Evaluation of Primary and Recurrent Breast Cancer after Giving Adjuvant Therapy in Correlation with the Receptor Status

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Breast cancer is the most common type of cancer among women. The molecular subtypes of breast cancer, depending on the Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor (HER-2) status, usually play a vital role for the adjuvant treatment. Interestingly, there is a good possibility of change of receptor status in the recurrence of same primary tumor. The study is designed April 2018 to March 2019 to see the concordance in triple-receptor expression (ER, PR, and HER-2) between the primary and the locally recurrent breast cancer patient and the results can be able to influence the management and prognosis of the breast cancer patients. This observational study was carried out in the department of surgical oncology, NICRH where total 48 patients were studied who were subjected to core biopsy of recurrent lesion for ER, PR and HER-2 status. A structured case record form was used to interview and collect data. Data analysis was done using SPSS version 26.0 to see concordance and discordance in triple-receptor expression between the primary and the locally recurrent breast cancer patient. Among 48 cases, 12(25.0%), 10(20.83%) and 2(4.16%) patients showed Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor (Her-2) discordance that are statistically significant in every receptor status. Majority discordance of ER, PR and Her-2 were associated with invasive duct cell carcinoma (IDC); ER & Her-2 discordance was equally associated with histological grade 2 and 3 whereas PR discordance had significant association with grade 3. Staging of disease showed that all ER, PR and Her-2 discordance were associated with stage ($p<0.05$). Besides, majority discordance was mostly associated with lumpectomy except Her-2 discordance. Besides, among the adjuvant treatment regimen chemotherapy along with radiotherapy was mostly associated with discordance of all receptors ($p<0.05$). Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor (HER-2) status of primary breast cancer showed 25.0%, 20.83% and 4.16% discordant in recurrent episodes in this study. Invasive duct cell carcinoma, histological grade 2 and 3, stage II, stage III, MRM and CT along with RT are major attributable factors in this study.

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Key words: Triple-receptor, Concordance, Discordance

Introduction

The original molecular classification of breast cancer has been derived from investigations of fresh frozen tissue based on the molecular expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (HER-2) and Ki-67. Breast cancer can be categorized as five major subtypes associated with different molecular alterations and distinct clinical outcome including therapeutic response luminal A, luminal B, HER-2 enriched, triple negative breast cancer (TNBC) and basal/normal like breast[1]. Selection of adjuvant treatment depends on molecular subtype of breast cancer. Twenty (20.0%) to thirty (30.0%) percent of early breast cancer cases will eventually relapse despite having more effective therapy[2]. At the time of relapse, treatment decisions are still supported the biological features of primary tumor, although a growing body of evidence indicates a scarcity of concordance in receptor status between primary and recurrent tumors in up to 40.0% of the cases[3,4].

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Endocrine therapy is the best therapeutic options for highly endocrine responsive tumor. Cytotoxic drugs (Transtuzumab in case of HER-2 over expression) are the treatment modalities of non-endocrine responsive tumor. Chemotherapy as well as hormone therapy are effective in case of ER positive and HER-2 negative disease[5]. Approximately one-third of breast malignancy patients develop recurrent tumors[6]. The treatment strategy for recurrent breast cancer is usually determined supported information from the pathological diagnosis of the first lesion. However, tumor phenotype, as represented by ER, PR and HER-2 status occasionally changes at recurrence[6]. So, pathological assessment of recurrent cancer can provide important information to plan therapeutic strategy. As the median survival in patients with obvious metastatic disease is 20 months only, the management policy of recurrent breast cancer requires evidence-based approaches[7]. Recent opinion supports reassessment of ER, PR, and HER-2 receptor in tumor tissue at the time of diagnosis of relapse to select appropriate treatment for each patient[8]. This idea largely based on retrospective evidence that loss of ER in recurrent breast cancer is an established predictor for poor response to endocrine therapy[9]. Where available from the primary cancer ER, PR, and HER2 have been used to direct subsequent therapy conventionally, presuming no change within the biological features of the recurrent disease compared with the original primary; this approach is no longer considered justifiable[8,10]. Even though molecular approaches is used with mixed results to collate primary and recurrent breast cancer[11], such transcriptome approaches have yet to be validated in the context of recurrent disease. Breast cancer is the most common type of cancer in Bangladesh[12]. Bangladesh is adopting large-scale population-based cancer registry or, a central cancer registry to provide a nationwide comprehensive data for cancer studies. National Institute of Cancer Research & Hospital (NICRH), Bangladesh is the leading institute providing comprehensive care for breast cancer patients. NICRH has its own cancer database providing a large share to the nationwide comprehensive data for cancer studies. Treatment decision regarding breast cancer is based on ER, PR, HER-2 status.

Methods

This study involved observational study conducted at the department of Surgical Oncology, National Institute of Cancer Research and Hospital (NICR&H), Dhaka, Bangladesh during the period of April 2018 to March 2019. The study population comprised patients suffering from recurrent breast carcinoma patients were selected from surgical oncology department on the basis of the inclusion and exclusion criteria. Inclusion criteria were - biopsy proven locally recurrent breast cancer patient, patient who have completed preoperative adjuvant chemotherapy or radio therapy and/or CT+RT and cases treated with neoadjuvant chemotherapy or radiotherapy prior to surgery. Exclusion criteria were - all distant recurrent patients with carcinoma breast. Study variable were receptor status (ER, PR, HER-2), histological type, tumour grade, stage of tumour, surgical treatment (BCS/MRM), adjuvant treatment etc. Total sample size was 48. After taking inform consent following enrollment in the study, patient was interviewed in detail and subsequently history, physical examination and necessary investigations of each patient were performed. A structured case record form was used to interview and collect data. All patients were subjected to core biopsy of recurrent lesion for ER, PR and HER-2 status. Data collection was done by direct interviewing of the cases. All the investigation findings were recorded accordingly from the patients' file by the investigators themselves. Standard statistical method was used. Data analysis was done using SPSS version 26.0. Categorical variables were tested by Pearson's chi square test (or, Fisher's Exact test when applicable) and operational variable were tested by students t-test. P value considered significant at <0.05.

Results

The study shows that among 48 patients out of 20(41.64%) ER positive status in primary tumor same 8(16.67%) were concordant in locally recurrent tumor. Rest 12(25.0%) turned into ER negative. Besides, out of 20(41.67%) PR positive cases in primary tumor same 10(20.83%) were concordant and rest 10(20.83%) were discordant. Finally, out of 36(75%) HER-2 positive cases in primary tumor same 34(70.83%) were concordant and 2(4.16%) was discordant. So, ultimately ER, PR and HER-2 status were found discordant in

12(25%), 10(20.83%) and 2(4.16%) patients out of 48patients respectively (Table I). Current study shows that out of 48 cases, 36(75.0%), 38(79.16%) and 46(95.83%) patients showed Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor (HER-2) concordance respectively. Subsequently, 12(25.0%), 10(20.83%) and 2(4.16%) patients showed significance respectively. These statistics showed significant difference between concordance and discordance in every receptor status (Figure 1).

Table I: Distribution of patients according to concordance and discordance of receptor status (n=48)

Receptor type	Primary tumor	Locally recurrent tumor		p value (Chi-square test)
		Concordance	Discordance	
	n (%)	n (%)	n (%)	
ER				
Positive	20 (41.67)	08 (16.67)	00 (00.0)	
Negative	28 (58.33)	28 (58.33)	12 (25.0)	<0.03
Total	48 (100.0)	36 (75.00)	12 (25.0)	
PR				
Positive	20 (41.67)	10 (20.83)	00 (00.0)	
Negative	28 (58.33)	28 (58.33)	10 (20.83)	<0.02
Total	48 (100.0)	38 (79.16)	10 (20.83)	
HER-2				
Positive	36 (75.00)	36 (70.83)	00 (00.0)	
Negative	12 (25.00)	10 (25.00)	02 (04.16)	<0.03
Total	48 (100.0)	46 (95.83)	02 (04.16)	

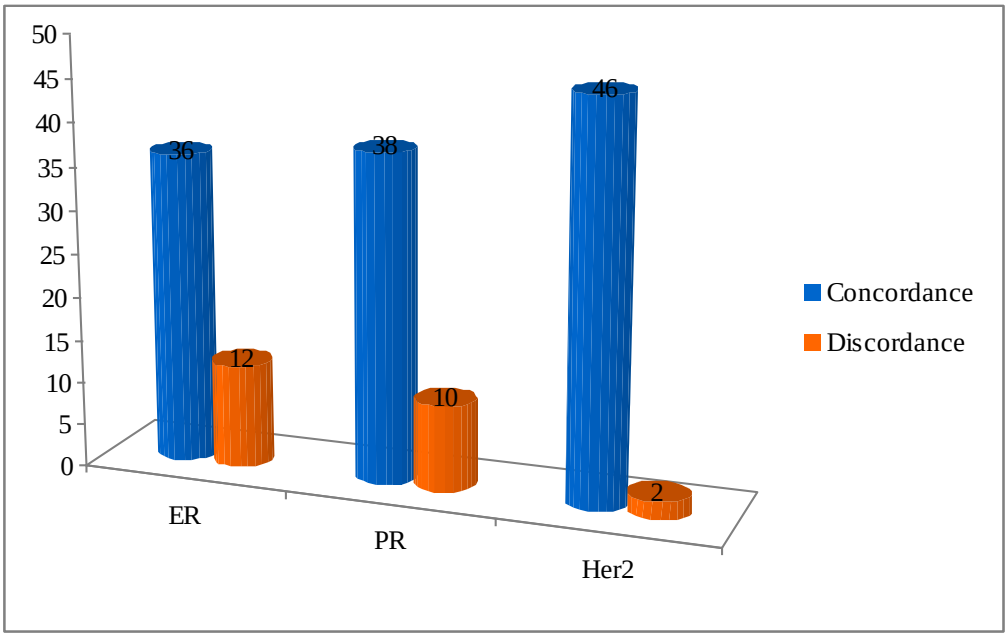

Figure 1: Distribution of patients according to concordance and discordance of ER, PR and HER-2 (n=48)

This study shows that majority discordance of ER, PR and HER-2 were associated with invasive duct cell carcinoma (IDC) Histological grade showed that ER discordance was equally associated with histological grade 2 and 3 whereas PR discordance had significant association with grade 3. Similar scenario like PR discordance was observed in HER-2 discordance. Staging of disease showed that all ER, PR and HER-2 discordance were associated with stage ($p<0.05$) (Table II). This study shows that majority discordance was mostly associated with MRM except Her2 discordance. Besides, among the adjuvant treatment regimen chemotherapy along with radiotherapy was mostly associated with discordance of all receptor ($p<0.05$) (Table III).

Table II: Change of receptor status in locally recurrent breast cancer in relation to histological type grade and stage of primary tumor (n=48)

Variables	All patients (n=48)	ER		PR		HER-2		p value ($\chi 2$ test)
		Concordance (n=36)	Discordance (n=12)	Concordance (n=38)	Discordance (n=10)	Concordance (n=36)	Discordance (n=2)	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Pathological type								
IDC	46	36 (78.26)	10 (21.73)	36 (82.60)	08 (17.39)	44 (95.65)	02 (04.34)	<0.05
ILC	02	00 (00.00)	02 (100.0)	02 (100.0)	02 (100.0)	02 (100.0)	00 (00.00)	
Histological grade								
1	04	04 (100.0)	00 (00.00)	02 (50.00)	02 (50.00)	04 (100.0)	00 (00.00)	
2	24	18 (75.00)	06 (25.00)	22 (91.67)	02 (08.33)	24 (100.0)	00 (00.00)	<0.05
3	20	14 (70.00)	06 (30.00)	14 (70.00)	06 (30.00)	04 (20.00)	02 (10.00)	
TNM stage								
T_{15}	00	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	
T_1	00	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	
T_2	04	04 (100.0)	00 (00.00)	04 (100.0)	00 (00.00)	04 (100.0)	00 (00.00)	<0.05
T_3	38	28 (73.68)	10 (26.31)	20 (52.63)	08 (21.05)	36 (94.73)	02 (05.26)	
T_4	06	04 (66.67)	02 (33.33)	02 (33.33)	02 (33.33)	06 (100.0)	00 (00.00)	
Stage								
0	00	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	
I	06	06 (100.0%)	00 (00.00)	06 (100.0)	00 (00.00)	06 (100.0)	00 (00.00)	<0.05
II	32	22 (68.75)	10 (31.25)	26 (81.25)	06 (18.75)	30 (93.75)	02 (6.25)	
III	10	08 (80.00)	02 (20.00)	06 (60.00)	04 (40.00)	10 (100.0)	00 (00.00)	

Table III: Change of receptor status in locally recurrent breast cancer in relation to treatment received in primary tumor (n=48)

Treatment received	All patients (n=48)	ER		PR		HER-2		p value ($\chi 2$ test)
		Concordance (n=36)	Discordance (n=12)	Concordance (n=38)	Discordance (n=10)	Concordance (n=46)	Discordance (n=2)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Surgical treatment								
MRM	40	32 (80.0)	8 (20.0)	34 (85.0)	6 (15.0)	40 (100.0)	0 (00.0)	<0.05
Lumpectomy	08	4 (50.0)	4 (50.0)	04 (50.0)	4 (50.0)	06 (75.0)	2 (25.0)	
Adjuvant treatment								
CT+RT+ HT	24	22 (91.67)	2 (08.33)	24 (100.0)	0 (00.0)	24(100.0)	0 (00.0)	<0.05
CT + RT	20	12 (50.0)	8 (66.67)	12 (60.0)	8 (40.0)	18 (90.0)	2 (10.0)	
CT	04	02 (50.0)	2 (50.00)	02 (50.0)	2 (50.0)	04 (100.0)	0 (00.0)	

Discussion

Multiple mechanisms causing a change in biomarkers expression between primary and recurrent breast cancer have been proposed: pre-analytical and analytical errors[13], intratumoral heterogeneity[14] and selective pressure of previous treatments[15]. Lastly, a switch in tumor biology cannot be excluded: despite breast cancer large-scale genomic features seem to remain stable during progression[16], alterations of individual genes may occur[17]. In this study, we determined our sample size as 49. There was dropout of one case. Among 48cases, 36(75.0%) and 12(25.0%) in case of ER in recurrent tumor showed concordance and discordance respectively to their previous receptor status in primary tumor. Here 20(41.67%) out of 48 cases had ER positive primary tumor among which only 8(16.67%) sustained later in recurrent cases and rest converted into ER negative. In case of 20(41.67%) PR positive out of 48 cases of primary tumor 10(20.83%) could preserve their previous nature in recurrent episode. Here 38(79.16%) were concordant and 10(20.83%) were discordant in PR of recurrent tumor. All 10(20.83%) were converted from PR positive to PR negative. Exception lied in HER-2 receptor status where it was observed that 1(4.16%) Her2 negative case became HER-2 positive in recurrent tumor. Interestingly, this was the only evidence of reverse discordance of receptor status comparison to ER, PR. Here the correlation between primary and recurrent tumor receptor status was found statistically significant. These findings were supported by a previous study[18]. Another study showed discordance of ER in 30% cases which is very similar to our findings (25.0%). In case of PR they found discordance of 38.0% cases and we observed the similar scenario in 20.83% cases which is lower but nearer to their findings[18]. Besides, a study conducted in Chicago showed that 71.0% patients had ER concordance and 56.0% patients had PR concordance[19]. Likewise, we have revealed in our study that 75.0% of our patients had ER concordance and 79.16% patients had PR concordance. Though, ER concordance of your study was almost similar to the previous study but PR concordance in our study is a title higher than that previous study[19]. In this study, we have upheld that ER, PR conversion from positive to negative and HER-2 was from negative to positive. Conversion from positive to negative status was related to a significantly worse overall survival (HR, 3.44; 95% CI, 1.36-8.33; p=0.008 for ER and HR, 8.33; 95% CI, 2.32-33.3; p=0.001 for PR)[20]. Biological differences between ER and PR may be the cause of the difference in HR. Good response to hormonal treatment is seen in the cases with strong ER expression and strong PR expression usually favors survival, especially in patients who are also ER positive[21]. In this study, it was beyond our scope to determine the prognostic indication in case of HR conversion as we did not approach for OS and DFS. Still though, the importance of determination of HR conversion in recurrent episode is very crucial for the further planning of treatment and survival analysis. According to our study results, IDC, were associated with ER, PR and HER-2 discordance ($p<0.05$). Histological grade revealed that 2 and 3 were associated with ER discordance whereas only 3 was associated with both PR and Her2 discordance ($p<0.05$). T staging revealed Stage 3 was associated with all ER, PR, HER-2 discordance ($p<0.05$) which were supported by previous study[22]. Finally, we have tried to observe the association of received treatment of primary tumor with HR conversion in case of recurrent tumor. Here it was revealed that the patients who received mastectomy as well as combination of chemotherapy plus radiotherapy showed mostly the receptor status discordance in subsequent episode ($p<0.05$). These results were supported by a previous study[23]. Henceforth, from the different aspects it may be emphasized here that breast cancer treatment is a personalized treatment. In case of recurrent episode, the cytopathology, histopathology, immunohistochemistry like all diagnostic work up must be done from very beginning as changed status may be observed. Hence, changed planning of treatment needs to be implemented. Finally, as this study has limitation of being single centered with small sample size, further large size multicentered study is required to confirm the study findings.

Conclusion

Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor (HER-2) status of primary breast cancer showed 25.0%, 20.83% and 4.16% discordant in recurrent episodes in this study. Invasive duct cell carcinoma, histological grade 2 and 3, stage II,

stage III, MRM and CT along with RT are major attributable factors in this study.

Recommendation

Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor (HER-2) study should be carried out for better understanding on the mechanism of change of expression between primary and recurrent breast cancer.

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