

Prognostic Evaluation of HER2-positive Early Breast Cancers Using Clinico-pathological Criteria

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Abstract. *Background/Aim:* HER2-positive breast carcinomas (BCs) generally behave more aggressively and show higher cytological and histological grade than HER2-negative BCs. However, the clinical properties of HER2-positive early BCs have not been studied extensively. Hence, the therapeutic significance of neoadjuvant chemotherapy (NAC) for this BC remains debatable. *Patients and Methods:* We retrospectively examined the clinicopathological features of 94 HER2-positive early BCs who perioperatively received anti-HER2 drugs, without undergoing NAC prior to surgery. *Results:* The patients' five year-disease free survival (DFS) and overall survival (OS) rates were 95.6% and 100%, respectively. Univariate analysis demonstrated significant differences in distant metastasis-free survival (DMFS) between clinical and pathological tumor stages (T stages). Pathological T1 stage and clinical T1 stage tumors showed significantly higher DMFS than pT2-3 and cT2-3 ($p=0.0002$ and 0.0294). Multivariate analysis disclosed no significant differences in DFS, OS, and DMFS with respect to preoperative clinical tumor stage, patient age, type of surgery, postoperative therapy, and pathological factors. Recurrences occurred in

nine patients: four (4.3%) and five (5.3%) patients showed local and distant recurrences, respectively. One patient with cT2 BC died of disease. Interestingly, four of the five BCs with distant recurrence pathologically demonstrated lymph vessel invasion. The prognoses of patients with HER2-positive stage cT1/2N0M0 BC were highly favorable. *Conclusion:* The indications for NAC in small, localized, and node-negative HER2-positive BC should be carefully assessed based on the presence of a larger tumor size, postoperative pathological evaluation of tumor size, and lymph vessel invasion.

Human epidermal growth factor receptor-2 (HER2) is present at low levels in the cell membrane of normal luminal epithelium. Its encoding gene, *HER2*, is amplified in 10-20% of invasive ductal carcinomas (IDCs), resulting in over-expression of HER2 protein (1, 2). These tumors are designated as HER2-positive breast carcinomas (BCs) and present an aggressive subtype of IDC, since HER2 over-expression can facilitate cancer cell proliferation, mobility, and angiogenesis (2). HER2-positive BCs generally have a high propensity for lymph node metastasis, even when diagnosed at an early stage (3, 4). Improving its therapeutic options to reduce the recurrence risk remains an unsolved issue and is an active area of interest. Therefore, studying the prognostic indicators of HER2-positive BC would be worthwhile.

HER2-positive BCs usually show high-grade histology and an aggressive phenotype, compared to negative BCs. Therefore, appropriate therapeutic strategies for these types of tumors are of great interest to clinicians and have been intensively discussed. It is well-known that neoadjuvant chemotherapy (NAC) improves the prognoses of patients with HER2-positive BC. According to National Comprehensive Cancer Network (NCCN) guidelines, NAC is recommended for HER2-positive stage cT2 or cN1 BCs and for more advanced cancers. Although several clinical trials have targeted for HER2-positive BCs (5-7), the number of patients with small, localized, and node-negative HER2-positive BCs were limited in these trials. These trials

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Key Words: HER2-negative early breast cancer, neoadjuvant chemotherapy, distant metastasis-free survival, tumor size, lymph vessel invasion.

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achieved a high pathologic complete response (pCR) ratio with high tolerability and a manageable safety profile with treatment of anthracycline. As previously mentioned in these reports, although the patients required concurrent treatment with anti HER2-therapy and chemotherapy using multi-drugs for advanced HER2-positive BC, the clinical outcomes of patients with early stage HER2-positive BC were reportedly quite favorable (8-10). Taking the adverse effects of neoadjuvant treatments and the favorable clinical outcomes even without such treatment into account, NAC might be an overtreatment for these BCs. Therefore, standardization of neoadjuvant therapy for HE2-positive early BC should be strictly established. It is important to avoid escalating treatment for HER2-positive BC. However, the risk factors and optimal therapeutic strategy for this cancer still remain to be clarified, especially in early HER2-positive BCs. Therefore, we retrospectively studied the clinico-pathological risk factors of early BCs staged as cT1/2N0M0 in order to clarify a therapeutic significance of NAC for patients who received only anti HER2-treatment without NAC.

Patients and Methods

Patients. We reviewed the clinical data base of Tokyo Medical Women’s University Yachiyo Medical Center (TYMC), and extracted 128 patients who underwent surgery for BC from January 2007 to December 2018. All patients preoperatively presented HER2-positive BC, which had size no more than 5 cm (cT1/2), and showed neither lymph node metastasis (cN0) nor distant metastasis (cM0). We excluded 15 patients who preoperatively received NAC and 29 patients who were not treated with anti-HER2 drugs in the perioperative period, and finally selected a total of 94 patients with HER2-positive BC stage cT1/2N0M0.

All data were collected in accordance with the protocol that was approved by the local ethics committees at Tokyo Women’s Medical University (Shinjuku, Tokyo, Japan; no. 2022-0002). This study adhered to the tenets of the Declaration of Helsinki. Patient data was anonymized at the time of analysis. General informed consent for research purposes was obtained from all patients prior to surgery.

Pathological evaluation. Surgically excised breast tissue was routinely processed for pathological examination and immunohistochemistry (IHC) for hormone receptors, HER2, and Ki-67 and fluorescence in situ hybridization (FISH) for *HER2*. Each pathological diagnosis was made based upon the *World Health Organization Classification of Tumours, Breast Tumours*, 5th edition (1). All samples were evaluated independently by two experienced pathologists (TN and KH). Nuclear grade was scored as previously reported (11).

Estrogen receptor (ER) and/or progesterone receptor (PgR) status was evaluated using IHC. BCs with more than 10% ER and/or PgR-positive neoplastic cells were considered positive. HER2 positivity or negativity was tested in combination with IHC and FISH according to ASCO/CAP HER2-guidelines (12). First, the HER2 protein was immunohistochemically evaluated as either negative (score 0 or 1+), positive (score 3), or equivocal (score 2+). Then, *HER2* gene amplification was determined in the group with equivocal IHC scores of 2+ group using FISH.

Table I. *Clinical characteristics of 94 patients with cT1/2N0M0 stage HER2-positive breast carcinoma.*

Characteristic	N (%)
Clinical T stage	
T1a	0 (0%)
T1b	8 (8.5%)
T1c	42 (44.7%)
T2	44 (46.8%)
Surgery	
Partial mastectomy	47 (50%)
Total mastectomy	47 (50%)
Lymph node biopsy	
SLNB	74 (78.7%)
SLNB→Ax	20 (21.3%)
Chemotherapy	
None	13 (13.8%)
Anthracycline	50 (61.7%)
Paclitaxel	5 (6.2%)
Anthracycline plus paclitaxel	24 (29.6%)
Others	2 (2.5%)
Hormone therapy	
Done	88 (93.4%)
Not done	6 (6.4%)
Anti-HER2 therapy	
None	0 (0%)
Trastuzumab	91 (96.8%)
Trastuzumab plus pertuzumab	3 (3.2%)

Statistical analysis. Disease-free survival (DFS), overall survival (OS) and distant metastasis-free survival (DMFS) were defined as the time from surgery to the first local or distant relapse, death from any reason and distant metastasis, respectively. Kaplan-Meier survival curves were plotted to calculate the DMFS rate. Then, comparisons of survival difference between different subgroups were performed using the log-rank test. Statistical significance was set at a two-tailed *p*-value of <0.05. Multivariate Cox proportional hazards regression models were created to estimate the hazard ration (HR) and 95% confidence intervals (CIs) of the following parameters: clinical and pathological T stage, lymph node metastasis, hormone receptor status, nuclear grade, and Ki-67 labeling index. Statistical analysis was performed using the commercially available software JMP pro14 (SAS Institute Inc., Cary, NC, USA).

Results

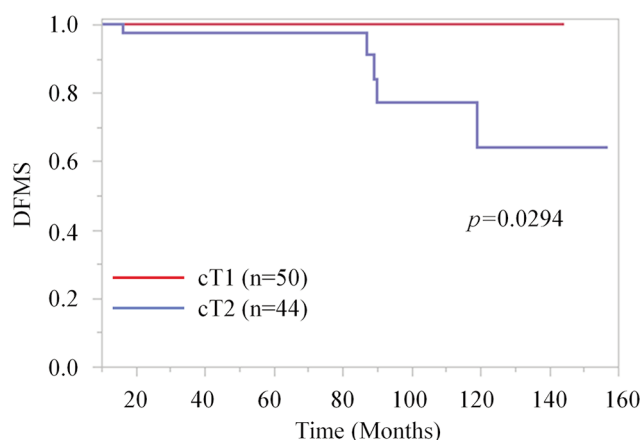
Clinical characteristics of the 94 patients with cT1/2N0M0-stage and HER2-positive BC are summarized in Table I. Mean age at diagnosis was 58 years-old. Regarding clinical stage, no patients were diagnosed as cT1a. Eight (8.5%), 42 (44.7%), and 44 (46.8%) cases were categorized as cT1b, cT1c, and cT2, respectively. Partial and total mastectomies were performed in 47 (50%) each. Sentinel lymph biopsy was performed in 74 (78.7%) cases, and sentinel plus

Table II. Pathological characteristics of 94 patients with cT1/2N0M0 stage HER2-positive breast carcinoma.

Characteristic	N (%)
Histology	
Invasive ductal carcinoma, no special type	85 (90.4%)
Invasive lobular carcinoma	3 (3.2%)
Others	6 (6.4%)
pT stage	
T1a	1 (1.0%)
T1b	14 (14.9%)
T1c	45 (47.9%)
T2	31 (33.0%)
T3	3 (3.2%)
pN stage	
N0	71 (75.5%)
N1mi	3 (3.2%)
N1	16 (17.0%)
N2	3 (3.2%)
N3	1 (1.1%)
Hormonal receptor	
Positive	55 (58.5%)
Negative	39 (41.5%)
Nuclear grade (NG)	
1	25 (23.4%)
2	33 (35.1%)
3	35 (37.2%)
NA	1 (1.1%)
Ki-67 labeling index	
Less than 10%	22 (23.4%)
10-30%	28 (29.8%)
More than 30%	23 (24.5%)
NA	21 (22.3%)

axillary lymph node biopsy was performed in 20 (21.3%) cases. A total 81 of 94 (86.2%) patients received postoperative chemotherapy: Anthracycline was administered to 50 patients (61.7%), paclitaxel to five (6.2%) patients, anthracycline plus paclitaxel to 24 (29.6%) patients, and other drugs to two (2.5%). Hormone therapy was administered to 94.6% of patients. Regarding anti-HER2 drugs, 61 (96.8%) patients were treated with trastuzumab and three (3.2%) with trastuzumab plus pertuzumab.

The pathological features of the valuated surgically excised specimens are summarized in Table II. Eighty-five (90.4%), three (3.2%), and six (6.4%) BCs were diagnosed as invasive ductal carcinoma of no special type, invasive lobular carcinoma, and others, respectively. With regard with pathological T stage, 60 of 94 (63.8%) BCs were pT1. Among them, one case (1.1%) was pT1a, 14 (14.9%) were pT1b, and 45 (47.9%) were pT1c. Thirty-one (33.0%) and three (3.2%) BCs were pT2 and pT3 stage. No lymph node metastasis was detected in 71 BCs (75.5%). Three (3.2%), 16 (17.0%), three (3.2%), and one (1.1%) BC were diagnosed as pN1mi, pN1, pN2, and pN3, respectively.

Figure 1. Kaplan-Meier estimate of distant metastasis-free survival (DMSF) according to clinical T (cT) stage. Patients with cT1 stage BC demonstrated significantly higher DMSF than cT2 ($p=0.0002$).

Hormone receptors were positive in 55 (58.5%) and negative in 39 (41.5%) cases. Twenty-five (23.4%), 33 (35.1%), and 35 (37.2%) BCs showed nuclear grades of 1, 2, and 3, respectively. Nuclear grade (NG) data was not available for one BC. Regarding Ki-67 labeling index, 22 (23.4%), 28 (29.8%), and 23 (24.5%) BCs had indexes of less than 10%, 10-30%, and more than 30%, respectively. Data on the index was not available in 21 BCs (22.3%).

Statistically, multivariate analysis failed to show a significant difference in DFS, OS and DMFS between subgroups for the following parameters: clinical and pathological stages, patients age, type of surgery, postoperative therapeutic status, and pathological factors. Univariate analysis disclosed significant correlations between DMFS and only two parameters: pathological and clinical tumor (pT and cT) stages. Patients with pT1 stage BC demonstrated significantly longer DMFS than those with pT2 or 3 stage BC ($p=0.0002$) (Figure 1). cT1-stage BCs had a significantly more favorable DMFS than cT2 or 3-stage BCs ($p=0.0294$) (Figure 2).

Recurrent and death events are summarized in Table III. The follow-up interval ranged from 19 to 157 months, with a median follow-up period of 65 months. One patient with cT2 stage BC died of the disease, indicating a five-year DFS of 95.6%. The five-year OS was 100%. BCs recurred in nine of 94 cases (9.6%), among which ipsilateral or contralateral local recurrence was detected in four cases (4.3%), and distant recurrence occurred in five cases (5.3%). Interestingly, all five BCs with distant recurrence were preoperatively clinical T2 stage, while the four BCs with local recurrence were clinically stage T1. Univariate analysis revealed that the prevalence rate of distant metastasis was significantly higher in the clinically T2 group than the clinically T1 group ($p=0.0198$) (Figure 3).

Table III. Patients with cT1/2N0M0 stage HER2-positive breast carcinoma resulting in recurrence or death.

Clinical T stage		cT1 (n=50)	cT2 (n=44)	Total (n=94)
Recurrence (total)		4 (4.3%)	5 (5.3%)	9 (9.6%)
Local	Ipsilateral	3 (3.2%)	0	3 (3.2%)
	Contralateral	1 (1.1%)	0	1 (1.1%)
Distant		0	5 (5.3%)	5 (5.3%)
Death		0	1 (1.1%)	1 (1.1%)

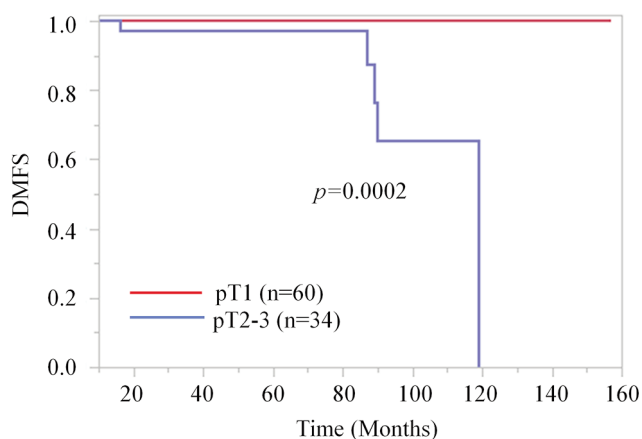


Figure 2. Kaplan-Meier estimate of distant metastasis-free survival (DMSF) according to pathological T (pT) stage. Patients with pT1 stage BC had significantly higher DMSF rates than those with pT2-3 stage BC ($p=0.0294$).

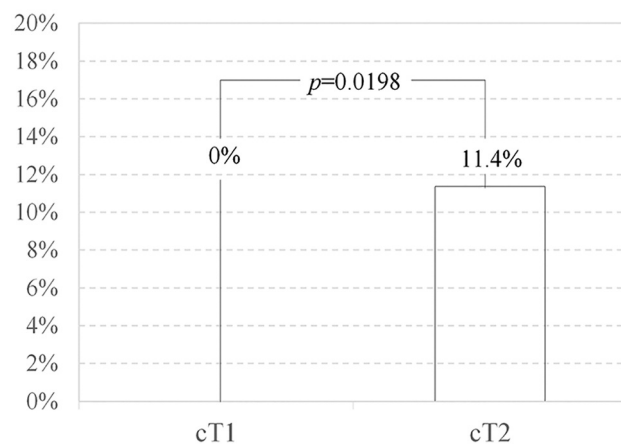


Figure 3. Frequency of distant recurrence in cT1 and cT2 stage BC. Distant recurrence occurred in 11.4% of cT2 stage BCs, and 0% of cT1 stage BCs. The prevalence of distant recurrence in cT2 stage BC was significantly higher than that in cT1 stage BC ($p=0.0198$).

Intriguingly, lymph vessel invasion was observed in four of the five BCs (80%) showing distant recurrence (Table IV). All five of these BCs were pathologically T2 stage and lacked blood vessel invasion. Their other pathological parameters were variable. The patients were aged from 44 to 77 years: hormone receptors were positive in three of the BCs and negative in two. Two and three BCs harbored a nuclear grade of 1 and 3. Their follow-up interval ranged from 16 to 119 months.

Discussion

The therapeutic strategy for HER2-positive BC remains a matter of debate for clinicians. Currently, response-guided therapy after neoadjuvant therapy (NAC) is recommended for cytoreduction of residual HER2-positive BC. The KATHERINE trial revealed that administration of trastuzumab emtansine prolonged invasive disease-free survival (iDFS) in 50% of patients who failed to obtain pCR after NAC (13). According to National Comprehensive Cancer Network (NCCN) guidelines, NAC is endorsed for HER2-positive BCs of stage T2 or N1 and higher. In this study, we examined

clinicopathological features of small, localized, node-negative BCs of patients who received anti-HER2 drug without NAC. As a consequence, the patients' prognoses were quite favorable, since 95.6% of the patients achieved 5-year DFS. In addition, the 5-year OS rate was 100% in the cohort of 94 cases. BCs recurred in nine cases (9.6%), among which five BCs showed distant recurrence. DMSFs were significantly more favorable in pT1 and cT1 stage BCs than pT2/3 and cT2/3 stage BCs, although there was no significant difference in DFS and OS between these groups.

Several clinical trials have been performed for patients with HER2-positive BC, to verify the significance of NAC (5-7). However, only few studies have assessed the efficacy of NAC specifically focusing on small, localized, node-negative HER2-positive BC. The APT trial was the first trial designed to assess adjuvant paclitaxel and trastuzumab treatment for small, node-negative and HER2-positive BCs (8). Eligible patients in the trial closely overlapped with those in this study, since we assessed BCs measuring 3 cm or less in the greatest dimension. According to long-term follow-up of that trial, the 5-year DFS was 95.6%, indicating

Table IV. Clinicopathological characteristics of 5 patients with cT1/2N0M0 stage HER2-positive breast carcinoma showing distant recurrence.

Case. no	Age	Hormone	cT2 receptor	pT2	pN	Nuclear grade	Ki-67	Lymph vessel invasion	Vascular invasion	Follow up (months)
1	44	Positive	2	2	1	3	NA	Present	Absent	89
2	55	Positive	2	2	1	3	22	Present	Absent	119
3	56	Positive	2	2	0	1	10	Present	Absent	90
4	73	Negative	2	2	0	1	3	Present	Absent	87
5	74	Negative	2	2	0	3	40	Absent	Absent	16

a favorable clinical outcome (9). Recurrence and cancer-related death scarcely occurred in the APT trial during long-term follow-up observation (10). Our results confirmed that the prognoses of patients with localized, node-negative, and HER2-positive BC is quite favorable. Currently, anti-HER2 drugs along with standard chemotherapy (anthracycline and/or taxane) is the recommended regimen for HER2-positive BCs. Therefore, dual anti-HER2 therapy and multi-drug chemotherapy might represent an unnecessary escalation in treatment for certain populations with small and localized HER2-positive BC.

In general, HER2-positive BCs are aggressive with a worse prognosis compared to HER2-negative BCs. The pathological background that potentially contributes to this unfavorable behavior can be explained by an increase in angiogenesis (14) and lymphangiogenesis (15, 16). In our study, all five BCs with distant recurrence were preoperatively categorized as clinical T2 stage. Interestingly, pathological examination of the excised specimens revealed that four of the five (4/5) BCs had lymphatic vessel invasion (LVI). Therefore, the presence of LVI might be a prognostic indicator in small, localized, node-negative and HER2-positive BC. LVI has been previously shown to be an independent prognostic indicator of local and distant recurrence in node-negative invasive BCs (17). Mohammed *et al.* confirmed the evidence from a large case series with long-term follow-up (4). They also verified that LVI was significantly associated with distant metastasis (4). In addition, HER2 positivity and high Ki-67 labeling index are, reportedly, significant predictors of LVI in invasive BCs (18). Hence, pathologists should carefully observe several whole sections of surgical specimens of BC in order to detect LVI, since the density of lymph vessels is reportedly higher in HER2-positive BCs than other subtypes of BCs (19).

A previous meta-analysis disclosed that the status of pCR is beneficial in determining the long-term prognosis of patients with invasive BC (20). Variable clinical trials have been performed with the aim to achieve pCR in HER2-positive BC. The NeoSphere study was designed to assess the effect of addition of pertuzumab to docetaxel and trastuzumab, resulting in a significantly improved frequency

of pCR (19). The regimen in the TRYPHAENA study contained pertuzumab and trastuzumab along with standard chemotherapy (5). The trial results showed successful attainment of a high percentage of pCR with high tolerability and cardiac safety. Cardiac safety was also verified in the neoadjuvant period of the BERENICE trial, although the regimen included anthracycline (7). However, the above-mentioned trials targeted patients with BC that were clinically staged as T1 or higher. Only 12% of clinical T1 and 32% of clinical N0 patients were studied in the KATHERINE trial (13). Hence, the number of patients with small-sized, localized, node-negative and HER2-positive BCs was limited in these trials. The number of patients examined in the current study was also insufficient, since the study was performed at a single institute. Hence, further multi-institutional studies focusing on such BCs are necessary to clarify the therapeutic efficacy of NAC on HER2-positive BC at an early clinical stage.

It is widely known that HER2 positivity is a risk factor for local recurrence of BC (21). In addition, intraductal spread of HER2-positive BCs tends to be extensive with high-grade histology compared with stage-matched HER2-negative BCs (3). Additionally, the multifocality of invasive lesions has been frequently observed in this type of BC (1, 2). These evidences might explain the high propensity for local recurrence in HER2-positive BCs. In this study, four of 94 BCs (4.3%) showed local recurrence, although the tumor size was preoperatively less than 2 centimeters (cT1) in all cases. The results of the present study, therefore, confirm those of previous reports. This suggests that complete excision with an adequate margin is absolutely imperative when performing BC excision, even if the HER2-positive BC is small in size and localized, without lymph node metastasis.

To summarize, there is increasing interest in clinical trials for HER2-positive BCs due to their aggressiveness (1-4). However, most trials targeted advanced stage BCs. Hence, the clinical and biological properties of early HER2-positive BCs still need to be fully elucidated. Our results suggested that this type of BC shows infrequent recurrence and cancer-related death, indicating that the clinical outcomes of these patients are quite favorable. The present study might also

imply that clinical larger tumor size (cT2), pathological tumor size (pT2/3), and lymph vessel invasion contribute to distant recurrence. Taken together, NAC might be necessary only for some patients with HER2-positive BC of stage cT1/2N0M0. Therefore, cT1N0 BC without pathological lymph vessel invasion should primarily undergo surgery before considering NAC. Future study focusing on small and localized HER2-positive BCs are required to develop optimal therapeutic personalized strategies and to avoid de-escalating and escalating treatment.

Conflict of Interest

All Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

NJ: study design and conceive, writing, review and editing; TN: study design and conceive, writing, pathological diagnosis, review and editing; MN: clinical data acquisition, review and editing; KY, AH, and FG: pathological diagnosis and data analyses; KH: pathological diagnosis, review and editing, supervision.

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