Title: Survival of HER2-positive primary breast cancer patients treated by neoadjuvant chemotherapy plus trastuzumab: a multicenter retrospective observational study (JBCRG-C03 study)

Author list:

Affiliations:
1. Department of Breast Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan
2. Outpatient Oncology Unit, Kyoto University Hospital, Kyoto, Japan
3. Department of Breast Oncology, Saitama Cancer Center, Saitama, Japan
4. Department of Breast Surgery, Hiroshima City Hospital, Hiroshima, Japan
5. Department of Breast and Endocrine Surgery, Toranomon Hospital, Tokyo, Japan
6. Department of Breast Oncology, Gunma Prefectural Cancer Center, Ota, Japan
7. Department of Breast Oncology, Jichi Medical University Hospital, Shimotsuke, Japan
8. Breast and Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan

9. Department of Breast Surgery, Hyogo Cancer Center, Akashi, Japan

10. Department of Breast Oncology, Niigata Cancer Center Hospital, Niigata, Japan

11. Department of Surgery, Kitasato University School of Medicine, Sagamihara, Japan

12. Breast Surgical Oncology, Social Medical Corporation Hakuaikai, Sagara Hospital, Kagoshima, Japan

13. Department of Breast Oncology, Aichi Cancer Center, Nagoya, Japan

14. Clinical Cancer Center, National Kyushu Cancer Center, Fukuoka, Japan

15. Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Centre, Komagome Hospital, Tokyo, Japan

16. Department of Surgery, Breast Oncology, Osaka National Hospital, Osaka, Japan

17. Department of Breast Surgery, National Hospital Organization Kure Medical Center, Kure, Japan

18. Institute for Advanced Biosciences, Keio University, Tsuruoka, Japan

19. Department of Health Care Policy and Health Economics, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

20. Department of Environment and Information Studies, Keio University, Fujisawa, Japan

21. Systems Biology Program, Graduate School of Media and Governance, Keio University,
Fujisawa, Japan

22. Department of Pathology, Tohoku University Hospital and School of Medicine, Sendai, Japan

23. Faculty of Health Care, Tenri Health Care University, Tenri, Japan

24. Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan

Correspondence to: Professor M. Toi, Department of Breast Surgery, Graduate School of Medicine, Kyoto University, 54 Kawaracho, Shogoin, Sakyō-ku, Kyoto, 606-8507, Japan. Tel: +81-75-751-3660; Fax: +81-75-751-3616; E-mail: toi@kuhp.kyoto-u.ac.jp

Word count: 2381 words (excluding title page, abstract, references, tables, figures and figure legends)

Number of tables: 3

Number of figures: 3

Supplementary material: 1 table
ABSTRACT

Purpose: We investigated the disease-free survival (DFS) of HER2-positive primary breast cancer patients treated with neoadjuvant chemotherapy plus trastuzumab, as well as predictive factors for DFS and pathologic response.

Patients and methods: Data from 829 female patients treated between 2001 and 2010 were collected from 38 institutions in Japan. Predictive factors were evaluated using multivariate analyses.

Results: The 3-year DFS rate was 87% (95% confidence interval [CI] 85-90). The pathologic complete response (pCR: ypT0/is + ypN0) rate was 51%. The pCR rate was higher in the ER/PgR-negative patients than in the ER/PgR-positive patients (64% vs 36%, \( P < 0.001 \)). Patients with pCR showed a higher DFS rate than patients without pCR (93% vs 82%, \( P < 0.001 \)). Multivariate analysis revealed 3 independent predictors for poorer DFS: advanced nodal stage (hazard ratio [HR] 2.63, 95%CI 1.36-5.21, \( P = 0.004 \) for cN2-3 vs cN0), histological/nuclear grade 3 (HR 1.81, 95%CI 1.15-2.91, \( P = 0.011 \)), and non-pCR (HR 1.98, 95%CI 1.22-3.24, \( P = 0.005 \)). In the ER/PgR-negative dataset, non-pCR (HR 2.63, 95%CI 1.43-4.90, \( P = 0.002 \)) and clinical tumor stage (HR 2.20, 95%CI 1.16-4.20, \( P = 0.017 \) for cT3-4 vs cT1-2) were independent predictors for DFS, and in the ER/PgR-positive dataset, histological
grade of 3 (HR 3.09, 95%CI 1.48-6.62, \( P = 0.003 \)), clinical nodal stage (HR 4.26, 95%CI 1.53-13.14, \( P = 0.005 \) for cN2-3 vs cN0), and young age (HR 2.40, 95%CI 1.12-4.94, \( P = 0.026 \) for \( \leq 40 \) vs >40) were negative predictors for DFS. Strict pCR (ypT0 + ypN0) was an independent predictor for DFS in both the ER/PgR-negative and -positive datasets (HR 2.66, 95%CI 1.31-5.97, \( P = 0.006 \) and HR 3.86, 95%CI 1.13-24.21, \( P = 0.029 \), respectively).

**Conclusions:** These results may help assure a more accurate prognosis and personalized treatment for HER2-positive breast cancer patients.

**Key words:** Breast cancer, HER2, neoadjuvant chemotherapy, pathologic complete response, prognostic factors, trastuzumab
INTRODUCTION

Amplification or overexpression of human epidermal growth factor receptor-2 (HER2) is associated with a high risk of breast cancer recurrence and metastasis [1]. Adjuvant use of cytotoxic chemotherapy and trastuzumab, a recombinant humanized monoclonal antibody that targets HER2, improves the overall survival (OS) and disease-free survival (DFS) of patients with HER2-positive primary breast cancer [2,3].

Neoadjuvant chemotherapy (NAC) reduces tumor size, which improves the rate of breast-conserving surgery, and provides information about chemosensitivity that helps with the design of postoperative therapy. Several meta-analyses have revealed that patients with a pathologic complete response (pCR) after NAC had higher survival rates than those without pCR, indicating that pCR represents a surrogate prognostic indicator [4-6].

Adding trastuzumab to NAC doubles the rate of pCR in patients with HER2-positive primary breast cancer [7-9]. The NOAH trial showed better 3-year event-free survival for chemotherapy plus trastuzumab versus chemotherapy alone [8]. In the TECHNO trial, patients with pCR after NAC plus trastuzumab showed better 3-year DFS than patients without pCR [10]; however, predictors for pCR and survival after treatment are unknown.

This multicenter retrospective study investigated the survival after NAC with trastuzumab
among patients with HER2-positive primary breast cancer in efforts to identify predictive factors.

PATIENTS AND METHODS

Patients

In this multicenter retrospective cohort study, the inclusion criteria were female sex, histologically confirmed HER2-positive invasive breast cancer diagnosed between 2001 and 2010, no distant metastasis, age 20-70 years, and received NAC containing trastuzumab. Eligible patients were identified from the institutional databases. Data were managed by the data center of the Japan Breast Cancer Research Group (JBCRG).

The study protocol was approved by the Institutional Review Board at Kyoto University Hospital and participating institutions. All patient data were anonymized and allocated numbers according to Japanese ethics guidelines for epidemiologic research.

Pathological assessment

Pathology specialists at each institution performed the pathological investigation.
HER2-positive status was defined as 3+ overexpression by immunohistochemical testing or HER2 amplification by fluorescent in situ hybridization (HER2/CEP17 ratio ≥ 2.0). At each institution, surgical specimens obtained following NAC were serially sectioned, stained with haematoxylin and eosin (H&E), and diagnosed by experienced pathologists. pCR was defined as the absence of residual invasive cancer cells in the breast and axillary lymph nodes (ypT0/is + ypN0). Strict pCR (spCR), another pCR definition, was defined as no invasive and non-invasive residuals in the breast and axillary nodes (ypT0 + ypN0).

**Statistical analysis**

All survival outcomes were measured from the date of starting NAC to the date of first event.

The primary survival outcome was DFS defined as time to occurrence of recurrence, secondary malignancy (including contralateral breast cancer, hematological malignancy, and sarcoma), or death as a result of any cause. Secondary survival outcomes were OS defined as time to death as a result of any cause, distant recurrence-free survival (DRFS) defined as time to any recurrence except for ipsilateral breast or regional lymph node, and death as a result of any cause.

The Kaplan-Meier method was used to estimate survival outcomes. $\chi^2$ tests for categorical data and log-rank tests for time-to-event endpoints provided two-sided p values, and p values < 0.05 were considered statistically significant. Cox proportional hazards regression analysis was
used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Logistic regression was used to estimate odds ratios (ORs) and 95% CIs. Covariates used in the multivariate model were age, body mass index, clinical tumor stage, clinical nodal stage, estrogen receptor (ER)/progesterone receptor (PgR) status, histological/nuclear grade, pCR/spCR, surgery type, radiation therapy, adjuvant hormonal therapy, adjuvant chemotherapy, and adjuvant trastuzumab. Menopausal status was not included in the model because of collinearity with age. Patients with missing data were excluded from the multivariate analysis (e.g. patients whose adequate pathologic responses were not confirmed due to insufficient local therapy or lack of information regarding local therapy type). All statistical analyses were performed using JMP® (ver. 10.0.2, SAS Institute Inc. Cary, NC). All analyses were supervised by a statistician (SM).

RESULTS

Patient characteristics

Data of 829 patients from 38 institutions in Japan were collected. Among them, 53 did not meet the inclusion criteria and were excluded, leaving a total of 776 patients for analysis (whole dataset). HER2-positive tumors could be subdivided into ER/PgR positive and negative, and we
therefore divided the patients into an ER/PgR-positive dataset (N = 334) and ER/PgR-negative
dataset (N = 439) and also performed the analyses for each dataset (Figure 1).

Baseline characteristics and treatment of the whole dataset are summarized in Table 1. Median age was 53 (range 25-70) years. Most patients had tumor stage T2 (61%) and were clinically node positive (67%). ER and PgR were negative in 57% of the patients. Most patients received anthracycline- and taxane-containing chemotherapy (87%), and trastuzumab was administered concurrently with taxane (80%). Breast-conserving surgery was performed in 64% of the patients, most of whom (91%) received radiation therapy. Radiation therapy was performed in 35% of the patients who received mastectomy. Adjuvant hormonal therapy was performed in 86% of the ER/PgR-positive patients. Most patients received adjuvant trastuzumab (90%).

Clinical outcomes

The median follow-up period was 42 (interquartile range 30-58) months. For the whole dataset, the 3-year DFS rate was 87% (95%CI 85-90) (Figure 2A). Three-year OS and DRFS were 97% (95%CI 96-98) and 91% (95%CI 89-93), respectively. pCR was achieved in 399 (51%) patients and spCR in 240 (31%) patients.

The 3-year DFS rate was almost the same among patients in the ER/PgR-positive and
-negative datasets (87% vs 88%, \( P = 0.888 \)) (Figure 2B). The pCR and spCR rates were higher in the ER/PgR-negative patients than in the ER/PgR-positive patients (64% vs 36% for pCR, \( P < 0.001 \); 38% vs 23% for spCR, \( P < 0.001 \), respectively).

**Prognostic factors for survival outcomes**

The results of Cox proportional hazard regression performed to evaluate the prognostic effect of baseline characteristics and pathologic tumor response to NAC with trastuzumab are shown in Table 2. In the whole dataset, independent predictors for poorer DFS were advanced clinical nodal stage (adjusted HR 2.63, 95%CI 1.36-5.21, \( P = 0.004 \) for cN2-3 vs cN0; adjusted HR 1.64, 95%CI 0.91-3.09, \( P = 0.100 \) for cN1 vs cN0), histological/nuclear grade 3 (adjusted HR 1.81, 95%CI 1.15-2.91, \( P = 0.011 \)), and failure to achieve pCR (adjusted HR 1.98, 95%CI 1.22-3.24, \( P = 0.005 \)). Neither age nor ER/PgR status was an independent predictor for DFS. Multivariate analysis including spCR yielded the same results. The DFS rate was higher among patients with pCR than those without pCR (93% vs 82%, \( P < 0.001 \)) (Figure 3A). Patients who achieved spCR had a higher DFS rate than those who did not (96% vs 84%, \( P < 0.001 \)) (Figure 3B).

In the ER/PgR-positive dataset, independent predictors for poorer DFS were advanced clinical nodal stage, histological/nuclear grade 3, young age (\( \leq 40 \)), and not achieving spCR. pCR was not an independent predictor for DFS on multivariate analysis (Table 2; Figure 3C, D).
For the ER/PgR-negative dataset, clinical tumor stage and both pCR and spCR were independent predictors for DFS (Table 2; Figure 3E, F).

Predictors for other survival outcomes are listed in Supplementary Table S1. Predictors for OS were clinical nodal stage, histological/nuclear grade, and spCR, but pCR was not an independent predictor. Predictors for DRFS were clinical nodal stage, histological/nuclear grade, young age, pCR, and spCR.

**Predictive factors for pCR**

The association of baseline characteristics with pCR/spCR following NAC plus trastuzumab was evaluated by multivariate logistic regression (Table 3). In the whole dataset, independent predictors for pCR were negative ER/PgR status (adjusted OR 3.42, 95% CI 2.42-4.86, $P < 0.001$) and clinical tumor stage T1-2 compared with T3-4 (adjusted OR 1.88, 95% CI 1.27-2.79, $P = 0.002$). Histological/nuclear grade 3 showed a statistically marginal association with pCR (adjusted OR 1.39, 95% CI 0.99-1.95, $P = 0.060$). The same factors were selected as independent predictors in the multivariate model for spCR.

In the ER/PgR-positive dataset, clinical tumor stage was a predictor for pCR and spCR. In the ER/PgR-negative dataset, clinical tumor stage was an independent predictor for both pCR and spCR. Histological/nuclear grade was marginally predictive of pCR and spCR.
DISCUSSION

In this analysis, we assessed survival after NAC plus trastuzumab among patients with HER2-positive breast cancer. Although clinical nodal status, histological/nuclear grade, and pCR/spCR were independent predictors for DFS, the prognostic impact differed depending on ER/PgR status. pCR was a predictor for DFS particularly in patients with ER/PgR-negative tumor, and spCR—a stricter definition of pCR—was an independent prognostic factor regardless of ER/PgR status.

Our data included more patients with clinical tumor stage T2 or higher (89%) and clinically node positive (67%). In this population, a three-year DFS rate of 87% was relatively good; however, a considerable number of patients experienced disease relapse during the follow-up period. Risk factors associated with disease relapse need to be clarified to conduct a clinical trial aimed at improving these patients’ prognosis.

In two phase III trials in which patients with HER2-positive disease were randomly allocated to NAC with trastuzumab or NAC only, the addition of trastuzumab to NAC resulted in a higher pCR rate and improved DFS [11,8]. The pCR rate in our study (51%) is comparable to those reported in previous trials of NAC with trastuzumab (30-67%) [7,8,12,10,13-15,9]. In our study,
ER/PgR status was the strongest predictor for pCR or spCR. Our results were consistent with those of two meta-analyses in which the pCR rate of NAC with trastuzumab was about 50% for patients with ER/PgR-negative disease and 30% for those with ER/PgR-positive disease [16,6].

In the TECHNO trial, a phase II trial of 217 patients with HER2-positive disease who received NAC with trastuzumab, failure to achieve pCR was a significant predictor for DFS in the multivariate analysis [10]. Kim et al. retrospectively investigated the prognostic value of pCR using data from 229 patients with HER2-positive tumor who were treated with NAC with trastuzumab [12]. They reported that pCR, clinical tumor stage, and lymphovascular invasion were independent predictors for DFS. In our study, pCR and spCR were predictors for DFS; in addition, conventional prognostic factors such as nodal stage and histological/nuclear grade were predictors for DFS.

In this study, the association of age with DFS was not statistically significant in the whole dataset, consistent with the results of the TECHNO trial and Kim et al. Partridge et al. reported that young age was not associated with worse DFS in patients with HER2-positive disease using large cohort data from the HERA trial [17]. When we divided the patients into ER/PgR-positive and -negative groups, multivariate analysis showed that young age (age ≤ 40) was an independent predictor for poorer DFS in the ER/PgR-positive dataset. Our result was consistent with earlier studies showing that younger age is an independent predictor for worse DFS,
especially in patients with ER/PgR-positive disease [18,19].

After dividing the patients into ER/PgR-positive and -negative datasets, we performed multivariate analysis for DFS using each dataset. About 30-40% of HER2-enriched subtype tumors are reported to be ER positive [20,21]. Among clinically HER2-positive tumors, up to 60% are classified as the HER2-enriched subtype, with the rest classified as luminal B, luminal A, or basal-like [22]. Adjuvant systemic therapy differs according to ER/PgR status [23]. Therefore, it seemed reasonable to perform the analysis based on ER/PgR status; however, the results should be interpreted carefully because of the relatively small event rate in each dataset.

In relation to the two aforementioned meta-analyses, pooled analysis from the German study group [6] indicated that pCR was a prognostic factor for the HER2-positive non-luminal subgroup, but not for those in the HER2-positive luminal subgroup. In the meta-analysis from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) [16], there was a stronger association of pCR with event-free survival in the HER2-positive non-luminal subgroup compared with those in the HER2-positive luminal subgroup. In our study, pCR was an independent predictor for DFS in the ER/PgR-negative dataset, but not ER/PgR-positive dataset, and spCR was an independent predictor for DFS regardless of ER/PgR status.

The limitations of this study include its retrospective design. Adjustment using multivariate analysis is mandatory to minimize selection bias. The relatively short observation period may
also limit the interpretation of our results. The median follow-up period of our study (42 months) covered the time when recurrence risk is high in HER2-positive disease [24]. A strength of our study was the large number of patients, which allowed us to conduct multivariate analysis separately according to ER/PgR status.

In conclusion, pCR/spCR, nodal status, and grade were predictors for DFS in patients with HER2-positive disease treated with NAC plus trastuzumab. Response to therapy and prognostic impact of the factors differed according to ER/PgR status. Our results may help identify patients who are not likely to achieve pCR or whose outcome would otherwise be unfavorable. New treatment approaches, such as the incorporation of novel anti-HER2 drugs, are needed for patients with high-risk disease.

**ACKNOWLEDGEMENTS**

We thank the patients who participated in this study. We also thank our colleagues who participated in this study and are not included in the list of authors, in alphabetical order: Y. Hasegawa (Hirosaki Municipal Hospital), K. Hisamatsu (Oikawa Hospital), Y. Horimoto (Juntendo University School of Medicine), Y. Kakugawa (Miyagi Cancer Center), A. Kitani (Tokyo Kyosai Hospital), Y. Kokawa (Wakayama Medical University), G. Kutomi (Sapporo
Medical University School of Medicine), Y. Moriguchi (Kyoto City Hospital), T. Morimoto (Yao Municipal Hospital), H. Nakagomi (Yamanashi Prefectural Central Hospital), K. Narui (Yokohama City University Medical Center), M. Ohara (Hiroshima Prefectural Hospital), T. Saito (Saitama Red Cross Hospital), T. Sato (Niigata Prefectural Central Hospital), H. Shigematsu (Research Institute for Radiation Biology and Medicine, Hiroshima University), K. Shingu (Iida Municipal Hospital), H. Sugiura (Nagoya City West Medical Center), M. Takahashi (Hokkaido Cancer Center), H. Takeuchi (National Hospital Organization Beppu Medical Center), K. Yamagami (Shinko Hospital), K. Yamazaki (Sapporo-Kotoni Breast Clinic), and K. Yoshida (Gifu University Hospital). We appreciate the contributions to data management of Tetsuhiro Sakai and Aya Maruyama from the JBCRG data center.

**FUNDING**

This work was supported by research grants from the Ministry of Health, Labour and Welfare of Japan (Nos. H18-3JIGAN-IPPAN-007 and H22- GANRINSHO-IPPAN-039).

**CONFLICT OF INTEREST**

H. Iwata, S. Ohno, N. Masuda, and S. Morita received honorarium from Chugai Pharmaceutical Co., Ltd. N. Masuda received honorarium from Eisai Co., Ltd. M. Toi is currently conducting
research sponsored by Chugai Pharmaceutical Co., Ltd. and received donation from Chugai Pharmaceutical Co., Ltd. All remaining authors have declared no conflicts of interest.
REFERENCES


epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen.


Table 1. Patient, disease, and treatment characteristics

<table>
<thead>
<tr>
<th>Factors</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All cases</strong></td>
<td>776</td>
<td>(100)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Min-Max)</td>
<td>53</td>
<td>(25-70)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Min-Max)</td>
<td>22.0</td>
<td>(15.0-47.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>(0.3)</td>
</tr>
<tr>
<td><strong>Menopausal status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>335</td>
<td>(43.2)</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>422</td>
<td>(54.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>19</td>
<td>(2.4)</td>
</tr>
<tr>
<td><strong>Clinical tumor size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>9</td>
<td>(1.2)</td>
</tr>
<tr>
<td>T1c</td>
<td>77</td>
<td>(9.9)</td>
</tr>
<tr>
<td>T2</td>
<td>476</td>
<td>(61.3)</td>
</tr>
<tr>
<td>T3</td>
<td>122</td>
<td>(15.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>-----</td>
<td>---</td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td>91</td>
<td>(11.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>(0.1)</td>
</tr>
</tbody>
</table>

**Clinical nodal status**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N0</strong></td>
<td>252</td>
<td>(32.5)</td>
</tr>
<tr>
<td><strong>N1</strong></td>
<td>366</td>
<td>(47.2)</td>
</tr>
<tr>
<td><strong>N2</strong></td>
<td>103</td>
<td>(13.3)</td>
</tr>
<tr>
<td><strong>N3</strong></td>
<td>54</td>
<td>(7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>(0.1)</td>
</tr>
</tbody>
</table>

**ER/PgR status**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive</strong></td>
<td>334</td>
<td>(43)</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>439</td>
<td>(56.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>(0.4)</td>
</tr>
</tbody>
</table>

**Histological/Nuclear grade**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>107</td>
<td>(13.8)</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>184</td>
<td>(23.7)</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>350</td>
<td>(45.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>135</td>
<td>(17.4)</td>
</tr>
</tbody>
</table>

**NAC regimen**
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline and taxane</td>
<td>676</td>
<td>(87.1)</td>
</tr>
<tr>
<td>Taxane only</td>
<td>78</td>
<td>(10.1)</td>
</tr>
<tr>
<td>Anthracycline only</td>
<td>7</td>
<td>(0.9)</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
<td>(1.8)</td>
</tr>
</tbody>
</table>

**Local therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy+XRT</td>
<td>96</td>
<td>(12.4)</td>
</tr>
<tr>
<td>Mastectomy alone</td>
<td>181</td>
<td>(23.3)</td>
</tr>
<tr>
<td>BCS+XRT</td>
<td>449</td>
<td>(57.9)</td>
</tr>
<tr>
<td>BCS alone</td>
<td>44</td>
<td>(5.7)</td>
</tr>
<tr>
<td>Needle biopsy+XRT</td>
<td>1</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Needle biopsy alone</td>
<td>1</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>(0.5)</td>
</tr>
</tbody>
</table>

**pCR (ypT0/is+ypN0)**

<table>
<thead>
<tr>
<th>Status</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>399</td>
<td>(51.4)</td>
</tr>
<tr>
<td>No</td>
<td>365</td>
<td>(47)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
<td>(1.5)</td>
</tr>
</tbody>
</table>

**spCR (ypT0+ypN0)**
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
<td>240</td>
<td>(30.9)</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>525</td>
<td>(67.7)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>11</td>
<td>(1.4)</td>
</tr>
</tbody>
</table>

**Adjuvant hormonal therapy**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
<td>281</td>
<td>(36.2)</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>440</td>
<td>(56.7)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>55</td>
<td>(7.1)</td>
</tr>
</tbody>
</table>

**Adjuvant trastuzumab therapy**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
<td>697</td>
<td>(89.8)</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>65</td>
<td>(8.4)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>14</td>
<td>(1.8)</td>
</tr>
</tbody>
</table>

**Adjuvant chemotherapy**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
<td>45</td>
<td>(5.8)</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>720</td>
<td>(92.8)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>11</td>
<td>(1.4)</td>
</tr>
</tbody>
</table>

BMI, body mass index; ER/PgR, estrogen receptor/progesterone receptor; NAC, neoadjuvant chemotherapy; XRT, radiation therapy; BCS, breast-conserving surgery; pCR, pathologic complete response.
Table 2. Adjusted hazard ratios of factors predicting DFS

<table>
<thead>
<tr>
<th>Factor</th>
<th>pCR (ypT0/is+ypN0)</th>
<th>spCR (ypT0+ypN0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Whole dataset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40 vs &gt;40</td>
<td>1.67</td>
<td>(0.95-2.81)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25≤ vs &lt;22</td>
<td>1.31</td>
<td>(0.74-2.24)</td>
</tr>
<tr>
<td>22≤, &lt;25 vs &lt;22</td>
<td>0.96</td>
<td>(0.56-1.61)</td>
</tr>
<tr>
<td>Clinical tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-4 vs T1-2</td>
<td>1.53</td>
<td>(0.93-2.49)</td>
</tr>
<tr>
<td>Clinical nodal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2-3 vs N0</td>
<td>2.63</td>
<td>(1.36-5.21)</td>
</tr>
<tr>
<td>N1 vs N0</td>
<td>1.64</td>
<td>(0.91-3.09)</td>
</tr>
<tr>
<td>ER/PgR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative vs positive</td>
<td>0.97</td>
<td>(0.47-2.08)</td>
</tr>
</tbody>
</table>

Histological/Nuclear grade
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Ratio</th>
<th>CI</th>
<th>p</th>
<th>Ratio</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 vs 1&amp;2</td>
<td>1.81</td>
<td>(1.15-2.91)</td>
<td>0.011</td>
<td>1.77</td>
<td>(1.12-2.84)</td>
<td>0.014</td>
</tr>
<tr>
<td>pCR/spCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-pCR vs pCR</td>
<td>1.98</td>
<td>(1.22-3.24)</td>
<td>0.005</td>
<td>2.90</td>
<td>(1.57-5.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ER/PgR-positive dataset</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40 vs &gt;40</td>
<td>2.40</td>
<td>(1.12-4.94)</td>
<td>0.026</td>
<td>2.33</td>
<td>(1.08-4.80)</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25≤ vs &lt;22</td>
<td>1.49</td>
<td>(0.63-3.38)</td>
<td>0.354</td>
<td>1.54</td>
<td>(0.66-3.45)</td>
<td>0.313</td>
</tr>
<tr>
<td>22≤, &lt;25 vs &lt;22</td>
<td>0.69</td>
<td>(0.25-1.67)</td>
<td>0.419</td>
<td>0.69</td>
<td>(0.25-1.68)</td>
<td>0.433</td>
</tr>
<tr>
<td><strong>Clinical tumor size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-4 vs T1-2</td>
<td>0.83</td>
<td>(0.35-1.88)</td>
<td>0.653</td>
<td>0.69</td>
<td>(0.28-1.62)</td>
<td>0.399</td>
</tr>
<tr>
<td><strong>Clinical nodal status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2-3 vs N0</td>
<td>4.26</td>
<td>(1.53-13.14)</td>
<td>0.005</td>
<td>4.54</td>
<td>(1.62-14.13)</td>
<td>0.004</td>
</tr>
<tr>
<td>N1 vs N0</td>
<td>2.55</td>
<td>(0.99-7.43)</td>
<td>0.053</td>
<td>2.83</td>
<td>(1.08-8.39)</td>
<td>0.034</td>
</tr>
<tr>
<td><strong>Histological/Nuclear grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 vs 1&amp;2</td>
<td>3.09</td>
<td>(1.48-6.62)</td>
<td>0.003</td>
<td>3.14</td>
<td>(1.49-6.85)</td>
<td>0.003</td>
</tr>
<tr>
<td>pCR/spCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-pCR vs pCR</td>
<td>1.20</td>
<td>(0.57-2.69)</td>
<td>0.634</td>
<td>3.86</td>
<td>(1.13-24.21)</td>
<td>0.029</td>
</tr>
</tbody>
</table>
**ER/PgR-negative dataset**

### Age

<table>
<thead>
<tr>
<th>vs</th>
<th>HR(95%CI)</th>
<th>p-value</th>
<th>HR(95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40 vs &gt;40</td>
<td>0.95 (0.35-2.18)</td>
<td>0.913</td>
<td>1.01 (0.38-2.28)</td>
<td>0.979</td>
</tr>
</tbody>
</table>

### BMI

<table>
<thead>
<tr>
<th>vs</th>
<th>HR(95%CI)</th>
<th>p-value</th>
<th>HR(95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25≤ vs &lt;22</td>
<td>0.94 (0.39-2.05)</td>
<td>0.886</td>
<td>0.97 (0.40-2.11)</td>
<td>0.942</td>
</tr>
<tr>
<td>22≤, &lt;25 vs &lt;22</td>
<td>1.10 (0.56-2.08)</td>
<td>0.774</td>
<td>1.10 (0.56-2.08)</td>
<td>0.779</td>
</tr>
</tbody>
</table>

### Clinical tumor size

<table>
<thead>
<tr>
<th>vs</th>
<th>HR(95%CI)</th>
<th>p-value</th>
<th>HR(95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3-4 vs T1-2</td>
<td>2.20 (1.16-4.20)</td>
<td>0.017</td>
<td>2.11 (1.11-4.04)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

### Clinical nodal status

<table>
<thead>
<tr>
<th>vs</th>
<th>HR(95%CI)</th>
<th>p-value</th>
<th>HR(95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2-3 vs N0</td>
<td>2.04 (0.85-5.07)</td>
<td>0.112</td>
<td>1.73 (0.73-4.27)</td>
<td>0.217</td>
</tr>
<tr>
<td>N1 vs N0</td>
<td>1.49 (0.70-3.38)</td>
<td>0.306</td>
<td>1.39 (0.66-3.13)</td>
<td>0.398</td>
</tr>
</tbody>
</table>

### Histological/Nuclear grade

<table>
<thead>
<tr>
<th>vs</th>
<th>HR(95%CI)</th>
<th>p-value</th>
<th>HR(95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 vs 1&amp;2</td>
<td>1.33 (0.74-2.48)</td>
<td>0.354</td>
<td>1.29 (0.72-2.41)</td>
<td>0.393</td>
</tr>
</tbody>
</table>

### pCR/spCR

<table>
<thead>
<tr>
<th>vs</th>
<th>HR(95%CI)</th>
<th>p-value</th>
<th>HR(95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-pCR vs pCR</td>
<td>2.63 (1.43-4.90)</td>
<td>0.002</td>
<td>2.66 (1.31-5.97)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

BMI, body mass index; ER/PgR, estrogen receptor/progesterone receptor; pCR, pathologic complete response; spCR, strict pathologic complete response; HR, hazard ratio.
Table 3. Adjusted odds ratios of factors predicting pCR

<table>
<thead>
<tr>
<th>Factor</th>
<th>pCR (ypT0/is+ypN0)</th>
<th>spCR (ypT0+ypN0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Whole dataset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40 vs ≤40</td>
<td>0.97</td>
<td>(0.60-1.58)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25≤ vs &lt;22</td>
<td>1.22</td>
<td>(0.78-1.91)</td>
</tr>
<tr>
<td>22≤, &lt;25 vs &lt;22</td>
<td>1.38</td>
<td>(0.94-2.04)</td>
</tr>
<tr>
<td>Clinical tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-2 vs T3-4</td>
<td>1.88</td>
<td>(1.27-2.79)</td>
</tr>
<tr>
<td>Clinical nodal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 vs N2-3</td>
<td>0.65</td>
<td>(0.40-1.07)</td>
</tr>
<tr>
<td>N1 vs N2-3</td>
<td>0.83</td>
<td>(0.53-1.31)</td>
</tr>
<tr>
<td>ER/PgR status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative vs positive</td>
<td>3.42</td>
<td>(2.42-4.86)</td>
</tr>
<tr>
<td>Histological/Nuclear grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>p-Value</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>ER/PgR-positive dataset</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40 vs ≤40</td>
<td>0.74 (0.40-1.39)</td>
<td>0.343</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25≤ vs &lt;22</td>
<td>1.65 (0.85-3.20)</td>
<td>0.140</td>
</tr>
<tr>
<td>22≤, &lt;25 vs &lt;22</td>
<td>1.43 (0.77-2.61)</td>
<td>0.253</td>
</tr>
<tr>
<td><strong>Clinical tumor size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-2 vs T3-4</td>
<td>1.76 (0.94-3.43)</td>
<td>0.078</td>
</tr>
<tr>
<td><strong>Clinical nodal status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 vs N2-3</td>
<td>0.98 (0.46-2.11)</td>
<td>0.954</td>
</tr>
<tr>
<td>N1 vs N2-3</td>
<td>0.80 (0.39-1.67)</td>
<td>0.547</td>
</tr>
<tr>
<td><strong>Histological/Nuclear grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 vs 1&amp;2</td>
<td>1.22 (0.73-2.05)</td>
<td>0.454</td>
</tr>
</tbody>
</table>

**ER/PgR-negative dataset**

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40 vs ≤40</td>
<td>1.43 (0.68-2.94)</td>
<td>0.344</td>
<td>1.73 (0.80-4.08)</td>
<td>0.170</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>OR</td>
<td>95% CI</td>
<td>p-value</td>
<td>OR</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------</td>
<td>---------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>25(\leq) vs &lt;22</td>
<td>0.95</td>
<td>(0.52-1.76)</td>
<td>0.871</td>
<td>1.29</td>
</tr>
<tr>
<td>22(\leq), &lt;25 vs &lt;22</td>
<td>1.35</td>
<td>(0.81-2.27)</td>
<td>0.248</td>
<td>1.47</td>
</tr>
<tr>
<td><strong>Clinical tumor size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-2 vs T3-4</td>
<td>1.93</td>
<td>(1.17-3.20)</td>
<td>0.010</td>
<td>1.89</td>
</tr>
<tr>
<td><strong>Clinical nodal status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 vs N2-3</td>
<td>0.48</td>
<td>(0.24-0.92)</td>
<td>0.027</td>
<td>0.98</td>
</tr>
<tr>
<td>N1 vs N2-3</td>
<td>0.89</td>
<td>(0.48-1.61)</td>
<td>0.692</td>
<td>1.75</td>
</tr>
<tr>
<td><strong>Histological/Nuclear grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 vs 1&amp;2</td>
<td>1.53</td>
<td>(0.97-2.42)</td>
<td>0.068</td>
<td>1.50</td>
</tr>
</tbody>
</table>

BMI, body mass index; ER/PgR, estrogen receptor/progesterone receptor; pCR, pathologic complete response; spCR, strict pathologic complete response; OR, odds ratio.
FIGURE LEGENDS

Figure 1. Flowchart of data collection and analysis

Figure 2. DFS curves of the (A) whole dataset and (B) ER/PgR-positive and -negative datasets

Figure 3. DFS curves of patients with pCR (ypT0/is + ypN0) versus non-pCR in the (A) whole dataset, (C) ER/PgR-positive dataset, and (E) ER/PgR-negative dataset. DFS curves of patients with spCR (ypT0 + ypN0) versus non-spCR in the (B) whole dataset, (D) ER/PgR-positive dataset, and (F) ER/PgR-negative dataset.
Collected
\( (N = 829) \)

Exclusion criterion \( (N = 53) \)
- cM1 \( (N = 1) \)
- Age > 70 \( (N = 15) \)
- HER2 unknown \( (N = 8) \)
- Outside the period \( (N = 29) \)

Whole dataset
\( (N = 776) \)

ER/PgR unknown
\( (N = 3) \)

ER/PgR positive dataset
\( (N = 334) \)

ER/PgR negative dataset
\( (N = 439) \)
A)

- Disease-free survival rate

- Time (months)

<table>
<thead>
<tr>
<th>HR for non-pCR vs pCR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>2.86</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.98</td>
</tr>
</tbody>
</table>
B)

![Graph showing disease-free survival rate over time (months) for spCR and Non-spCR groups.](image)

<table>
<thead>
<tr>
<th>HR for non-pCR vs pCR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>3.90</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted</td>
<td>2.90</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
C)

![Graph showing disease-free survival rate over time](image)

<table>
<thead>
<tr>
<th></th>
<th>HR for non-pCR vs pCR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>2.15</td>
<td>0.020</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.20</td>
<td>0.643</td>
</tr>
</tbody>
</table>

Disease-free survival rate vs. time (months)
D)

Disease-free survival rate

<table>
<thead>
<tr>
<th>HR for non-pCR vs pCR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>7.08</td>
</tr>
<tr>
<td>Adjusted</td>
<td>3.86</td>
</tr>
</tbody>
</table>

Time (months)
E) Disease-free survival rate

<table>
<thead>
<tr>
<th></th>
<th>HR for non-pCR vs pCR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>3.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted</td>
<td>2.63</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Time (months)
Table S1. Summary of P-values of clinicopathological factors by the multivariate Cox regression for survival outcomes

<table>
<thead>
<tr>
<th>Factor</th>
<th>DFS</th>
<th>OS</th>
<th>DRFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40 vs &gt;40</td>
<td>0.074</td>
<td>0.112</td>
<td>0.027</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25≤ vs &lt;22</td>
<td>0.351</td>
<td>0.149</td>
<td>0.465</td>
</tr>
<tr>
<td>22≤, &lt;25 vs &lt;22</td>
<td>0.891</td>
<td>0.793</td>
<td>0.672</td>
</tr>
<tr>
<td>Clinical tumor size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-4 vs T1-2</td>
<td>0.093</td>
<td>0.591</td>
<td>0.098</td>
</tr>
<tr>
<td>Clinical nodal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2-3 vs N0</td>
<td>0.004</td>
<td>0.003</td>
<td>0.042</td>
</tr>
<tr>
<td>N1 vs N0</td>
<td>0.100</td>
<td>0.006</td>
<td>0.128</td>
</tr>
<tr>
<td>ER/PgR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative vs Positive</td>
<td>0.933</td>
<td>0.137</td>
<td>0.450</td>
</tr>
<tr>
<td>Histological/Nuclear grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 vs 1&amp;2</td>
<td>pCR</td>
<td>non-pCR vs pCR</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------</td>
<td>---------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>0.011</td>
<td>0.032</td>
<td>0.018</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40 vs &gt;40</td>
<td>0.088</td>
<td>0.156</td>
<td>0.026</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25≤ vs &lt;22</td>
<td>0.348</td>
<td>0.159</td>
<td>0.502</td>
</tr>
<tr>
<td>22≤, &lt;25 vs &lt;22</td>
<td>0.993</td>
<td>0.857</td>
<td>0.681</td>
</tr>
<tr>
<td>Clinical tumor size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-4 vs T1-2</td>
<td>0.160</td>
<td>0.725</td>
<td>0.147</td>
</tr>
<tr>
<td>Clinical nodal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2-3 vs N0</td>
<td>0.004</td>
<td>0.002</td>
<td>0.048</td>
</tr>
<tr>
<td>N1 vs N0</td>
<td>0.070</td>
<td>0.004</td>
<td>0.101</td>
</tr>
<tr>
<td>ER/PgR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative vs Positive</td>
<td>0.842</td>
<td>0.148</td>
<td>0.380</td>
</tr>
<tr>
<td>Histological/Nuclear grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 vs 1&amp;2</td>
<td>0.014</td>
<td>0.044</td>
<td>0.025</td>
</tr>
<tr>
<td>spCR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
non-pCR vs pCR  <0.001  0.048  0.001

BMI, body mass index; DFS, disease-free survival; DRFS, distant recurrence-free survival;

ER/PgR, estrogen receptor/progesterone receptor; OS, overall survival; pCR, pathologic complete response; spCR, strict pathologic complete response.