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ORIGINAL ARTICLE

# Discordance of hormone receptor, human epidermal growth factor receptor-2, and Ki-67 between primary breast cancer and synchronous axillary lymph node metastasis

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## Summary

***Purpose:*** *We herein report the discordance rate between primary breast cancer and synchronous axillary node metastasis, its characteristics and its prognostic impact.*

***Methods:*** *One hundred and four patients with invasive breast cancer with synchronous axillary node metastasis who underwent surgery were included. Estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor-2 (HER2), and Ki-67 were stained by immunohistochemistry in both primary and node metastasis. The cut-off values of the ER/PgR and Ki-67 labeling index were set at 10% and 14%, respectively. HER2 was classified according to the ASCO/CAP guidelines.*

***Results:*** *Cases positive for ER, PgR, and HER2 were 65.4%, 51.0%, and 27.9% and those with a high Ki-67 labeling index were 47.1% in primary breast cancer, respectively, while they were 47.1%, 30.8%, 16.3%, and 75.0% in node metastasis, respectively. The discordance rates between primary and node were 28.8% for ER (positive in primary→negative in node/negative→positive 22.1%/6.7%), 31.7% for PgR (26.9%/4.8%), 13.5% for HER2 (12.5%/1.0%), and 43.3% for Ki-67 (high in primary→low in node/low→high 12.5%/30.8%). The proportions of labeled cells in primary/node were as follows: ER 42.7%/25.2%, PgR 32.1%/14.0%, Ki-67 20.3%/37.1% (p<0.01 each). Regarding the cut-off value of Ki-67 in node metastasis as defined by a receiver operating characteristic (ROC) analysis, the patients with values >33.2% tended to have a poor recurrence-free survival (RFS) (p=0.08).*

***Conclusions:*** *The expression of hormone receptors tended to weaken while the proliferative status remained strong in axillary metastasis. A high Ki-67 labeling index in axillary lymph node metastasis may be a risk factor for recurrence.*

***Key words:*** *axillary lymph node, breast cancer, estrogen receptor, human epidermal growth factor receptor-2, Ki-67, progesterone receptor*

## Introduction

Breast cancer is classified into four intrinsic subtypes according to gene expression profiling by complementary DNA microarrays, making its natural history and responsiveness to treatments clear [1,2]. In clinical settings, many institutes use a surrogate subtype classification based on immunohistochemistry of ER, PgR, HER2, and Ki-67 to predict sensitivity to drugs and to determine the application and types of systemic therapy [3]. However, some discrepancies in the subtypes and

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prognostic information between genetic and immunohistochemical identifications have been reported [4,5].

Several studies have explored the expression of biomarkers in primary breast cancer and metachronous recurrent/metastatic disease [6-10]. Bogina et al. reported that the discordance of ER, PgR, and HER2 between these two entities, including liver, lung, pleura, bone, alimentary tract, and node metastases, was 6.4%, 21.4%, and 3.7%, respectively [6]. The association between changes in the biomarkers and patients' prognoses has been retrospectively evaluated [10,11], and the conversion of the ER and PgR status at the time of recurrence, particularly if the change is from positive (primary lesion) to negative (metastatic lesion), has been shown to have a negative impact on survival. Thus, the discordance of biomarkers between primary breast cancer and metastasis may affect the therapeutic sensitivity and treatment planning. The National Comprehensive Cancer Network (NCCN) guideline recommends biopsies at the first disease recurrence or stage IV disease along with the determination of the ER, PgR, and HER2 status [12].

We evaluated the expression of ER, PgR, HER2, and Ki-67 in primary breast cancer and corresponding synchronous axillary lymph node metastasis in order to clarify the rate, characteristics, and prognostic impact of the discordance. In previous reports involving the above-mentioned markers, some metachronous metastatic lesions might have been affected by preceding adjuvant/neoadjuvant systemic therapy. Because we evaluated only cases without preceding systemic therapy, innate changes in the biology during the metastatic process will become evident in the present study.

## Methods

We reviewed the clinical and laboratory data of 104 consecutive patients with primary invasive breast cancer with axillary lymph node metastasis who underwent lumpectomy/mastectomy with axillary lymph node dissection between January 2000 and December 2010 in Nagasaki University Hospital. The study was approved by the Institutional Review Board, and the requirement to obtain informed consent was waived. Patients were excluded if they were treated with systemic therapy before surgery. The information, including patient age, histological type, and tumor size, was obtained from medical reports. A history of systemic adjuvant therapy was not specified in most cases because the medical records had been lost.

*Pathological evaluations*

Primary breast cancer was staged pathologically according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours [13]. We carried out immunohistochemistry both in primary breast cancer and axillary lymph node metastasis for this study. In cases with multiple lymph node metastases, we considered samples obtained from the site of the maximal metastasis.

Five sections were prepared from each paraffin block. One slide was stained with hematoxylin and eosin (HE), and the remaining slides were kept for immunohistochemical staining. In the immunohistochemical analysis, sections were incubated with antibodies against ER (clone SP1; Ventana Medical Systems, Inc., Tucson, AZ, USA), PgR (clone 1E2; Ventana Medical Systems, Inc.), HER2 (C-erbB-2) (clone 4B5; Ventana Medical Systems, Inc.), and Ki-67 (clone MIB1; DAKO, Tokyo, Japan). Blots were developed by the labeled streptavidin biotinylated antibody method using an automated staining system (BenchMark XT; Ventana Medical Systems, Inc.). Scoring of immunohistochemistry was carried out by a single observer (H. K.).

Nuclear staining was considered positive for ER, PgR, and Ki-67. The ER- and PgR-positive cell counts under 20 fields with a magnification of 100 were determined, and only ≥10% stained cells were regarded as positive. The HER2 expression was scored according to the ASCO/CAP guidelines [14]. A dual *in situ* hybridization (DISH) analysis was carried out in HER2 2+ samples. A DISH DNA Probe Cocktail Assay was performed using the Ventana Benchmark XT staining system. Fluorescence *in situ* hybridization (FISH) in HER2 2+ samples of primary breast cancer had been carried out in clinical practice after July 2004. In this study DISH analysis was carried out in HER2 2+ samples of primary breast cancer until July 2004 and those of axillary lymph node metastasis throughout the study period. The HER2/chromosome 17 ratio was calculated and scored according to the ASCO/CAP guidelines: ratio <1.8, HER2 gene not amplified; ratio >2.2, HER-2 gene amplified; ratio between 1.8 and 2.2, uncertain. If HER2 was scored at 3+ or the gene was amplified, we defined the sample as positive. The Ki-67 labeling index was measured in approximately 1,000 malignant invasive cells counted in hot spots in a high-power field (400×), and 14% was determined as the cut-off value according to definitions adopted by the 2013 St. Gallen Consensus Panel [15].

Next, we performed a ROC analysis to assess the association between the Ki-67 in axillary lymph node metastasis and recurrence in order to determine the cut-off value of the Ki-67 in axillary lymph node metastasis.

*Statistics*

The data are presented as the median (range) or average±standard deviation, unless otherwise mentioned. Student's *t*-test was used for comparisons of continuous variables between two groups, and Fisher's exact probability test was used for comparisons of categorical variables. The consistency of ER, PgR, HER2, and Ki-67 between primary breast cancer and axillary lymph node metastasis was tested using the kappa test. Recurrence-free survival (RFS) was assessed with the use of Kaplan-Meier method and log-rank test. A p value

**Table 1.** Background characteristics of patients

| *Characteristics* | *n (%)* |
|---|---|
| Age (years), median (range) | 55.5 (28-83) |
| pT | |
| T1 | 32 (30.8) |
| T2 | 49 (47.2) |
| T3 | 14 (13.5) |
| T4 | 8 (7.7) |
| Unknown | 1 (1.0) |
| Stage | |
| II | 60 (57.7) |
| III | 34 (32.7) |
| Unknown | 12 (11.5) |
| Cases with metachronous metastasis | 23 (22.1) |
| Duration until metastasis (months), median (range) | 22 (3-108) |
| Initial site of metastasis (n) | |
| Bone | 4 |
| Lung | 3 |
| Liver | 3 |
| Lymph node | 2 |
| Peritoneum | 1 |
| Brain | 1 |
| Ipsilateral breast | 1 |
| Bone + lung | 1 |
| Bone + brain | 1 |
| Lymph node + lung + liver +bone | 1 |
| Unknown | 5 |

<0.05 was considered as statistically significant. All of the statistical analyses were performed using the Stat-Mate III software program for Macintosh (ATMS Co., Ltd., Tokyo, Japan).

## Results

The background characteristics of patients are shown in Table 1. The median observational period was 127 months (range 72-203). The median age of the patients at surgery was 55.5 years (range 28-83). Of the 104 patients, 23 (22.1%) experienced metastasis at 22 months (range 3-108) after operations.

Table 2 shows the expression of each biomarker in primary breast cancer and axillary lymph node metastasis. In 65.4% and 51.0% of the patients, the primary breast cancer was positive for ER and PgR, respectively; however, the proportions of patients with positivity in axillary lymph node metastasis were relatively small (47.1% for ER and 30.8% for PgR, p<0.01 each). Furthermore, the proportions of ER- or PgR-labeled cancer cells in axillary lymph node metastasis were significantly smaller than in primary breast cancer (25.2% vs. 42.7% for ER, p<0.01; 14.0% vs. 32.1% for PgR, p<0.01). In contrast, the pattern of expression of Ki-67 was the opposite, with the proportion of Ki-67-labeled cancer cells being significantly higher in axillary lymph

**Table 2.** The biomarker status

| *Biomarker* | *Primary breast cancer* | *Axillary lymph node metastasis* | *p value* |
|---|---|---|---|
| ER | | | |
| Positive cases | 68 (65.4%) | 49 (47.1%) | <0.01* |
| % of labeled cells | 42.7 ± 36.7 | 25.2 ± 30.5 | < 0.01 |
| PgR | | | |
| Positive cases | 53 (51.0%) | 32 (30.8%) | <0.01* |
| % of labeled cells | 32.1 ± 31.7 | 14.0 ± 22.9 | <0.01 |
| HER2 | | | |
| Positive cases | 29 (27.9%) | 17 (16.3%) | <0.01* |
| Ki-67 | | | |
| high cases | 49 (47.1%) | 78 (75.0%) | n.s.* |
| % of labeled cells | 20.3 ± 20.7 | 37.1 ± 28.0 | < 0.01 |

n.s.: not significant, *the consistency of biomarkers between primary breast cancer and axillary lymph node metastasis was analyzed by kappa test

**Table 3.** Changes in the expression of the biomarkers between primary breast cancer and axillary lymph node metastasis

| *Biomarker* | *Discordance rate* | *Primary breast cancer → axillary lymph node metastasis* | |
|---|---|---|---|
| | | *(+) → (-)* | *(-) → (+)* |
| ER | 30 (28.8%) | 23 (22.1%) | 7 (6.7%) |
| PgR | 33 (31.7%) | 28 (26.9%) | 5 (4.8%) |
| HER2 | 14 (13.5%) | 13 (12.5%) | 1 (1.0%) |
| Ki-67 | 45 (43.3%) | 13 (12.5%) | 32 (30.8%) |

(+) and (-) refer to positive and negative for ER, PgR, and HER2, and to high and low for Ki-67, respectively.

**Table 4.** Association between the biomarker status and recurrence-free survival

| *All cases* | | | *5-year RFS (%)* | *p value* |
|---|---|---|---|---|
| Stage I | | | | |
| ER | primary breast cancer | positive | 76.7 | 0.84 |
| | | negative | 75.0 | |
| | axillary lymph node metastasis | positive | 68.9 | 0.41 |
| | | negative | 81.2 | |
| PgR | primary breast cancer | positive | 75.1 | 0.64 |
| | | negative | 77.5 | |
| | axillary lymph node metastasis | positive | 67.7 | 0.39 |
| | | negative | 80.5 | |
| HER2 | primary breast cancer | positive | 61.5 | 0.1 |
| | | negative | 81.9 | |
| | axillary lymph node metastasis | positive | 56.3 | 0.07 |
| | | negative | 80.4 | |
| Ki-67 | primary breast cancer | high | 74.1 | 0.24 |
| | | low | 78.3 | |
| | axillary lymph node metastasis | high | 73.5 | 0.34 |
| | | low | 83.8 | |
| Stage II | | | | |
| ER | primary breast cancer | positive | 89.5 | 0.13 |
| | | negative | 75.0 | |
| | axillary lymph node metastasis | positive | 82.1 | 0.89 |
| | | negative | 83.6 | |
| PgR | primary breast cancer | positive | 84.3 | 0.51 |
| | | negative | 80.8 | |
| | axillary lymph node metastasis | positive | 88.9 | 0.33 |
| | | negative | 80.2 | |
| HER2 | primary breast cancer | positive | 70.0 | 0.07 |
| | | negative | 93.8 | |
| | axillary lymph node metastasis | positive | 80 | 0.31 |
| | | negative | 83.1 | |
| Ki-67 | primary breast cancer | high | 70.8 | 0.04 |
| | | low | 93.5 | |
| | axillary lymph node metastasis | high | 79.8 | 0.76 |
| | | low | 89.5 | |
| Stage III | | | | |
| ER | primary breast cancer | positive | 69.6 | 0.88 |
| | | negative | 66.7 | |
| | axillary lymph node metastasis | positive | 59.3 | 0.47 |
| | | negative | 76.5 | |
| PgR | primary breast cancer | positive | 71.8 | 0.99 |
| | | negative | 64.3 | |
| | axillary lymph node metastasis | positive | 57.1 | 0.43 |
| | | negative | 75.0 | |
| HER2 | primary breast cancer | positive | 70.7 | 0.48 |
| | | negative | 66.7 | |
| | axillary lymph node metastasis | positive | 64.8 | 0.85 |
| | | negative | 69.6 | |
| Ki-67 | primary breast cancer | high | 72.2 | 0.76 |
| | | low | 63.5 | |
| | axillary lymph node metastasis | high | 68.8 | 0.99 |
| | | low | 66.7 | |

**Table 5.** Association between the newly determined cut-off value of Ki-67 in axillary lymph node metastasis and recurrence-free survival

| | *Ki-67 labeling index (%)* | *5-year RFS (%)* | *p value* |
|---|---|---|---|
| All cases | >33.2 | 74.9 | 0.08 |
| | ≤33.2 | 85.4 | |
| Stage II | >33.2 | 78.3 | 0.22 |
| | ≤33.2 | 88.7 | |
| Stage III | >33.2 | 68.4 | 0.58 |
| | ≤33.2 | 75.0 | |

RFS: recurrence-free survival. Each cut-off value for the Ki-67 was determined by a receiver operating characteristic analysis.

node metastasis than in primary breast cancer (37.1% vs. 20.3%, p<0.01). The expression of HER2 decreased through the process of axillary metastasis in a similar way to ER and PgR (27.9% vs. 16.3%, p<0.01). The proportion of biomarker discordance between primary breast cancer and axillary lymph node metastasis for ER, PgR, HER2, and Ki-67 was 28.8%, 31.7%, 13.5%, and 43.3%, respectively (Table 3). In detail, the expressions of ER, PgR, and HER2 showed changes from positive in primary breast cancer to negative in axillary lymph node metastasis more frequently than the reverse (ER 22.1% vs. 6.7%; PgR 26.9% vs. 4.8%; HER2 12.5% vs. 1.0%). However, Ki-67 changed from a low level in primary breast cancer to a high level in axillary lymph node metastasis more frequently than from positive to negative (12.5% vs. 30.8%).

Regarding the RFS (Table 4), although it did not differ significantly according to the status of biomarkers in either primary or axillary lymph node metastasis in evaluations with all cases, HER2-positive status in cases of axillary lymph node metastasis tended to be associated with a poor prognosis (p=0.07). In patients with stage II disease, high Ki-67 in primary breast cancer was associated with a poor RFS (p=0.04), and positive HER2 in primary breast cancer tended to be associated with a poor RFS (p=0.07). When we evaluated the RFS with our newly determined cut-off values in axillary lymph node metastasis obtained by ROC analysis, cases with values >33.2% (n=50 [48.1%]) showed a poor prognosis with marginal significance (p=0.08) (Table 5).

## Discussion

In the present study, the discordance rate of the expression between primary breast cancer and synchronous axillary lymph node metastasis was 28.8% for ER, 31.7% for PgR, 13.5% for HER2, and 43.3% for Ki-67. In addition to the above dichotomous results, the proportion of cells labeled with each biomarker in primary breast cancer/axillary lymph node metastasis was 42.7%/25.2% for ER, 32.1%/14.0% for PgR, and 20.3%/37.1% for Ki-67.

In previous reports, the rates of discordance between primary breast cancer and metachronous metastasis were 10-30% for ER, 25-55% for PgR, and 10-15% for HER2 [9,16-18]. Positivity in primary cancer to negativity in metastasis seemed to be a more frequent pattern for ER and PgR than the opposite. Discordance of HER2 expression was infrequent compared to that of ER and PgR, and the patterns of HER2 change were not uniform. The change from HER2-positive primary breast cancer to HER2-negative metastasis was promoted by adjuvant chemotherapy, but not by trastuzumab [19]. Thus, a history of systemic therapies may influence the change in the biomarkers, as clones in heterogeneous cancer cells resistant to drugs might survive and grow.

There have been few reports on synchronous distant metastasis that was not affected by systemic therapy. Although their study had a small number of patients, Liu et al. reported that the ER, PgR, and HER2 status between primary breast cancer and synchronous liver metastasis was consisted in most cases during the natural metastatic process [17]. Furthermore, there have been some reports on investigations of biomarkers in synchronous axillary lymph node metastasis. The discordance rate in this setting varied: 4-52% for ER [20-24], 11-52% for PgR [21-24], and 9-30% for HER2 [20-24]. The dominant pattern of ER was a shift from positive in primary to negative in lymph node, whereas the patterns of PgR and HER2 seemed to vary [21-24].

As for Ki-67, the proportion of labeled cells increased in metachronous metastasis compared with primary breast cancer, suggesting the predominance of a more aggressive phenotype [9,10,25]. In synchronous axillary lymph node metastasis, the expression of Ki-67 was reported to vary. Some authors reported that there were no significant differences [23,26], while others found that the Ki-67 expression was significantly increased in axillary lymph node metastasis [27,28]. Although the exact mechanism underlying the discordance of biomark-

ers has not been elucidated, cancers are usually heterogeneous, and aggressive subpopulations might travel to remote sites and metastasize. Alternatively, cancer cells might acquire molecular alterations, including biomarkers, when entering the blood/lymphatic stream and colonizing distant sites.

The influence of discordance of biomarkers on the prognosis has been investigated to some degree. Liedtke et al. reported that cases of recurrence with all-negative ER, PgR, and HER2 (triple-negative) derived from non-triple-negative primary breast cancer had a poor survival, probably due to inappropriate use of targeted therapies, compared with cases with hormone receptor-positive breast cancer of both primary and recurrence [16]. In another report, PgR loss in recurrence seemed to be correlated with a worse prognosis [6]. Salvage hormone therapy is still worth trying for patients whose hormone receptors status changes from positive to negative [11]. Despite few reports on the relationship between the prognosis and biomarkers in synchronous axillary lymph node metastases, PgR loss seemed to decrease the survival [22]. Ki-67 was reported as an independent prognostic marker in axillary lymph node metastasis as well as in primary breast cancer, with a higher index being associated with a poor prognosis [26,27]. In our study, Ki-67 in primary breast cancer with a 14% cut-off value was associated with the prognosis (RFS) in cases of stage II breast cancer but not in axillary lymph node metastases. Because the 2013 St. Gallen Consensus Panel noted that standardized cut-offs for Ki-67 have not been established and that laboratory-specific values should be used [15], we conducted ROC analysis to obtain a new cut-off value for axillary lymph node metastasis. Our analyses showed that a 33.2% cut-off value in axillary lymph node metastasis showed marginal significance with regard to the RFS. Furthermore, in our evaluation of ER-positive cases alone, the patients with Ki-67 >33.2% in axillary lymph node metastasis tended to have a poor RFS (5-year RFS 74.8 vs. 87.2%, p=0.09, data not shown). The Ki-67 labeling index in axillary lymph node metastasis may be helpful for determining the kind of adjuvant systemic therapy, e.g. indications for cytotoxic agents in some patients with luminal type breast cancer. HER2 positivity in axillary lymph node tended to be associated with a poor RFS in our analysis of all cases. Because the anti-HER2 monoclonal antibody trastuzumab was not administered to patients with HER2 positive primary breast cancer as adjuvant therapy before 2007, the therapeutic background was not uniform in our study. The significance of the expression of HER2 in axillary lymph node metastasis will be elucidated in further studies.

Several limitations associated with the present study warrant mentioning. First, we compared the results of DISH assays in HER2 2+ samples from cases of lymph node metastasis with that of FISH in some cases of primary breast cancer that had been carried out in the course of clinical practice. The results of FISH and DISH in the determination of HER2 have reportedly shown some discordance, with DISH potentially underestimating or FISH potentially overestimating the HER2/chromosome 17 ratio [29]. Second, we estimated the HER2 expression according to the 2007 ASCO/CAP guidelines and not the 2013 guidelines, as all of the cases underwent surgery by 2010. Third, because we evaluated patients that underwent operation for a relatively long time (around 10 years), we were unable to determine details with regard to their background of adjuvant systemic therapy in all cases, which may have influenced the RFS.

In this study, we failed to determine the significance of the discordance of biomarkers or each biomarker itself in axillary lymph node metastasis on the clinical courses, including the sensitivity to medications or the prognosis. Clarifying these issues will require conducting studies with larger numbers of subjects and detailed records of adjuvant systemic therapy and prognosis. Future studies should explore how to select adjuvant/neoadjuvant therapies, including targeted and cytotoxic agents, according to the biomarkers in primary breast cancer and/or axillary lymph node metastasis.

## Conflict of interests

The authors declare no conflict of interests.

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