Comparison of Hormone Receptor Status in Primary and Recurrent Breast Cancer

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Abstract

Background: Systematic treatments such as hormone and chemotherapy are selected according to tumor characteristic after major therapeutic approaches such as surgery. This study attempted to analyze and compare the status of Estrogen Receptor (ER) and Progesterone Receptor (PR) in primary and recurrent sites of breast cancer in patients.

Methods: We reviewed all medical records of breast cancer women who were treated between January 1995 and December 2008. One hundred eighty two out of 2241 patients (8.12%) had a metastatic breast cancer. Amongst them 48 patients had tumor and biopsy-driven samples, however 13 samples were destroyed and only 35 samples were investigated in this study, therefore 35 malignant biopsy specimens of breast cancer patients were examined by immunohistochemistry essay for ER and PR. Binominal proportional test and Chi square test were conducted to determine the significant correlation between positive cases of hormone receptors among primary and metastases sites.

Results: Hormone Receptor in the primary tumor (HR1) of 9 patients (25.7%) was positive (ER1 and/or PR1) and in the recurrent areas (HR2) of 8 patients (22.9%) was positive (either ER2 or PR2 positive). Kappa coefficients of diagnostic agreement in primary and recurrent cases were 0.077 and 0.125 for estrogen and progesterone, respectively which indicated that the amount of coefficient of agreement is not considerable between primary and recurrent sites.

Conclusion: The current study indicated that receptor status in recurrent tumors did not pose predictable value based on the analysis of hormone receptors in primary stage, so it is not an appropriate basis to set up therapeutic protocol in the metastatic patients. Therefore, tissue sampling and hormone receptor re-analyzing of metastatic sites should be considered in these cases.

Keywords: Breast neoplasm; Progesterone receptors; Estrogen receptors; Metastasis

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Introduction

Diagnosis of metastatic breast cancer is usually made by combination of clinical signs and symptoms and by imaging evaluation. In most cases, tumor biopsy is not used to confirm the suspected metastatic lesion. Therefore, systematic management such as hormone therapy and chemotherapy are performed after treatment approaches such as surgery. It is accepted that certain features of tumors such as Estrogen Receptor (ER) and Progesterone Receptor (PR) might vary during the recurrence of the disease. Retrospective studies for estrogen and progesterone receptors status suggest 15-40% discordance between primary tumor and metastatic tissue in breast cancer patients [1].

Hormone receptor statuses are considered to be the most valuable and effective predictive factors in breast cancer patients while other studies have indicated that patients with tumors presenting no ER and PR receptors will not benefit from hormone therapy. Currently some techniques such as immunohistochemistry are employed for these patients with several advantages including: non-affectability of internal estrogens, possibility of

implementation on paraffinic samples, being compatible with histological findings in a manner with no need to examine ER on non-cancerous samples. Tumor size as a restrictive factor for accurate appraisal of samples has not taken into account in this method [2].

Immunohistochemistry has proved to be superior to biochemical assays in determining the response to hormone therapy [3]. However, many laboratories still report ER and PR status as positive or negative using a cutoff point when less than 10 % of cells stained for ER or PR. Many trials have shown correlation of ER and PR status with prognosis. Five years after diagnosis, women with ER and PR positive tumors have a relapse rate of 5% to 10% higher than those with ER negative tumors, but this difference decreases and ultimately disappears as time passes during follow-up [4].

The results of an analysis by Early Breast Cancer Trialists' Group (EBCTG) coupled with review of 60 studies on 8000 women suffering from non-metastatic breast cancer during 15 years showed that hormone therapy in women with positive hormone breast cancer can reduce annual breast cancer recurrence and mortality rate up to 41% and 34%, respectively. In metastatic cases, hormone therapy is also found helpful in hormone positive receptor tumors and is effective in related response up to 50% [5].

This study attempted to analyze and compare the status of ER and PR in primary tumors and recurrent sites of breast cancer in our patients. The result of this study may be helpful to stop practitioners from overusing or not using hormone therapy and also to provide comparing results for hormone receptor variations in recurrent tumors.

Materials and Methods

All medical records of breast cancer women who admitted in Omid Hospital in Mashhad, Iran were reviewed during 1995 to 2008. One hundred eighty two out of 2241 patients (8.12%) had a metastatic breast cancer. Among them 48 had tumor and biopsy-driven samples; however, 13 samples were destroyed and only 35 samples were investigated in this study. These patients experienced a recurrence during their treatment course. Focusing on ER and PR status, their biopsy samples were examined by immunohistochemistry. The samples with cellular staining rate less than 10 % were reported negative, and those above that considered positive.

Recurrent areas were categorized into local recurrence and distant metastasis, which were available in the patients' medical records. The duration between diagnosis and the first recurrence was described as “Disease Free Survival”. Based on the patients' medical records, their disease stage was also measured before the first treatment.

Statistical Analysis

Analysis of the data, binominal proportional and Chi square analysis were employed to determine the significant correlation of positive rate in hormone receptors of primary and metastatic sites. Kappa Coefficient Agreement was used to determine the amount of Kappa Coefficient of Diagnostic Agreement in different sites. In this study, P-value less than 0.05 was regarded as a significant difference. SPSS software (version 16) performed the statistical analysis.

Results

The Mean ±SD and median age of 35 cases of this study were 51±12.06 and 52, respectively. The most common primary stages of observed tumor were T2 (17 patients, 48.6%), T3 (9 patients, 25.7%), T4 (5 patients, 14.3%), T1 (4 patients, 11.4%) sequentially. The most common lymphatic stages were N1 (14 patients, 40%), N0 (11 patients, 31.4%), N2 (7 patients, 20%), N3 (3 patients, 8.6%) (Table 1). Estrogen Receptor in primary tumor (ER1) of 9 patients was positive (25.7%) while in 26 (74.3%) patients was negative.

Also, Progesterone Receptor in primary tumor (PR1) of the same nine patients (25.7%) was positive and in the others was negative. Therefore, we concluded that hormone receptor, in the primary stage of tumor in 9 patients (25.7%) was positive (either ER1 or PR1). Estrogen Receptor (ER2) in the recurrence area of six patients (17%) was positive whereas Progesterone Receptor (PR2) in the recurrence area of just five patients (14.3%) was positive. Finally, Hormone Receptor in the recurrence area (HR2) in 8 patients (22.9%) was positive (either ER2 or PR2) and was negative in the rest (Table 2).

The duration of Disease Free Survival (DFS) was between 7 and 96 months (23.54±19.17). The most common type of recurrence was local recurrence involving 26 patients (74.3%). Nine patients (25.7%) were diagnosed with distant recurrence in which the most common affected areas were bone (involving 4 patients=11.4%), lung (involving 2 patients=5.7%), brain (involving 2 patient=5.7%), and liver (involving one patient=2.9%).

Long DFS (DFS> 24 months) showed no correlation with ER1 (P=0.416), PR1 (P=0.416), and ER2 (P=0.32), but significant statistical correlation with positive PR2 (P=0.026). Among nine patients with

Table 1. Primary stages of breast cancer

T* stage	Freq (%)	N** Stage	Freq (%)
1	4 (11.4%)	0	11 (31.4%)
2	17(48.6%)	1	14 (40%)
3	9 (25.7%)	2	7 (20%)
4	5 (14.3%)	3	3 (8.6%)

* T: Tumor
** N: Lymph Nodes

Table 2. Hormone Receptor status in primary (ER1, PR1) and recurrent (ER2, PR2) breast cancer

ER1*	Freq (%)	PR1**	Freq (%)	ER2	Freq (%)	PR2	Freq (%)
+	9 (25.7%)	+	9 (25.7%)	+	6 (17.1%)	+	5 (14.3%)
-	26 (74.3%)	-	26 (74.3%)	-	29 (82.9%)	-	30 (85.7%)

*ER: Estrogen Receptors
**PR: Progesterone Receptors

positive HR1, six patients (67%) had negative HR2 in their metastatic sites. This variation (from 100% to 33%) was estimated as significant in binominal proportional test (P<0.001, Proportion test=0.99).

Among patients with negative HR1 (26 cases), 5 patients (19.2%) had positive HR2 in their metastatic sites and the rest (80.8%) had negative hormone receptors. This variation in hormone receptor status was also significant (P<0.001, Proportion test=0.99). Kappa coefficient of diagnostic agreement in primary and recurrent modes was 0.077 and 0.125 for estrogen and progesterone, respectively, which indicated that the amount of coefficient of agreement was not considerable between primary and recurrence sites. In other word, hormone status results of recurrent sites cannot be predicated from status of the primary tumor.

Discussion

In our study 35 patients were investigated, of which 9 patients (25.7%) were reported to have positive Estrogen Receptor in their primary tumors (ER1) while the other 26 patients (74.3%) had negative Estrogen Receptors. Likewise, 9 patients (25.7%) were reported to have positive Progesterone Receptor in their primary tumors (PR1) whereas 26 patients (74.3%) had negative estrogen receptor.

In a study conducted in the US in 2005, ER and PR receptor status was investigated in primary tumors and metastases of 200 patients suffering from breast invasive carcinoma. They found a significant correlation between these two receptors in primary tumors and in metastatic areas (P<0.001). However, there was no concordance between ER receptor in primary tumors and metastases in 60 patients (30%). There was also no concordance observed in PR receptors in 68 patients (38%) out of 173 patients. The patients with ER positive in primary and metastatic tumors had similar survival with those with ER negative in primary tumor but positive in metastatic tumor.

However, those patients whose ER varied from positive in primary tumor to negative in metastatic tumor had rather shorter survival (P<0.05). The results of this study indicated that there was a significant correlation between survival and variations in Progesterone Receptor (PR) in primary and metastatic tumors. This study also revealed a clear discordance between primary tumors and its metastases for ER and PR. ER status of metastatic tumor was a better predictive factor for survival. So oncologists need to have thorough knowledge and profound awareness of receptor status in metastatic tumors if they want to offer treatments for breast carcinoma more successfully [6].

In another study conducted in Chicago, ER and PR status of primary and metastases tumors of 84 patients were investigated. Among these 84 patients 59 patients (71%) had ER concordance. There was also 56% concordance among progesterone receptors. Treatments such as adjuvant chemotherapy, adjuvant radiotherapy and hormone therapy had no impact on concordance/discordance between these receptors in primary and metastatic

tumors. DFS in tumors in which ER was positive in primary but negative in metastatic tumor was significantly less common than those tumors in which ER was negative in primary but positive in metastatic tumors (P=0.04). In this study, researchers concluded that increasing of invasive features of a tumor might be due to variation in receptor status from positive in primary to negative in metastatic tumors [7].

In a study conducted in Finland, PR and ER status of primary breast malignancy and metastatic carcinoma of 50 patients were examined. Immunohistochemistry was the main technique to use and receptor status discordance in recurred and primary tumors was observed. Lack of ER was significantly correlated with shorter survival and poor response to hormone therapy treatment (P=0.085). The researchers concluded that analysis of ER and PR status in recurrent breast tumors will contribute to prediction power of these two indicators [8].

In an experiment carried out in China, status of 3 receptors of ER, PR, and HER2 was analyzed in primary and metastatic tumors of 65 breast invasive carcinoma patients using Immunohistochemistry. There was far more ER positive in primary tumors than in metastatic ones (P<0.01) while there was no significant difference between primary and metastatic tumors for the other two receptors (PR and HER2). The scientists concluded that there was a marked difference between ER positive rate in primary tumors and metastatic ones, and this fact can play a crucial role to make a decision to offer more effective treatment [9].

In a study conducted in Croatia, 60 patients suffering from breast cancer were examined. The main aim of this study was to determine similarity and/or difference between tumor cell sub-colonies in axillary lymph node and primary area of disease (breast) for factors such as Ki-67, expression of estrogen and progesterone receptors, protein P53, proto-oncogene bcl-2 and cathepsin D. Although they observed a higher tumor growth fraction in tumor cells (P=0.045) and more expression of proto-oncogene bcl-2 (P=0.014) in tumor cell of axillary lymph node rather than in breast, there was not a noticeable difference in expression of ER and PR receptors, protein P53, and cathepsin D in these two areas [10].

In our study 9 patients who were HR1 positive, 6 patients (67%) had negative HR2 in their metastases and this variation (from 100% to 33%) was estimated significant in binomial proportional test (P<0.001, Proportion test=0.99). In other word, we observed 33% discordance in hormone receptor status between primary tumor and metastasis one, which is similar to other studies.

Conclusion

Our recent study indicated that receptor status in recurrence cannot be predicted based on the analysis of hormone receptors in primary stage and it is not an appropriate base for selecting the proper treatment for metastatic patients. Therefore, tissue sampling and hormone receptor re-analyzing of metastatic sites should be considered in these cases.

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Conflict of Interest

The authors have no conflict of interest in this article.

Authors' Contribution

Hamid Saeedi Saedi and Mohammad-Reza Ghavam Nasiri designed the study. Hamid Saeedi Saedi wrote the article, and Soodabeh ShahidSales collected the data, revised the article and the manuscript; Ali Taghizadeh contributed to the analysis and data interpretation; Nama Mohammadian contributed to the pathologic results.

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