Effect of adjuvant chemotherapy in patients with ER + /HER2- breast cancer, assessed by propensity score matching: significance of nuclear grade and nodal status

Original article

Effect of adjuvant chemotherapy in patients with ER+/HER2- breast cancer, assessed by propensity score matching: significance of nuclear grade and nodal status

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ABSTRACT

Background: Survival benefits of chemotherapy (CT) differ among patients with estrogen receptor-positive (ER+) breast cancer. This study investigated the survival benefits of CT for ER+ and human epidermal growth factor receptor 2-negative (HER2-) breast cancer (BC) patients by propensity score matching (PSM).

Methods: Patients with stages I-IIIER+/HER2- BC were enrolled in this study. The primary endpoints were 5-year recurrence-free survival (RFS) and overall survival (OS) in the non-CT and CT groups of the selected population matched by PS. The PS was analyzed by a logistic regression model with factors those influence provided indication of chemotherapy (tumor size, nuclear grade [NG], progesterone receptor, and nodal status).

Results: This study enrolled 895 patients between 2000 and 2015. The median follow-up period was 5.7 years. Overall, the 5-year RFS was 94.3% and 90.1% in the non-CT and CT-treated groups, respectively (p=0.106). The 5-year OS was 97.5% in the non-CT group and 95.6% in the CT group (p=0.047). Using PSM, 236 patients were selected. After matching, both the 5-year RFS and the 5-year OS were higher in the CT group than in the non-CT group (96.8% vs. 82.7%, p=0.003 and 100% vs. 91.9%, p<0.001, respectively). Particularly in the case of the node-negative/NG3 and 1-3 node positive/NG2 patients after PSM, the 5-year RFS was significantly higher in the CT group than in the non-CT group (p=0.041 and p=0.006, respectively).

Conclusion: After PSM, CT significantly improved both the RFS and OS of ER+/HER2- BC patients, especially for node-negative/NG3 and 1-3 node positive/NG2 patients.

Introduction

Estrogen receptor-positive (ER+), human epidermal growth factor receptor 2 -negative (HER2-) breast cancer (BC) is the most commonly diagnosed breast cancer subtype. Adjuvant chemotherapy for ER+/ HER2- early BC is traditionally decided based on tumor size, nodal status, histologic grade, immunohistochemistry (IHC) assessment of ER, and the progesterone receptor (PgR) and Ki-67 labeling indexes (LI). Although adjuvant chemotherapy (CT) reduces the risk of recurrence of BC [1-3], the degree of benefit differs among the subtypes of ER+/ HER2- BC because of their heterogeneity [4].

According to the 2015 St. Gallen Consensus Panel, 1-3 positive nodes are not an absolute indicator for CT in patients with ER+ HER2-negative breast cancer [5]. At the St. Gallen Consensus Panel 2017, it was agreed that CT is preferred except in cases of high ER expression, low proliferation and low nuclear grade (NG) - classified as 'luminal A like' with low tumor burden and no nodal involvement or low genomic risk based on gene expression profile (GEP) assays [6].

GEP assays could be most beneficial for patients with tumors measuring between 1 cm and 3 cm, with zero to three positive lymph nodes, and an intermediate proliferative fraction [most commonly assessed by Ki-67 labeling index] - often classified as an intermediate group [6]. GEP assays such as the 21-gene recurrence-score assay (Oncotype DX, Genomic Health) and others are validated prognostic/ predictive tools for early ER+/ HER2- BC [7-14]. These assays can play an important role in early ER+/HER2- BC detection as they inform the physician and patient on early recurrence risks, assist in choosing the optimal treatment option by avoiding unnecessary treatments and thus might help in providing a patient-tailored treatment [15]. However, GEP assays have not been approved in Japan or most other countries, although some developed countries have approved them. These countries depend on clinicopathological parameters such as tumor size, nodal status, NG and Ki-67 LI to make decisions on adjuvant CT.

When GEP assays are unavailable, although it is ideal to perform a randomized control study to investigate effects of CT for Luminal-A like BC; it is difficult to plan such trials. Hence, we investigated the significance of CT in ER+/HER2- BC using propensity score matching (PSM), which significantly can reduce bias. PSM is a valuable method to adjust treatment bias in observational studies [16, 17].

Propensity score (PS) is calculated by performing multivariate logistic regression analysis with variables that may influence the treatment decision. This probability is defined as PS and a high score equates to a high probability of receiving the treatment. Patients with equal PS were selected from two groups - with or without treatment (matching). After matching, background variables of patients were well balanced.

Accordingly, we analyzed the survival benefit of CT for ER+/HER2- breast cancer based on clinicopathological factors especially nodal status and NG using PSM.

Patients and Methods

2.1. Study population

We included 895 female patients with stage I-III ER+/HER2- breast cancer who underwent surgery between 2000 and 2015 at Tokyo Women's Medical University Medical Center East. Patients with bilateral breast cancer, ER<10%, and preoperative treatment were excluded. Immunohistochemical staining for ER/PgR/HER2 was performed on pre-operative biopsy samples in all cases.

2.2. Endpoints

The primary endpoints were the 5-year recurrence-free survival (RFS) and overall survival (OS) in non-CT and CT groups of the selected population matched by PS. The secondary endpoints were 5-year OS and RFS in the entire population (before matching), and 5-year RFS classified by nuclear grade and nodal status after matching.

2.3. Statistical analysis

Statistical analysis was performed using JMP Ver.13 software (SAS Institute Inc., Cary, NC, USA). Patients were divided into two groups according to the administration of adjuvant CT: CT-treated (CT group) and CT-untreated (non-CT group).

The χ^2 test was used to determine significant differences in the distribution of categorical variables between the two groups - with and without CT. The RFS and OS rates were determined using Kaplan-Meier curves. The log-rank test was used to assess the differences in survival distribution between groups. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CI) were estimated by Cox proportional hazard regression model. The PSM methodology was used to reduce the treatment

selection bias in the non-random assignment [18]. The PS of the present study is the probability of receiving CT as estimated by a logistic regression model that includes factors that influence the decision of whether or not to administer CT [progesterone receptor (PgR) status, tumor size, NG, nodal status, lymphatic infiltration (ly)]. Patients with similar PS were selected from the CT and non-CT groups (1:1 matching).
After matching, patients of the CT and non-CT groups had a similar distribution of PS and consequently the two matched groups are similar in terms of the clinicopathological factors.

2.4. Ethical statement

This study was approved by the ethical committee of the Tokyo Women's Medical University. Written informed consent was obtained from all patients included in the study (SRB/IRB approval number: No. 4677).

Results

- Before PSM-

Characteristics of study population and therapy

The median age of the cohort at the time of surgery was 59 years (range, 28-95 years). 223 patients (24.9%) were node positive and 126 patients (14.1%) had NG3 disease. All patients received endocrine therapy, and 24.1% received adjuvant CT. Information about CT regimen was available for all patients who received CT. In detail, 35 patients (16.2%) received anthracycline-containing regimens, 79 patients (36.6%) received taxane-containing regimens, and 63 patients (29.2%) received both anthracycline and taxane containing regimen.

There were significant differences in age, menopausal status, tumor size, PgR status, Ki-67 LI, NG, nodal status and ly between the CT and non-CT groups. CT-treated patients were significantly younger (median age 53 vs 61 years; $p<0.001$), with more premenopausal women (43.0% vs 33.4%; $p=0.001$), large tumors (T2-4 rate: 57.4% vs 38.4%; $p<0.001$), lower rate of PgR (73.6% vs 83.5%; $p=0.010$), higher proliferation rate of Ki67 labeling index (13.4% vs 5.4%; $p<0.001$), higher proportion of NG3 grade (30.0% vs 9.0%; $p<0.001$), and a higher number of positive-nodes (64.4% vs 12.4%; $p<0.001$) (Table 1).

RFS and OS analysis

The median follow-up duration was 5.7 years. Among 895 patients, 79 patients had recurrence (8.8%). Local recurrences were observed in 22 patients (2.5%), distant recurrences in 43 patients (4.8%) and local plus distant recurrences in 14 patients (1.6%). Of the 47 patients who died (5.3%), 36 patients died due to breast cancer (4.0%) and 11 patients died of other causes (1.2%).

The 5-year RFS was 94.3% in non-CT treated patients (non-CT group) and 90.1% in CT-treated patients (CT group) (hazard ratio [HR] for recurrence, 1.47; 95% confidence interval [CI], 0.90 -2.33; p=0.106).

The 5-year OS was 97.5% in the non-CT group and 95.6% in the CT group (HR for death, 1.80; 95% CI, 0.99-3.21; p=0.047) (Figs. 1 a, b).

Univariate and multivariate analysis of RFS

In the univariate analysis; PgR status, tumor size, NG, and nodal status were statistically significant prognostic factors for RFS. When entering these factors, CT and age into multivariate analysis, PgR status, tumor size, NG, and nodal status have an independent prognostic value in predicting RFS (data not shown).

-After PSM-

Characteristics of study population and therapy

To evaluate the impact of adjuvant treatment on clinical outcomes in a more homogeneous population, we analyzed survival outcome in a subgroup of 236 patients matched by PSM (118patients each in the CT and non-CT group, respectively).

There were significant differences in age, menopausal status, and nodal status. Patients in the CT group were younger (median age 54 vs 70 years; p<0.001), with more premenopausal women (44.9% vs 24.5%; p<0.001), and high number of positive-nodes (58.4% vs 34.7%; p<0.001) (Table 2). However, the difference in positive-node numbers decreased markedly by PSM. PgR status, tumor size, NG, Ki-67 LI and ly were well balanced between the two groups. In the CT group, 24 patients (20.3%) received anthracycline-containing regimens, 62 patients (52.5%) received taxane-containing regimens, 25 patients (21.2%) received both anthracycline and taxane containing regimen, and 7 patients received other regimens (CMF, S-1, tegafur plus uracil).

RFS and OS analysis

In contrast to the entire population, the 5-year RFS was significantly higher in the CT group than in the non-CT group (96.8% vs. 82.7%; HR for recurrence, 0.29; 95% CI, 0.11-0.68; p=0.003) after PSM. As well as RFS, the 5-year OS rate was also significantly higher in the CT group than in the non-CT group (100% vs. 91.9%; HR for death, 0.06; 95% CI, 0.003-0.35; p<0.001) (Figs. 2 a, b).

Univariate and multivariate analysis of RFS

In the univariate analysis, CT, and NG were statistically significant prognostic factors for RFS. Furthermore, multivariate analysis was performed with covariates of CT, NG, age, tumor size, and nodal status. As a result, tumor size, NG, and CT were independent prognostic factors in predicting RFS (Table 3).

RFS analysis classified by NG

Subgroup analysis classified by NG were performed in patients after PSM (Figs. 3a, b). A significant benefit of CT was observed only for NG3 patients. The 5-year RFS was 100% in the CT group and 78.2% in the non-CT group (HR for recurrence, 0.28; 95% CI, 0.06-0.94; p=0.038; Fig. 3b).

There was no apparent benefit of CT in NG1 and NG2 patients. In patients with NG1, the 5-year RFS was 95.8% in the non-CT group and 100% in the CT group (HR for recurrence was not estimated). For patients with NG2, the 5-year RFS was favorable in the CT group but with no significant difference between the two groups. 5-year RFS was 90.8% in CT group and 77.2% in the non-CT group (HR for recurrence, 0.41; 95% CI, 0.10-1.37; p=0.151; Fig 3a).

RFS analysis classified by nodal status

When patients were PS matched according to nodal status, CT was found to be significantly beneficial only for patients with 1 to 3 positive nodes (n1-3). The 5-year RFS was 100% in the CT group and 76.4% in the non-CT group (HR for recurrence, 0.12; 95% CI, 0.01-0.58; p=0.008). For node negative (n0) patients, the 5-year RFS was 92.6% in the CT group and 85.5% in the non-CT group (HR for recurrence, 0.368; 95%

CI, 0.01-1.68; p=0.359). In the case of patients with 4 or more positive nodes (n≧4), the 5-year RFS was favorable for the CT group with no significant difference between the two groups. 5-year RFS was 100% in the CT group and 62.5% in the non-CT group (HR for recurrence was not estimated).

RFS analysis classified by nodal status and NG

We analyzed the RFS of patients classified by a combination of nodal status and NG. In the case of patients with n0, significant benefit of CT was observed for those with NG3; the 5-year RFS was 100% in the CT group and 79.2% in the non-CT group (HR for recurrence, 0.23; 95% CI, 0.03-0.94; p=0.041) (Fig. 4 a). There was no apparent benefit of CT for NG1 and NG2 patients. There was no recurrence in patients with n0 and NG1 in both the CT and non-CT groups. For patients with n0 and NG2, the 5-year RFS was 85.1% in the CT group and 76.2% in the non-CT group (HR for recurrence, 1.31; 95% CI, 0.25-6.02; p=0.721).

A significant advantage of CT was observed in patients with n1-3 and NG2. The 5-year RFS was 100% in the CT group and 41.7% in the non-CT group (HR for recurrence <0.01; 95% CI, not estimated; p=0.006) (Fig. 4b). For patients with n1-3 and NG1, the 5-year RFS was 100% in the CT group and 88.9% in the non-CT group (HR for recurrence, $6.27e^{-10}$; 95% CI, not estimated; p=0.092).

In the case of patients with n1-3 and NG3, the 5-year RFS was favorable for the CT group, but with no significant difference between the groups. 5-year RFS was 100% in the CT group and 75.0% in the non-CT group (HR for recurrence, 0.52; 95% CI, 0.02-5.45; p=0.585).

Discussion

A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in 2011 showed that anthracycline-based CT improved breast cancer recurrence and mortality, independent of age, nodal status, ER status, tumor diameter/differentiation, or tamoxifen use [19]. However, PgR status, HER2, and Ki-67 were not included as covariates in this analysis.

However, several studies have suggested that the reduction of recurrence risk by adjuvant CT in ER+ /HER2- BC was limited compared to other subtypes [20,21]. In the present study, no benefit of CT was observed for RFS and OS in the entire population.

However, these results would be subjected to treatment bias as CT was administered even for patients with a high risk of recurrence. When the variables of clinicopathological factors were well balanced by PSM, the addition of CT significantly improved both RFS and OS.

The West German Study Group (WSG) Plan B trial is one of the first prospective studies that evaluated histological grade and IHC markers as predictive factors of CT effect [13]. This trial showed high 5-year disease-free survival (DFS) (94.2%) and OS (99.1%) in pN0-1 patients with low genomic risk, a 21-gene recurrence score (RS) of ≦11, high clinical risk, and those treated with endocrine therapy (ET) [22].

The MINDACT (Microarray in Node Negative Disease May Avoid Chemotherapy) trial is another prospective trial integrating a gene-expression assay (with 70 genes) and randomized assignment of chemotherapy in early-stage BC [23]. This trial also showed that the 5-year distant-DFS rate was 94.7% without adjuvant CT in patients with high clinical risk (Adjuvant! Online 9.0) and low genomic risk, suggesting that 46% of the clinically high-risk population (including 46% pN1 and/or 28.6% NG3 tumors) would not require CT. In the present study, for patients with node-negative/NG3 and 1-3 node positive/NG2 disease, the 5-year RFS was significantly higher in the CT group than in the non-CT group ($p=0.041$ and $p=0.006$, respectively) by subgroup analysis after PSM. However, it should be taken into consideration that some patients might receive unnecessary CT regimens.

Consistent with the WSG Plan B trial, our study demonstrated that PgR status, tumor size, nuclear grade, and nodal status have an independent prognostic value in predicting RFS (Ki-67 was not included in our study). In addition, our study showed that CT was also a statistically significant prognostic factor and that these clinicopathological factors play a critical role in disease management. The St. Gallen Consensus Panel 2017 stated that grading or Ki-67 could be used to distinguish between luminal A and B in ER+/HER2- BC, and that these factors may affect the recommendation for CT [6]. Nevertheless, evaluation of Ki-67 is controversial because of the lack of data on optimal measurement methods and cutoff [5] as well as the substantial inter-observer variability in Ki-67 staining [24-26]. In the WSG Plan B trial, concordance between RFS and Ki-67 risk assessment is relatively high in the Ki67≦

10% and ≧40% groups [22]. Hence, in an experienced laboratory when financial resources are limited, treatment decisions for CT can be guided by a combination of not only nodal status and NG, but also Ki-67.

Our study has several limitations. It is a single center retrospective evaluation, and treatment allocation was therefore not randomly assigned. Using PSM, we could adjust the treatment bias in this observational study. However, we could not take into consideration Ki-67 in calculating PS and RFS subgroup analysis because Ki-67 was not measured in half of the patient population. Consequently, we did not obtain adequate numbers of patients for this analysis. In the future, a further study will be necessary where all patients will be measured for Ki-67.

In the present study, 39 patients before PSM (7 patients after PSM) received non-standard chemotherapy regimens; cyclophosphamide, methotrexate, and fluorouracil (CMF), S-1, and tegafur plus uracil (UFT). Meta-analysis by the EBCTCG in 2011 reported that the effectiveness of four cycles of doxorubicin, cyclophosphamide (AC) vs. 6 cycles of CMF on survival outcome were equivalent; furthermore, the 10-year recurrence rate was reduced by one-third, and breast cancer mortality rate was reduced by 20-25% among patients treated with CMF compared with the control arm [19]. The National Surgical Adjuvant Study for Breast Cancer (N-SAS BC) 01 trial is the randomized phase III trial that compared UFT with CMF in patients with node-negative, high-risk breast cancer. This trial suggested that 2 years of UFT was comparable to 6 cycles of CMF; the 5-year RFS was 88% in the CMF arm and 87.8% in the UFT arm, and the 5-year OS was 96.0% and 96.2%, respectively [27]. One patient received S-1 because she was included in a clinical trial using S-1 (POTENT trial). This trial showed that addition of S-1 to endocrine therapy significantly improved invasive disease-free survival [28].

Therefore, we included the patients that received these regimens in the present study. However, these regimens have a limit and are recommended in elderly women or patients with comorbidity only.

According to the results of the WSG Plan B trial and MINDACT trial, only n0-3 patients with high clinical risk but low genomic risk had a favorable prognosis following ET treatment. Relying on traditional clinicopathological factors will fail to identify such patients who could receive benefits of CT. GEP assays would be

particularly useful for n0-3 patients with an intermediate/high clinical risk. Therefore, GEP assays are expected to be easily available in Japan in the near future.

In conclusion, our study showed that adjuvant chemotherapy improved both RFS and OS in ER+ HER2- early BC especially for n0/NG3 and n1-3/NG2 patients when expensive GEP assays are not available.

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Compliance with Ethical Standards:

Funding: This study was funded by none.

Conflict of interest: We have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Mansour EG, Gray R, Shatila, et al. Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer: an intergroup study. N Engl J Med 1989;320:485-90.
2. Mansour EG, Gray R, Shatila, et al. Survival advantage of adjuvant chemotherapy in high-risk node-negative breast cancer: ten-year analysis-an intergroup study. J Clin Oncol 1998;16:3486-92.
3. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor positive breast cancer. J Natl Cancer Inst 1997;89:1673-82.
4. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumors. Nature 2000;406:747-52.
5. Coates A. S, Winer E. P, Goldhirsch A, et al. Tailorling therapies-improving the management of early breast cancer: St. Gallen international Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015;26:1533-46.
6. Curigliano G, Burstein H. J, Winer E. P, et al. De-escalating and escalating treatments for early-stage breast cancer: St. Gallen international Expert Consensus on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol 2017;28:1700-12.
7. Paik S, Shak S, Tang G, et al. A Multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-26.
8. Paik S, Tang G, Sgak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24:3726-34.
9. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer in chemotherapy: a retrospective analysis of a randomized trial. Lancet Oncol 2010;11:55-65.
10. Toi M, Iwata H, Yamanaka T, et al. Clinical significance of the 21-gene signature (Oncotype DX) in hormone receptor-positive early stage primary breast cancer in the Japanese population. Cancer 2010;116:3112-18.
11. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive post-menopusal patients with breast cancer treated with anastrozole or tamozifen; a Trans ATAC study. J Clin Oncol 2010;28:1829-34.

12. Sprano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2018;379:111-121.
13. Guiz O, Nitz UA, Chirstgen M et al. West German Study Group Phase III Plan B Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markaers by Central and Local Pathology Assessment. J Clin Oncol 2016;34:2341-49.
14. Petkov VI, Miller DP, Howlader N, et al. Breast-cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. NPJ Breast Cancer 2016;2:16017.
15. Sestak I, Buus R, Matsumoto H, et al. Comparison of the performance of 6 prognostic signatures for a randomized clinical trial. JAMA Oncol 2018;4:545-53.
16. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41-55.
17. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984;79:516-524.
18. Alfred F, The Effectiveness of Right Heart Catheterization in the Initial Care of Critically Ill Patients. JAMA 1996;276:889-97.
19. Early Breast Cancer Trialistis' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analysis of ling term outcome among 100,000 women in 123 randomized trials. Lancet 2012;379: 432-44.
20. Aebi S, Sun Z, Braun D, et al; Differential efficacy of three cycles of CMF followed by tamoxifen in patients with ER-positive and ER-negative tumors: long-term follow up on IBCSG trial IX. Ann Oncol 2011;22:1981-7.
21. Pritchard KI, Shepherd LE, O' Malley FP, et al; National Cancer Institute of Canada Clinical Trials Group. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 2006;354:2103-11.
22. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high - risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomized phase3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat 2017;165:573-583.
23. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med 2016;375:717-29.

24. Dowsett M, Nielsen TO, A'Herm R, et al. Assessment of Ki67 in breast cancer: Recommendations from the international Ki67 in Breast Cancer working group. J Natl Cancer Inst 2011;103:1656-64.
25. Polley M-YC, Leung SCY, McShane LM, et al. An international Ki67 reproducibility study. J Natl Cancer Inst 2013;105:1897-1906.
26. Andre F, Amendos M, Goubar A, et al. Ki67-no evidence for its use in node positive breast cancer. Nat Rev Clin Oncol 2015;12:296-301.
27. Watanabe T, Sano M, Takashima S, et al. Oral Uracil and Tegafur Compared With Classic Cyclophosphamide, Methotrexate, Fluorouracil As Postoperative Chemotherapy in Patients With Node-Negative, High-Risk Breast Cancer: National Surgical Adjuvant Study for Breast Cancer 01 Trial. J Clin Oncol 2009; 27: 1368-1374.
28. Toi M, Imoto S, Ishida T, et. al. Addition of S-1 to endocrine therapy in the post-operative adjuvant treatment of hormone receptor-positive and human epidermal growth factor receptor 2-negative primary breast cancer: A multicenter, open-label, phase 3 randomized trial (POTENT trial). Cancer Res 2020; 80 (4 Supplement) GS1-09.

Figure legends

Fig. 1 Kaplan-Meier plots for five-year recurrence-free survival (RFS) (a) and overall survival (OS) (b) in the entire population.

No significant benefit of CT was observed when considering the entire cohort.

Fig. 2 Kaplan-Meier plots for five-year recurrence-free survival (RFS) (a) and overall survival (OS) (b) in patients matched by propensity score.

The addition of chemotherapy significantly improved both RFS and OS post PS matching.

Figure 3 Kaplan-Meier plots for five-year recurrence-free survival (RFS) in patients with NG2 (a) and NG3 (b) post propensity score matching. The five-year RFS was significantly higher in the CT group than in the non-CT group in NG3 patients.

Fig. 4 Kaplan-Meier plots for five-year recurrence-free survival (RFS) in patients with n0/NG3 (a) and n1-3/NG2 (b) post propensity score matching.

The five-year RFS was significantly higher in the CT group than in the non-CT group in both the node-negative/NG3 and the 1-3 node positive/NG2 patients.