 80.6% probability.

A significant difference was found between the probability of survival in Her2– in comparison with Her2+ subtypes of Her2 tumor type (92.2% vs. 57.1%) respectively.

In the same way, overall survival was demonstrated among the ER/PR Her2 subtypes within the first 3 years following diagnosis after receiving the treatment. While probability of surviving was best for the ER+, PR + or –/ Her2– subtype followed by ER– PR–/Her2– (94.2%) and (84.8%) respectively. On the other hand ER– PR–/Her2+ subtype suffered low probability of survive (25.0%).

Our data provide that after Cox proportional hazard regression for determinants of the time to mortality, after adjustment for the effect of other covariates, the Her2 tumor type was only an independent determinant for the time to mortality.

Studies showed that over expression of ER and PR showed a decreased hazard of death **[20]**. Mortality diminished with increasing category of ER protein staining (p=.001 for trend), in Cox proportional hazards models, ER percent positive was no longer related to breast cancer death after adjustment for only age, tumor size, number of positive nodes, and tumor grade, thus adjustment for ER intensity or for PR was not responsible for the loss of significance **[18]**. Furthermore, over expression/amplification of HER2 was found to correlate with a superior survival in a variety of studies, including those in patients with de novo metastatic breast cancer **[21]**. Correlation of HER-2/neu over-expression and tumor grade was also studied by Veronesi et al. **[22]** with a sample size of 1,210 cases. According to their study also, HER-2/neu over-expression was associated with a higher tumor grade, as observed in 3.9%, 20.4%, and 38.9% grade 1, 2, and 3 tumors respectively, whereas in our study positivity was shown in 0%, 22.89%, and 31.58%. Similarly, a study conducted in Italy **[23]** showed overexpression of HER-2/neu in 29.7% of breast cancers, significantly correlating with larger tumor size and a decreasing level of ER. Another study by Ozdogan et al. **[23]** in Antalya-Turkey provided comparable results.

The prognostic relevance of ER and PR has been a matter of debate for many years. Recently, an analysis on 4000 patients enrolled in four clinical trials with a follow-up of 24 years described that ER-positive tumors have a lower annual hazard of recurrence compared to ER-negative tumors during the first 5 years (9.9% vs. 11.5, p 0.01). Beyond 5 years, hazards in ER-positive cancers are higher and remain stable after 10 years from primary diagnosis, regardless lymph node status **[24]**. PR is a well-known prognostic factor of time to recurrence and overall survival **[25]**.

HER2 in the absence of systemic therapy, HER2 overexpression is associated with poorer prognosis regardless of the axillary lymph node involvement. HER2 retains a negative prognostic effect even in tumors ≤ 1 cm with negative lymph nodes **[26]**.

Conclusion:

We have found that the extent of nodal involvement and hormone receptor expression are very important prognostic and predictive factors in breast cancer management and recurrence.

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العوامل الإكلينيكية التكهنية لحالات سرطان الثدى

شملت الدراسة مائة سيدة مصابة بسرطان الثدى بمستشفى الدمرداش بجامعة عين شمس. وقد تم تحليل بياناتهن الطبية بأثر رجعى. وتم إستعراض السمات الإكلينيكية المتعلقة بالمرض بما فى ذلك العمر وحجم الورم والحالة العقدية والإنتشار والدرجة والمراحل الإكلينيكية وحالة إنقطاع الطمث ونوع العملية والغزو اللمفاوى الوعائى وظهور العلامات PR, ER وHER-2 والعلاج النظامى والعلاج الإشعاعى.

تبين من نتائج الدراسة الحالية وجود علاقة كبيرة بين درجة العقد الليمفاوية وتطور التكرار فى مجموعة الثالثة للمرضى مقارنةً مع مجموعات المرضى N1, N0 وN2.

أظهرت نتائج الدراسة تكرار الإصابة بالمرضى ذوى النتائج الإيجابية ER+ وPR+ بصورة أقل من غيرهم ذوى النتائج السلبية ER–، PR– على التوالى، وكان هناك فرق كبير إحصائياً مع البقاء على قيد الحياة لمدة ٣ سنوات خالية من الآمراض. وعلى العكس من ذلك، فقد عانت كل مريضة Her2+ من تكرار الإصابة بسرطان الثدى مقارنةً بمرضى Her2. ونظراً لآن تكرار المرض فى الآنواع الفرعية الآربعة ER/PR/Her2 كان متغيراً تماماً، فقد لوحظ آن جميع آنواع المرضى ER+ PR+/Her2– وER+ PR–/Her2– يعانون من تكرار الإصابة بسرطان الثدى.

فى الختام، لقد وجدنا آن مدى تورط العقدى والتعبير عن مستقبلات الهرمون عاملان مهمان للغاية فى التنبؤ بسرطان الثدى وتكرارهما.