Original Study

Prognostic Impact of Discordance in Hormone Receptor Status Between Primary and Recurrent Sites in Patients With Recurrent Breast Cancer

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Abstract

In 153 patients with breast cancer with recurrence, the discordance rates for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status between primary and recurrent sites were 18%, 26%, and 7% under the same standardized method, respectively. Loss of hormone receptor expression and conversion to triple negative at the recurrence sites were independent indicators of worse clinical outcome.

Introduction: Recent retrospective studies have reported discordance rate of hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) statuses between primary and recurrent tumors and prognostic values of discordance. However, the results of these reports may possibly include analytical error. **Patients and Methods:** We analyzed 153 patients from whom pathological specimens of tumor tissues were available from both primary and recurrent sites. For all specimens, immunohistochemistry was performed for these statuses with a standardized method. Two experienced pathologists evaluated these specimens in a blinded fashion. **Results:** The discordance rates for estrogen receptor, progesterone receptor, and HER2 were 18%, 26%, and 7%, respectively. Subtype changes based on HR and HER2 status occurred in 21% of patients. Clinical outcome was significantly worse in the patients with the tumors that were primarily HR-positive (HR^+) converted to HR-negative (HR^-) at recurrent sites than in the patients with the tumors in which HR status did not change or converted from HR^- to HR^+ ($P = .001$). Clinical outcome was also significantly worse in the patients with the primarily HR^+ tumor that converted to triple negative in the recurrence sites than in the patients with a constantly HR^+ tumor ($P < .001$). By the Cox multivariate analyses, loss of HR expression and conversion to triple negative at the recurrence sites were independent indicators of worse clinical outcome. **Conclusion:** Discordance in HR and HER2 status often occurred between primary and recurrent breast cancer and had independent prognostic impact in the patients with recurrent breast cancer.

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Introduction

The statuses of hormone receptors (HRs) and human epidermal growth factor receptor 2 (HER2) in the primary breast cancer are the most important markers for the treatment decisions of the patients with recurrent breast cancer. However, recent retrospective studies have reported that discordance sometimes occurs in these biological markers between primary and recurrent tumors.[1-4] It is unclear whether or not survival improved when patients with recurrent breast cancer are treated in accordance with these receptor statuses in the recurrent tumors.

Recently, several retrospective analyses have suggested that discordance of HR and HER2 statuses between the primary and recurrent tumors is associated with poor clinical outcome.[1,5-10] However, many results have a possibility of including an analytical error. The aim of this study is to assess estrogen receptor (ER), progesterone receptor (PR), and HER2 statuses using the same standardized methods with an autostainer and evaluation by 2

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Table 1 Clinicopathologic Characteristics of Patients in the Present Study

Parameter	n (%)
Total	153
Median age at diagnosis, year (range)	54 (30-81)
Menopausal status	
Premenopausal	59 (39)
Postmenopausal	94 (61)
Tumor size at primary tumor (TNM)	
T1	67 (44)
T2	62 (40)
≥T3	24 (16)
Lymph node status	
0	67 (44)
1, 2, 3	36 (24)
≤4	45 (29)
Unknown	5 (3)
Histologic grade	
1	19 (12)
2	58 (38)
3	76 (50)
Histologic type	
Invasive ductal carcinoma	134 (88)
Invasive lobular carcinoma	10 (7)
Others	9 (5)
Lymphovascular invasion	
Positive	78 (51)
Negative	75 (49)
Initial surgical therapy	
Mastectomy	87 (57)
Partial resection	66 (43)
Neoadjuvant therapy	
Yes	35 (23)
No	118 (77)
Adjuvant chemotherapy	
Yes	120 (78)
No	30 (20)
Unknown	3 (2)
Adjuvant hormone therapy	
Yes	111 (73)
No	38 (25)
Unknown	4 (2)
Trastuzumab therapy	
Yes	18 (12)
No	131 (86)
Unknown	4 (2)
Radiation therapy	
Yes	111 (73)
No	38 (25)
Unknown	4 (2)
ER in the primary site	
Positive	110 (72)
Negative	43 (28)
PR in the primary site	
Positive	82 (54)
Negative	71 (46)
HER2 in the primary site	
3+	18 (12)
2+ (≥FISH 2.0)	6 (4)
2+ (<FISH 2.0)	8 (5)
1+, 0	121 (79)
Initial recurrent sites of biopsy	
Chest wall	39 (26)
In breast	42 (27)
Regional lymph node	23 (15)
Lung	13 (8)
Bone	9 (6)
Liver	8 (5)
Brain	4 (3)
Distant lymph node	7 (5)
Other metastatic sites	8 (5)

experienced pathologists in a blinded fashion. Then, the prognostic values of such discordance were examined in patients with recurrent breast cancer in a single institution. Knowledge of the discordance rate and identification of independent prognostic factors can contribute to improving treatment for recurrent breast cancer.

Materials and Methods

We retrospectively reviewed the records of 7248 patients who underwent surgery for primary breast cancer between 1985 and 2013 in the database of the Department of Breast Surgery in the National Cancer Center Hospital, Tokyo. In these 7248 patients, 153 patients underwent either core needle biopsy or surgical excision for recurrent breast cancer. Ultrasound-guided core needle biopsies were performed with a 16-gauge needle by skillful breast surgeons. For the patients who received neoadjuvant chemotherapy, we retrieved the pretreatment biopsy specimens.

For these 153 patients, we were able to retrieve files for 137 (89.5%) patients from the Department of Pathology, National Cancer Center Hospital. Formalin-fixed paraffin-embedded tumor tissues specimens of the primary and recurrent sites were available from these 137 patients. These specimens were cut into 3-μm-thick sections and subjected to immunohistochemical (IHC) staining for ER, PR, and HER2. ER and PR were performed using the following mouse monoclonal anti-ER antibody (clone 1D5; Dako, Glostrup, Denmark), mouse monoclonal anti-PR antibody (clone PgR636, Dako), and rabbit polyclonal anti-HER2 antibody (HercepTest, Dako), respectively. IHC was performed with standardized methods