

The rate of Estrogen receptors ,progesterone receptors and pidermal growth factor 2 receptors discordance between primary and recurrent breast cancer and its effect on survival

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Abstract

Background: Treatment of recurrent breast cancer, like treatment of early-stage breast cancer, is based on consideration of tumor biology and clinical history. Thus, characterization of tumor hormonal and HER2 status is critical for all patients, and a detailed assessment of past treatment, including timing of therapies as well as patient symptoms and functional assessment, is essential. Determination of hormone receptor status and HER2 status should be repeated in all cases of first recurrence when diagnostic tissue is obtained because there may be discordance between the primary and recurrent tumors.

Aim of study: 1-To determine the rate of discordance of estrogen ,progesteron and epidermal growth factor2 (HER2) receptors between primary and recurrent breast cancer.
2-To study the effect of the discordance on patient's disease free survival

Patients and method: The study was conducted retrospectively and included 100 Iraqi female patients attended Baghdad oncology teaching hospital between January 2012 and December 2017 for whom estrogen receptors , progesteron receptors status were known at time of diagnosis and had been obtained on new tissue biopsy at time of recurrence.

Results: 1-The rate of discordance for estrogen receptors ,progesteron receptors and HER2 receptors between primary and recurrent tumor are 24%,27%,17% respectively

2-There was not statistically significant difference in the disease free survival between concordant and discordant cases for both estrogen receptors and progesteron receptors while there is a significant difference in form of increase disease free survival of the epidermal growth factor 2 receptors discordant cases compared to concordant ones.

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Conclusion:The effect hormonal receptors discordance on disease free survival not statistically significant ,while the gain of HER2 receptors after recurrence is associated with better survival.

Key words: ER,PR Discordance,HER2 discordance ,Disease free survival

Introduction

Breast cancer is a major public health problem for women throughout the world. In the United States, breast cancer remains the most frequent cancer in women and the second most frequent cause of cancer death. In 2017, it was estimated there were 255,180 new cases of breast cancer, with 41,070 deaths⁽¹⁾

Overall, it is the most common cancer among general Iraqi population & the second most frequent cancer. The latest Iraqi cancer registry shows that 4115 cases of breast cancer were registered among an estimated population of about 32.5 million ;accounting for 19.5% of newly diagnosed cancer and an incidence of 22 per 100000 females population.⁽²⁾

The estrogen(ER) and progesterone receptors(PR) are weak prognostic indicators, but they are highly predictive of response to endocrine therapy⁽³⁾

Among all breast cancers, 55% are ER-positive/PR-positive, 16% are ER-positive/PR-negative, and 4% are ER-negative/PR-positive.⁽⁴⁾

HER2 is a member of the epidermal growth factor receptor (EGFR) tyrosine kinase family, overexpression of the HER2 185-kd protein is a consequence of gene amplification, which occurs in approximately 20% of all breast cancers. HER2 status is defined by ASCO/CAP guidelines, which were updated in 2013⁽⁵⁾

The NCCN Panel recommends that metastatic disease at presentation or first recurrence of disease should be biopsied as a part of the workup for patients with recurrent or stage IV disease. This ensures accurate determination of metastatic/recurrent disease and tumor histology and allows for biomarker

determination and selection of appropriate treatment.⁽⁶⁾

Determination of hormone receptor status and HER2 status should be repeated in all cases when diagnostic tissue is obtained. ER and PR assays may be falsely negative or falsely positive, and there may be discordance between the primary and metastatic tumors.⁽⁷⁾

The reasons for the discordance may relate to change in biology of disease differential effect of prior treatment on clonal subsets, tumor heterogeneity, or imperfect accuracy and reproducibility of assays.⁽⁸⁾

The accuracy and reliability of immunohistochemical testing is based on multiple factors, such as the method of tissue fixation, method of staining, and subjective scoring; all of which can have an effect in the final interpretation of the result affect⁽⁹⁾

Discordance between the receptor status of primary and recurrent disease has been reported in a number of studies. The discordance rates are in the range of 3.4% to 60% for ER-negative to ER-positive; 7.2% to 31% for ER-positive to ER-negative; and 0.7% to 11% for HER2.⁽¹⁰⁾

Patients and methods

This study was conducted retrospectively and it included 100 Iraqi female patients were attending Baghdad oncology teaching hospital between January 2012 and December 2017, all of them had breast cancer recurrence at time of collecting the data ,their data were collected and their files were reviewed in a duration between January 2019 and January 2020.

Inclusion criteria

All patients in this study had received chemotherapy and had breast cancer recurrence at time of presentation .

Exclusion criteria 1. History of bilateral breast cancer. 2. History of denovo metastasis(stage 4 at time of diagnosis). 3. Patients without obtainable information. 4. History of non breast second malignancies. 5. Patients received neoadjuvant chemotherapy

Data collection tools One tool used to collect the required data and this tool was self constructed questionnaire form prepared to collect information from the participants regarding selected variables. The data was collected by from patient's records regarding the primary tumor(age at presentation ,menopausal status , primary breast cancer were staged according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7 th and 8th edition , Grading of tumors was done according to Nottingham grading system⁽¹¹⁾ , ER, PR, HER2 status was obtained from patient medical records. The type of recurrence (local or distal recurrence) and duration (in months) from time of diagnosis of primary tumor to time of recurrence were obtained from patient's records. The hormonal status(ER,PRand HER2) at recurrence was also recorded. The patients were divided in two groups according to the presence or absence of the discordance. Tissue sample was taken from each patient either by excisional biopsy or true cut biopsy and examined by H&E staining to confirm relapse of primary tumor. After the confirmation of the recurrence , immunohistochemistry was done in the pathology department of Baghdad oncology teaching hospital to assess for ER,PR and HER2 status at recurrence

The proportion of positive cells and intensity were summed to produce total score 0 or 2 through 8 .A score of 0 or 2 was regarded as negative ,whereas a score

of 3 to 8 ,as positive⁽¹²⁾ HER2 protein overexpression was determined by using IHC with HER2 test (Dako Denmark,A/S ,Ventana medical system ,D-68305)was done using the standards system of scoring between 0 to 3, values of 0 and 1 was regarded as negative, 3 as positive, and for equivocal intensity of 2, further confirmation was done by Chromogenic in situ hybridization (CISH)⁽¹³⁾The patients were divided in two groups according to the presence or absence of the discordance and their data were studied and analyzed.

Statistical analysis

Data was analyzed using statistical package for the social sciences (SPSS version 23) computer software program. Descriptive statistics presented as frequency tables, Continuous variables were expressed as mean \pm standard deviation and categorical variables as numbers and percentages. Analytic statistics as chi-square test to find association between two categorical variables and fisher exact test when chi-square test was inapplicable. Statistical survival analysis was done by log rank and Kaplan- Meier test. The P-value below or equal to 0.05was considered to be statistically significant

Results

A total of 100 patients with recurrent breast cancer were enrolled in this study, the mean age of presentation (\pm SD) of those patients was 48.5(\pm 11.5) years, range was between 25-82 years where 22 patients were below 40 years, 32 patients were between 40-49 years, 27 patients were between 50-59 years and 19 patients were above 60 years, figure1.

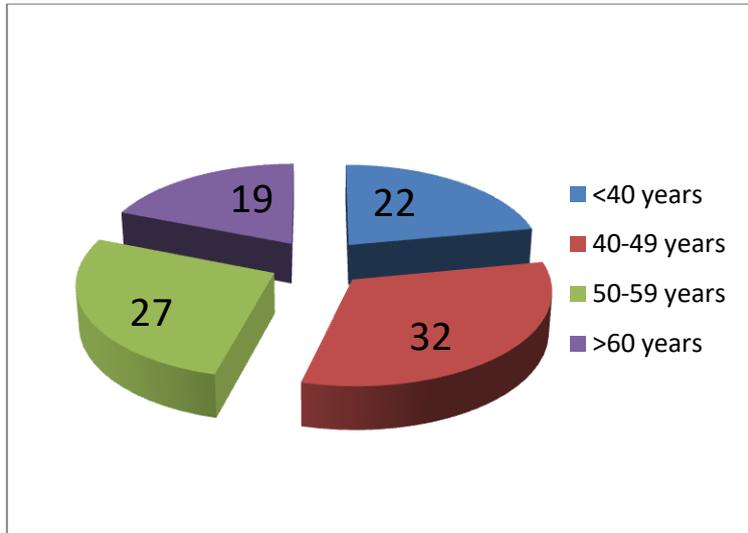


Figure1 Pie chart for distribution of studied patients on age at presentation.

Table 1 distribution of studied patients on some variable.

Variables		Number
Histopathological type	IDC	82
	ILC	10
	Mixed type	8
Primary tumor diameter	T1	16
	T2	61
	T3	16
	T4	7
Regional lymph nodes	N0	19
	N1	32
	N2	29
	N3	20

The rate of discordance in molecular testing between primary and recurrent invasive carcinoma is 24% in estrogen receptor (ER) biomarker where 19.5%(8)

of patients with negative ER shifted to positive ER at recurrent status and 27.1% (16) of patients with positive ER shifted to negative ER at recurrent status, table 2.

Variables	ER at recurrence		Total	
	- ve	+ve		
ER at diagnosis	-ve	33(80.5%)	8(19.5%)	41
	+ve	16(27.1%)	43(72.9%)	59
Total		49	51	100

Table2 Estrogen receptor (ER) biomarker at diagnosis and recurrent status.

The mean months of DFS was higher in patients with concordance ER status at recurrence (20.7 months) than the patients

with discordance ER status at recurrence (16.9 months) with no significant difference in the mean between two group (p=0.13),table 3 and figure 2.

Table 3 Mean months of DFS in relation to ER status at recurrence.

Variable		Mean months	95% confidence interval		P value
			Lower bound	Upper bound	
ER status at recurrence	Concordance	20.7	17.7	23.7	0.13#
	Discordance	16.9	12.4	21.4	
Overall		19.8	17.3	22.3	

log Rank test. Significant ≤ 0.05 .

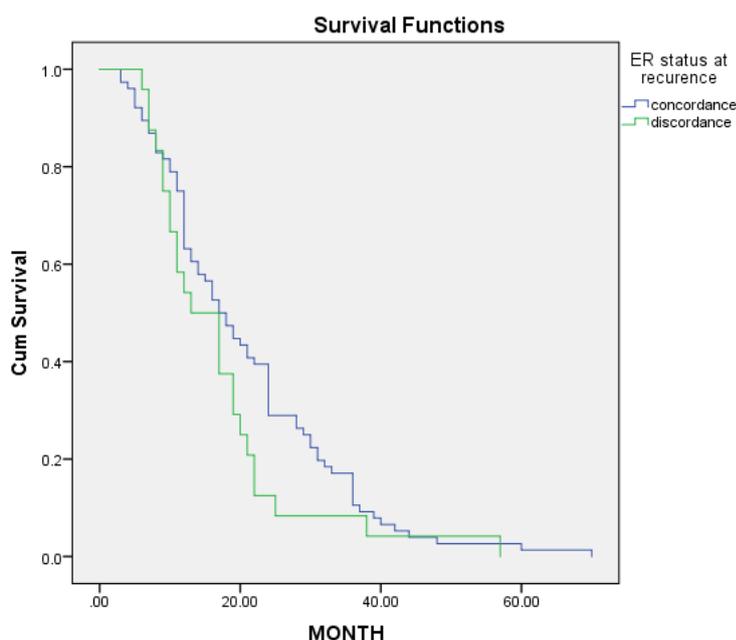


Figure 2 Kaplan- Meier survival analysis in relation of ER status at recurrence.

The rate of discordance in molecular testing between primary and recurrent invasive carcinoma is 27% in progesterone receptor (PR) biomarker where 19%(8) of patients with negative PR

shifted to positive PR at recurrent status and 32.8% (19) of patients with positive PR shifted to negative PR at recurrent status, table 4.

Table 4 Progesterone receptor (PR) biomarker at diagnosis and recurrent status.

Variables		PR at recurrence		Total
		- ve	+ve	
PR at diagnosis	-ve	34(81%)	8(19%)	42
	+ve	19(32.8%)	39(67.2%)	58
Total		53	47	100

The mean months of DFS was higher in patients with concordance PR status at recurrence (20.6 months) than the patients with discordance PR at recurrence (17.7

months) with no significant difference in the mean between two group (p=0.24),table 5and figure 3

Variable	Mean months	95% confidence interval		P value
		Lower bound	Upper bound	
PR status at recurrence				
Concordance	20.6	17.5	23.7	0.24#
Discordance	17.7	13.3	22	
Overall	19.8	17.3	22.3	

Table 5 Mean months of DFS in relation to PR status at recurrence

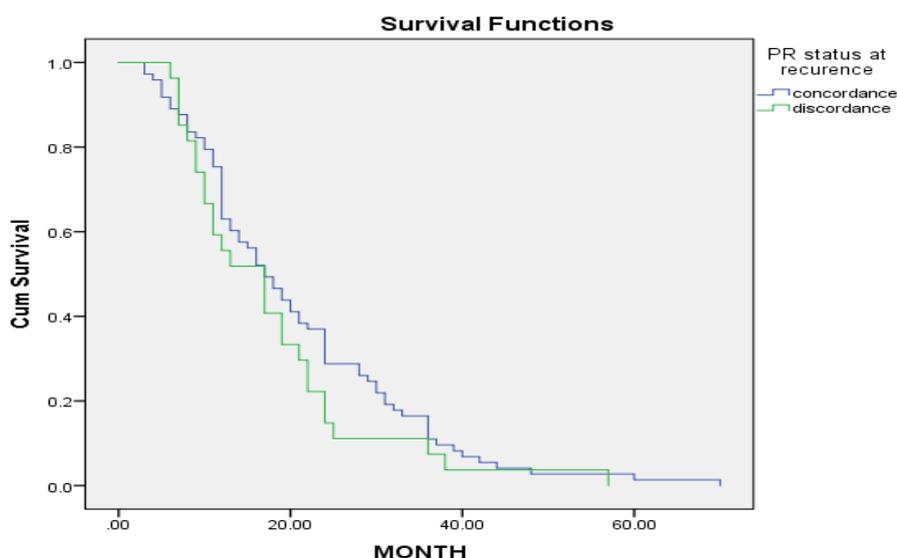


Figure 3 Kaplan- Meier survival analysis in relation of PR status at recurrence. The rate of discordance in molecular testing between primary and recurrent invasive carcinoma is 17% in human epidermal growth factor receptor 2 (HER2) biomarker where 19.2%(14) of patients with negative HER2 shifted to

positive HER2 at recurrent status and 11.1% (3) of patients with positive HER2 shifted to negative HER2 at recurrent status,

table 6 Table 6 Human epidermal growth factor receptor 2 (HER2) biomarker at diagnosis and recurrent status.

Variables	HER2 at recurrence		Total
	- ve	+ve	
HER2 at diagnosis			
-ve	59(80.8%)	14(19.2%)	73
+ve	3(11.1%)	24(88.9%)	27
Total	62	38	100

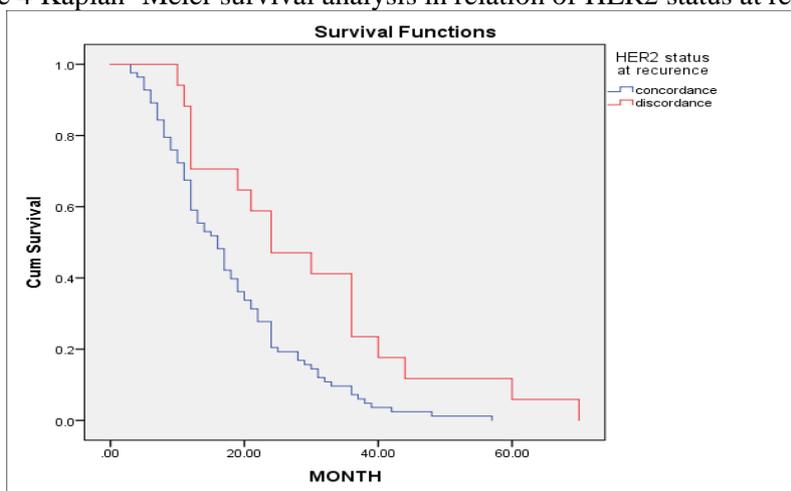
The mean months of DFS was lower in patients with concordance HER2 status at recurrence (17.9 months) than the patients with discordance HER2 status at recurrence (29.2 months) with a significant

difference in the mean between two group of patients (p=0.003),table 7 and figure 4.

Table 7 Mean months of DFS in relation to HER2 status at recurrence.

Variable		Mean months	95% confidence interval		P value
			Lower bound	Upper bound	
HER2 status at recurrence	Concordance	17.9	15.5	20.2	0.003#
	Discordance	29.2	20.9	37.5	
Overall		19.8	17.3	22.3	

Figure 4 Kaplan- Meier survival analysis in relation of HER2 status at recurrence



Discussion

The rate of ER & PR discordance

The rate of ER & PR discordance This study included 100 patients for whom hormonal status (esterogen receptor ER and progesterone receptor PR) status and epidermal growth factor her2 neu status was assessed in both primary and metastatic (local and distant)

In this study the rate of ER discordance between primary and recurrent breast cancer was 24% ,the rate PR discordance between primary and recurrent breast cancer was 27% .

In a study conducted at University of Cincinnati Medical Center,Cincinnati,USA this study conducted retrospectively and ER,PR analysis at time of diagnosis and at

recurrence were available from 200 patients ,the rate of ER discordance was 30% and the rate of PR discordance was 39.3%.⁽¹⁴⁾

In study from the MD Anderson Cancer Centre which retrospectively reviewed 182 breast cancer for whom ER,PR were available both of the primary and the recurrence to determine whether it was important to repeat the IHC for ER,PR at recurrence ,in this study the rate of both ER and PR discordance was 25%.⁽¹⁵⁾

The rate of Her2 neu discordance

In this study the rate of her2 neu discordance between primary and recurrent breast cancer was 17%.

A study conducted at Department of Breast & Endocrine Surgery, Kumamoto

City Hospital, Japan which included 97 female breast cancer patients, the rate of her2 neu discordance was 14.4%.⁽⁴⁷⁾

The effect of ER , PR & her2 neu discordance on survival

In this study we calculated the disease free survival in months (DFS: which is defined as the duration from time of first diagnosis to time of recurrence) for the patients who remained ER, PR, HER2 neu concordant after the recurrence and for those who have discordance after the recurrence to compare between them to see who remained disease free for a longer duration.

The effect of ER & PR discordance on survival

For the patients who remained ER concordant their DFS was 20.7 months while those with ER discordance their DFS was 16.9 months. For patients who remained PR discordant their DFS was 20.6 months while those with PR discordance their DFS was 17.7 months. As we can see that those with ER concordant remained disease free approximately 4 months longer than those with ER discordant patients and those with PR concordant remained disease free approximately 3 months longer compared to those with PR discordant although the difference between the mean DFS of the two groups was not statistically significant ($P=0.13$ and 0.24) for ER groups and PR groups respectively but it still can indicate poor prognosis with trend toward worst survival. In study conducted at the Galway Hospitals group between 2001 and 2014 and included 132 patients, the aim of the study was to determine impact of ER, PR, HER2 discordance on post-recurrence survival and potential treatment options, in this study Overall survival (OS) was comparable between the ER discordant group and the ER concordant group (60.2 vs. 59.3 months), DFS was shorter in the discordant group, but this was not statistically significant (21.6 vs. 17.4

months, $p=0.36$). There was no statistically significant difference in OS or DFS between the PR discordant and concordant groups (OS 67.1 vs. 55.7 months, $p=0.096$, DFS 23.3 vs. 19.1 months, $p=0.096$).⁽¹⁷⁾ The result in the previous study is comparable to this study.

The effect of HER2 neu discordance on survival: In this study the DFS for the patients who remained HER2 concordant after recurrence was 17.9 months and for those who had discordance the DFS was 29.2 months which was statistically significant ($P=0.003$)

In a study conducted at Karolinska University Hospital Stockholm Sweden which included 151 breast cancer female patients showed significant increase in the risk of dying in patients with HER2 discordant cases compared to HER2 positive concordant cases⁽¹⁸⁾

As we can notice the difference between the study above and this study in which the DFS was significantly longer in the discordant cases compared to concordant, this difference between the result in our study and the study above can be explained by the following: in the study above only 6% of the patients who were HER2 negative shifted to positive while 19% of HER2 positive cases shifted to negative which means the percentage of the patients who loss HER2 expression about three times the percentage of the patient who gain HER2 expression after recurrence which is known to be associated with poor survival and poor outcome⁽¹⁹⁾, while in this study it was the opposite as we can notice from the result mentioned previously that 19.2% of HER2 negative patients gained HER2 and shifted to HER2 positive while only 11% of the patients with HER2 positive shifted to negative.

Another study conducted at Medical Oncology Department, Hospital of Prato, Istituto Toscano Tumori, Prato, Italy which included review of 60 her2

discordance studies and concluded that loss of her2 associated with worst DFS and OS while her2 discordance was not associated with shorter DFS.⁽¹⁹⁾

The study above also support the result in this study.

Conclusion

1-the rate of ER ,PR & HER2 discordance between primary and recurrent breast cancer in Baghdad oncology teaching hospital is similar to other well established results.

2-the DFS of those patients with ER & PR discordance are worse than those with ER & PR concordant cases although it is not statistically significant. 3-the DFS of those patients with HER2 discordance are better than than those with HER2 concordant.

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