

Do Recent Advances in Diagnostic and Therapeutic Procedures Negate the Benefit of Postmastectomy Radiotherapy in N1 Patients With a Low Risk of Locoregional Recurrence?

Jee Suk Chang, MD, Jeongshim Lee, MD, Kyung Hwan Kim, MD, Joo Hyuk Sohn, MD, PhD, Seung Il Kim, MD, PhD, Byeong-Woo Park, MD, PhD, Hyun Cheol Chung, MD, PhD, Ki Chang Keum, MD, PhD, Chang-Ok Suh, MD, PhD, and Yong Bae Kim, MD, PhD

Abstract: Recent advances in breast cancer management might make the use of postmastectomy radiotherapy (PMRT) redundant in the treatment of pT1/T2N1 patients. We investigated the impact of PMRT on disease-free survival (DFS) in these patients who have a low risk of locoregional recurrence (LRR) after contemporary multidisciplinary management.

Between 1998 and 2011, 1123 patients underwent upfront surgery for pathologically diagnosed pT1/T2N1 breast cancer, at a single institution. A retrospective review was performed on 692 patients who had a mastectomy with axillary lymph node (LN) clearance. Most patients received adjuvant systemic chemotherapy and/or endocrine therapy. PMRT was administered to 17.8% of the patients. The median follow-up time was 98 months.

The entire cohort was divided into 2 groups, the early-era (1998–2003) and late-era (2004–2011) cohorts. Grouping was based on the use of modern therapies since 2004 including sentinel LN (SLN) biopsy, anthracycline/taxane-based chemotherapy, and aromatase inhibitors. Late-era patients had a significantly lower 5-year LRR compared with early-era patients (3.2% vs 10.3%, respectively; $P < 0.001$). In late-era patients, although PMRT did not significantly reduce the 5-year LRR rate (1% vs 3.8%, respectively), it did improve the 5-year DFS rate (96.1% vs 87.5%, respectively). After controlling for all clinicopathological variables, PMRT was independently associated with improved DFS. In subgroup analysis, depending on the presence of micro- or macrometastasis in the axillary nodes, the benefit of PMRT was most apparent in patients with macrometastasis (hazard ratio, 0.19). In the late-era cohort with no PMRT, the 3-year distant metastasis risk increased according to LN tumor burden

(0%, 5.2%, and 9.8% in micrometastasis, SLN macrometastasis, and non-SLN macrometastasis, respectively).

Advanced surgical and systemic therapies might not negate the benefit of PMRT in recently diagnosed pN1 patients who have a very low risk for LRR. Our data indicate that the overall recurrence risk combined with the LRR should be considered for an indication of PMRT, and raises the question of whether the receipt of PMRT would improve outcome in patients with micrometastasis.

(*Medicine* 94(33):e1259)

Abbreviations: AC ± T = cyclophosphamide, doxorubicin, and/or paclitaxel, CI = confidence interval, DFS = disease-free survival, DM = distant metastasis, EBCTCG = Early Breast Cancer Trialists' Collaborative Group, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, LN = lymph node, LRR = locoregional recurrence, OS = overall survival, PMRT = postmastectomy radiotherapy, PR = progesterone receptor, SLN = sentinel lymph node.

INTRODUCTION

In breast cancer patients, anatomic staging, especially nodal status, is considered a significant factor for the prognosis of locoregional recurrence (LRR) and selection of adjuvant radiation therapy after mastectomy. The survival benefit of post-mastectomy radiotherapy (PMRT) in node-positive breast cancer patients has been well established through multiple-randomized trials.^{1–3} The results of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses confirmed that PMRT consistently reduced the risk of LRR by two-thirds and increased disease-free survival (DFS) and cancer-specific survival.⁴ Although there is an international consensus that PMRT should be indicated for patients with tumors that measure >5 cm or for those with ≥4 positive lymph nodes (LNs), the role of PMRT in patients who have tumors that measure ≤5 cm and 1 to 3 positive LNs (pT1–2N1) is highly controversial because axillary LN dissection seems likely to outweigh the potential benefit of PMRT.

Recently updated EBCTCG reports have reaffirmed the benefit of PMRT in a subset of N1 patients who had axillary dissection at least level II, irrespective of adjuvant systemic therapy (mostly cyclophosphamide, methotrexate, and fluorouracil).¹ However, resistance to apply the results of older studies to present practice remains, and the routine use of PMRT has not been recommended. This is because the absolute risks of any recurrence or death have decreased during recent decades because of improved screening and treatment

Editor: Leizhen Wei.

Received: May 1, 2015; revised: June 23, 2015; accepted: July 8, 2015. From the Department of Radiation Oncology (JSC, JL, KHK, KCK, C-OS, YBK); Division of Medical Oncology, Department of Internal Medicine (JHS, HCC); Department of Surgery (SIK, B-WP); and Yonsei Song-Dang Institute for Cancer Research, Yonsei University College of Medicine, Seoul, Republic of Korea (HCC, YBK).

Correspondence: Yong Bae Kim, Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea (e-mail: ybkim3@yuhs.ac).

JSC and JL contributed equally to this work.

This paper was presented at the Korean Society for Radiation Oncology 2014 meeting and received 1st place "Poster Award," October 2014.

The authors have no funding and conflicts of interest to disclose. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001259

protocols. In other words, the characteristics of patients with pT1/T2N1 have changed favorably overtime. The widespread use of sentinel LN (SLN) biopsy combined with extensive pathologic analysis has resulted in frequent identifications of nodal micrometastasis, and a higher proportion of patients have now been treated using modern systemic agents. Studies in the 1980s reported the LRR rate of patients who did not undergo PMRT to be 17.7%, whereas recent studies reported rates of 6% to 10%.^{1–3} In this respect, the present absolute benefits of PMRT for patients with T1/T2N1 breast cancer are likely to be small.

A subgroup analysis of the Danish Breast Cancer Cooperative Group 82 b and c trials suggested that reduced LRR in response to PMRT translated as a larger reduction in cancer mortality in women with N1 breast cancer compared with those with ≥ 4 positive LNs.⁴ Recent data from the National Cancer Institute of Canada Clinical Trials Group MA.20 and the European Organization for Research and Treatment of Cancer 22922 trials indicated that optimized locoregional control is crucial for long-term survival, especially in patients with a relatively lower competing risk of distant metastasis (DM).^{5,6} From their standpoint, PMRT does not only limit itself to locoregional control, but also to the prevention of systemic progression. Here, we verified the hypothesis that modern improvements in diagnostic and therapeutic procedures have resulted in a lower risk of LRR and superior survival in patients with T1/T2N1 breast cancer who were treated with mastectomy and axillary LN dissection. We subsequently evaluated the contribution of PMRT to survival outcomes regarding overall recurrence as well as LRR.

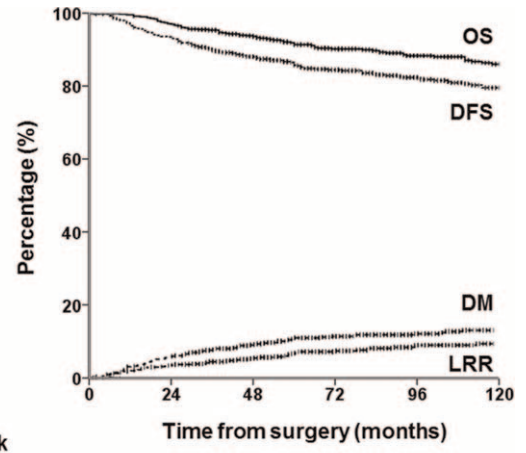
METHODS

Patients

This retrospective observational study was approved by the Institutional Review Board of Severance Hospital in Seoul, Korea. Patient consent was not required, because the collected data were existing information. We identified 1123 consecutive patients who underwent upfront surgery and who were diagnosed with pathological T1N1/T2N1 breast cancer between January 1998 and December 2011. Patients who underwent breast conservation surgery (n = 431) were excluded. The data from the remaining 692 patients were reviewed retrospectively. Preoperative evaluation consisted of a complete history, a physical examination, complete blood counts, mammography, breast ultrasonography, a bone scan, and computed tomography scans or magnetic resonance imaging, if indicated. Systemic staging with [18F]-fluorodeoxyglucose-positron emission tomography was performed in 109 patients (15.8%). Immunohistochemical staining for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) was performed. Breast cancer molecular subtypes were categorized as luminal A (ER+, moderate to strong PR+, and HER2-); luminal B (ER+, negative or weak PR+, and HER2+/-); HER2 (ER- and PR- and HER2+); and triple negative (ER- and PR-, HER2-).^{7,8}

Treatment

All 692 patients underwent modified radical mastectomy. Although SLN sampling was first implemented at our institution in 2000, it was not commonly employed until 2003; thus, SLN sampling was only performed in 357 patients (51.6%). Those with biopsy-confirmed or suspicious axillary nodal metastasis on positron emission tomography imaging were spared. Surgeons did not refer all T1/T2N1 patients to radiation



No. at risk	Time from surgery (months)					
	0	24	48	72	96	120
OS	692	668	576	444	338	236
DFS	692	643	539	412	309	216
DM	692	650	551	422	326	226
LRR	692	654	555	420	315	219

FIGURE 1. Kaplan–Meier (KM) overall survival (OS) and disease-free survival (DFS) rates, and the 1–KM cumulative incidence of locoregional recurrence (LRR) and distant metastasis (DM).

oncologists; PMRT was offered to patients with high-risk features such as multiple positive LNs. Three-dimensional conformal PMRT was applied to the chest and regional nodal areas (supraclavicular, axillary, and internal mammary nodes) using the reverse hockey stick technique with a total dose of 50.4 Gy in 28 fractions.

Before the publication of the Cancer and Leukemia Group B 9344 study (1998–2003), if patients had comorbidities such as cardiac disease or a poor performance status, our institutional policy for adjuvant chemotherapy for node-positive patients was to offer 6 cycles of fluorouracil, doxorubicin, cyclophosphamide or 6 cycles of cyclophosphamide, methotrexate, and fluorouracil.⁹ After the Cancer and Leukemia Group B study (2004–2011), most node-positive patients were offered a combination of cyclophosphamide (600 mg/m²) and doxorubicin (60, 75, or 90 mg/m²) for 4 cycles with or without an additional 4 cycles of paclitaxel (175 mg/m²) (cyclophosphamide, doxorubicin, and/or paclitaxel [AC ± T]). Trastuzumab therapy was indicated for patients with HER2-overexpressing tumors. In accordance with these policies, adjuvant systemic therapy was selected after discussion with a medical oncologist.

Statistical Analyses

The cumulative incidences of LRR and DM were estimated using the 1–Kaplan–Meier method, and the survival probabilities of DFS and overall survival (OS) were estimated using the Kaplan–Meier method. The time to recurrence or death was calculated from the date of the mastectomy. Comparisons were performed using a *t*-test (continuous variables) or the Chi-square test (nominal variables). Univariate analyses for survival outcomes were performed using the log-rank test. Multivariate analyses for survival outcomes were performed using the Cox regression model with stepwise backward elimination (alpha = 0.20). The level of statistical significance was set at *P* < 0.05. All statistical analyses were performed with SPSS version 20.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

TABLE 1. Comparison of Patient, Tumor, and Treatment Characteristics According to the Treatment Era (N = 692)

Age (yr)	<45	1998–2003 (n = 280)		2004–2011 (n = 412)		P
		109	38.9%	124	30.1%	
	≥45	171	61.1%	288	69.9%	
	Mean ± SD		48.4 ± 9.9		51.1 ± 11.4	0.001
T stage	T1	107	38.2%	203	49.3%	0.004
	T2	173	61.8%	209	50.7%	
T size, cm	Mean ± SD		2.42 ± 0.95		2.13 ± 0.88	<0.001
Histological grade	1	27	10.7%	71	20.8%	0.002
	2	169	66.8%	188	55.1%	
	3	57	22.5%	82	24.0%	
EIC	Negative	146	63.8%	246	61.5%	0.574
	Positive	83	36.2%	154	38.5%	
Size of LN metastasis	Micro	4	1.4%	120	29.1%	<0.001
	Macro	276	98.6%	292	70.9%	
No. of positive lymph nodes	1	137	48.9%	256	62.1%	0.001
	2	88	31.4%	108	26.2%	
	3	55	19.6%	48	11.7%	
Percentage of positive LNs	<25%	272	97.1%	345	94.8%	0.138
	≥25%	8	2.9%	19	5.2%	
Estrogen receptor status	Negative	98	35.5%	101	24.5%	0.002
	Positive	178	64.5%	311	75.5%	
Progesterone receptor status	Negative	141	51.1%	144	35.0%	<0.001
	Positive	135	48.9%	268	65.0%	
HER2 overexpression	Negative	145	59.2%	294	74.8%	<0.001
	Positive	100	40.8%	99	25.2%	
Sentinel LN biopsy	Yes	25	8.9%	332	80.6%	<0.001
No. of LN dissection	Mean ± SD		18.4 ± 6.5		15.9 ± 7.0	<0.001
Chemotherapy		259	92.5%	373	90.5%	
CMF		186	66.4%	62	15.0%	<0.001
AC ± T		62	22.1%	298	72.3%	
Unspecified		11	3.9%	13	3.2%	
Trastuzumab	No	100	100.0%	71	73.2%	<0.001
	Yes	0	0.0%	26	26.8%	
Hormone therapy		180	65.5%	297	72.1%	0.064
Postmastectomy RT	No	254	90.7%	315	76.5%	<0.001
	Yes	26	9.3%	97	23.5%	

AC = adriamycin cyclophosphamide, CMF = cyclophosphamide methotrexate 5-fluorouracil, EIC = extensive intraductal component, HER2 = human epidermal growth factor receptor type 2, LN = lymph node, RT = radiotherapy, SD = standard deviation, T = paclitaxel docetaxel.

RESULTS

The clinicopathological characteristics of the 692 patients are shown in Supplementary Table 1, <http://links.lww.com/MD/A350>. Briefly, SLN-positive patients underwent axillary LN dissection (mean number of LN resected, 17.1 ± 6.8). Most patients received adjuvant systemic chemotherapy (632, 91.3%) and/or endocrine therapy (477, 69.4%). Trastuzumab was administered in 26 (13.2%) patients with HER2-overexpressing tumors. PMRT was administered to 123 (17.8%) patients.

The median follow-up time among surviving patients was 98 months (range, 2–197 months). Recurrence was observed in 126 patients (18.2%). A total of 87 (12.6%) patients died. The overall incidence of LRR and DM as the first failure pattern was 7.5% (n = 52) and 12.9% (n = 89), respectively, including 31 patients who suffered from simultaneous LRR and DM. The 5-year cumulative incidences of LRR and DM were 5.9% and 10%, and the 10-year rates were 9.3% and 13%, respectively (Figure 1). The 5-year DFS and

OS were 86.5% and 91.9%, respectively, and the 10-year rates were 79.5% and 86%, respectively.

Entire Cohort (1998–2011)

The entire cohort was divided into 2 groups, the early-era (1998–2003) and late-era (2004–2011) cohorts, because modern therapies including SLN biopsy, taxane-based chemotherapy, and aromatase inhibitors have been commonly used since 2004 at our institution (Table 1). Comparisons of patient characteristics for each cohort are listed in Table 1. Patient characteristics have changed favorably overtime (eg, older patients, less T2, smaller tumor size, lower grade tumors, increased detection of micrometastasis, fewer positive LNs, and a higher proportion of hormone-receptor positive tumors). In addition, in late-era group SLN biopsy use was widespread facilitating increased detection of micrometastasis in LNs, and fewer numbers of positive LNs, postoperatively. Furthermore, in the late-era group, patients were more likely to be treated

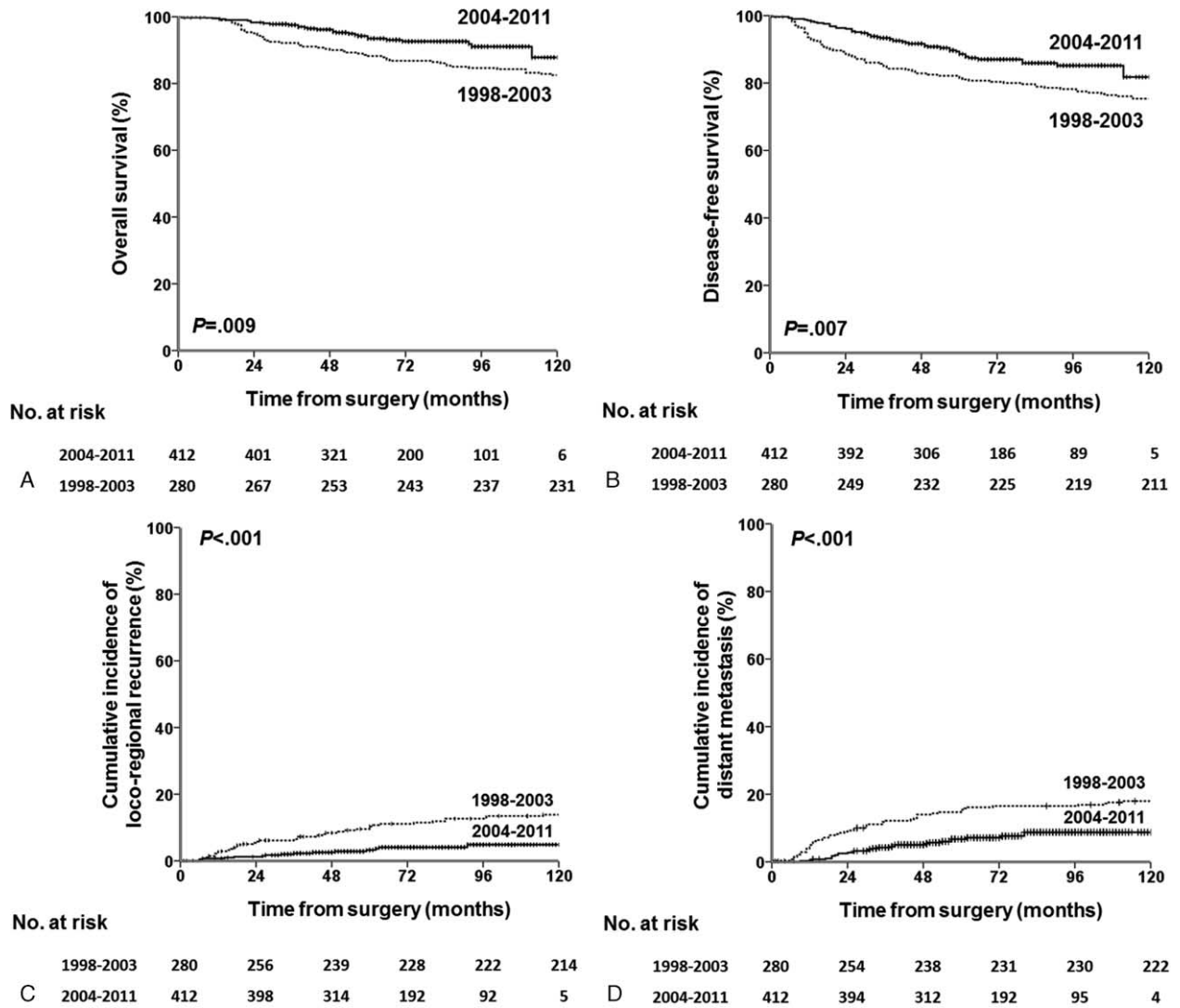


FIGURE 2. (A) Overall survival, (B) disease-free survival, (C) locoregional recurrence, and (D) distant metastasis in all patients with T1N1/T2N1 breast cancer (N=692) according to treatment era (1998–2003 vs 2004–2011).

using a modern chemotherapy regimen (AC ± T), anti-HER2 targeted agents, and PMRT (all $P < 0.05$). The median follow-up of the early-era and late-era cohorts were 155 (range, 124–197) months and 73 (range, 2–122) months, respectively.

Compared with the early-era cohort, the late-era cohort had significantly better 5-year OS (88.6% vs 94.2%, $P = 0.009$) and 5-year DFS (82.1% vs 89.3%, $P = 0.007$) (Figure 2A, B). Improvement in DFS in the late-era cohort was a consequence of a significant reduction in LRR and DM ($P < 0.001$, Figure 2C, D). Notably, the 5-year LRRs were 10.3% (95% confidence interval [CI] 6.8%–13.8%) and 3.2% (95% CI 1.4%–5.0%) for the early-era and late-era cohorts, respectively.

Multivariate Cox regression analyses were performed to analyze the factors independently associated with LRR, DM, DFS, and OS (Table 2). Older age (≥ 45 years), smaller LN ratio ($< 25\%$), use of SLN biopsy, and administration of AC ± T were significantly and independently associated with improved DFS. T-stage, tumor grade, and use of PMRT were related to DFS, but

with borderline significance. Administration of the AC ± T was significantly and independently associated with improved LRR control, and having a nonhigh grade tumor showed borderline significance. In an analysis of DM, old age (≥ 45 years), T1 tumor stage, nonhigh grade tumor, a smaller LN ratio ($< 25\%$), SLN biopsy, and the chemotherapy regimen administered were significantly and independently associated with improved DM control.

Late Cohort (2004–2011)

To provide more clinically relevant information for current practice from a relatively homogenous patient group, we assessed the effect of PMRT on clinical outcomes limited to the data from late-era group. Based on our previous experience, LN status was the first consideration when determining the use of PMRT. Understandably, patients treated with PMRT had more LN macrometastasis and positive LNs than those who were not treated with PMRT (all $P < 0.05$, Table 3). AC ± T chemotherapy was more frequently administered to patients

TABLE 2. Multivariate Cox Proportional Hazards Survival Analysis in the Entire Cohort According to Each Clinicopathological and Treatment Variable

Covariate	LRR Analysis			DM Analysis			DFS Analysis		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Year of mastectomy									
04–11 vs 98–03	0.68	0.28–1.63	0.387	0.79	0.40–1.51	0.457	0.71	0.42–1.20	0.203
Age, years									
<45 vs ≥45	1.54	0.81–2.91	0.187	2.25	1.38–3.68	0.001	1.83	1.22–2.75	0.003
T stage									
T2 vs T1	1.33	0.74–2.42	0.342	1.74	1.04–2.90	0.034	1.44	0.98–2.13	0.064
Grade									
III vs I-II	1.84	0.97–3.47	0.061	2.01	1.22–3.33	0.006	1.49	0.98–2.27	0.064
Lymph node involvement									
2 vs 1	1.22	0.63–2.36	0.549	1.18	0.69–2.00	0.551	1.39	0.91–2.13	0.125
3 vs 1	1.00	0.43–2.34	0.993	1.02	0.52–1.99	0.951	1.30	0.77–2.20	0.324
Lymph node tumor deposits									
Macro vs micro	1.09	0.34–3.52	0.889	2.09	0.71–6.14	0.178	1.26	0.63–2.50	0.516
Percentage of positive LNs									
≥25% vs <25%	2.96	0.86–10.23	0.087	4.67	1.96–11.1	0.001	2.82	1.23–6.12	0.009
ER/PR status									
Positive vs Negative	0.70	0.38–1.27	0.239	0.74	0.46–1.21	0.23	0.71	0.48–1.06	0.091
Use of SLN biopsy									
Yes vs No	0.90	0.41–1.99	0.799	0.35	0.18–0.69	0.002	0.55	0.33–0.92	0.022
Adjuvant chemotherapy									
CMF vs no	0.63	0.26–1.49	0.29	1.90	0.57–6.33	0.294	0.64	0.35–1.17	0.151
AC ± T vs No	0.19	0.06–0.58	0.003	1.33	0.38–4.64	0.652	0.36	0.18–0.70	0.003
Unspecified vs No	0.30	0.04–2.47	0.26	4.30	1.00–18.6	0.05	0.81	0.29–2.28	0.691
Use of PMRT									
Yes vs No	0.50	0.11–2.26	0.365	0.54	0.22–1.35	1.9	0.46	0.20–1.03	0.059

AC = adriamycin cyclophosphamide, CI = confidence interval, CMF = cyclophosphamide methotrexate 5-fluorouracil, DFS = disease-free survival, DM = distant metastasis, ER/PR = estrogen/progesterone receptor, HR = hazard ratio, LN = lymph node, LRR = locoregional recurrence, PMRT = postmastectomy radiotherapy, SLN = sentinel lymph node, T = paclitaxel docetaxel.

who underwent PMRT (85.6% vs 68.3%, $P = 0.003$). Otherwise, disease and treatment characteristics were well balanced between those who underwent PMRT and those who did not (all $P > 0.05$).

The 5-year LRR rates were not significantly different between those who underwent PMRT and those who did not at 1% and 3.8%, respectively (Figure 3A). The 5-year DM rates were not significantly different (Figure 3B). The 5-year DFS rates were 96.1% and 87.5%, respectively, and the 10-year DFS rates were 96.1% and 79.5%, respectively ($P = 0.015$) (Figure 3C). The 5-year OS rates for patients who underwent PMRT and those that did not were 100% and 91.9%, respectively ($P = 0.013$) (Figure 3D).

In the multivariate analysis, PMRT ($P = 0.038$), nonhigh grade tumor ($P = 0.025$), and AC ± T chemotherapy ($P = 0.007$) were significantly and independently associated with improved DFS (Table 4). To better assess the impact of PMRT, we analyzed the data by excluding patients who did not undergo chemotherapy. In these patients, PMRT (hazard ratio [HR], 0.22; 95% CI 0.05–0.91) and macrometastasis (vs micrometastasis; HR, 2.89; 95% CI 1.20–6.94) were significantly and independently associated with DFS. Multivariate analysis could not be applied to assess the effect of PMRT on OS, since there were no deaths in the PMRT group. To gain insight into associations between the PMRT effect and size (macro- vs

micrometastasis) or number of positive LNs, we performed subgroup analyses. The benefits of PMRT in DM control (HR, 0.13; 95% CI 0.02–0.99) and DFS (HR, 0.19; 95% CI 0.05–0.78) were most apparent in patients with macrometastasis compared to those with micrometastasis (Table 5).

In the late-era cohort, in patients with N1 disease who did not undergo PMRT, the effect of LN tumor burden on the risk of the tumor recurrence was assessed and is summarized in Supplementary Table 2, <http://links.lww.com/MD/A350>. The 3-year LRR rate was not significantly different as a function of LN tumor burden, whereas the DM risk increased according to LN tumor burden. The 3-year DM rate was 0%, 5.2%, and 9.8% for those with micrometastasis, SLN macrometastasis, and non-SLN macrometastasis, respectively.

DISCUSSION

The 2005 EBCTCG pooled analysis showed a survival benefit of PMRT when the 5-year LRR risk exceeded 10%.¹⁰ Their analysis evaluated the benefit of PMRT in patients who underwent a mastectomy according to node positivity. Although PMRT yielded similar proportional reductions in LRR irrespective of node positivity, the absolute reductions in LRR in node-positive women were large and resulted in a clear survival benefit. Therefore, PMRT was indicated in N2 disease;

TABLE 3. Comparison of Patient, Tumor, and Treatment Characteristics According to Postmastectomy Radiotherapy Use in 412 Patients Who Were Treated in the Late Era (2004–2011)

Age, year	<45	PMRT (–) (n = 315)		PMRT (+) (n = 97)		P
		95	30.2%	29	29.9%	
T stage	≥45	220	69.8%	68	70.1%	0.779
	T1	154	48.9%	49	50.5%	
	T2	161	51.1%	48	49.5%	
Histological grade	1	55	20.1%	16	23.9%	0.778
	2	153	55.8%	35	52.2%	
	3	66	24.1%	16	23.9%	
EIC	Negative	190	62.5%	56	58.3%	0.465
	Positive	114	37.5%	40	41.7%	
Size of LN metastasis	Micro	100	31.7%	20	20.6%	0.035
	Macro	215	68.3%	77	79.4%	
No. of positive lymph nodes	1	209	66.3%	47	48.5%	0.006
	2	73	23.2%	35	36.1%	
	3	33	10.5%	15	15.5%	
Percentage of positive LNs	<25%	281	95.3%	64	92.8%	0.401
	≥25%	14	4.7%	5	7.2%	
Estrogen receptor status	Negative	79	25.1%	22	22.7%	0.631
	Positive	236	74.9%	75	77.3%	
Progesterone receptor status	Negative	110	34.9%	34	35.1%	0.981
	Positive	205	65.1%	63	64.9%	
HER2 overexpression	Negative	222	74.7%	72	75.0%	0.96
	Positive	75	25.3%	24	25.0%	
Chemotherapy		281	89.2%	92	94.9%	0.003
CMF		57	18.1%	5	5.2%	
AC ± T		215	68.3%	83	85.6%	
Unspecified		9	2.9%	4	4.1%	
Trastuzumab	No	53	72.6%	18	75.0%	0.818
	Yes	20	27.4%	6	25.0%	
Hormone therapy		230	73.0%	67	69.1%	0.449

AC = adriamycin cyclophosphamide, CMF = cyclophosphamide methotrexate 5-fluorouracil, EIC = extensive intraductal component, HER2 = human epidermal growth factor receptor type 2, LN = lymph node, PMRT = postmastectomy radiotherapy, T = paclitaxel docetaxel.

however, the benefit of PMRT in N1 disease, which is assumed to have a relatively low absolute LRR risk, remained debatable. Recently, an updated meta-analysis showed that LRR reduction in response to PMRT mediated a significant survival benefit in patients with N1 disease, regardless of systemic chemotherapy.¹

Here, patients with T1/T2N1 disease who were treated more recently (2004–2011) had lower risks of DM and LRR, and had better survival compared with those who were treated earlier (1998–2003). In recently treated patients who were at very low risk for LRR, PMRT significantly improved DFS. These findings indicate that recent advances in surgical and systemic therapies might not negate the benefit of PMRT in N1 patients, and that a very low LRR rate should not be a surrogate endpoint to exclude patients from PMRT.

A recent meta-analysis indicated that the 5-year LRR in a series of patients who underwent PMRT between 1964 and 1986 was 2.8%,¹ which was similar to that for the recently treated patients in the present study (1%). In contrast, in the past, the 5-year LRR in patients who did not undergo PMRT was as high as 16.5%, whereas this has continually decreased over time and was considerably low in our late-era cohort (3.8%).^{2,3,11} A number of possibilities could underlie improvements in the 5-year LRR, DFS, OS, and the rate of DM. First, the Korean

national cancer-screening program for breast cancer became active during 2003–2005, meaning that the patient characteristics of those with N1 disease have changed favorably over time.¹² Second, improvements in pathological diagnostic methods have increased the detection of micrometastasis, which might have been classified previously as N0 disease. Third, the median age of Korean breast cancer patients has increased overtime, which might affect treatment outcomes.¹² Furthermore, increased use of more effective adjuvant systemic therapies likely resulted in superior outcomes in recently treated patients.^{13,14}

To assess the impact of PMRT in the late-era cohort rather than entire cohort was more clinically relevant, although the cut-off point of 2003 was somewhat arbitrary. In the late-era cohort, PMRT was not associated with a significant reduction in LRR or DM risk, but was significantly associated with improvements in DFS and OS, which resulted from possible reduction of both LRR and DM by PMRT. In addition, PMRT prevented subsequent progression of subclinical disease within the chest wall and regional nodes (eg, supraclavicular and internal mammary nodes) to systemic disseminations. These findings are congruent with 2 recent clinical trials that addressed the clinical benefit of adjuvant radiotherapy in breast-conserved patients.

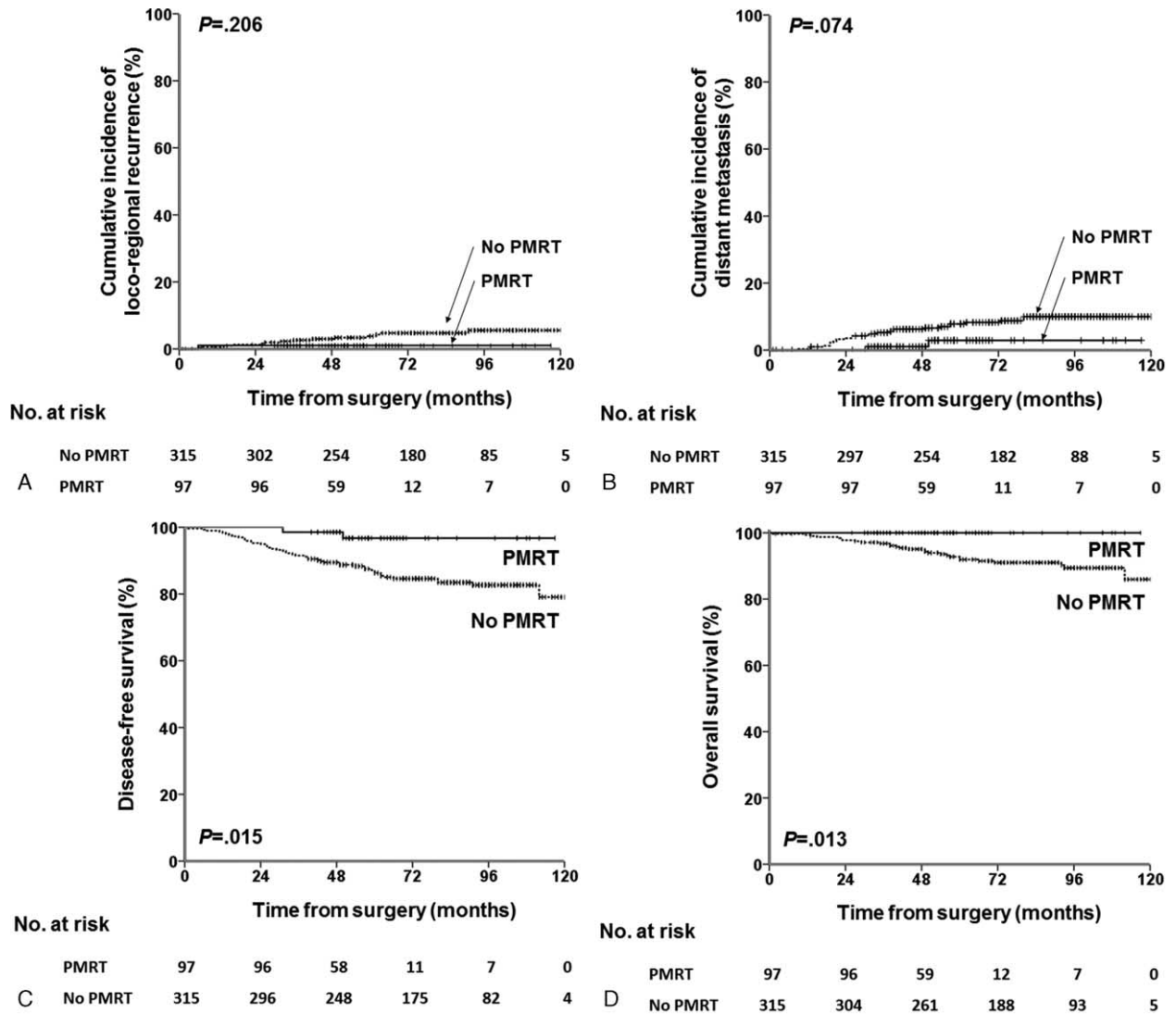


FIGURE 3. (A) Loco-regional recurrence, (B) distant metastasis, (C) disease-free survival, and (D) overall survival in the late-era group (2004–2011) patients with T1N1/T2N1 breast cancer (n=412) according to the use of postmastectomy radiotherapy (PMRT).

The National Cancer Institute of Canada Clinical Trials Group MA.20 trial enrolled patients with high-risk N0 and N1 disease and randomly assigned them to treatment with or without regional RT.⁵ In the preliminary report, regional radiotherapy reduced the 5-year DM rate by 4.3% and reduced the LRR rate by 2%. The European Organization for Research and Treatment of Cancer 22922/10925 trial showed similar results; regional radiotherapy reduced the 10-year DFS rate by 3%.⁶ In our study, both AC ± T and PMRT were independently associated with an improvement in DFS. This supports the hypotheses that radiotherapy and systemic therapy have different time-dependent effects¹⁵ and that the effects of radiotherapy and systemic therapy are synergistic or additive rather than competitive.¹⁶

The benefit of PMRT on DFS was most apparent in patients with macrometastasis compared with that in those with micrometastasis. In addition, the risk of DM or any recurrence was lower in patients with low LN tumor burden (micrometastasis) compared to that in those with macrometastasis. Mitendorf et al¹⁷ reported similar survival in patients with

micrometastasis compared with node-negative patients. Since SLN biopsy was validated as standard operating procedure in 2003, efforts have been made to assess the SLN using serial sectioning of entire SLN rather than using 3 sections per axillary LN.^{18,19} Such extensive pathologic analysis results in the frequent identification of micrometastatic foci (≤2 mm, N1mi), and in our opinion, the use of PMRT in patients with small-volume LN disease should be conservative, potentially avoiding local therapy overtreatment.

Risk-adaptive-personalized treatment is the current standard treatment in mastectomy patients with N1 disease. The current international consensus does not recommend routine use of PMRT unless there are additional adverse features.⁸ However, the indication and frequency of PMRT use varies significantly between institutions, and many investigators have identified various risk factors of LRR including young age (eg, ≤45 years),^{20,21} large tumor size (eg, T2 or >3 cm),^{11,21} LN ratio (eg, >15%–25%),^{20,22–24} ER-status,^{20,25} lymphovascular invasion,^{25,26} extranodal extension, a medially located tumor,²⁰

TABLE 4. Stepwise Univariate and Multivariate Analyses Using Cox Regression Method for Disease-Free Survival in 412 Patients Who Were Treated in the Late Era (2004–2011)

Variables		Univariate Analysis			Multivariate Analysis*		
		HR	95% CI	P	HR	95% CI	P
Age, year	<45 vs ≥45	1.23	0.69–2.21	0.486	NI		
T stage	T2 vs T1	1.25	0.71–2.19	0.443	NI		
Histological grade	G3 vs G1/2	2.02	1.12–3.65	0.02	2.02	1.09–3.72	0.025
EIC	Positive vs negative	1.26	0.69–2.28		NI		
Size of lymph node metastasis	Macro vs Micro	1.64	0.84–3.21	0.146	1.98	0.95–4.13	0.066
No. of positive lymph nodes	3 vs 1–2	1.18	0.53–2.63	0.683	NI		
Percentage of positive lymph nodes	≥25% vs <25%	1.21	0.38–3.90	0.747	NI		
Estrogen receptor status	Positive vs negative	0.68	0.37–1.23	0.199	NI		
Progesterone receptor status	Positive vs negative	0.61	0.35–1.06	0.08	NI		
HER2 overexpression	Positive vs negative	1.00	0.52–1.92	0.998	NI		
Chemotherapy	No (reference)						0.047
	CMF	0.75	0.31–1.82	0.529	0.59	0.24–1.44	0.243
	AC ± T	0.36	0.16–0.79	0.011	0.33	0.15–0.74	0.007
	Unspecified	0.77	0.16–3.62	0.739	0.55	0.11–2.67	0.461
Postmastectomy radiotherapy	Yes vs No	0.26	0.08–0.84	0.024	0.22	0.05–0.92	0.038

AC = adriamycin cyclophosphamide, CI = confidence interval, CMF = cyclophosphamide methotrexate 5-fluorouracil, EIC = extensive intra-ductal component, HER2 = human epidermal growth factor receptor type 2, HR = hazard ratio, Macro = macrometastasis, Micro = micrometastasis, T = paclitaxel docetaxel.

*Variables were entered into multivariate Cox regression model in a stepwise backward elimination method if P was <0.20 and were removed at any point if P was >0.20.

inadequate axillary surgery,¹¹ and an earlier treatment era (eg, before 1997).¹¹ However, our results suggest that a risk-adaptive approach should be considered based on overall recurrence risk rather than LRR risk. In this regard, the results of the United Kingdom Medical Research Council-SUPREMO trial, which is a large randomized trial investigating the benefit of PMRT in modern treatment regimens that has the primary end-point of OS, are eagerly awaited.²⁷

Our study has several limitations including those inherent in retrospective analysis. The statistical analyses are incomplete because multivariate analysis for LRR and OS could not be performed because none of the patients undergoing PMRT died. In addition, patients who underwent PMRT had more LNs that

were positive and were, therefore, more likely to receive AC ± T chemotherapy, leading to potential selection bias. However, it is noteworthy that PMRT had a protective effect after controlling for these potentially confounding factors. Routine use of internal mammary node irradiation in our study should be taken into consideration to interpret the benefit of PMRT, which may be important because all previous positive trials of PMRT used internal mammary node irradiation.

In summary, patients with T1/T2N1 breast cancer who were treated recently had a lower risk of LRR and DM with excellent survival outcomes compared with those treated in the past. PMRT significantly and independently improved DFS, although reductions in LRR were not large or significant in

TABLE 5. Univariate Cox Proportional Hazards Survival Analysis Among Patients in the Late-Era Cohort (2004–2011) According to Metastasis Size and Positive Lymph Node Number

PMRT vs No PMRT	N	LRR Analysis		DM Analysis		DFS Analysis	
		HR	95% CI	HR	95% CI	HR	95% CI
Late-era cohort	412	0.29	0.04–2.23	0.29	0.07–1.23	0.26	0.08–0.84
[0,1-8]LN tumor deposits							
Micrometastasis	120	0.04	0.00–>100	2.38	0.23–24.5	0.59	0.07–4.66
Macrometastasis	292	0.33	0.04–2.56	0.13	0.02–0.99	0.19	0.05–0.78
[0,1-8]No. of positive LN							
1	256	0.04	0.00–163	0.04	0.00–12.1	0.04	0.00–3.73
2	108	0.53	0.06–4.53	0.42	0.05–3.51	0.45	0.10–2.05
3	48	NA		0.75	0.08–7.34	0.37	0.04–3.01

CI = confidence interval, DFS = disease-free survival, DM = distant metastasis, HR = hazard ratio, LN = lymph node, LRR = locoregional recurrence, NA = not applicable, PMRT = postmastectomy radiotherapy.

those treated with contemporary multidisciplinary management. We believe that the present study does not convincingly support the routine use of PMRT in all patients with T1/T2N1 breast cancer. However, it does support the results of the recent EBCTCG meta-analysis that PMRT improves LRR-free survival, DFS, and cancer-specific survival in node-positive patients in contemporary practice.¹ Similar concerns regarding regional radiotherapy in breast-conserved patients might be meaningful. Further studies, ideally, well-designed and controlled, need to be conducted to confirm our findings.

ACKNOWLEDGMENTS

The authors thank Hye Sun Lee, MS, Department of Biostatistics, Yonsei University College of Medicine, for statistical consultation and analysis of the data. The authors would like to thank Editage for editorial assistance. This work was supported by a grant from the National R & D Program for Cancer Control, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (0820010).

REFERENCES

1. Ebcetg, McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014;383:2127–2135.
2. Recht A, Gray R, Davidson NE, et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 1999;17:1689–1700.
3. Taghian A, Jeong JH, Mamounas E, et al. Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. *J Clin Oncol*. 2004;22:4247–4254.
4. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiother Oncol*. 2007;82:247–253.
5. Whelan TJ, Olivetto IA, Parulekar WR, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015;373:307–316.
6. Poortmans PM, Collette S, Kirkove C, et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. *N Engl J Med*. 2015;373:317–327.
7. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes – dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol*. 2011;22:1736–1747.
8. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol*. 2013;24:2206–2223.
9. Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol*. 2003;21:976–983.
10. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687–1717.
11. McBride A, Allen P, Woodward W, et al. Locoregional recurrence risk for patients with T1,2 breast cancer with 1-3 positive lymph nodes treated with mastectomy and systemic treatment. *Int J Radiat Oncol Biol Phys*. 2014;89:392–398.
12. Kim Z, Min SY, Yoon CS, et al. The basic facts of Korean breast cancer in 2011: results of a nationwide survey and breast cancer registry database. *J Breast Cancer*. 2014;17:99–106.
13. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev*. 2012;4:CD006243.
14. Early Breast Cancer Trialists' Collaborative GPeto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379:432–444.
15. Jatoi I, Anderson WF, Jeong JH, et al. Breast cancer adjuvant therapy: time to consider its time-dependent effects. *J Clin Oncol*. 2011;29:2301–2304.
16. Marks LB, Prosnitz LR. One to three" or "four or more"?: selecting patients for postmastectomy radiation therapy. *Cancer*. 1997;79:668–670.
17. Mittendorf EA, Ballman KV, McCall LM, et al. Evaluation of the stage IB designation of the American Joint Committee on Cancer staging system in breast cancer. *J Clin Oncol*. 2015;33:1119–1127.
18. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med*. 2003;349:546–553.
19. Viale G, Maiorano E, Mazzaro G, et al. Histologic detection and clinical implications of micrometastases in axillary sentinel lymph nodes for patients with breast carcinoma. *Cancer*. 2001;92:1378–1384.
20. Truong PT, Olivetto IA, Kader HA, et al. Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;61:1337–1347.
21. Fodor J, Polgar C, Major T, et al. Locoregional failure 15 years after mastectomy in women with one to three positive axillary nodes with or without irradiation: the significance of tumor size. *Strahlenther Onkol*. 2003;179:197–202.
22. Truong PT, Berthelet E, Lee J, et al. The prognostic significance of the percentage of positive/dissected axillary lymph nodes in breast cancer recurrence and survival in patients with one to three positive axillary lymph nodes. *Cancer*. 2005;103:2006–2014.
23. Duraker N, Demir D, Bati B, et al. Survival benefit of post-mastectomy radiotherapy in breast carcinoma patients with T1-2 tumor and 1-3 axillary lymph node(s) metastasis. *Jpn J Clin Oncol*. 2012;42:601–608.
24. Kim SI, Cho SH, Lee JS, et al. Clinical relevance of lymph node ratio in breast cancer patients with one to three positive lymph nodes. *Br J Cancer*. 2013;109:1165–1171.
25. Yang PS, Chen CM, Liu MC, et al. Radiotherapy can decrease locoregional recurrence and increase survival in mastectomy patients with T1 to T2 breast cancer and one to three positive nodes with negative estrogen receptor and positive lymphovascular invasion status. *Int J Radiat Oncol Biol Phys*. 2010;77:516–522.
26. Su YL, Li SH, Chen YY, et al. Post-mastectomy radiotherapy benefits subgroups of breast cancer patients with T1-2 tumor and 1-3 axillary lymph node(s) metastasis. *Radiol Oncol*. 2014;48:314–322.
27. Kunkler IH, Canney P, van Tienhoven G, et al. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial. *Clin Oncol (R Coll Radiol)*. 2008;20:31–34.