

## ORIGINAL ARTICLE

# Association of Human Epidermal Growth Factor Receptor 2 with Radiotherapy Resistance in Patients with T1N0M0 Breast Cancer

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**Purpose:** Preclinical studies have shown that human epidermal growth factor receptor 2 (HER2) status is associated with resistance to radiotherapy (RT). In this study, we evaluated the overall survival of a T1N0M0 breast cancer cohort in Korea according to the use of RT and the HER2 status. **Methods:** We analyzed data collected from 11,552 patients with invasive breast cancer who were enrolled in the Korean Breast Cancer Society Registration Program between 1999 and 2007. Data on the TNM stage, estrogen receptor status, progesterone receptor status, HER2 status, operation method, and the use of RT were analyzed. **Results:** The median follow-up period was 51 months. A significant improvement in overall survival after RT was observed only in the HER2(-) group. In this group, the 10-year overall survival rate

was 95.5% for patients who did not receive RT and 96.3% for patients who received RT ( $p=0.037$ ). In contrast, in the HER2(+) group, RT was not associated with a survival benefit ( $p=0.887$ ). Multivariate analysis showed that RT was significantly associated with a reduction in mortality in the HER2(-) group (hazard ratio, 0.738; 95% confidence interval, 0.549–0.993;  $p=0.045$ ). **Conclusion:** We found that postoperative RT was not associated with a survival benefit in HER2(+) breast cancer patients, suggesting that HER2(+) breast cancers could be RT resistant.

**Key Words:** Breast neoplasms, Human epidermal growth factor receptor 2, Radiotherapy, Survival

## INTRODUCTION

Radiotherapy (RT) is an important treatment modality in breast cancer management. Multiple clinical trials have demonstrated long-term RT-related mortality benefits in patients with breast cancer [1-4]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed a meta-analysis to determine the effects of RT after breast-conserving surgery (BCS). In this analysis, RT reduced the 15-year risk of breast cancer death from 25.2% to 21.4%, an absolute reduction of 3.8% (95% confidence interval [CI], 1.6–6.0;  $p=0.00005$ ) [4]. Several important trials have evaluated the effects of postmas-

tectomy RT. The Danish Breast Cancer Cooperative Group (DBCG) protocols 82b and 82c, the British Columbia trial, and the EBCTCG meta-analysis showed that postmastectomy RT was associated with a significant improvement in overall survival [1,3,5,6]. Taken together, these results suggest that RT-induced locoregional control can result in improved overall survival.

The human epidermal growth factor receptor 2 (HER2) is amplified or overexpressed in 20% to 25% of patients with breast cancer [7,8]. Recent reports suggest that HER2 expression is associated with a high rate of locoregional recurrence [9-11]. Although the relationship between HER2 status and treatment failure is generally accepted, the exact mechanism is not entirely understood. Some preclinical studies showed that HER2 plays a major role in the modulation of radiation sensitivity [12-14]. Breast cancer cells develop resistance to RT when transfected with the *HER2* gene [12,14]. Further, specific inhibition of HER2 mRNA by siRNA increased the radiosensitivity of HER2(+) SKBR3 breast cancer cells [13]. How-

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ever, few clinical studies on this subject have been reported. The DBCG conducted a subgroup analysis of overall survival according to molecular subtype in high-risk patients who participated in trials based on the DBCG protocols 82b or 82c [15]. In this analysis, patients with hormone receptor (HR)(-)/HER2(+) status did not show any survival improvement after treatment with total mastectomy plus partial axillary dissection and RT. Although the participants were high-risk patients, this analysis suggested that HER2(+) tumors are possibly resistant to RT.

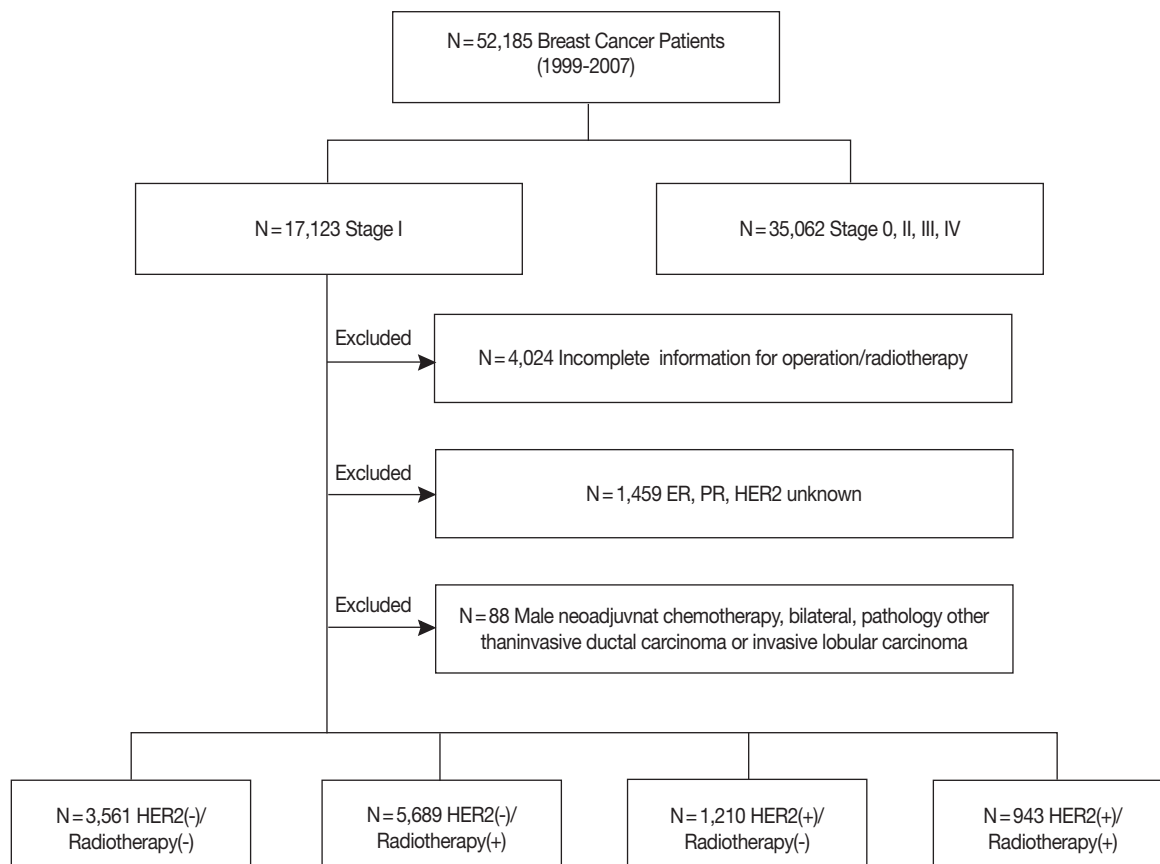
To evaluate the effects of RT on survival according to the HER2 status in early breast cancer patients, we retrospectively analyzed data from the nationwide Korean breast cancer patient cohort.

## METHODS

### Patients

The Korean Breast Cancer Society (KBCS) registry database was used to identify node-negative patients with newly diagnosed invasive breast cancer with a tumor less than  $\leq 2$  cm

between January 1999 and December 2007. The KBCS registry has prospectively collected nationwide breast cancer data since 1996 [16-19]. The Online Korean Breast Cancer Registration Program was launched in 2001. Physicians personally enter clinicopathological data of newly diagnosed biopsy-proven primary breast cancer patients into the web-based database. The database contains information regarding the patients' sex and age, the surgical method used, the histologic findings, status of biologic markers (including HER2 status), adjuvant treatment, and cancer stage (according to the sixth American Joint Committee on Cancer classification). Patient survival data, including the dates and causes of death, were obtained from the Death Certification of the Korean National Statistical Office and the Korean Central Cancer Registry of the Ministry of Health and Welfare. The Korean Central Cancer Registry is linked to the Korea National Statistical Office, which has recorded complete death statistics by using a unique identification numbers that are assigned to all Korean residents [16-19]. Between January 1999 and December 2007, 52,185 patients were registered in this database. The database includes more than 40% of the incidence data from The Korea



**Figure 1.** Patient selection flow chart.

ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2.

National Cancer Incidence Database (KNCID), and the completeness of the KNCID for 2009 was 97.2%, as determined by the Ajiki method [20]. Detailed information on the KBCS registry has been provided elsewhere [16-20]. The last date of follow-up was December 31, 2008. This study was approved by the Institutional Review Board of the Korea Cancer Center Hospital (approval number: K-1305-002-017).

Of the 52,185 patients identified, we excluded those patients with incomplete information regarding estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, operation method, and use of RT and male patients. Patients with bilateral disease, malignant phyllodes tumor, lymphoma, sarcoma, squamous cell carcinoma, prior malignancy, and prior treatment with neoadjuvant chemotherapy were also excluded. Thus, a total of 11,552 patients were included in this analysis (Figure 1).

### HER2 and hormone receptor status

HER2 positivity was defined as a rating of 3+ on immunohistochemistry (IHC) and/or gene amplification on fluorescence *in situ* hybridization (FISH). ER and PR status was defined as positive or negative by physicians according to each institution's standard methods and cutoff values. Tumors that were ER or PR positive were defined as hormone receptor (HR) positive, and tumors that were ER and PR negative were defined as HR negative.

### Statistical analysis

Data analysis was performed using SPSS version 14.0 (SPSS Inc., Chicago, USA). The chi-square test was used to assess differences in the clinicopathological factors between the groups. Survival rates were estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. The Cox proportional hazards model was used to perform multivariate analyses. Statistical significance was accepted for *p*-values of less than 0.05.

## RESULTS

### Patient characteristics

Patient and tumor characteristics and data on the adjuvant systemic treatment received are summarized in Table 1. The mean age of the patients was 49.0 ± 10.1 years, and 6,646 patients (57.5%) were younger than 50 years. Of the 11,552 patients, 18.6% had HER2(+) disease and 72.3% had HR(+) disease. RT had been administered to 6,781 patients (58.7%). The proportion of patients who had undergone BCS was 61.5%, and 92.6% of these patients had received postoperative RT. Among the patients who had undergone mastectomy, only

**Table 1.** Clinicopathologic characteristic of patients

Characteristic	No. (%)
Total no.	11,552 (100.0)
Age at diagnosis (yr)*	49.0 ± 10.1
<50	6,646 (57.5)
≥50	4,757 (41.2)
Unknown	149 (1.3)
Histology	
Invasive ductal cancer	11,312 (97.9)
Invasive lobular cancer	240 (2.1)
T stage	
T1mic	420 (3.6)
T1a	825 (7.1)
T1b	2,366 (20.5)
T1c	7,637 (66.1)
Unknown	304 (2.6)
Hormone receptor status	
ER- and PR-	3,199 (27.7)
ER+ and/or PR +	8,353 (72.3)
HER2	
0, 1+, 2+	9,399 (81.4)
3+ or FISH+	2,153 (18.6)
Breast operation and radiotherapy	
Breast-conserving surgery	7,106 (61.5)
Mastectomy	4,446 (38.5)
Chemotherapy	
No	5,466 (39.5)
Yes	6,683 (57.9)
Unknown	303 (2.6)
Endocrine therapy	
No	3,092 (26.8)
Yes	7,803 (67.5)
Unknown	657 (5.7)
Radiotherapy	
No	4,771 (41.3)
Yes	6,781 (58.7)

ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; FISH=fluorescence *in situ* hybridization.

\*Mean ± SD.

201 (4.5%) had received postoperative RT. Further, 57.9% of the patients had received adjuvant chemotherapy, and 67.5% had received endocrine therapy. Five patients (0.2%) with HER2(+) tumors had been treated with adjuvant trastuzumab therapy. No patients had received adjuvant lapatinib therapy.

Table 2 summarizes the clinicopathological characteristics according to the use of RT and HER2 status. In the HER2(-) group, 61.5% of the patients had received RT. The HER2(-)/RT(+) group had a larger proportion of patients younger than 50 years (*p* < 0.001), a larger number of patients with HR(-) disease (*p* = 0.028), and fewer patients who were treated with adjuvant chemotherapy than the HER2(-)/RT(-) group. In the HER2(+) group, 943 patients (43.8%) had received RT. The HER2(+)/RT(-) group had a larger proportion of younger patients (*p* = 0.004), fewer patients with HR(-) disease, and a

**Table 2.** Clinicopathologic characteristics according to radiation therapy based on HER2 status

Characteristic	HER2(-) (n=9,399)			HER2(+) (n=2,153)		
	RT(-) (n=3,561) No. (%)	RT(+) (n=5,838) No. (%)	<i>p</i> -value	RT(-) (n=1,210) No. (%)	RT(+) (n=943) No. (%)	<i>p</i> -value
Age at diagnosis (yr)						
< 50	1,865 (52.4)	3,563 (62.6)	<0.001	652 (53.9)	566 (60.0)	0.004
≥ 50	1,696 (47.6)	2,126 (37.4)		558 (46.1)	377 (40.0)	
T stage						
T1mic	111 (3.2)	86 (1.5)	<0.001	152 (13.0)	71 (7.7)	<0.001
T1a	259 (7.5)	365 (6.4)		135 (11.5)	66 (7.2)	
T1b	704 (20.3)	1,332 (23.4)		185 (15.8)	145 (15.8)	
T1c	2,390 (69.0)	3,911 (68.7)		700 (59.7)	636 (69.3)	
Hormone receptor status						
ER- and PR-	774 (21.7)	1,384 (23.7)	0.028	652 (53.9)	389 (41.3)	<0.001
ER+ and/or PR+	2,787 (78.3)	4,454 (76.3)		558 (46.1)	554 (58.7)	
Operation						
Breast-conserving surgery	459 (12.9)	5,682 (97.3)	<0.001	67 (5.5)	898 (95.2)	<0.001
Mastectomy	3,102 (87.1)	156 (2.7)		1,143 (94.5)	45 (4.8)	
Adjuvant chemotherapy						
No	1,595 (45.0)	2,190 (39.2)	<0.001	472 (39.3)	309 (33.7)	0.008
Yes	1,951 (55.0)	3,394 (60.8)		729 (60.7)	609 (66.3)	
Adjuvant trastuzumab						
No	-	-		1,208 (99.8)	940 (99.7)	0.659
Yes	-	-		2 (0.2)	3 (0.3)	

HER2=human epidermal growth factor receptor 2; RT=radiation therapy; ER=estrogen receptor; PR=progesterone receptor.

higher frequency of treatment with adjuvant chemotherapy than the HER2(+)/RT(+) group. Operation methods according to RT were significantly imbalanced in both the HER2(-) and HER2(+) groups.

A total of 181 death events occurred during a median follow-up period of 51 months (range, 1–140 months). The 10-year overall survival rate was 96.0% (Figure 2A). Overall survival did not differ significantly between patients with HER2(+) tumors and those with HER2(-) tumors ( $p=0.208$ ), as shown in Figure 2B. The operation method used was not associated with overall survival ( $p=0.201$ ) (Figure 2C). In contrast, overall survival differed significantly between patients treated with RT and those not treated with RT. The patients treated with RT had a significantly better overall survival ( $p=0.040$ ) (Figure 2D).

#### Univariate survival analyses according to HER2 status and the use of radiotherapy

Among patients with HER2(-) disease, the 10-year overall survival rate was higher in those younger than 50 years (96.5% vs. 95.4%,  $p=0.029$ ), in those with HR(+) disease (97.1% vs. 92.6%,  $p<0.001$ ), and in those treated with RT (96.3% vs. 95.5%,  $p=0.037$ ). No significant difference in overall survival was found between patients treated with adjuvant chemotherapy and those treated without adjuvant chemotherapy.

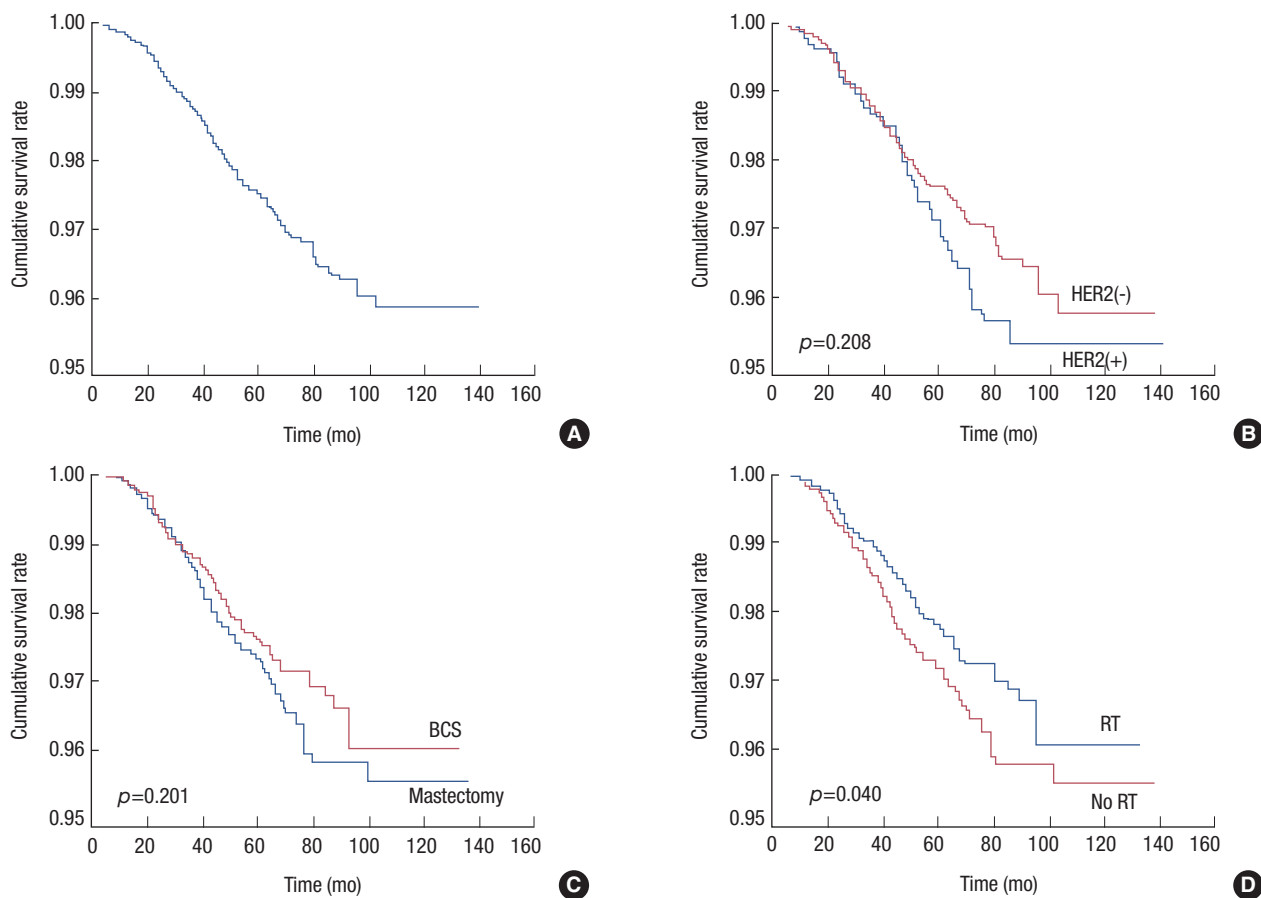
In contrast, among HER2(+) patients, no significant differ-

ence was found among patients with regard to various risk factors, including the age at diagnosis, HR status, adjuvant chemotherapy, and the use of RT. The 10-year overall survival rate in the HER2(+) patient group was 95.7% for patients who did not receive RT and 95.3% for those who received RT ( $p=0.887$ ) (Table 3, Figure 3).

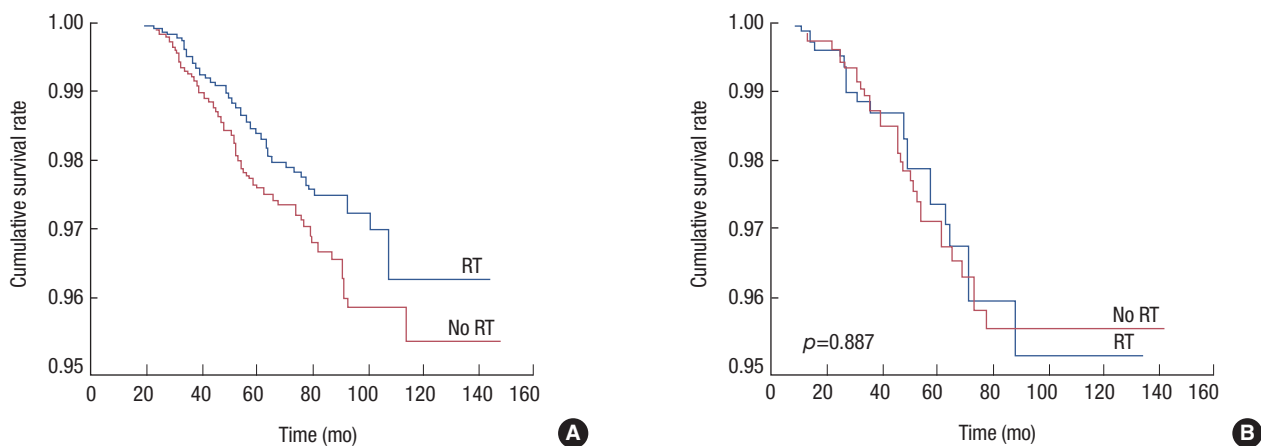
Overall survival was analyzed according to the molecular subtype and RT use. Among patients with HR(+)/HER2(-) disease, the 10-year overall survival rate was greater in those treated with RT than in those not treated with RT (97.6% vs. 96.5%,  $p=0.021$ ). However, no significant difference was found in overall survival between patients treated with RT and those treated without RT among patients with HR(+)/HER2(+) disease (93.9% vs. 96.8%,  $p=0.182$ ), HR(-)/HER2(+) disease (97.8% vs. 94.6%,  $p=0.087$ ), or HR(-)/HER2(-) disease (93.2% vs. 92.0%,  $p=0.372$ ).

#### Multivariate survival analysis in patients with HER2(-) tumors

To identify the factors that predict overall survival in the subgroup of patients with HER2(-) tumors, multivariate analysis was performed. Variables that were statistically significant in univariate analysis were included in multivariate analysis. These were age at diagnosis, HR status, mass size, and use of RT. Multivariate analysis showed that the use of RT could predict overall survival in patients with HER2(-) disease (hazard ratio [HR], 0.738; 95% CI, 0.549–0.993;  $p=0.045$ ) (Table 4).



**Figure 2.** (A) Overall survival for all patients. (B) Overall survival according to human epidermal growth receptor 2 (HER2) status. (C) Overall survival according to operation methods. (D) Overall survival according to whether radiotherapy (RT) or not. BCS=breast-conserving surgery.



**Figure 3.** Effect of radiotherapy (RT) on breast cancer mortality after curative operation (A) in the human epidermal growth receptor 2 (HER2) (-) group and (B) in the HER2(+) group.

In addition, an age of  $\geq 50$  years at diagnosis (HR, 1.410; 95% CI, 1.044–1.904;  $p = 0.025$ ) and HR(+) status (HR, 0.351; 95% CI, 0.260–0.472;  $p < 0.001$ ) retained statistical significance as

predictors of overall survival. In the HER2(+) group, no factors were found to significantly predict overall survival in univariate analysis. Therefore, multivariate analysis was not per-

**Table 3.** Univariate analysis of factors associated with overall survival based on HER2 status and radiation therapy use

Risk factor	HER2(-)					HER2(+)				
	No. of patients	No. of death	5-year survival (%)	10-year survival (%)	p-value	No. of patients	No. of death	5-year survival (%)	10-year survival (%)	p-value
Age at diagnosis (yr)										
< 50	5,428	88	98.1	96.5	0.029	1,218	33	97.1	95.5	0.853
≥ 50	3,822	91	97.3	95.4		935	22	96.9	95.5	
T stage										
T1mic	197	0	100.0	100.0	<0.001	223	3	98.1	-	0.180
T1a	624	5	98.8	-		201	1	99.5	99.5	
T1b	2,036	21	98.4	98.4		330	7	97.4	95.6	
T1c	6,301	150	97.3	95.1		1,336	42	96.5	94.8	
Hormone receptor status										
ER- and PR-	2,158	86	95.0	92.6	<0.001	1,041	26	96.7	95.7	0.990
ER+ and/or PR+	7,241	95	98.6	97.1		1,112	29	97.4	95.5	
Adjuvant chemotherapy										
No	3,785	60	98.2	96.5	0.078	781	23	96.8	94.2	0.301
Yes	5,345	117	97.4	95.6		1,338	30	97.2	96.6	
Radiotherapy										
No	3,561	88	97.4	95.5	0.037	1,210	33	96.8	95.7	0.887
Yes	5,838	93	97.9	96.3		943	22	97.4	95.3	

HER2=human epidermal growth factor receptor 2; ER=estrogen receptor; PR=progesterone receptor.

**Table 4.** Multivariate analysis of factors associated with overall survival on patients with HER2 negative tumor

Risk factor	HR	95% CI		p-value
		Lower	Upper	
Age at diagnosis (yr)				
< 50	1.0			0.025
≥ 50	1.410	1.044	1.904	
Hormone receptor status				
ER- and PR-	1.0			<0.001
ER+ and/or PR+	0.351	0.260	0.472	
T stage				
T1mic	1.0			0.008
T1a	4,824.651	0	2.727	
T1b	5,477.907	0	3.087	
T1c	11,046.499	0	6.220	
Radiotherapy				
No	1.0			0.045
Yes	0.738	0.549	0.993	

HER2=human epidermal growth factor receptor 2; HR=hazard ratio; CI=confidence interval; ER=estrogen receptor; PR=progesterone receptor.

formed for this group.

## DISCUSSION

In the present study, we showed that breast cancer patients with HER2(+) disease do not obtain an overall survival benefit from postoperative RT, unlike those with HER2(-) disease. To our knowledge, this is the first large-scale clinical analysis to show that HER2(+) tumors display a tendency for RT resis-

tance in patients with T1N0M0 breast cancer. This result has clinical relevance because the use of RT after BCS is increasing with the trend in the general use of screening mammography.

Although some preclinical data support the hypothesis that the HER2 status is positively associated with RT resistance, the available clinical data on this subject are limited. The DBCG conducted a subgroup analysis of 1,000 patients from the DBCG studies based on protocols 82b and 82c, in which the inclusion criteria were positive lymph nodes and/or tumors of > 5 cm in size and/or tumor invasion of the skin or pectoralis muscle fascia [15]. All patients had received total mastectomy, axillary dissection, and 8 cycles of CMF (cyclophosphamide, methotrexate, and fluorouracil) as adjuvant chemotherapy. In subgroup analysis, IHC staining was used to evaluate the ER, PR, and HER2 statuses, and tissue microarrays were used for FISH analyses of HER2 expression. The median follow-up time was 17 years. The 4 subgroups were defined according to ER, PR, and HER2 expression: HR(+)/HER2(-), HR(+)/HER2(+), HR(-)/HER2(-), and HR(-)/HER2(+). Postmastectomy RT did not improve overall survival for the HR(-)/HER2(+) subtype, whereas it significantly improved overall survival for the HR(+)/HER2(-) subtype. In the present nationwide analysis of T1N0M0 patients, we found that no RT-related survival benefits were observed in the HER2(+) group, whereas RT conferred survival benefits in the HER2(-) group. This result closely agrees with those of the DBCG subgroup analyses based on the 82b and 82c protocols, although these analyses were conducted on very differ-

ent populations. In contrast to the present study and the DBCG subgroup analyses based on the 82b and 82c protocols, Rozan et al. [21] reported that HER2 overexpression was not associated with RT use in a neoadjuvant setting. The authors evaluated tumor responses to FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) chemotherapy or RT. Of 329 patients, 156 were assigned to the neoadjuvant RT group, in which HER2 expression was not significantly associated with tumor response. However, the small number of patients limits the utility of these results; only 26 patients (16.7%) had tumors that were strongly positive for HER2.

Previous reports have suggested that breast cancer subtypes were associated with the risk of local and regional recurrence or survival [4,9,11,22,23]. However, the mechanism by which HER2 positivity predicts a poor prognosis is unknown. To evaluate the relationship between the use of RT and survival, the patients evaluated must not have pre-existing distant micrometastatic disease [24]. Therefore, the target population should include patients with very early-stage disease. In the present study, only patients with T1N0M0 disease were included in the analysis. Despite the relatively short follow-up period and the generally low number of death events in this population, the survival rate differed significantly between the HER2(-)/RT(+) and HER2(-)/RT(-) groups.

The study presented herein was a retrospective analysis, and therefore, it has several limitations. First, a clinical and pathological imbalance existed between the groups. Second, the operation method was excluded from multivariate analysis because it was an intervening variable of RT. However, it is well established that the operation method does not affect the overall survival of patients with early breast cancer. Veronesi et al. [25] found that after 20 years of follow-up, the long-term survival rate of patients who underwent BCS did not differ from that of patients who underwent radical mastectomy. In the National Surgical Adjuvant Breast and Bowel Project B-06, 1,851 patients were assigned randomly to one of several treatment groups: total mastectomy, lumpectomy only, lumpectomy, and breast irradiation. The findings reported after 20 years showed no significant differences between the groups with regard to disease-free survival, distant disease-free survival, and overall survival [26]. In accordance with these prospective randomized trials, the data from the present study also showed that overall survival was not affected by the operation method ( $p=0.201$ ). A third limitation of our study was that locoregional recurrence was not analyzed. Because the recurrence data were entered freely by the physicians at each institute, data were incomplete in several cases. In contrast with the recurrence data, the Korean Breast Cancer Society online registry database contains complete and accurate data

on death events that are obtained biannually from the Korean National Statistical Office and the Korean Central Cancer Registry of the Ministry of Health and Welfare according to unique identification numbers. Finally, according to the EBCTCG meta-analysis, on average, approximately 1 breast cancer death was avoided by year 15 for every 4 recurrences that were avoided by year 10 as a result of RT [4]. Thus, the median follow-up time of 51 months in our study is a relatively short time with which to provide definitive answers regarding the absolute survival benefits of RT.

Our data showed that HER2 positivity was related to RT resistance in patients with T1N0M0 breast cancer. These results suggest that HER2-targeted therapies are potentially useful as radiosensitizers for patients with HER2(+) tumors. However, the relatively short follow-up period and lack of locoregional recurrence data should be considered when interpreting these findings. In a preclinical study, RT resistance induced by *HER2* gene transfection was overcome by trastuzumab both in *in vitro* and *in vivo* studies [12]. Inhibition of PI3K-Akt-mTOR signaling (HER2 pathway) has been shown to increase radiosensitivity in HER2(+) breast cancer cell lines [13,27]. In addition, lapatinib, a small molecule tyrosine kinase inhibitor of HER1 and HER2, acts as a radiosensitizer in HER2(+) breast cancer xenografts [28]. Unfortunately, clinical information regarding the radiosensitization effects of HER2-targeted therapy is currently unavailable. At present, trastuzumab and lapatinib are commonly used in clinical practice as standard therapies for the treatment of HER2(+) breast cancer. However, the optimal sequence for RT and trastuzumab in an adjuvant setting for breast cancer treatment is not yet established. Phase II trials showed that concurrent therapy with trastuzumab and RT was well tolerated [29,30]. A large prospective randomized clinical trial might provide insight into whether the combination of RT and HER2-targeted therapy could improve the survival of patients with HER2(+) tumors.

## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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