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# Trends in the Application of Postmastectomy Radiotherapy for Breast Cancer With 1 to 3 Positive Axillary Nodes and Tumors $\leq 5$ cm in the Modern Treatment Era

## A Retrospective Korean Breast Cancer Society Report

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**Abstract:** Despite high-level evidence, the benefit of postmastectomy RT in these patients in recent years has not been fully elucidated. We investigated postmastectomy radiotherapy (RT) use and evaluated clinicopathologic and treatment factors influencing RT use in Korean women with pT1-2N1 breast cancer.

We identified women diagnosed with pT1-2N1 breast cancer between 1994 and 2009 using the Korean Breast Cancer Registry. Factors associated with RT use were evaluated using logistic regression analysis. The median follow-up was 95 months.

Of the 6196 women, 11.9% underwent postmastectomy RT. RT was applied more frequently in women with 3 positive lymph nodes (adjusted odds ratio [OR], 2.69) and larger tumors (OR per centimeter, 1.10). RT use was not significantly associated with well-established risk factors (e.g., tumor grade, hormone receptor status, and lymphovascular space invasion). Although RT utilization increased gradually during the study period (OR per year, 1.07), factors associated with RT were similar over time. The estimated 5-year overall survival increased significantly from 84.1% in 1994 to 2000 to 94.6% in 2005 to 2009.

This population-based analysis revealed that the indications for postmastectomy RT in pT1-2N1 breast cancer in Korea are based solely on conventional anatomical factors, although their survival has increased significantly in the modern treatment era. There is a significant unmet need for better risk stratification in these patients and for tailored RT with the incorporation of tumor biology-associated factors.

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**Abbreviations:** AC = doxorubicin and cyclophosphamide, ACOSOG = American College of Surgeons Oncology Group, DSS = disease-specific survival, ECOG = Eastern Cooperative Oncology Group, EORTC = European Organization for Research and Treatment of Cancer, KBCR = Korean Breast Cancer Registry, LRR = locoregional recurrence, LVI = lymphovascular space invasion, NCIC-CTG = National Cancer Institute of Canada Clinical Trials Group, NSABP = National Surgical Adjuvant Breast and Bowel Project, OS = overall survival, PET = positron-emission tomography, pN1mi = micrometastases, RT = radiotherapy, SLNB = sentinel lymph node biopsy, T-based = paclitaxel-containing regimens.

## INTRODUCTION

In patients with breast cancer, nodal status is a significant factor for the prognostication and selection of adjuvant radiotherapy (RT).<sup>1</sup> Randomized trials have demonstrated survival benefits for patients with node-positive breast cancer who underwent mastectomy and adjuvant RT, compared with those who underwent mastectomy alone.<sup>2-4</sup> Despite high-level evidence, the use of postmastectomy RT is still controversial in women with the involvement of 1 to 3 axillary lymph nodes (pN1). With contemporary multidisciplinary management, overall survival (OS) has been increasing in patients treated since 2000 compared with that in those treated in earlier trials,<sup>5-7</sup> and the locoregional recurrence (LRR) risk is likely to be correspondingly lower in these patients.<sup>5-7</sup> In this respect, the present absolute benefits of postmastectomy RT for pT1-2N1 breast cancer are likely to be small.

Given the excellent recent treatment outcomes, there is no consensus on the definite indication for postmastectomy RT in patients with pN1 breast cancer. A number of risk factors for LRR following mastectomy alone, including large tumor size, unfavorable tumor biology, or young age, have been reported.<sup>7-9</sup> This knowledge can guide careful patient selection for postmastectomy RT to avoid unnecessary local therapy because RT may have detrimental impacts in terms of breast cosmetics, late toxicity, and associated costs.<sup>10</sup> A better understanding of RT use is important to optimize patient care.

We hypothesized that because OS has increased, patients may have been selected more appropriately for postmastectomy RT in Korea. Therefore, the objective of this study was to determine the survival in patients with pT1-2N1 breast cancer and describe the trend of RT use in Korea using the Korean

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Breast Cancer Registry nationwide database. In addition, we evaluated the impact of clinicopathologic and treatment factors on RT use.

## METHODS

### Data Source and Collection

The Korean Breast Cancer Society has assembled information on breast cancer since 1996. The details of the Korean Breast Cancer Registry (KBCR) have been described previously.<sup>11–13</sup> In brief, nationwide, breast surgeons in 110 teaching hospitals have voluntarily participated in the KBCR program. These surgeons prospectively collect data on sex, age, surgical method used, and cancer stage as essential items, and operative and pathologic findings, laboratory and imaging findings, biologic markers, and adjuvant treatment as optional items. This registry comprised about 92.0% of all newly diagnosed breast cancer patients in Korea in 2011. Survival data, including dates and causes of death, were obtained from the Korean Central Cancer Registry, Ministry of Health and Welfare, Korea. The KBCR is linked to the Korean National Statistical Office with complete death statistics using unique identification numbers assigned to all Korean residents, and was recently updated in 2013. The KBCR does not include information regarding tumor recurrence.

### Description of the Study Cohort

Patients were eligible for analysis if they were diagnosed with invasive ductal carcinoma of the breast and underwent

mastectomy between January 1, 1994 and December 31, 2009. Exclusion criteria are shown in Figure 1. We excluded patients without information on the receipt of postmastectomy RT. The final study cohort comprised 6196 women with complete data. The median follow-up period was 95 months (range, 37–229 months) and 5-year follow-up data were available in 84% of patients. The review board of the Korean Breast Cancer Society approved this study. The institutional review board of Severance Hospital concluded that no informed consents were needed for this observational and retrospective study.

### Statistical Analyses

The proportion of women who underwent postmastectomy RT over specific periods was the primary endpoint. Univariate and multivariate logistic regression analyses were conducted to assess whether there was an association between the year of mastectomy, age, tumor size, number of lymph nodes involved, tumor grade, hormone-receptor status, lymphovascular space invasion (LVI), method of axillary clearance, number of retrieved nodes, use of adjuvant chemotherapy, breast reconstructive surgery, and receipt of postmastectomy RT. To further investigate whether patterns changed over time, the year of mastectomy was categorized into 3 periods (1994–2000, 2001–2004, and 2005–2009), and the same analyses were conducted. Secondary endpoints included OS (from mastectomy to any cause of death) and disease-specific survival (DSS, from mastectomy to death from breast cancer, women who died of other causes were censored at the time of death). Univariate and multivariate Cox proportional hazards survival analyses were

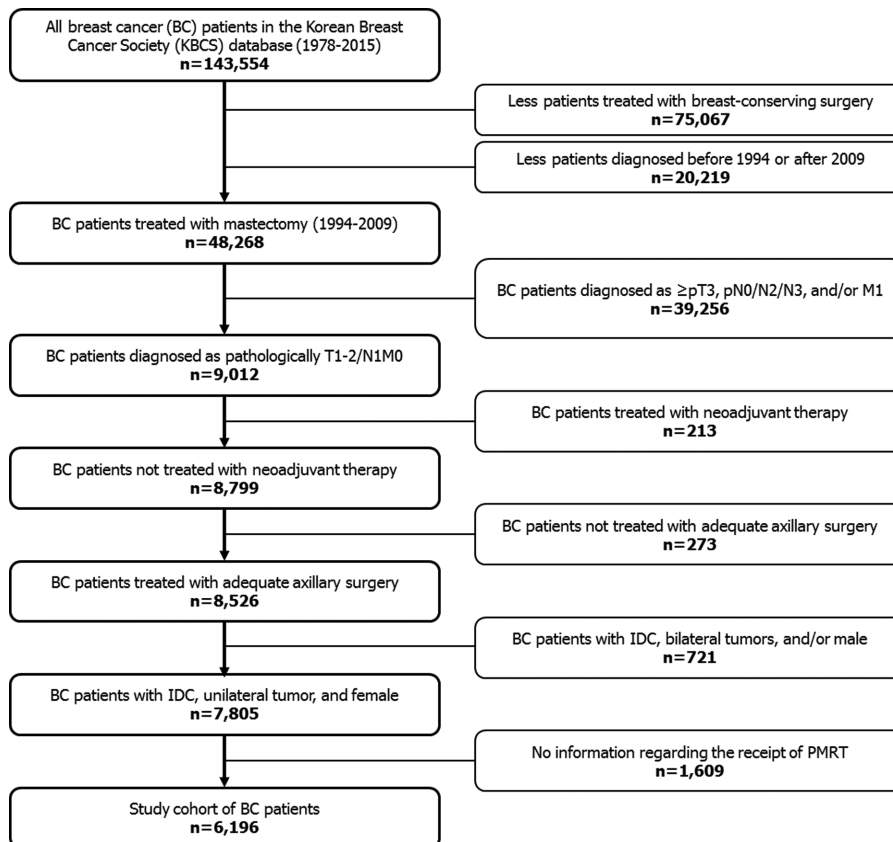


FIGURE 1. Selection of the study cohort. PMRT = postmastectomy radiation therapy.

performed to model the association of variables with OS or DSS. Conditional landmark analysis was used to eliminate guarantee-time bias introduced by misclassification of patients without adjuvant treatments who had died before reaching last follow-up.<sup>14</sup> The level of statistical significance was set at 5%. All statistical analyses were performed using SPSS version 20.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

## RESULTS

### Patient Clinicopathologic and Treatment Characteristics

The baseline clinicopathologic and treatment characteristics of this study cohort are described in Table 1. The median patient age at diagnosis was 48 years (range, 24–94 years). Among patients with available pathology (n = 4576), 49.3% of patients had LVI. No patients underwent sentinel lymph node biopsy (SLNB) alone for pT1-2N1 after mastectomy within the study period. Among patients who underwent chemotherapy (n = 5763), 35.8%, 23.5%, and 33.6% of patients received paclitaxel-containing regimens (T-based), doxorubicin and cyclophosphamide (AC), and others (e.g., cyclophosphamide/methotrexate/fluorouracil), respectively.

### Factors Associated With Postmastectomy RT

Factors associated with having undergone postmastectomy RT were as follows: age <40 years (vs. age 50–64 years; adjusted odds ratio [aOR], 1.95; 95% confidence interval [CI], 1.50–2.53; *P* < 0.001); age 40–49 (vs. age 50–64 years; aOR, 1.25; 95% CI, 1.00–1.56; *P* = 0.054); larger tumor size (per centimeter; aOR, 1.11; 95% CI, 1.01–1.21; *P* = 0.025); and 3 positive lymph nodes (aOR, 2.71; 95% CI, 2.20–3.33; *P* < 0.001). Factors inversely associated with having undergone postmastectomy RT were as follows: age ≥65 years (vs. age 50–64 years; aOR, 0.55; 95% CI, 0.35–0.85; *P* = 0.007); a greater number of retrieved lymph nodes (aOR, 0.98; 95% CI, 0.96–0.99; *P* < 0.001); and breast reconstructive surgery (aOR, 0.44; 95% CI, 0.30–0.65; *P* < 0.001) (Table 2). Multivariate analyses revealed a significant independent association between the proportion of patients undergoing postmastectomy RT and time (increasing each year) (aOR, 1.05; 95% CI, 1.02–1.09; *P* = 0.003).

### Subgroup Analysis of RT Use by Treatment Period

In the subgroup analysis, the postmastectomy RT utilization rate significantly increased as the treatment period advanced, with higher proportions of patients undergoing RT in the modern treatment period eras (*X*<sup>2</sup> trend test, *P* < 0.001, Table 3). The differences between RT use trends and patterns in adverse features during 1994 to 1999, 2000 to 2004 vs 2005 to 2009 are listed in Table 3. Age and the number of positive lymph nodes correlated with RT receipt regardless of the period, as would be expected. However, unexpectedly, the proportion of patients with small tumors (<2 cm) who underwent postmastectomy RT significantly increased between 1994 and 2000 and between 2005 and 2009 (5.8% vs. 13.8%, respectively). Postmastectomy RT use was not likely to be affected by tumor grade, hormone receptor status, or LVI across any study period.

### Survival Analyses

Figure 2 and Table 4 shows the estimated survival among all patients according to period. The estimated 5-year OS and

**TABLE 1.** Clinicopathologic and Treatment Characteristics, pT1-2N1 Breast Cancer, 1994–2009, Korean Breast Cancer Society

Characteristics	No. of Patients	%
Age, y		
<40	1129	18.1
40–49	2394	38.8
50–64	2023	32.7
≥65	640	10.4
Tumor size, cm		
<1	395	6.4
1–1.9	1385	22.4
2–2.9	2216	35.8
3–3.9	1317	21.3
4–5	756	12.2
Unknown	127	2.0
Number of involved lymph node		
1	3189	51.5
2	1808	29.2
3	1199	19.4
Grade		
I	631	10.2
II	2790	45.0
III	2132	34.3
Unknown	643	10.4
ER status		
Negative	2179	35.2
Positive	3778	61.0
Unknown	239	3.9
PR status		
Negative	2585	41.7
Positive	3375	54.5
Unknown	236	3.8
LVI		
Absent	2322	37.5
Present	2254	36.4
Unknown	1620	26.1
Axillary clearance		
ALND	4356	70.3
SLNB + ALND	1840	29.7
Number of removed lymph node		
Median	16	
Range	1–69	
Mean (SD)	16.8 (7.8)	
Adjuvant chemotherapy		
No	419	6.8
Yes	5763	93.0
Unknown	14	0.2
Adjuvant endocrine therapy		
No	1785	28.8
Yes	4111	66.3
Unknown	300	4.8
Adjuvant radiation therapy		
No	5459	88.1
Yes	737	11.9
Breast reconstructive surgery		
No	5665	91.4
Yes	531	8.6
Vital status		
Dead	907	14.6
Alive	5289	85.4

ALND = axillary lymph node dissection, ER = estrogen receptor, LVI = lymphovascular invasion, PR = progesterone receptor, SD = standard deviation, SLNB = sentinel lymph node biopsy.

**TABLE 2.** Unadjusted and Adjusted Odds Ratios for Association With Receipt of Adjuvant Radiation Therapy for pT1-2N1 Breast Cancer for Each Clinicopathologic and Treatment Characteristic\*

Covariate	No. of Patients	RT (%) Receipt	Univariable			Multivariable		
			Odds Ratio	95% CI	P	Odds Ratio	95% CI	P
Year of mastectomy (per year)	6196		1.08	1.05–1.10	<0.001	1.05	1.02–1.09	0.003
Age, y								
<40	1121	15.3	1.59	1.28–1.97	<0.001	1.95	1.50–2.53	<0.001
40–49	2394	12.6	1.27	1.06–1.54	0.012	1.25	1.00–1.56	0.054
50–64	2023	10.2	1 [Reference]		—	1 [Reference]		—
≥65	640	6.4	0.60	0.43–0.86	0.004	0.55	0.35–0.85	0.007
Tumor size (per centimeter) <sup>†</sup>	6196		1.09	1.01–1.18	0.021	1.11	1.01–1.21	0.025
Number of involved LN								
1–2	4997	9.7	1 [Reference]		—	1 [Reference]		—
3	1199	21.0	2.48	2.09–2.93	<0.001	2.71	2.20–3.33	<0.001
Grade <sup>‡</sup>								
I	631	12.8	1 [Reference]		—	1 [Reference]		—
II	2790	11.6	0.89	0.69–1.15	0.376	0.82	0.61–1.10	0.179
III	2132	11.4	0.87	0.66–1.14	0.308	0.80	0.58–1.10	0.172
ER/PR status <sup>‡</sup>								
Positive	4181	11.6	1 [Reference]		—	1 [Reference]		—
Negative	1784	12.6	1.09	0.92–1.30	0.296	1.05	0.84–1.31	0.658
LVI <sup>‡</sup>								
Absent	2322	13.0	1 [Reference]		—	1 [Reference]		—
Present	2254	13.5	1.04	0.88–1.24	0.631	0.95	0.79–1.15	0.591
Axillary clearance								
ALND	4356	11.0	1 [Reference]		—	1 [Reference]		—
SLNB + ALND	1840	14.0	1.31	1.11–1.54	0.001	1.24	1.02–1.51	0.035
Number of removed LN (per no.) <sup>†</sup>	6196		0.98	0.97–0.99	0.001	0.98	0.96–0.99	<0.001
Adjuvant chemotherapy <sup>‡</sup>								
No	419	5.3	1 [Reference]		—	1 [Reference]		—
Yes	5763	12.4	2.55	1.65–3.94	<0.001	1.55	0.87–2.78	0.140
Breast reconstructive surgery <sup>‡</sup>								
No	5665	12.3	1 [Reference]		—	1 [Reference]		—
Yes	531	7.2	0.55	0.39–0.77	0.001	0.44	0.30–0.65	<0.001

ALND = axillary lymph node dissection, CI = confidence interval, ER = estrogen receptor, LN = lymph node, LVI = lymphovascular invasion, PR = progesterone receptor, RT = radiation therapy, SLNB = sentinel lymph node biopsy.

\*Odds ratios based on logistic regression modeling. Model covariates included year of surgery, age, tumor size, nodal status, grade, ER/PR status, LVI, receipt of SLNB, number of LN retrieved, receipt of adjuvant chemotherapy, and receipt of breast reconstructive surgery.

<sup>†</sup>P values were calculated after unknown values were excluded.

DSS significantly increased from 84.1% and 85.4% for 1994 to 2000 to 94.6% and 95.6% for 2005 to 2009, respectively (adjusted hazard ratio per year, 0.86; 95% CI, 0.83–0.88).

Table 5 presents the multivariate Cox proportional hazards survival analyses at the 16-month landmark point including all variables listed in Table 1. Postmastectomy RT was not associated with any differences in mortality rates. Factors associated with superior OS included later year of mastectomy, age (<50 years), SLNB followed by axillary lymph node dissection, breast reconstructive surgery, and greater numbers of retrieved lymph nodes. Factors associated with inferior OS included age (≥65 years), larger tumor size, higher grade tumor, negative hormone receptor status, and positive LVI. Findings were similar for DSS. Table 6 shows an additional subset analysis

for patients who received adjuvant chemotherapy to determine whether the chemotherapy regimen affected the survival outcome. AC or T-based regimens were significantly associated with superior OS and DSS compared with other regimens.

## DISCUSSION

The present study highlights national practice patterns in RT utilization following mastectomy in patients with pT1-2N1 breast cancer in Korea, and the factors associated with RT use, which can both be useful in guiding current clinical practice in the right direction. Surprisingly, we found that only 11.9% of patients received RT after mastectomy, but that the numbers of patients receiving RT increased gradually per year from 1994 to

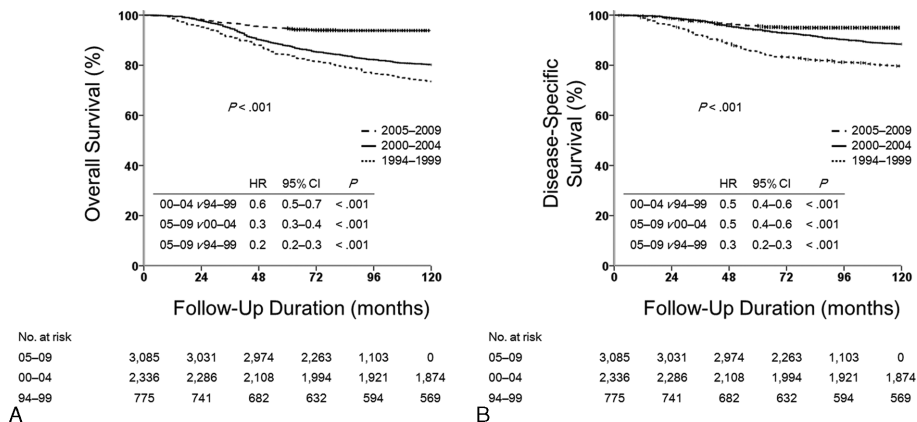
**TABLE 3.** Use of Adjuvant Radiation Therapy for pT1-2N1 Breast Cancer in Adverse Features During 1994–2000 Versus 2001–2004 Versus 2005–2009

	1994–2000 (n = 775)		2001–2004 (n = 2336)		2005–2009 (n = 3085)	
	N	%	N	%	N	%
Overall rate of RT use % who received RT	57/775	7.4	244/2336	10.4	436/3085	14.1
Age, y						
<40	24/193	12.4	51/429	11.9	96/499	19.2
40–49	21/308	6.8	122/923	13.2	159/1163	13.7
50–64	9/219	4.1	58/746	7.8	139/1058	13.1
≥65	3/55	5.5	11/235	4.7	27/350	7.7
Tumor size, cm						
<1	2/32	6.3	14/117	12.0	45/246	18.3
1–1.9	9/158	5.7	37/435	8.5	98/792	12.4
2–2.9	19/277	6.9	79/882	9.0	122/1057	11.5
3–3.9	11/170	6.5	67/566	11.8	85/581	14.6
4–5	14/111	12.6	31/282	11.0	68/363	18.7
Lymph node involvement						
1–2	34/624	5.4	158/1852	8.5	293/2521	11.6
3	23/151	15.2	86/484	17.8	143/564	25.4
Grade						
I	5/66	7.6	24/214	11.2	52/351	14.8
II	20/324	6.2	113/1045	10.8	190/1421	13.4
III	7/201	3.5	81/792	10.2	154/1139	13.5
ER/PR status						
Positive	12/196	6.1	81/718	11.3	131/870	15.1
Negative	30/448	6.7	152/1535	9.9	303/2198	13.8
LVI						
Absent	13/117	11.1	86/680	12.6	204/1525	13.4
Present	19/89	21.3	90/869	10.4	196/1296	15.1

ER = estrogen receptor, LVI = lymphovascular invasion, PR = progesterone receptor, RT = radiation therapy.

2009. During this period, women with larger tumors and more positive lymph nodes were likely to receive RT, but we did not observe significant differences in relation to other well-established risk factors including LVI, high-grade tumor, and estrogen receptor-negative status. For women treated in the 2000s, who had a significantly better OS and DSS than those treated in the 1990s, this concerning trend of patient selection for RT may be against “choosing wisely.”

A number of possibilities could underlie the improvements in the survival outcome over time. Prior to 2010, the KBCR database did not record pathologic information on small volume axillary disease. However, given our findings that SLNB was independently associated with a higher OS and that the number of patients undergoing SLNB increased over time, an increase in the detection of small volume nodal metastasis, including micrometastases (pN1mi), by extensive pathologic evaluation following SLNB



**FIGURE 2.** Survival outcomes for patients with pT1-2N1 breast cancer. Kaplan–Meier curves for (A) overall survival and (B) disease-specific survival. HR = hazard ratio.



**TABLE 4.** Five-Year Overall and Disease-Specific Survivals for Patients With pT1-2N1 Breast Cancer According to Time Period, 1994–2009, Korean Breast Cancer Society

Time Period	5-Y OS*	95% CI	5-Y DSS <sup>†</sup>	95% CI
94–99	84.1%	81.6–86.6%	85.4%	82.9–87.9%
00–04	87.8%	86.4–89.2%	94.1%	93.1–95.1%
05–09	94.6%	93.8–95.4%	95.6%	94.8–96.4%

CI = confidence interval, DSS = disease-specific survival, OS = overall survival.

\*Overall survival (Group 05–09 vs. 94–99, Bonferroni corrected *P* values [*P<sub>c</sub>*] <0.001, Group 05–09 vs. 00–04, *P<sub>c</sub>* <0.001, Group 00–04 vs. 94–99, *P<sub>c</sub>* <0.001).

<sup>†</sup>Disease-specific survival (Group 05–09 vs. 94–99, *P<sub>c</sub>* <0.001, Group 05–09 vs. 00–04, *P<sub>c</sub>* <0.001, Group 00–04 vs. 94–99, *P<sub>c</sub>* <0.001).

could be the most plausible reason for improved survival. In an analysis of >8000 patients from 2 large cohorts, Mittendorf et al<sup>15</sup> reported that patients with pN1mi and pN0 disease have similar survival outcomes. Parallel findings were reported in 2 other recent analyses from the American College of Surgeons Oncology Group (ACOSOG) Z0010 and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 trials.<sup>16,17</sup> An ongoing RxPonder trial evaluating the utility of Oncotype Dx in patients with 1 to 3 positive lymph nodes and hormone receptor-positive tumors recently amended the protocol to exclude patients with pN1mi. Taken together, we feel that the benefit of RT was diminished in these patients and that postmastectomy RT should not be determined primarily by the presence of pN1mi disease.<sup>18</sup>

Our findings showed that patients treated in later years were more likely to undergo a modern chemotherapy (AC ± T) regimen, and that modern chemotherapy was significantly associated with improved OS. This suggests that advances in adjuvant systemic treatments might also contribute to improved survival outcomes.<sup>19</sup> With growing evidence supporting modern chemotherapy and targeted agents, it seems essential to determine the relative contribution of each component of adjuvant treatment.<sup>20</sup> Earlier trials that showed the 10-year LRR rate in those who did not undergo RT was 17.7%, although most of those patients also underwent a CMF chemotherapy regimen.<sup>5</sup> On the other hand, trials from the NSABP and the Eastern Cooperative Oncology Group reported a 10-year LRR rate of <10% in those who did not undergo RT, and most of them received modern chemotherapy.<sup>6,7</sup> This further supports the hypothesis that there is less room for improvement by RT in those undergoing modern chemotherapy.

These findings raise the question of whether RT could be omitted in T1-2N1 patients who undergo modern systemic therapy postmastectomy, especially in the era of SLNB and in those expected to have a very low risk for LRR. However, there are data emphasizing the importance of RT in these patients. A recent study by Chang et al<sup>18</sup> showed a significant improvement in disease-free survival by postmastectomy RT in recently treated patients who were at extremely low risk of LRR, indicating recent treatment advances might not mitigate the benefit of RT in these N1 subsets of patients. Interestingly, recent data from both the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) MA.20 and the European Organization for Research and Treatment of Cancer 22922 trials indicated that the addition of comprehensive regional nodal irradiation in the treatment of breast-conserved patients

provided a small but statistically significant benefit in disease-free survival.<sup>21,22</sup> N1 patients constituted 90% of the NCIC-CTG MA.20 cohort and 43% of the European Organization for Research and Treatment of Cancer 22922 cohort. While data from the SUPREMO trial are awaited, which specifically investigates whether postmastectomy RT improves survival in patients with an intermediate risk of local recurrence, including N1 patients, physicians should pay careful attention to the selection of candidates for postmastectomy RT.<sup>23</sup>

In this study, we found that RT was underutilized in Korean patients with pT1-2N1 breast cancer patients, and that its use was considerably lower than that in North American patients (11.9% vs. 19–25%, respectively).<sup>24,25</sup> This stands in contrast to current international guidelines, including NCCN in recent years inclusive of 2016, even after allowing for improved survivals of these subsets of patients recently.<sup>26</sup> Our findings with respect to gradual increases in RT use also suggest conservative responsiveness of the breast cancer community to emerging evidence. While 1 overriding cause is difficult to determine, substantial underutilization of RT in N1 mastectomy patients can largely be explained by the results of a study by Jagsi et al.<sup>27</sup> That large, population-based study found high rates of RT use in breast conserved patients, but lower rates among mastectomy patients. For most mastectomy patients with strong indications for RT who failed to undergo PMRT, patient self-report indicated that physicians either did not discuss RT or said that it was unnecessary. Concerns about the adverse effects, inconveniences, and associated costs of RT may also contribute to underutilization of adjuvant postmastectomy RT in Korean patients. However, the potential for toxicity from breast RT has decreased with the introduction of more advanced RT technologies including RT planning with computed tomography-based RT simulation and three-dimensional conformal RT delivery. Especially, CT-based RT simulation planning assists radiation oncologists in delineating the organs at risk more precisely, in estimating the complication probabilities, and in minimizing the irradiated volume. Intensity-modulated radiation therapy, which has the advantage of improving dose homogeneity and sparing normal tissue, was covered by the Korean National Health Insurance for postmastectomy RT in breast cancer in July 2015, which may alleviate concerns regarding toxicity to some degree.<sup>28</sup> Although large randomized trials that established the role of hypofractionated RT in breast cancer excluded postmastectomy patients, there are retrospective studies supporting the use of hypofractionated RT in these patients, which compliment an ongoing phase III randomized trial (NCT00793962).<sup>29</sup> With respect to patients' convenience, hypofractionated RT might be possible treatment approach to reduce both cost and burden.

In a time of growing concern about local therapy under or over treatment, continued efforts are needed to investigate clinical, metabolic, and molecular markers for better risk stratification and appropriate patient selection. In our study, the number of positive lymph nodes, number of lymph nodes resected, tumor size, and age were found to be predictive clinical factors associated with RT use, which was similar to the findings of a systematic review of the NSABP trials.<sup>7</sup> The lymph node ratio, which combined number of positive lymph nodes with the number of lymph nodes removed, could identify patients who might benefit most from RT.<sup>30,31</sup> In our study, RT use was more common among younger than older women, reflecting the concern that younger age is in itself a risk factor for local recurrence following mastectomy.<sup>32</sup> However, peculiarly enough, young age has not clearly been shown to be a predictor of survival from our cohort that included only

**TABLE 5.** Multivariable Cox Proportional Hazards Analyses of Overall Survival and Disease-Specific Survival at the 16-Month Landmark Point, pT1-2N1 Breast Cancer, 1994–2009, Korean Breast Cancer Society

Covariate	No. of Patients	OS Analysis					DSS Analysis				
		HR	95% CI		P	HR	95% CI		P		
Year of mastectomy (per year)	6118	0.84	0.81	—	0.87	<0.001	0.86	0.82	—	0.89	<0.001
Age, y											
<40	1107	0.62	0.44	—	0.86	0.004	0.41	0.26	—	0.65	<0.001
40–49	2374	0.81	0.63	—	1.03	0.080	0.75	0.56	—	1.00	0.050
50–64	1995		1 [Reference]			—		1 [Reference]			—
≥65	625	1.63	1.21	—	2.21	0.001	1.39	0.95	—	2.03	0.085
Tumor size (per centimeter)	6118	1.19	1.07	—	1.31	0.001	1.32	1.17	—	1.49	<0.001
Number of involved LN											
1–2	4941		1 [Reference]			—		1 [Reference]			—
3	1177	1.03	0.80	—	1.33	0.807	0.94	0.69	—	1.29	0.717
Grade											
I	629		1 [Reference]			—		1 [Reference]			—
II	2765	1.66	1.08	—	2.55	0.021	2.08	1.14	—	3.77	0.016
III	2094	2.03	1.30	—	3.16	0.002	2.51	1.36	—	4.63	0.003
ER/PR status											
Positive	4151		1 [Reference]			—		1 [Reference]			—
Negative	1744	1.83	1.35	—	2.47	<0.001	1.56	1.07	—	2.28	0.020
LVI											
Absent	2307		1 [Reference]			—		1 [Reference]			—
Present	2220	1.51	1.23	—	1.85	<0.001	1.63	1.27	—	2.11	<0.001
Axillary clearance											
ALND	4289		1 [Reference]			—		1 [Reference]			—
SLNB + ALND	1829	0.66	0.51	—	0.86	0.002	0.74	0.54	—	1.00	0.051
Number of removed LN (per no.)	6118	0.98	0.97	—	0.99	0.002	0.97	0.95	—	0.99	<0.001
Adjuvant chemotherapy											
No	392		1 [Reference]			—		1 [Reference]			—
Yes	5712	0.71	0.47	—	1.05	0.089	0.93	0.54	—	1.62	0.809
Adjuvant endocrine therapy											
No	1745		1 [Reference]			—		1 [Reference]			—
Yes	4076	0.95	0.71	—	1.28	0.752	0.79	0.54	—	1.14	0.199
Breast reconstructive surgery											
Yes	527		1 [Reference]			—		1 [Reference]			—
No	5591	0.31	0.14	—	0.65	0.002	0.19	0.06	—	0.61	0.005
Adjuvant radiation therapy											
No	5391		1 [Reference]			—		1 [Reference]			—
Yes	727	1.16	0.85	—	1.57	0.345	1.24	0.86	—	1.78	0.246

ALND = axillary lymph node dissection, CI = confidence interval, DSS = disease-specific survival, ER = estrogen receptor, HR = hazard ratio, LN = lymph node, LVI = lymphovascular invasion, NA = not applicable, OS = overall survival, PR = progesterone receptor, SLNB = sentinel lymph node biopsy.

early stage women. Given the fact that younger women usually present with larger tumors and higher percentage of positive lymph nodes, much care is needed to consider age in post-mastectomy RT decision making in women with early-stage disease.<sup>33</sup> Recently, many investigators have identified other risk factors for LRR in institutional cohorts who did not undergo RT, such as high-grade tumor, estrogen receptor negativity, and LVI.<sup>34–36</sup> The present study also found that these well-established risk factors were associated with poor survival outcome, but that they did not affect RT utilization. Previous

study have shown that biologic factors including tumor grade and estrogen receptor status could be used as prognostic markers and even more so in those with small-volume nodal disease.<sup>15</sup> These results indicate that estrogen receptor status, tumor grade, and LVI should be considered alongside T and N stage in multidisciplinary discussions to decide whether to implement RT.

Recent studies reported the utility of pretreatment positron-emission tomography (PET) for predicting high-risk patients who could be candidates for RT among patients with

**TABLE 6.** Univariable Cox Proportional Hazards Survival Analysis According to Chemotherapy Regimen Among pT1-2N1 Breast Cancer Patients Who Received Chemotherapy and Had Available Data on Regimen, 2000–2009, Korean Breast Cancer Society

Covariate	No. of Patients	OS Analysis				DSS Analysis			
		5-Y (%)	HR	95% CI	P	5-Y (%)	HR	95% CI	P
Regimen									
T-based	2219	95.6	0.46	0.37–0.58	<0.001	96.9	0.44	0.34–0.58	<0.001
AC-based	1395	90.2	0.76	0.63–0.91	0.003	95.7	0.62	0.48–0.78	<0.001
Others (e.g., CMF)	1479	88.6	1 [Reference]		—	92.5	1 [Reference]		—

AC = adriamycin cyclophosphamide, CI = confidence interval, CMF = cyclophosphamide methotrexate 5-fluorouracil, DSS = disease-specific survival, HR = hazard ratio, OS = overall survival, T = paclitaxel docetaxel.

T1-2N1 disease.<sup>37,38</sup> In this series, hypermetabolic features in baseline PET represented a high-risk group having larger tumors, more positive lymph nodes, a higher LNR, high-grade tumors, hormone-receptor negativity, or triple-negative status, and these factors were associated with an increased LRR risk as well as poor disease-free survival. Several genetic signatures have been reported to predict risk of distant metastases, expanding the application of genetic analysis for assessing LRR risk.<sup>39–41</sup> Mamounas et al<sup>40</sup> retrospectively analyzed >1500 specimens from patients with N0 and estrogen-positive disease from the NSABP B-14 and B-20 trials, and found that the LRR risk was significantly associated with recurrence score risk groups that were quantified using Oncotype DX genetic analysis. Similar findings were reproduced in patients with ductal carcinoma in situ.<sup>42</sup> Although these new findings regarding PET imaging and gene signatures need to be validated in the prospective setting or in node-positive patients, their implementation in clinical practice would prevent both RT under- and overtreatment with truly personalized treatment protocols.

There are some limitations to the present study. Given its retrospective observational study design, there were unmeasured patient factors related to prognosis, which might have influenced RT use. The KBCR database does not contain details of RT dose, fractionation, field, and technique. However, our previous study reporting RT patterns of care suggested that it is likely that a large proportion of our patients received RT in a relatively homogenous manner.<sup>43</sup> Other limitations of this study included the lack of KBCR data on details of performance status, socioeconomic and demographic characteristics, patient preferences, physician interaction, and comorbidities. The impact of HER2 status and trastuzumab could not be analyzed in this study. As with all national large databases, miscoding of variables is possible. The KBCR database represents the majority of breast cancer patients in Korea, while the SEER database represents only approximately 26% of cancer patients in the United States.<sup>44</sup>

In summary, among women diagnosed with pT1-2N1 breast cancer in Korea, the percentage undergoing postmastectomy RT over a 15-year period was relatively low, but gradually increased during the study period. Although an international consensus recommends postmastectomy RT for N1 patients if there are additional adverse features, our study found that several important well-established risk factors have been de-emphasized in actual clinical practice in Korea. Our concern is that, with advances in surgical techniques and modern chemotherapy regimens, patients are now expected to have far superior survival outcomes with a low LRR risk when compared with those treated in previous years; therefore, more careful patient selection is

needed. There is a significant unmet need to educate surgeons and medical and radiation oncologists for better risk stratification of such patients with the incorporation of tumor biologic factors, well-established risk factors, and conventional anatomic factors. As mentioned by Jaggi et al,<sup>27</sup> surgeon participation in the RT decision has a strong impact on RT use, especially among mastectomy patients. Further effort is needed to investigate effective predictive markers for RT as well as to optimize the postmastectomy RT technique, dose, and volume.

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