Impact of Trastuzumab on Ipsilateral Breast Tumor Recurrence for Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer after Breast-Conserving Surgery

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ABSTRACT

Purpose: Trastuzumab is effective in early and advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancer. However, few studies have reported the effect of trastuzumab on ipsilateral breast tumor recurrence (IBTR), whose incidence is higher in the HER2-positive subtype than in other subtypes.

Methods: We retrospectively investigated 959 patients who underwent breast-conserving surgery (BCS), chemotherapy, and radiotherapy for HER2-positive breast cancer between 2000 and 2017. IBTR was compared between the patients who received neoadjuvant or adjuvant trastuzumab (Tmab group) for a total duration of 1 year and those who received no trastuzumab (N-Tmab group).

Results: Propensity score matching designated 426 and 142 patients in the Tmab and N-Tmab groups, respectively. The median follow-up period for all patients after matching was 73.79 months. The IBTR-free survival rate was significantly higher in the Tmab group than in the N-Tmab group (10-year IBTR-free survival rate, 92.9% vs. 87.3%; \( p = 0.002 \)). The multivariate analysis showed a significant association between the N-Tmab and Tmab group (hazard ratio, 3.03; 95% confidence interval, 1.07–8.59) and IBTR in addition to close or positive resection margin and hormone receptor (HR) positivity. The subgroup analysis showed that adjuvant treatment with trastuzumab significantly reduced IBTR among the patients with HR-negative or lymph node-negative breast cancer.

Conclusion: Significantly reduced IBTR after BCS was observed in the patients who received 1 year of adjuvant/neoadjuvant trastuzumab treatment for HER2-positive breast cancer.

Keywords: Breast neoplasms; Local neoplasm recurrence; Trastuzumab
INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20%–30% of breast cancers. This HER2-positive subtype is known to be aggressive and more resistant to standard chemotherapy than other subtypes [1]. However, it is much more likely to respond to treatments that target the HER2 protein [2,3].

Trastuzumab (Herceptin®, Genentech Corporation, US/Hoffman-Roche, Basel, Switzerland) is a monoclonal antibody that targets HER2 on the surface of cancer cells. It inhibits growth signals being delivered into the cell and also activates the immune system to destroy cancer cells [4]. Clinical trials have shown that the addition of trastuzumab to standard therapy improves the outcomes of metastatic and early HER2-positive breast cancer. Since the US Food and Drug Administration approved the use of trastuzumab in 1998, it is currently recommended in the major clinical practice guidelines [5,6].

Although the systemic effect of trastuzumab is well established, there are few reports of its local control on the ipsilateral breast. This is important because HER2-positive breast cancers have been reported to have a higher ipsilateral breast tumor recurrence (IBTR) rate after breast-conserving surgery (BCS) and radiotherapy (RT) than other breast cancer subtypes in studies conducted before the trastuzumab era [7]. Kim et al. [8] reported that especially in young patients, the HER2-positive subtype had a higher IBTR rate than the luminal type.

In this retrospective study, we aimed to investigate the effect of trastuzumab on IBTR by comparing between trastuzumab-treated and non-treated patients. We conducted propensity score matching (PSM) to reduce confounding factors and minimize selection bias.

METHODS

Patients

We obtained data on the baseline and clinicopathologic characteristics of patients who underwent curative surgery for invasive breast cancer between January 2000 and December 2017 from the database of Seoul National University Hospital Breast Care Center [9]. To minimize selection bias, we used the following inclusion criteria: (1) history of BCS and completion of scheduled RT following surgery and (2) tumor size of > 1 cm without axillary lymph node (LN) metastasis or > 0.5 cm with axillary LN metastasis according to the Korean National Health Insurance coverage criteria for trastuzumab use in early breast cancer, and exclusion criteria: history of neither neoadjuvant nor adjuvant chemotherapy for any reason, bilateral breast cancer, synchronous or metachronous malignancies in other organs, male breast cancer, and recurrent breast cancer.

Intravenous trastuzumab was administered every 3 weeks (8 mg/kg loading dose, and 6 mg/kg maintenance dose) for a total duration of 1 year, including neoadjuvant and/or adjuvant settings. Patients taking other HER2-targeted agents, such as pertuzumab, lapatinib, neratinib, or trastuzumab-emtansine, were excluded to evaluate the pure effect of trastuzumab. Initial breast cancer was pathologically staged according to the 7th American Joint Committee on Cancer staging criteria [10]. Surveillance after primary treatment followed the protocol of our institution. This study was approved by the institutional review board (IRB) of Seoul National University Hospital (IRB No. H-2006-114-1133). The protocol was reviewed...
and approved by our institution, and the study followed the Declaration of Helsinki and good clinical practice guidelines. The requirement for informed consent was waived.

**Definition of HER2-positive breast cancer**

The primary test for HER2 overexpression in the cancer cells of the patients was immunohistochemistry (IHC). Results of 0 or 1+ were considered HER2-negative, while results of 3+ were considered HER2-positive. In case of equivocal results (2+) on IHC, the specimen was re-evaluated via fluorescence in situ hybridization (FISH) by quantifying the number of copies of the HER2 gene in the tumor cells using the PathVysion HER2 DNA Probe Kit™ (Abbott Molecular, Des Plaines, USA). When the HER2/chromosome enumeration probe 17 (CEP17) ratio was > 2.0 on FISH, cancer was regarded as HER2-positive according to the manufacturer’s criteria referencing the American Society of Clinical Oncology/College of American Pathologists guideline [9]. In this study, patients with HER2 2+ results on IHC with missing FISH results were excluded.

**Definition of recurrence and recurrence-free survival (RFS)**

IBTR was defined as the first recurrence in any quadrant of the ipsilateral breast after BCS, including that concurrent with any regional or distant metastasis (DM). Skin metastases were excluded. Regional recurrence (RR) included the first recurrence in the ipsilateral chest wall, mastectomy scar, skin of the ipsilateral breast, and ipsilateral regional LNs, such as axillary, supraclavicular, infraclavicular, and internal mammary nodes. RFS was defined as the interval between the date of surgical treatment and the date of pathologic confirmation or radiologic diagnosis of any recurrence. To focus on the effect of trastuzumab on IBTR, we censored the patients with RR or DM as the first events at the time of recurrence for IBTR-free survival analysis. As trastuzumab is usually administered for 1 year after surgery, we excluded patients with a follow-up period of less than 1 year.

**Statistical analyses**

The demographics and clinicopathologic factors were compared using one-way analysis of variance for continuous variables and Pearson’s χ² test for categorical variables. The log-rank test was used to analyze the differences between the curves of RFS derived from the Kaplan-Meier method. Cox proportional hazard regression with forward selection was used to adjust other factors affecting the recurrence rate and to estimate the adjusted hazard ratio. PSM was performed using the “MatchIt” R package (version 3.6.3; R Foundation, Vienna, Austria) [11]. Statistical significance was set at p-values of < 0.05. All analyses were performed using SPSS (version 25.0; SPSS, Inc., IBM, Armonk, USA), and curves of figures were drawn using GraphPad Prism™ (version 8.0; GraphPad Software, San Diego, USA).

**RESULTS**

**Patient demographics and characteristics**

We identified 959 patients who had HER2-positive breast cancer and met the inclusion criteria. For all patients, the mean age at the time of operation was 48.8±9.2 years (range, 24.0~78.0 years), and the median follow-up period was 78.8 months (range, 12.7~239.6 months). The clinical characteristics of the patients are listed in Table 1.

Among all patients, 737 (76.9%) completed the trastuzumab treatment as initially planned, and 195 (20.3%) did not receive trastuzumab treatment. The patients (n=27) who did not...
complete the planned 1-year trastuzumab treatment were excluded from further analysis. The reasons for discontinuation of trastuzumab treatment are listed in Supplementary Table 1.

In the comparison of the 2 groups, the patients in the trastuzumab (Tmab) group were significantly older at the time of operation and had undergone surgery more recently, less...
axillary LN dissection, higher T/N stage, less lymphovascular invasion, and higher Ki-67 index than the patients in the no trastuzumab (N-Tmab) group (Table 2). Additionally, the Tmab group received more neoadjuvant chemotherapy, while the N-Tmab group received more adjuvant chemotherapy. To minimize the effect of confounding factors, we conducted PSM with factors, including age at the time of operation, type of axillary surgery, T/N stage, lymphovascular invasion status, and Ki-67 expression; 1:3 instead of 1:1 PSM was used to collect data for a larger sample size and to analyze with greater statistical power. Finally, 426 and 142 patients were designated to the Tmab and N-Tmab groups, respectively. The clinicopathologic features were not significantly different between the 2 groups in the PSM cohort, except the year of surgery, type of axillary surgery, and chemotherapy status.

**Relationship between trastuzumab treatment and RFS**

The median follow-up periods of the 426 patients in the Tmab group and 142 patients in the N-Tmab group were 69.2 months (range, 14.9–191.4 months) and 102.4 months (range, 13.2–227.6 months), respectively. There were 14 and 17 IBTR events among the Tmab and N-Tmab groups, respectively. The Kaplan-Meier curves for the IBTR-free survival rate of all 568 patients are shown in Figure 1. In the log-rank test, the Tmab group showed a higher IBTR-free survival rate than did the N-Tmab group (10-year IBTR-free survival rate, 92.9% vs. 87.3%; \( p = 0.002 \)).

**Multivariate analysis for IBTR**

The year of surgery, N stage, resection margin status, Ki-67 level, and administration of trastuzumab were associated with the IBTR rate in the log-rank test (Table 3). The Cox regression analysis adjusting for the abovementioned variables revealed that trastuzumab use was a significant factor for a lower IBTR rate (hazard ratio, 0.33; 95% confidence interval, 0.12–0.93; \( p = 0.037 \)). Moreover, involved or close resection margin and hormone receptor (HR)-positive tumors remained significant independent predictors for a higher IBTR rate in HER2-positive breast cancer.
### Table 2. Clinical characteristics of patients according to treatment of trastuzumab before and after propensity score matching

| Characteristics                      | Tmab group (n = 737) | N-Tmab group (n = 195) | p-value | Tmab group (n = 426) | N-Tmab group (n = 142) | p-value |
|--------------------------------------|----------------------|------------------------|---------|----------------------|------------------------|---------|
| Age at surgery (yr)                  | 49.6 ± 9.1           | 46.3 ± 9.4             |         | 48.3 ± 9.0           | 45.6 ± 9.4             |         |
|                                      | < 50                 | 360 (48.8)             |         | 250 (58.7)           | 93 (65.5)              | 0.151   |
|                                      | ≥ 50                 | 377 (51.2)             |         | 176 (41.3)           | 49 (34.5)              |         |
| BMI (kg/m²)                          |                      | 0.935                  |         |                      | 0.625                  |         |
| Within normal                        | 490 (66.5)           | 128 (65.6)             |         | 299 (70.2)           | 101 (71.1)             |         |
| Underweight (< 18.5)                | 22 (3.0)             | 6 (3.1)                | 14 (3.3) | 5 (3.5)              |                       |         |
| Overweight (≥ 25.0)                 | 220 (29.9)           | 54 (27.7)              | 111 (26.1) | 30 (21.1)           |                       |         |
| Unknown                              | 5 (0.7)              | 7 (3.6)                | 2 (0.5)  | 6 (4.2)              |                       |         |
| Year of surgery                      |                      | < 0.001                |         | < 0.001              |                       |         |
| 2000–2008                            | 74 (10.0)            | 177 (90.8)             |         | 55 (12.9)            | 124 (87.3)             |         |
| 2009–2017                            | 663 (90.0)           | 18 (9.2)               |         | 371 (87.1)           | 18 (12.7)              |         |
| Axilla surgery                       |                      | < 0.001*               |         | < 0.001*             |                       |         |
| SLNB                                 | 469 (63.6)           | 70 (35.9)              | 229 (53.8) | 62 (43.7)           |                       | 0.037   |
| ANLD                                 | 268 (36.4)           | 125 (64.1)             | 197 (46.2) | 80 (56.3)           |                       |         |
| T stage†                             |                      | 0.012*                 |         | 0.215                |                       |         |
| T1                                   | 241 (32.7)           | 84 (43.1)              | 186 (43.7) | 55 (38.7)           |                       |         |
| T2                                   | 418 (56.7)           | 99 (50.8)              | 207 (48.6) | 80 (56.3)           |                       |         |
| T3–4                                 | 78 (10.6)            | 12 (6.2)               | 33 (7.7)  | 7 (4.9)              |                       |         |
| N stage†                             |                      | < 0.001*               |         | < 0.001*             |                       |         |
| N0                                   | 305 (41.4)           | 113 (57.9)             | 241 (56.6) | 83 (58.5)           |                       |         |
| N1                                   | 258 (35.0)           | 61 (31.3)              | 140 (32.9) | 41 (28.9)           |                       |         |
| N2                                   | 139 (18.9)           | 17 (8.7)               | 44 (10.3)  | 15 (10.6)           |                       |         |
| N3                                   | 35 (4.7)             | 6 (2.1)                | 1 (0.2)   | 3 (2.1)              |                       |         |
| Histologic grade                     | 0.783                |                       | 0.488                |                       |                       |         |
| I                                    | 10 (13.6)            | 2 (1.0)                | 3 (0.7)    | 2 (1.4)              |                       |         |
| II                                   | 240 (32.6)           | 58 (29.7)              | 127 (29.8) | 36 (25.4)           |                       |         |
| III                                  | 445 (60.4)           | 120 (61.5)             | 286 (67.1) | 99 (69.7)           |                       |         |
| Unknown                              | 34 (4.6)             | 53 (27.2)              | 10 (2.3)   | 5 (3.5)              |                       |         |
| Lymphovascular invasion              | 0.001*               |                       | 0.187                |                       |                       |         |
| Present                              | 233 (31.6)           | 68 (34.9)              | 177 (41.5) | 68 (47.9)           |                       |         |
| Absent                               | 470 (63.8)           | 74 (37.9)              | 249 (58.5) | 74 (52.1)           |                       |         |
| Unknown                              | 34 (4.6)             | 53 (27.2)              | -          | -                   |                       |         |
| Resection margin                     | 0.980                |                       | 0.561                |                       |                       |         |
| Clear                                | 692 (93.9)           | 183 (93.8)             | 396 (93.0) | 134 (94.4)          |                       |         |
| Involved or close                    | 45 (6.1)             | 12 (6.2)               | 30 (7.0)    | 8 (5.6)             |                       |         |
| Hormone receptor status              | 0.797                |                       | 0.156                |                       |                       |         |
| Positive                             | 412 (55.9)           | 107 (54.9)             | 251 (58.9) | 74 (52.1)           |                       |         |
| Negative                             | 325 (44.1)           | 88 (45.1)              | 175 (41.1) | 68 (47.9)           |                       |         |
| Ki-67 index                          | 0.027*               |                       | 0.881                |                       |                       |         |
| < 10%                                | 385 (52.2)           | 119 (61.0)             | 261 (61.3) | 88 (62.0)           |                       |         |
| ≥ 10%                                | 349 (47.4)           | 75 (38.5)              | 165 (38.7) | 54 (38.0)           |                       |         |
| Unknown                              | 3 (0.4)              | 1 (0.5)                | -          | -                   |                       |         |
| Neoadjuvant CTx                       | < 0.001              |                       | 0.004                |                       |                       |         |
| Yes                                  | 322 (43.7)           | 25 (11.2)              | 106 (24.9) | 19 (13.4)           |                       |         |
| No                                   | 415 (56.3)           | 170 (74.8)             | 320 (75.1) | 123 (86.6)          |                       |         |
| Adjuvant CTx                         | < 0.001              |                       | 0.001                |                       |                       |         |
| Yes                                  | 473 (64.2)           | 193 (99.0)             | 346 (81.2) | 140 (98.6)          |                       |         |
| No                                   | 264 (35.8)           | 2 (1.0)                | 80 (18.8)    | 2 (1.4)             |                       |         |
| RTx boost                            | 0.066                |                       | 0.054                |                       |                       |         |
| Yes                                  | 589 (79.9)           | 144 (73.8)             | 347 (81.5) | 105 (73.9)          |                       |         |
| No                                   | 148 (20.1)           | 51 (26.2)              | 79 (18.5)    | 37 (26.1)           |                       |         |
| Adjuvant HTx                          | 0.626                |                       | 0.095                |                       |                       |         |
| Yes                                  | 420 (57.0)           | 107 (54.9)             | 256 (60.1) | 74 (52.1)           |                       |         |
| No                                   | 317 (43.0)           | 88 (45.1)              | 170 (39.9) | 68 (47.9)           |                       |         |

Values are means ± standard deviation or number (%).

Tmab = trastuzumab; N-Tmab = no trastuzumab; PSM = propensity score matching; BMI = body mass index; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; CTx = chemotherapy; RTx = radiation treatment; HTx = hormone treatment.

*Values were calculated for propensity score matching; †Patients who had received neoadjuvant chemotherapy were evaluated with clinical stage.
The beneficial effect of trastuzumab on IBTR was different according to the HR status. As shown in Figure 2, there was no significant difference in HR-positive breast cancer between the

### Table 3. Log-rank and Cox regression analyses for ipsilateral breast tumor recurrence-free survival

| Characteristics                  | Log-rank analysis | Cox regression analysis |
|----------------------------------|-------------------|-------------------------|
|                                  | Hazard ratio (95% CI) | p-value | Hazard ratio (95% CI) | p-value |
| Age at surgery (yr)†             |                   |            |                       |         |
| < 50                             | Ref.              | 0.854      |                        |         |
| ≥ 50                             | 1.07 (0.51–2.27)  |            |                        |         |
| BMI (kg/m²)                      |                   |            |                       |         |
| Within normal                    | Ref.              | 0.594      |                        |         |
| Underweight (< 18.5)             | 2.08 (0.48–8.97)  |            |                        |         |
| Overweight (≥ 25.0)              | 1.16 (0.49–2.75)  |            |                        |         |
| Year of surgery                  |                   |            |                       |         |
| 2000–2008                        | Ref.              | 0.018†     | 0.808                  |         |
| 2009–2017                        | 0.41 (0.20–0.88)  |            | 0.88 (0.30–2.54)       |         |
| Axilla surgery                   |                   | 0.471      |                        |         |
| SLNB                             | Ref.              |            |                        |         |
| ANLD                             | 0.77 (0.38–1.58)  |            |                        |         |
| T stage                           |                   | 0.958      |                        |         |
| T1                               | Ref.              |            |                        |         |
| T2                               | 1.08 (0.52–2.24)  |            |                        |         |
| T3–4                             | 0.89 (0.20–3.97)  |            |                        |         |
| N stage                           |                   |            |                       |         |
| N0                               | Ref.              | 0.015†     | 0.068                  |         |
| N1                               | 0.20 (0.06–0.68)  |            | 0.24 (0.07–0.80)       |         |
| N2–3                             | 0.65 (0.20–2.17)  |            | 0.79 (0.24–2.65)       |         |
| Histologic grade                 |                   | 0.384      |                        |         |
| I–II                             | Ref.              |            |                        |         |
| III                              | 1.49 (0.60–3.67)  |            |                        |         |
| Lymphovascular invasion         |                   | 0.326      |                        |         |
| Present                          | Ref.              |            |                        |         |
| Absent                           | 0.70 (0.34–1.43)  |            |                        |         |
| Resection margin                 |                   |            |                       |         |
| Clear                            | Ref.              | 0.001†     | < 0.001                |         |
| Involved or close                | 5.39 (2.41–12.06) |            | 4.92 (2.14–11.32)      |         |
| Hormone receptor status          |                   |            |                       |         |
| Positive                         | Ref.              | 0.007†     | 0.006                  |         |
| Negative                         | 2.72 (1.28–5.78)  |            | 2.94 (1.37–6.34)       |         |
| Ki-67 index                      |                   |            |                       |         |
| < 10%                            | Ref.              | 0.096†     | 0.067                  |         |
| ≥ 10%                            | 1.80 (0.89–3.65)  |            | 2.00 (0.95–4.17)       |         |
| Neoadjuvant CTx                  |                   | 0.210      |                        |         |
| Yes                              | Ref.              |            |                        |         |
| No                               | 2.11 (0.64–6.97)  |            |                        |         |
| Adjuvant CTx                     |                   | 0.500      |                        |         |
| Yes                              | Ref.              |            |                        |         |
| No                               | 0.61 (0.14–2.59)  |            |                        |         |
| RTx boost                        |                   | 0.139      |                        |         |
| Yes                              | Ref.              |            |                        |         |
| No                               | 1.79 (0.82–3.88)  |            |                        |         |
| Trastuzumab                      |                   | 0.002†     | 0.037                  |         |
| Yes                              | Ref.              |            |                        |         |
| No                               | 2.94 (1.42–6.07)  |            | 3.03 (1.07–8.59)       |         |

CI = confidence interval; BMI = body mass index; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; CTx = chemotherapy; RTx = radiation treatment

*Hazard ratio was calculated with univariate Cox regression analysis; †Values were calculated for Cox regression analysis.

**Subgroup analysis according to the HR, resection margin, and axillary node status**

The beneficial effect of trastuzumab on IBTR was different according to the HR status. As shown in Figure 2, there was no significant difference in HR-positive breast cancer between the
Tmab and N-Tmab groups (10-year IBTR rate, 96.7% vs. 94.0%, log-rank $p = 0.410$). Conversely, among the 243 patients with HR-negative breast cancer, the Tmab group had a significantly higher IBTR-free survival rate (10-year IBTR rate, 88.3% vs. 80.2%, log-rank $p = 0.004$).

The Tmab group showed a higher IBTR-free survival rate regardless of the resection margin status. However, trastuzumab treatment had a greater effect on IBTR when the resection margin was close or positive (10-year IBTR rate, 84.9% vs. 43.8%, log-rank $p = 0.015$, Figure 3A and B).

Additionally, while there was no difference according to trastuzumab use among the axillary LN-positive patients (10-year IBTR-free survival rate, 97.0% vs. 96.5%, $p = 0.604$), the Tmab group had a significantly higher IBTR-free survival rate among the LN-negative patients (10-year IBTR-free survival rate, 89.6% vs. 81.5%, $p = 0.003$, Figure 3C and D).

**DISCUSSION**

In this study, we showed that the patients with HER2-positive breast cancer who received neoadjuvant and/or adjuvant trastuzumab treatment had a lower IBTR rate after BCS than those who did not receive trastuzumab treatment. Our result supports the importance of using trastuzumab for 1 year to reduce in-breast recurrence for HER2-positive cancer.

The systemic effect of trastuzumab for HER2-positive breast cancer has been well established in metastatic breast cancer and early breast cancer. The HERA trial randomized patients into 1 and 2 years of trastuzumab and observation groups and showed that administration of trastuzumab for 1 year increased the disease-free survival rate from 77.4% to 85.8% ($p < 0.001$) and 72.2% to 78.6% ($p < 0.001$) after 2 and 4 years of follow-up, respectively [2]. The positive effect of trastuzumab remained beyond 10 years of follow-up (69.0% vs. 63.0%, $p < 0.001$) [3]. Further, the NSABP B-31 and NCCTG N9831 trials analyzed the effect of trastuzumab after doxorubicin and cyclophosphamide administration followed by paclitaxel administration [12]. Adding trastuzumab to chemotherapy improved the 10-
year disease-free survival and overall survival from 75.2% to 84% ($p < 0.001$) and 62.2% to 73.7% ($p < 0.001$), respectively.

For determining the efficacy of trastuzumab on locoregional recurrence (LRR), a few prospective and retrospective studies have been conducted. Cao et al. [13] retrospectively evaluated 278 patients with stage II/III cancer who underwent RT and observed a significant difference in LRR according to trastuzumab use (3-year LRR, 2.4% vs. 7.5%, $p = 0.019$). Kiess et al. [14] reported similar results that trastuzumab can prolong the 3-year locoregional RFS from 92% to 98% after BCS for node-negative HER2-positive breast cancer. Lanning et al. [15] analyzed data from 501 women and found a significantly lower 5-year LRR rate in the trastuzumab-treated group after adjusting for other variables (hazard ratio, 0.21; $p = 0.04$). Kim et al. [16] also found that trastuzumab had an effect on LRR in HR+/HER2+ tumors;
however, contrary to our study results, no effect on LRR in HR-/HER2+ tumors was seen. Importantly, most of these studies did not focus on IBTR, despite the fact that HER2-positive breast cancer is known to have a higher IBTR rate than other subtypes. The guidelines of Society of Surgical Oncology-American Society for Radiation Oncology [17] stated a positive effect of trastuzumab on IBTR after BCS based on the findings of 2 studies [18,19]. However, the 2 referenced studies lack the evidence to support the effect of trastuzumab on IBTR and analyzed its effect on only RFS and overall survival. To date, only assumptions on the effects on IBTR exist, and there is currently no statistical evidence to support it.

According to a previous study conducted in Korea in which the records of 520 patients were analyzed, the 7-year LRR rate was significantly lower in the trastuzumab-treated group than in the non-treated group (4.4% vs. 10.1%, $p = 0.014$); however, there was no evidence of a beneficial effect among patients with estrogen receptor (ER)-positive tumors and a low LN-positive ratio (2.1% vs. 4.2%, $p = 0.75$) [20]. Because our institution participated in this multicenter study, a substantial proportion of the patients analyzed in our study was also included in the previous study. However, we included more patients with a longer follow-up period and used 1:3 PSM instead of 1:1 PSM. In addition, only patients who underwent BCS were included for analysis in this study. We focused on IBTR and set stringent inclusion criteria for the tumor size and axillary node status. Finally, while the previous study included patients who received more than 6 months of trastuzumab treatment, our study excluded patients who did not complete the initially planned regimen for 1 year.

A significant proportion of IBTR seems to result in DM and reduced survival of patients [21]. It is well known that radiation after BCS can reduce IBTR. Expression of HER2/neu shows increased resistance to RT via the focal adhesion kinase-mediated pathway in vitro and in vivo [22]. Anti-HER2 therapy downregulates several HER2 signaling pathways, resulting in radio-sensitization of HER2 breast cancer [23,24]. It can be hypothesized that the synergistic effect of RT and trastuzumab might have elicited reduced IBTR in HER2-positive breast cancer. In our study, the administration of trastuzumab was an independent variable associated with IBTR after adjusting for other factors, such as RT, resection margin status, age at the time of operation, T/N stage, histologic grade, and lymphovascular invasion, which have been reported to affect IBTR.

There are several explanations for the different results according to the ER status. First, ER-positive cancers are more resistant to trastuzumab owing to diverse levels of bidirectional genomic crosstalk between ER and HER2 pathways [25]. Previous studies have demonstrated that highly manifested ER pathways can be an escape route for anti-HER2 treatment, resulting in de novo drug resistance and negating the effect [26]. In addition, Xia et al. [27] reported that continuous exposure to anti-HER2 treatment enhances ER signaling by facilitating transcriptional activity (depressing FOXO3a and increasing caveolin-1). Acquired resistance enforces the ER and plays a major role in regulating the cancer cells. Second, ER signaling stimulates the G1/S phase transition in the cell cycle and diminishes DNA repair inducing radiosensitivity [28]. It results in favorable prognosis of RT for ER-positive breast cancer, making the effects of trastuzumab smaller than those for ER-negative cancer. In contrast, HER2-overexpressed cancer was reported to be radioresistant by cell adhesion and anoikis resistance, indicating that the importance of trastuzumab might be remarkable [22]. Finally, the magnitude of the HER2/CEP17 ratio on HER2/neu gene amplification is heterogeneous among HER2-positive breast cancers. The clinical significance of the HER2/CEP17 ratio is important in that a lower ratio predicts a worse RFS and overall survival after trastuzumab treatment [29]. As ER negativity was previously reported to be significantly
associated with a high HER2/CEP17 ratio [30], ER-negative breast cancer might have been more strongly affected by trastuzumab. Unfortunately, not all patients in our study underwent the FISH test; thus, the data for the HER2/CEP17 ratio are missing.

This study has several limitations. It was a long-term retrospective study conducted at a single institution. Owing to the inherent nature of a retrospective study, selection bias is bound to occur. To eliminate the selection bias and confounding effects, we conducted PSM to minimize the difference in the variables between the 2 groups. Despite our efforts, the number of patients who received neoadjuvant treatment was not able to be matched owing to large differences in the original cohort. Additionally, as trastuzumab has been recommended for HER2-positive breast cancer since 2007, and insurance coverage had been expanded for tumors exceeding 1 cm without LN metastasis since 2010 in Korea, the follow-up period of the Tmab group was shorter than that of the N-Tmab group (median, 65.9 vs. 100.9 months; \( p < 0.001 \)). This selection bias may have affected the results as breast cancer recurs even more than several years after surgery. In this study of 41 patients with IBTR, 8 patients showed recurrence after 7 years of surgery; 3 patients had HR-positive tumors, and 5 patients had HR-negative tumors. To circumvent this problem, we performed the landmark analysis discarding the follow-up at 5, 7, and 10 years after surgery (Supplementary Figure 1). The median follow-up period was not significantly different between the 2 groups at the 5th year follow-up; however, the beneficial effect of trastuzumab on IBTR significantly remained at all points of landmark. Further, we regarded RR and DM as non-informative censored data to exclude the effect of systemic therapy on subsequent IBTR, despite the shorter RFS of the patients with RR and DM than that of the patients with IBTR during the same period (Supplementary Figure 2). The N-Tmab group had a poorer DM-free survival than the Tmab group; thus, the IBTR rate may have been overestimated when competing risks were considered. This may be the reason for the lower IBTR rate for the patients with node-positive tumors than for the other patients. Nonetheless, several studies have reported that the node status is not associated with IBTR-free survival [8,13]. Moreover, diverse chemotherapy and RT regimens, except for RT boost, were not considered in this study. As most patients in the Tmab group were treated more recently than did the patients in the N-Tmab group, significant improvements of treatments, such as the operative technique, method of pathologic confirmation for the resection margin, and adjuvant treatments, including regimen of chemotherapy, might have resulted in better outcomes and led to bias. To reduce the bias, we analyzed the year of surgery using a Cox proportional hazard model. Finally, patients who discontinued their trastuzumab treatment before the end of the originally planned cycles were excluded from this study. However, the number of patients who discontinued the trastuzumab treatment was too small that the effect of early discontinuation could not be analyzed.

In conclusion, administration of trastuzumab for 1 year is an independent factor associated with reduced IBTR after BCS and RT in patients with HER2-positive breast cancer. The benefit of trastuzumab is more prominent in HR-negative cancer or axillary LN-negative breast cancer.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Reasons for discontinuation of trastuzumab
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Supplementary Figure 1
Kaplan-Meier curves showing IBTR-free survival rate after landmark analysis. To minimize the confounding effect of different follow-up period, we conducted landmark analysis at 5-, 7-, and 10-year of surgery. The median follow-up period was significantly different between 2 groups at 7- and 10-year, but it was not at the point of 5-year. All Kaplan-Meier curves show significant difference of IBTR-free survival between 2 groups at all points.
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Supplementary Figure 2
Kaplan-Meier curves showing recurrence-free survival of all patients depending on metastasis sites. The Kaplan-Meier curves show RR-free survival (A), and DM-free survival (B) of all 568 patients according to trastuzumab administration.
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