INTRODUCTION

In patients with breast cancer, nodal status is a significant factor for the prognostication and selection of adjuvant radiotherapy (RT). 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. 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, and the locoregional recurrence (LRR) risk is likely to be correspondingly lower in these patients. 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. 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. 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 Breast Cancer Registry. The present population-based analysis revealed that the indications for RT in these patients in recent years have 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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Trends in the Application of Postmastectomy Radiotherapy for Breast Cancer With 1 to 3 Positive Axillary Nodes and Tumors <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.

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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.

INTRODUCTION

In patients with breast cancer, nodal status is a significant factor for the prognostication and selection of adjuvant radiotherapy (RT). 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. 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, and the locoregional recurrence (LRR) risk is likely to be correspondingly lower in these patients. 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. 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. 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 Breast Cancer Registry.
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. 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](https://example.com/figure1.png)

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. \(^{14}\) 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 (\(X^2\) 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 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. \(^ {14}\) 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).

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**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 |
| ALND            |                 |   |
| Absent          | 2322            | 37.5 |
| Present         | 2254            | 36.4 |
| Unknown         | 1620            | 26.1 |
| SLNB + ALND     | 4356            | 70.3 |
| Number of removed lymph node |         |   |
| Median          | 16              |   |
| Range           | 1–69            |   |
| Mean (SD)       | 16.8 (7.8)      |   |
| Adjuvant chemothrapy |             |   |
| 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.
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
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

### 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            | 9/115   | 5.7    | 37/435  | 5.1     | 30/896  | 12.4    |
| 2–2.9            | 19/277  | 6.9    | 79/882  | 9.0     | 122/1057| 11.5    |
| 3–3.9            | 11/171  | 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.

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.

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could be the most plausible reason for improved survival. In an analysis of >8000 patients with 2 large cohorts, Mittendorf et al\textsuperscript{15} 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.\textsuperscript{16,17} 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 would be diminished in these patients and that postmastectomy RT should not be determined primarily by the presence of pN1mi disease.\textsuperscript{18}

Our findings showed that patients treated in later years were more likely to undergo a modern chemotherapy (AC \pm 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.\textsuperscript{19} With growing evidence supporting modern chemotherapy and targeted agents, it seems essential to determine the relative contribution of each component of adjuvant treatment.\textsuperscript{20} 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.\textsuperscript{7} 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.\textsuperscript{5,7} 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\textsuperscript{18} 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.\textsuperscript{21,22} 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.\textsuperscript{23}

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).\textsuperscript{24,25} This stands in contrast to current international guidelines, including NCCN in 2016, even after allowing for improved survival of these subsets of patients recently.\textsuperscript{26} 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.\textsuperscript{27} 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 delivering dosimetry to 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.\textsuperscript{28} 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).\textsuperscript{29} 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.\textsuperscript{7} 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.\textsuperscript{30,31} 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.\textsuperscript{32} However, peculiarly enough, young age has not clearly been shown to be a predictor of survival from our cohort that included only

| 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\textsuperscript{a} | 95% CI | 5-Y DSS\textsuperscript{b} | 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% |

\textsuperscript{a}Overall survival (Group 05–09 vs. 94–99, Bonferroni corrected P values [P'] <0.001, Group 05–09 vs. 00–04, P <0.001, Group 00–04 vs. 94–99, P <0.001).

\textsuperscript{b}Disease-specific survival (Group 05–09 vs. 94–99, P <0.001, Group 05–09 vs. 00–04, P <0.001, Group 00–04 vs. 94–99, P <0.001).
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.\(^3\)\(^3\) 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.\(^3\)\(^4\)\(^–\)\(^6\) 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.\(^1\)\(^5\) 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 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.
T1-2N1 disease. 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. Mamounas et al 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 ducal carcinoma in situ. 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 KBRC 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. Other limitations of this study included the lack of KBRC 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 patient factors related to prognosis, which might have influenced RT use. The KBRC database does not contain 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 KBRC 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.

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 Jagsi et al., 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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