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Correspondence to

Hongki Gwak

Division of Breast and Thyroid Surgical Oncology, Department of Surgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 16247, Korea.
E-mail: hkgwak@gmail.com

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ORCID iDs

Jean Schneider <https://orcid.org/0000-0002-3449-7591>
Hyouk Jin Lee <https://orcid.org/0000-0002-6579-3529>
Seok Jin Nam <https://orcid.org/0000-0003-1072-8954>
Soo Jung Lee <https://orcid.org/0000-0003-0066-4109>
Jin Hyang Jung <https://orcid.org/0000-0003-2607-1686>
Sung Hoo Jung <https://orcid.org/0000-0001-7058-0870>
Seung Taek Lim <https://orcid.org/0000-0003-2186-6578>
Ye Won Jeon <https://orcid.org/0000-0002-5181-8211>
Hongki Gwak <https://orcid.org/0000-0002-5132-588X>

Relative Survival Benefit by Hormonal Receptor Status of Adding Trastuzumab to Neoadjuvant Chemotherapy in Breast Cancer Patients

Jean Schneider ¹, Hyouk Jin Lee ², Seok Jin Nam ³, Soo Jung Lee ⁴, Jin Hyang Jung ⁵, Sung Hoo Jung ⁶, Seung Taek Lim ⁷, Ye Won Jeon ⁷, Hongki Gwak ⁷

¹College of Natural Sciences, University of Texas at Austin, Austin, TX, USA

²Segyero Hospital, Busan, Korea

³Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

⁴Department of Surgery, Yeungnam University Hospital, Daegu, Korea

⁵Department of Surgery, Kyungpook National University School of Medicine, Daegu, Korea

⁶Department of Surgery, Jeonbuk National University Medical School, Jeonju, Korea

⁷Division of Breast and Thyroid Surgical Oncology, Department of Surgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea

ABSTRACT

Purpose: Neoadjuvant chemotherapy (NAC) involving trastuzumab markedly increases pathologic complete response (pCR) rates in patients with human epidermal growth factor receptor 2-positive (HER2+) breast cancer. Despite increasing pCR rates, long-term survival gains are controversial owing to distinctive biologic behavior mediated by the presence of hormonal receptors (HRs) that may interact with HER2 receptors. We, therefore, investigated the differences in relative survival gain provided by neoadjuvant trastuzumab-based chemotherapy on HR positive (HR+) status of patients.

Methods: We retrospectively analyzed Patient clinical characteristics were compared using women with stage II or III HER2+ breast cancer who underwent NAC followed by a breast cancer surgery between 2008 and 2013. The survival benefits of adding trastuzumab to NAC were analyzed by classifying patients into HR+ and HR negative (HR-) groups.

Results: Of 666 patients included in the study, 374 (52.1%) were HR+ and 319 (47.9%) were HR-. In the HR+ group, trastuzumab treatment led to higher pCR rates and significantly better breast cancer specific survival (BCSS) and overall survival (OS) than no trastuzumab treatment. However, among patients with HR- breast cancer, trastuzumab treatment showed no statistically significant difference between BCSS and OS following multivariate analysis.

Conclusion: We found that the addition of trastuzumab to NAC improved relative survival benefit in HER2+/HR+ patients than in HER2+/HR- patients, even though the pCR rate increases were lower. Although pCR has been regarded as a surrogate marker for estimating long-term survival benefits after NAC, it alone may not translate into real long-term oncologic outcomes in particular cancer subtypes after trastuzumab-based NAC. Further longer-term evaluation of the objective survival benefit after NAC driven by a dual HER2 block according to HR status is warranted.

Keywords: Breast neoplasms; Induction chemotherapy; Receptor, ErbB-2; Survival; Trastuzumab

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Schneider J, Gwak H;
Data curation: Schneider J; Formal analysis:
Gwak H; Supervision: Lee HJ, Nam SJ, Lee SJ,
Jung JH, Jung SH, Lim ST, Jeon YW; Writing
- original draft: Schneider J, Gwak H; Writing -
review & editing: Schneider J, Gwak H.

INTRODUCTION

The therapeutic effect of neoadjuvant chemotherapy (NAC) on early breast cancer is similar to that of adjuvant chemotherapy [1]. Currently, NAC is being individualized for patients with breast cancer according to intrinsic subtypes [2,3]. As several representative randomized controlled trials (RCTs) have demonstrated the efficacy of NAC combined with anti-human epidermal growth factor receptor 2 (HER2) agents in patients with HER2+ early breast cancer, this is currently the standard treatment for this subtype [4-6].

Pathologic complete response (pCR) is considered a surrogate marker for predicting long-term survival benefits in patients receiving NAC [2,7]. Although NAC with trastuzumab resulted in significantly higher pCR rates in those with HER+ breast cancer, several studies have not demonstrated a long-term overall survival (OS) benefit when patients were stratified by HR status. In addition, outcomes were based on post-hoc analyses following clinical trials [4,8-13]. Hormonal receptor positive (HR+)/HER2+ and HR negative (HR-)/HER2+ breast cancers are biologically distinct [14]. HR-/HER2+ cancer demonstrates more sensitivity to NAC and shows better pCR rates [15]. To the best of our knowledge, clinical trials comparing the long-term survival benefit of NAC with trastuzumab according to HR status, particularly in Asian populations, have not yet been published.

Not long after NAC with trastuzumab was approved for daily practice, pertuzumab was integrated into the standard NAC for HER2+ breast cancer for dual blockade. However, many Asian countries faced financial hurdles in reimbursing medical expenses of patients with HER+ breast cancer treated with trastuzumab with or without pertuzumab. These countries must allocate budget efficiently to help patients with HER2+ breast cancer according to the clinical trials reflecting the patients' biologic and ethnic characteristics. Initiating new RCTs for NAC without trastuzumab is not feasible for malignancies for which anti-HER2 agents are the standard treatment [16]. Therefore, a retrospective study with a fairly organized and well-maintained database is the only option for analyzing the effect of NAC plus trastuzumab on long-term survival according to HR status.

METHODS**Compliance with ethical standards**

This study protocol was approved by the Institutional Review Board of the Catholic University of Korea (VC18RCSI0163). The Korean Breast Cancer Society (KBCS) prospectively collected all patient data. All participants in this study provided written informed consent for the storage of their medical information in the database and the use of this information for research purposes.

Data source and study population

Since 1996, the KBCS has been prospectively collecting patient data that were reported by surgeons at 102 general hospitals, including 41 university hospitals and 61 accredited training hospitals. Data audits were routinely performed to guarantee the quality of the database by the KBCS registration committee. Survival and cause of death were censored by the National Statistical Office of the Republic of Korea.

We selected female patients aged ≥ 20 years with HER2+ stage II or III primary breast cancer diagnosed between 2008 and 2013. HER2 positivity was defined as either 3+ overexpression as observed via immunohistochemical staining or HER2 amplification as observed via fluorescent *in situ* hybridization (HER2/CEP17 ratio ≥ 2.0). HR positivity was defined as $>1\%$ staining for either estrogen or progesterone receptors or both. This study included patients who received trastuzumab-based NAC and then underwent breast cancer surgery. Patients who received HER2-targeted NAC other than trastuzumab were excluded. Only patients with complete data regarding clinical and pathologic parameters were included. The final study population comprised 666 patients.

From the KBCS database, which processes personal information anonymously from the initial phase of data gathering, we extracted information regarding patient age, date of diagnosis, date of surgery, date of death, cause of death, type of surgery, clinical stage, pathologic stage, NAC regimen, treatment response (pCR or non-pCR), HR status, HER2 status, histologic grade, adjuvant hormonal therapy, and adjuvant radiotherapy. Clinical and pathologic TNM stages were classified according to the sixth classification of the American Joint Committee on Cancer.

Statistical analysis

Patient clinical characteristics were compared using the χ^2 test and Student's *t*-test. pCR was defined as the absence of residual invasive cancer cells in the breasts and axillary lymph nodes (ypT0/is + ypN0). Survival was defined as the time interval from the date of diagnosis to death. Survival was estimated using the Kaplan-Meier method and was compared using the log-rank test (2-sided, $p < 0.05$). Cox proportional regression models were used to estimate the hazard ratio of breast cancer specific survival (BCSS) and OS (95% confidence interval [CI]). All statistical analyses were performed using SPSS Statistics, version 18.0 (SPSS Inc., Chicago, USA).

Data availability statement

The datasets generated or analyzed during the current study are not publicly available due to the patient privacy requirements but are available from the corresponding author upon reasonable request.

RESULTS

Patients

The final study population comprised 666 patients with a mean age of 48.2 ± 10.0 years and a median length of follow-up of 54 (45.6–82) months. Among 666 patients, 347 (52.1%) and 319 (47.9%) had HR+ and HR- status, respectively (**Figure 1**). Most patients (620; 93.1%) had invasive ductal carcinoma.

Treatment

After surgery, all patients continued the recommended trastuzumab treatment with adjuvant chemotherapy, and 90.8% of patients in the HR+ group received adjuvant hormonal therapy. The rate of breast-conserving surgery was significantly higher in the trastuzumab-based NAC group than in the non-trastuzumab-based NAC group. Patient baseline characteristics and treatments according to HR status are depicted in **Table 1**.

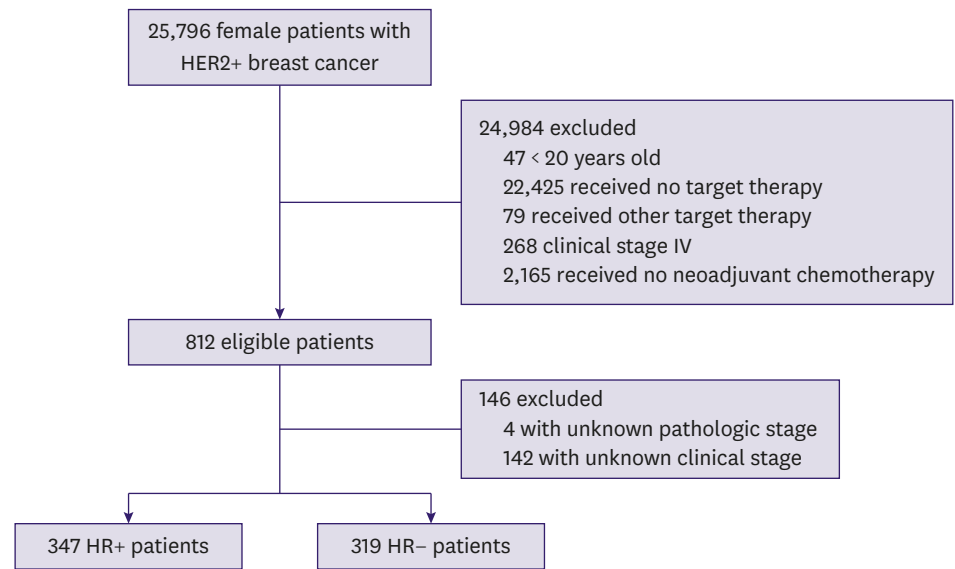


Figure 1. Flow chart of patient population. Data collection was performed between 2008 and 2013. HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

Table 1. Patient characteristics by HR status

Characteristics	Total (n = 666)	HR positive (n = 347)		p-value	HR negative (n = 319)		p-value
		Trastuzumab (n = 221)	Non-trastuzumab (n = 126)		Trastuzumab (n = 208)	Non-trastuzumab (n = 111)	
Age (yr)	48.2 ± 10.0	45.8 ± 9.8	47.6 ± 8.8	0.156	49.3 ± 10.3	51.6 ± 10.0	0.058
20–49	378 (56.8)	151 (68.3)	72 (57.1)	0.047	111 (53.4)	44 (39.6)	0.025
≥ 50	288 (43.2)	70 (31.7)	54 (42.9)		97 (46.6)	67 (60.4)	
Clinical stage				0.001			< 0.001
II	231 (34.7)	95 (43.0)	32 (25.4)		84 (40.4)	20 (18.0)	
III	435 (65.3)	126 (57.0)	94 (74.6)		124 (59.6)	91 (82.0)	
Histologic grade				0.522			0.261
G1/G2	288 (43.2)	127 (57.5)	63 (50.0)		59 (28.4)	39 (35.1)	
G3	247 (37.1)	65 (29.4)	39 (31.0)		100 (48.1)	43 (38.7)	
NA	131 (19.7)	29 (13.1)	24 (19.0)		49 (23.6)	29 (26.1)	
Histologic type				0.373			0.033
IDC	620 (93.1)	212 (95.9)	117 (92.9)		191 (91.8)	100 (90.1)	
ILC	9 (1.4)	1 (0.5)	2 (1.6)		1 (0.5)	5 (4.5)	
NA, other	37 (5.6)	8 (3.6)	7 (5.6)		16 (7.7)	6 (5.4)	
Surgery				0.051			0.003
BCS	250 (37.5)	92 (41.6)	39 (31.0)		90 (43.3)	29 (26.1)	
Mastectomy	416 (62.5)	129 (58.4)	87 (69.0)		118 (56.7)	82 (73.9)	
NAC regimen				0.012			0.193
T + A	490 (73.6)	155 (70.1)	62 (76.2)		151 (72.6)	88 (79.3)	
T	153 (23.0)	62 (28.1)	40 (17.5)		51 (24.5)	18 (16.2)	
NA	23 (3.5)	4 (1.8)	13 (6.3)		6 (2.9)	5 (4.5)	
Hormone therapy				0.281			
Yes	315 (90.8)	210 (95.0)	105 (83.3)				
No	15 (4.3)	8 (3.6)	7 (5.6)				
NA	17 (4.9)	3 (1.4)	14 (11.1)				
pCR rate	15.9	15.8	5.6	0.006	26.4	8.1	< 0.001

Data are shown as mean ± standard deviation or number (%).

HR = hormone receptor; BCS = breast-conserving surgery; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; NA = not applicable; NAC = neoadjuvant chemotherapy; pCR = pathologic complete remission.

Pathologic complete response

The pCR was reported in 90 of 429 patients (21.0%) in the trastuzumab-based NAC group and 16 of 237 patients (6.8%) in the non-trastuzumab group ($p < 0.001$). Irrespective of HR status, the pCR rate was significantly higher in the trastuzumab-based NAC group than in the non-trastuzumab group (HR+: 15.8 vs. 5.6%; $p = 0.006$; HR-: 26.4 vs. 8.1%; $p < 0.001$).

Survival analysis

Both patients with HR+/HER2+ and HR-/HER2+ breast cancer in the trastuzumab-based NAC group had significantly better OS than those in the non-trastuzumab-based NAC group (log-rank; HR+: $p = 0.020$; HR-: $p = 0.007$). However, HR+ HER+ patients in the trastuzumab-based NAC group demonstrated significantly better BCSS than HR- HER+ patients in the non-trastuzumab-based NAC group (log-rank; HR+ HER+: $p = 0.009$; HR- HER+: $p = 0.066$) (**Figure 2**). Univariate Cox proportional hazard analysis showed a significant BCSS benefit following trastuzumab treatment in the HR+/HER2+ group (HR+/HER2+: hazard ratio, 0.232; 95% CI, 0.070–0.773; HR-/HER2+: hazard ratio, 0.533; 95% CI, 0.269–1.055) and an OS benefit in both the HR groups (HR+/HER2+: hazard ratio, 0.354; 95% CI, 0.142–0.884; HR-/HER2+: hazard ratio, 0.513; 95% CI, 0.290–0.910). Multivariate Cox regression analysis revealed significantly better BCSS (HR+/HER2+: hazard ratio, 0.221;

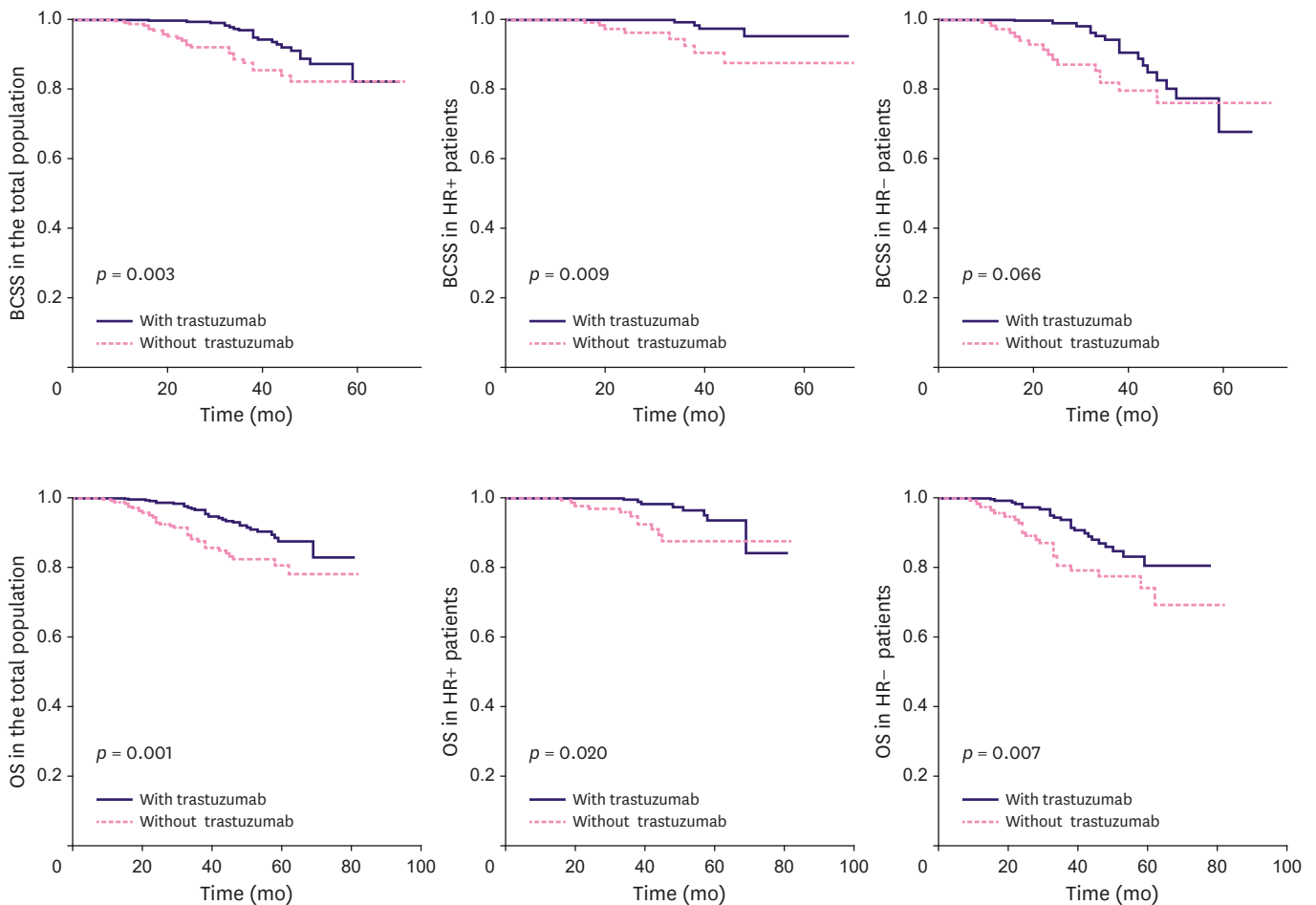


Figure 2. Kaplan-Meier estimates of BCSS and OS according to HR status. BCSS = breast cancer-specific survival; HR = hormone receptor; OS = overall survival.

Table 2. Multivariate analysis of survival after adding trastuzumab to NAC according to pathologic complete remission and HR status

	HR positive		HR negative	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
All				
BCSS	0.221 (0.055–0.886)	0.033	0.500 (0.220–1.138)	0.098
OS	0.359 (0.133–0.966)	0.043	0.522 (0.269–1.015)	0.055
With pCR				
BCSS	NA		0.271 (0.027–2.734)	0.271
OS	NA		0.271 (0.027–2.734)	0.271
Without pCR				
BCSS	0.382 (0.146–1.001)	0.050	0.622 (0.337–1.147)	0.128
OS	0.418 (0.165–1.055)	0.065	0.657 (0.360–1.202)	0.173

BCSS = breast cancer specific survival; CI = confidence interval; HR = hormone receptor; NA = not applicable; NAC = neoadjuvant chemotherapy; OS = overall survival; pCR = pathologic complete remission.

95% CI, 0.055–0.886; HR-/HER2+: hazard ratio, 0.500; 95% CI, 0.220–1.138) and relatively improved OS in HR+/HER2+ trastuzumab-based NAC group only (HR+/HER2+: hazard ratio, 0.359; 95% CI, 0.133–0.966; HR-/HER2+: hazard ratio, 0.522; 95% CI, 0.269–1.015). For HER2+patients with HR+/HER2+ breast cancer showing pCR after trastuzumab-based NAC, statistical analysis could not be conducted owing to the small number of events. Among patients without pCR, those with HR+/HER2+ breast cancer showed significantly better BCSS than those with HR-/HER2+ breast cancer (**Table 2**).

DISCUSSION

In the 2014 report of the NOAH trial, 151 patients with HR-/HER2+ breast cancer and 84 patients with HR+/HER2+ breast cancer were analyzed to determine the survival benefit of trastuzumab administered as neoadjuvant systemic therapy with chemotherapeutic agents. However, statistical head-to-head comparison according to HR positivity was not reported. In the 2010 GeparQuattro report, 261 HER2+patients with HR+/HER2+ breast cancer and 182 HER2+patients with HR-/HER2+ breast cancer were enrolled [5]. The pCR rate after trastuzumab-based NAC was significantly higher in HER2+patients with HR-/HER2+ breast cancer. However, long-term survival outcomes stratified by HR positivity were not reported. Therefore, we planned to analyze the differences in oncologic outcomes after adding trastuzumab to NAC between patients with HR+/HER2+ and HR-/HER2+ breast cancer by comparing the hazard ratio.

In a subgroup analysis of the NOAH trial, no benefit of neoadjuvant trastuzumab was noted regarding OS in the HR+/HER2+ subgroups (HR+/HER2+: hazard ratio, 1.05; 95% CI, 0.53–2.10). However, in our study, multivariate analysis demonstrated a significant survival benefit of neoadjuvant trastuzumab in patients with HR+ status only, despite a mere 10.2% increase in pCR. This finding indicates a relatively greater benefit for patients, which reflected as improved BCSS and OS that may be expected for those with HR+/HER2+ status than for those with HR-/HER2+ status.

As the US Food and Drug Administration had accepted pCR as a surrogate marker to support the accelerated approval of chemotherapeutics, most recent trials have focused on the pCR rate [7]. Therefore, many RCTs have used pCR as a surrogate marker to determine the efficacy [8]. However, the OS benefit of a drug that is assessed using pCR at a trial level is controversial [12,17]. In the CTneoBC pooled analysis, a markedly increased pCR was not associated with a corresponding benefit in OS. A significant increase in the pCR rate with

no disease-free survival or OS benefit was also demonstrated in the NeoALTO trial with lapatinib [9]. The low OS, despite the marked increase in the pCR rate, may be related to patient heterogeneity and breast cancer intrinsic subtype [10]. There is a lack of consensus that pCR is the surrogate marker for predicting long-term survival, especially in luminal-type breast cancer [18,19]. Similar to other studies, our study demonstrated that the pCR rate was higher in the HR-/HER2+ group than in the HR+/HER2+ group. However, no comparable long-term relative survival benefit was noted among patients with HR-/HER2+ breast cancer compared with patients with HR+/HER2+ breast cancer despite the marked increase in the pCR in the former.

Although we cannot delineate the exact mechanism that differentiates our findings from those of previous trials, there are a few plausible explanations. Breast cancer in Asian individuals has a distinctive molecular genomic basis, tends to occur at a younger age, and has a worse prognosis than that in Caucasian individuals. An ongoing study revealed that Asian individuals have lower estrogen receptor (ER) gene expression within the ER+ subtypes and an increased prevalence of TP53 mutations [20]. Another example of probable genetic differences between Asians and Caucasians can be found in patterns of non-small cell lung carcinoma. The frequency of the mutation rate of epidermal growth factor receptor is higher in Asians, resulting in the need for different treatment strategies [21,22]. Unfortunately, research on neoadjuvant HER2-targeted treatment is limited owing to the low number of Asian patients with breast cancer who are enrolled in trials.

In this study, it was imperative to balance patient subsets for comparisons to avoid selection biases that might lead to erroneous conclusions. The proportion of stage II and lower histologic grades is higher in the HR+/HER2+ trastuzumab-based NAC subsets than in HR-/HER2+ counterparts. By contrast, the proportion of patients younger than 50 years was significantly higher in the HR+ HER2+ trastuzumab-based NAC group. Therefore, we compared the hazard ratio between these 2 subsets after multivariate analyses to determine comparative survival gain by patients after trastuzumab-based NAC treatment stratified by HR positivity, while mitigating the effects of unbalanced characteristics due to the inherent pitfalls of the retrospective study using a preset database.

The relative survival gain in patients with HR-/HER2+ breast cancer was not significant according to the results of the multivariate analysis in this study, possibly because of the small sample size. Another possible reason may be molecular changes observed after NAC, such as the loss of HER2 expression [23,24]. The negative phenotype conversion rate from HER2+ to HER2- after NAC was higher in the HR+/HER2+ group, implying that the molecular subtype shifts from luminal HER2+ to luminal A. This change could be translated into increased survival.

The limitations of this retrospective study included the exclusion of missing data, which is a typical inherent pitfall of large-scale databases such as ours. Starting in December 2013, the Korean government began reimbursing expenses related to trastuzumab neoadjuvant treatment combined with NAC for breast cancer. The median follow-up period was slightly less than 5 years. Although the risk of early distant metastases within 5 years after diagnosis is similar in HER2+ breast cancer irrespective of HR status, the hazard ratio of late distant metastases \geq 5 years after diagnosis is higher in the HR- HER2+ subtype [19]. Therefore, improved survival of patients with the HR+ HER2+ subtypes can be prolonged after 5 years [24]. The advantage of our study is its high consistency in the perioperative management

of the patients, as the pattern of local and systemic treatments have been monitored by the Korean government to ensure that treatments recommended by international guidelines are not overlooked. Even though head-to-head and well-balanced RCTs are mandatory for definitive delineation of relative oncologic outcome gains patients with for HER2+ status with endocrine dependency, this type of RCT is not possible for 2 reasons [16]. First, omitting the neoadjuvant trastuzumab for patients with HER2+ status is impossible owing to ethical issues. Second, the dramatically reduced number of events in the pCR group requires a large number of patients to be enrolled to make statistical analysis possible.

As pCR cannot be achieved in all patients undergoing NAC with trastuzumab or pertuzumab, further research regarding molecular typing in non-pCR groups should be pursued to determine the optimal populations that may receive survival benefit from neoadjuvant target therapy. Considering that patients with HR+ status generally show better survival outcomes than patients with HR- status, survival effects of some possible molecular changes such as HER2 loss and crosstalk between HR and HER2 in patients without pCR after NAC with trastuzumab may warrant further research on various molecular subtypes.

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