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Original Article

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Comparison of Breast Conserving Surgery Followed by Radiation Therapy with Mastectomy Alone for Pathologic N1 Breast Cancer Patients in the Era of Anthracycline Plus Taxane-Based Chemotherapy: A Multicenter Retrospective Study (KROG 1418)

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Purpose

We compared the oncologic outcomes of breast-conserving surgery plus radiation therapy (BCS+RT) and modified radical mastectomy (MRM) under anthracycline plus taxane-based (AT) regimens and investigated the role of adjuvant radiation therapy (RT) in patients with pathologic N1 (pN1) breast cancer treated by mastectomy.

Materials and Methods

We retrospectively reviewed the medical records of 2,011 patients with pN1 breast cancer who underwent BCS+RT or MRM alone at 12 institutions between January 2006 and December 2010. Two-to-one propensity score matching was performed for balances in variables between the groups.

Results

The median follow-up duration for the total cohort was 69 months (range, 1 to 114 months). After propensity score matching, 1,074 patients (676 in the BCS+RT group and 398 in the MRM-alone group) were analyzed finally. The overall survival, disease-free survival, locoregional failure-free survival, and regional failure-free survival (RFFS) curves of the BCS+RT group vs. MRM-alone group were not significantly different. The subgroup analysis revealed that in the group with both lymphovascular invasion (LVI) and histologic grade (HG) III, the BCS+RT showed significantly superior RFFS (p=0.008). Lymphedema (p=0.007) and radiation pneumonitis (p=0.031) occurred more frequently in the BCS+RT group than in the MRM-alone group, significantly.

Conclusion

There are no differences in oncologic outcomes between BCS+RT and MRM-alone groups under the AT chemotherapy regimens for pN1 breast cancer. However, BCS+RT group showed superior RFFS to MRM-alone group in the patients with LVI and HG III. Adjuvant RT might be considerable for pN1 breast cancer patients with LVI and HG III.

Key words
Breast neoplasms, Pathologic N1, Breast conserving surgery, Radiotherapy, Mastectomy, Anthracyclines, Taxane, Survival

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Introduction

Randomized trials comparing breast-conservation surgery (BCS) plus adjuvant radiation therapy (RT) with mastectomy alone in early-stage breast cancer have shown no differences in oncologic outcomes [1-6]. On the other hand, several recent population-based studies reported that BCS plus RT (BCS+RT) resulted in better oncologic outcomes than mastectomy according to T or N category [7-11]. The role of adjuvant RT after mastectomy for pN1 breast cancer is also a controversial issue. Key randomized trials showed better oncologic outcomes in the post-mastectomy RT (PMRT) group compared with the non-PMRT group for breast cancer with nodal metastasis [12,13]. Subgroup analysis by the Danish Breast Cancer Cooperative Group (DBCG) 82 B&C randomized trial [13] and meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [14] reported that PMRT had the benefit of local control for subgroups with 1-3 axillary nodal metastases. The National Comprehensive Cancer Network (NCCN) clinical practice guideline recommends strong consideration of PMRT for N1 breast cancer [15]. However, the chemotherapeutic regimens of these studies are not the modern one, but mostly the CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) regimen, which is less effective [16,17].

Anthracycline plus taxane-based (AT) chemotherapy is the currently recommended adjuvant treatment in the breast cancer, especially with nodal metastasis [15]. This regimen showed benefits in local control as well as overall survival (OS) comparing with previous chemotherapy regimens [18,19]. In the era of the AT regimen, the role of PMRT for pN1 disease is still unclear [20,21]. Therefore, we performed this study to compare oncologic outcomes between BCS+RT and modified radical mastectomy (MRM) alone under the AT regimen and to investigate the role of adjuvant RT in patients with pN1 breast cancer treated by mastectomy.

Materials and Methods

1. Patients

We retrospectively reviewed the medical records of 2,011 patients with pathologic N1 breast cancer who underwent BCS+RT or MRM alone at 12 institutions in South Korea between Jan 2006 and Dec 2010.

Information was obtained from medical records regarding pathologic tumor features, including molecular subtype, tumor size, resection margin, lymphovascular invasion (LVI), nuclear grade (NG), histologic grade (HG), number of lymph nodes (LN) with metastasis, and extracapsular extension (ECE). Patients were excluded because of non-AT chemotherapy (n=47), BCS without adjuvant RT (n=37) and PMRT (n=157), and insufficient medical records (n=296). Finally, 1,474 patients were included in the analysis.

2. Treatment

BCS+RT was performed for 1,047 patients (71.0%). The median dose of adjuvant RT on the whole breast was 50 Gy (range, 45 to 50.4 Gy). Tumor bed boost with median dose of 10 Gy (range, 5 to 16 Gy) was applied to 1,026 patients. RT to the supraclavicular fossa with a median dose of 50 Gy (range, 45 to 50.4 Gy) was performed in 320 patients (30.6%), and 37 (3.5%) of them received RT to the internal mammary area with a median dose of 50.4 Gy (range, 45 to 50.4 Gy). RT plans followed the general principles of RT to the whole breast. Median number of axillary LN dissections performed was 16 (range, 1 to 47). Most patients (99.8%) were treated with an AC (adriamycin and cyclophosphamide) plus T (taxane) regimen, while others were administrated the FAC (fluorouracil, adriamycin, and cytoxan) plus T regimen (0.1%) or EC (epirubicin and cyclophosphamide) plus T regimen (0.1%).

MRM alone was performed for 427 patients (29.0%). All patients in the MRM-alone group received a median of 19 axillary LN dissections (range, 2 to 43). AC plus T was administered to most patients (99.8%) in the MRM group. Other patients received the FEC (fluorouracil, epirubicin, and cytoxan) plus T regimen (0.2%). None of this group underwent adjuvant RT.

3. Statistical analysis

OS, disease-free survival (DFS), locoregional failure-free survival (LRFFS), and regional failure-free survival (RFFS) were defined as the interval from surgery to death, cancer recurrence, locoregional recurrence, and regional recurrence, respectively. The chi-square test or Fisher exact test was used to compare patient characteristics and patterns of failure between the BCS+RT and MRM-alone group. The Kaplan-Meier method was used to estimate survival curves. Log-rank tests were performed to compare survival between groups for various variables. Cox regression analysis was chosen for multivariate analysis to determine the independent prognostic factors for outcomes. A two-sided p-value of < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS ver. 22.0 (IBM Corp., Armonk, NY). Analyses were also performed for subgroups defined according to the number of risk factors identified as significant in multivariate analyses for DFS.

Table 1. Baseline characteristics of study patients

Characteristic	Before matching			After matching		
	BCS+RT (n=1,047)	MRM alone (n=427)	p-value	BCS+RT (n=676)	MRM alone (n=398)	p-value
Age (yr)	47.4±8.6	48.9±9.4	0.004	48.1±8.9	48.7±9.3	0.319
Menopausal status						
Premenopause	676 (64.6)	251 (58.8)	0.043	415 (61.4)	238 (59.8)	0.604
Postmenopause	371 (35.4)	176 (41.2)		261 (38.6)	160 (40.2)	
Site						
Left	504 (48.1)	217 (50.8)	0.380	330 (48.8)	199 (50.0)	0.732
Right	543 (51.9)	210 (49.2)		346 (51.2)	199 (50.0)	
Pathology						
IDC	984 (94.0)	413 (96.7)	0.044	648 (95.9)	384 (96.5)	0.601
Non-IDC	63 (6.0)	14 (3.3)		28 (4.1)	14 (3.5)	
Pathologic T category						
1	507 (48.4)	160 (37.5)	0.000	280 (41.4)	160 (40.2)	0.897
2	532 (50.8)	265 (62.1)		393 (58.1)	236 (59.3)	
3	8 (0.8)	2 (0.5)		3 (0.4)	2 (0.5)	
No. of LN metastases						
1	603 (57.6)	231 (54.1)	0.070	381 (56.4)	218 (54.8)	0.722
2-3	444 (42.4)	196 (45.9)		295 (43.6)	180 (45.2)	
LN management						
SLNB only	78 (7.4)	24 (5.6)	0.258	46 (6.8)	22 (5.5)	0.438
ALND	969 (92.6)	403 (94.4)		630 (93.2)	376 (94.5)	
Positive LN ratio						
≤ 0.1	506 (48.3)	233 (54.6)	0.034	338 (50.0)	219 (55.0)	0.101
> 0.1	541 (51.7)	194 (45.4)		338 (50.0)	179 (45.0)	
LVI						
No	370 (35.3)	273 (63.9)	0.000	397 (58.7)	244 (61.3)	0.068
Yes	677 (64.7)	154 (36.1)		279 (41.3)	154 (38.7)	
Nuclear grade						
1-2	599 (57.2)	200 (46.8)	0.000	324 (47.9)	200 (50.3)	0.412
3	448 (42.8)	227 (53.2)		352 (52.1)	198 (49.7)	
Histologic grade						
I-II	642 (61.3)	216 (50.6)	0.000	301 (44.5)	185 (46.5)	0.482
III	405 (38.7)	211 (49.4)		375 (55.5)	213 (53.5)	
Molecular subtype						
Luminal A	459 (43.8)	192 (45.0)	0.736	375 (55.4)	216 (54.3)	0.736
Non-luminal A	588 (56.2)	235 (55.0)		301 (44.6)	182 (45.7)	
ECE						
No	578 (55.2)	267 (62.5)	0.012	382 (56.5)	239 (60.1)	0.247
Yes	469 (44.8)	160 (37.5)		294 (43.5)	159 (39.9)	

Values are presented as mean±standard deviation or number (%). BCS, breast conserving surgery; RT, radiation therapy; MRM, modified radical mastectomy; IDC, invasive ductal carcinoma; LN, lymph node; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; LVI, lymphovascular invasion; ECE, extracapsular extension.

Two-to-one propensity score matching was performed to eliminate imbalances in variables between the two treatment groups. Matching variables were age, menopause status, site, pathology, pathologic T staging, number of LNs with metastasis, LVI, NG, HG, molecular subtype, and ECE. R Statistical Software ver. 3.2.3 (The R foundation for Statistical Analyses, Vienna, Austria) was utilized in propensity score matching.

Table 2. Patterns of the first failure according to field of radiotherapy

Sites of the first failure	BCS+RT (n=676)	MRM alone (n=398)	p-value
Isolated loco-regional only	10 (1.5)	6 (1.5)	0.971
Local only	5 (0.7)	2 (0.5)	1.000
Regional only	5 (0.7)	4 (1.0)	0.733
Distant only	28 (4.1)	23 (5.8)	0.223
Simultaneous loco-regional and distant	12 (1.8)	13 (3.3)	0.118
Total	50 (7.4)	42 (10.6)	0.074

Values are presented as number (%). BCS, breast conserving surgery; RT, radiation therapy; MRM, modified radical mastectomy.

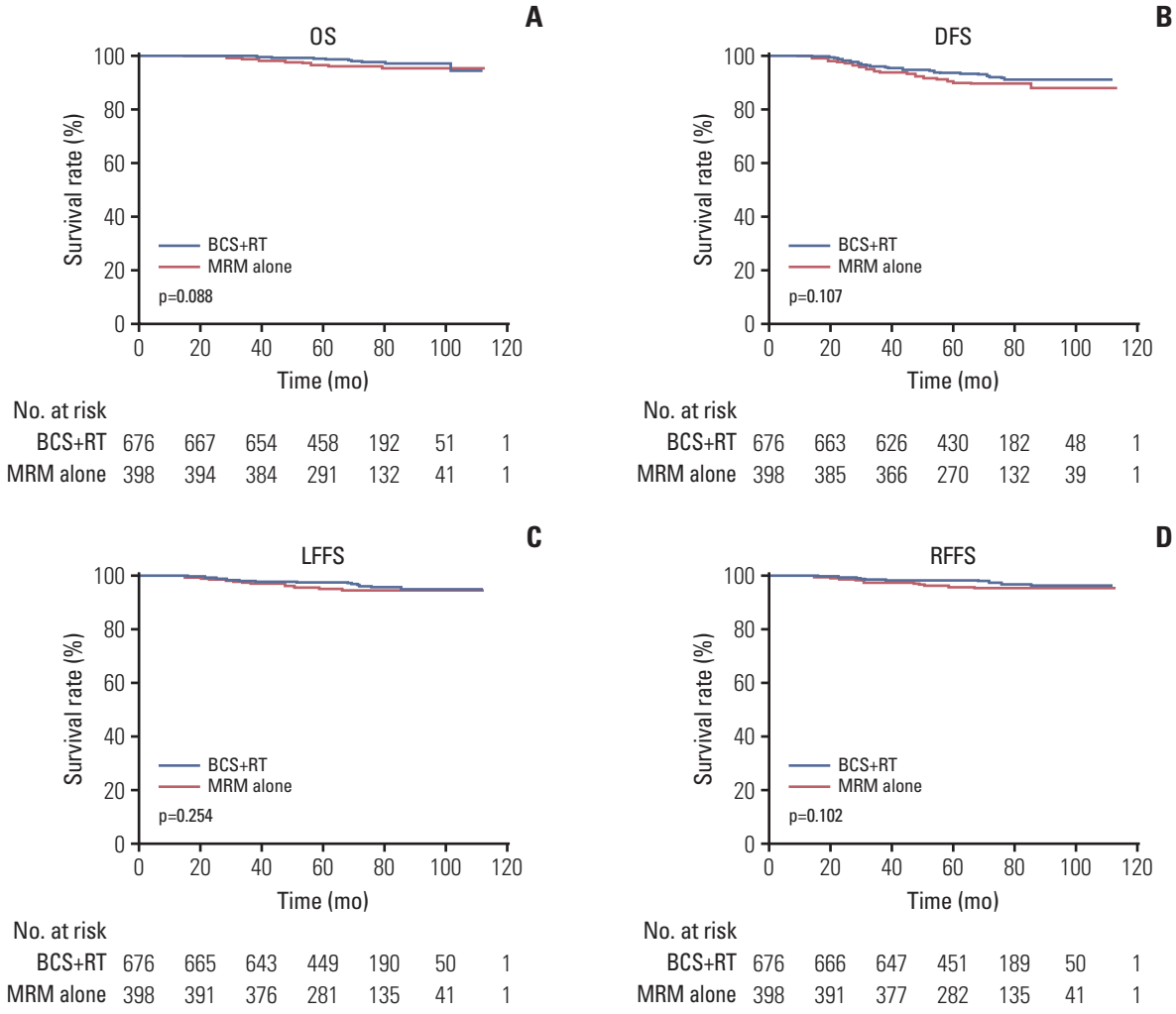

Fig. 1. Survival curves according to treatment group. Overall survival (OS) (A), disease-free survival (DFS) (B), locoregional failure-free survival (LFFS) (C), and regional failure-free survival (RFFS) (D). BCS+RT, breast conserving surgery plus radiation therapy; MRM, modified radical mastectomy.

Table 3. Univariate and multivariate analysis (OS)

Characteristic	Univariate analysis		Multivariate analysis	
	5-Year OS rate (%)	p-value	HR (95% CI)	p-value
Age (yr)				
≤ 55	97.7	0.828	-	-
> 55	97.5		-	
Menopause status				
Premenopause	98.6	0.072	0.592 (0.295-1.190)	0.141
Postmenopause	96.0		-	
Site				
Left	97.3	0.737	-	-
Right	97.9		-	
Pathology				
IDC	97.6	0.725	-	-
Non-IDC	97.7		-	
Pathologic T category				
1	97.9	0.731	-	-
2-3	97.4		-	
No. of LN metastases				
1	97.8	0.443	-	-
2	97.4		-	
LVI				
No	98.0	0.342	-	-
Yes	97.2		-	
Nuclear grade				
1-2	98.9	0.002	0.544 (0.174-1.704)	0.296
3	96.2		-	
Histologic grade				
I-II	99.0	0.004	0.773 (0.269-2.220)	0.632
III	95.9		-	
Molecular subtype				
Luminal A	99.1	0.001	0.327 (0.129-0.825)	0.018
Non-luminal A	96.3		-	
ECE				
No	97.6	0.771	-	-
Yes	97.7		-	
Modality				
BCS+RT	98.6	0.088	0.597 (0.297-1.200)	0.147
MRM alone	96.1		-	

OS, overall survival; HR, hazard ratio; CI, confidence interval; IDC, invasive ductal carcinoma; LN, lymph node; LVI, lymphovascular invasion; ECE, extracapsular extension; BCS, breast conserving surgery; RT, radiation therapy; MRM; modified radical mastectomy.

4. Ethical statement

This study was approved by the Institutional Review Board (IRB) of each hospital and performed in accordance with the principles of the Declaration of Helsinki. Each IRB approved a waiver of informed consent.

Results

1. Patient characteristics

The median follow-up duration for the total cohort was 69 months (range, 1 to 114 months). The 5-year rates of OS, DFS, LRFFS, and RFFS of the total cohort were 98.0%, 92.4%,

Table 4. Univariate and multivariate analysis (DFS)

Characteristic	Univariate analysis		Multivariate analysis	
	5-Year DFS rate (%)	p-value	HR (95% CI)	p-value
Age (yr)				
≤ 55	91.9	0.987	-	-
> 55	92.3		-	
Menopause status				
Premenopause	92.5	0.248	-	-
Postmenopause	91.0		-	
Site				
Left	90.7	0.171	1.239 (0.818-1.875)	0.311
Right	93.2		-	
Pathology				
IDC	91.9	0.598	-	-
Non-IDC	93.2		-	
Pathologic T category				
1	95.0	0.001	0.665 (0.415-1.064)	0.089
2-3	89.6		-	
No. of LN metastases				
1	93.2	0.126	0.823 (0.545-1.244)	0.356
2-3	90.4		-	
LVI				
No	94.6	< 0.001	0.472 (0.304-0.731)	0.001
Yes	88.7		-	
Nuclear grade				
1-2	95.4	< 0.001	0.715 (0.389-1.314)	0.280
3	88.0		-	
Histologic grade				
I-II	96.4	< 0.001	0.254 (0.134-0.481)	0.001
III	86.1		-	
Molecular subtype				
Luminal A	94.4	0.024	0.849 (0.544-1.326)	0.472
Non-luminal A	90.0		-	
ECE				
No	91.8	0.771	-	-
Yes	92.0		-	
Modality				
BCS+RT	93.3	0.107	0.702 (0.463-1.065)	0.096
MRM alone	89.7		-	

DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; IDC, invasive ductal carcinoma; LN, lymph node; LVI, lymphovascular invasion; ECE, extracapsular extension; BCS, breast conserving surgery; RT, radiation therapy; MRM; modified radical mastectomy.

97.0%, and 97.6%, respectively. Among the total cohort, there were significant differences in age, menopausal status, pathology, pathologic T category, LVI, NG, HG, and ECE between the BCS+RT and MRM-alone groups. After propensity score matching, a total of 1,074 patients (676 in the BCS+RT group and 398 in the MRM-alone group) were included for analysis. The patient characteristics are summarized in Table 1. The number of dissected LNs were 16 (range, 1 to 42) in BCS+RT group and 18 (range, 2 to 42) in MRM-alone group.

Table 5. Univariate and multivariate analysis (RFFS)

Characteristic	Univariate analysis		Multivariate analysis	
	5-Year RFFS rate (%)	p-value	HR (95% CI)	p-value
Age (yr)				
≤ 55	97.2	0.915	-	-
> 55	98.0		-	
Menopause status				
Premenopause	97.3	0.571	-	-
Postmenopause	97.4		-	
Site				
Left	96.9	0.571	-	-
Right	97.8		-	
Pathology				
IDC	97.2	0.218	-	-
Non-IDC	100		-	
Pathologic T category				
1	98.2	0.120	0.890 (0.417-1.900)	0.764
2-3	96.7		-	
No. of LN metastases				
1	97.1	0.638	-	-
2-3	97.7		-	
LVI				
No	98.6	0.004	0.340 (0.159-0.726)	0.005
Yes	95.9		-	
Nuclear grade				
1-2	98.8	0.021	0.527 (0.205-1.356)	0.184
3	95.7		-	
Histologic grade				
I-II	99.4	< 0.001	0.138 (0.047-0.408)	< 0.001
III	94.6		-	
Molecular subtype				
Luminal A	98.5	0.193	0.902 (0.431-1.887)	0.785
Non-luminal A	96.4		-	
ECE				
No	97.3	0.503	-	-
Yes	97.3		-	
Modality				
BCS+RT	98.3	0.102	0.523 (0.262-1.044)	0.066
MRM	95.7		-	

RFFS, regional failure-free survival; HR, hazard ratio; CI, confidence interval; IDC, invasive ductal carcinoma; LN, lymph node; LVI, lymphovascular invasion; ECE, extracapsular extension; BCS, breast conserving; RT, radiation therapy; MRM; modified radical mastectomy.

2. Treatment outcome

Among 1,074 patients, 92 (8.6%) experienced disease recurrence. The patterns of first failure were not significantly different between the groups (Table 2). The OS, DFS, LRFFS, and RFFS rates of the BCS+RT group vs. MRM-alone group at 5 years were 98.6% vs. 96.1% (p=0.088), 93.3% vs. 89.7% (p=0.107), 97.6% vs. 95.2% (p=0.254), and 98.3% vs. 95.7% (p=0.102), respectively (Fig. 1). On multivariate analysis, luminal A type was identified as an independent prognostic factor associated with better OS (Table 3). The multivariate analyses revealed that LVI and HG were independent prognosticators associated with DFS and RFFS (Tables 4 and 5).

Three subgroups were determined according to the num-

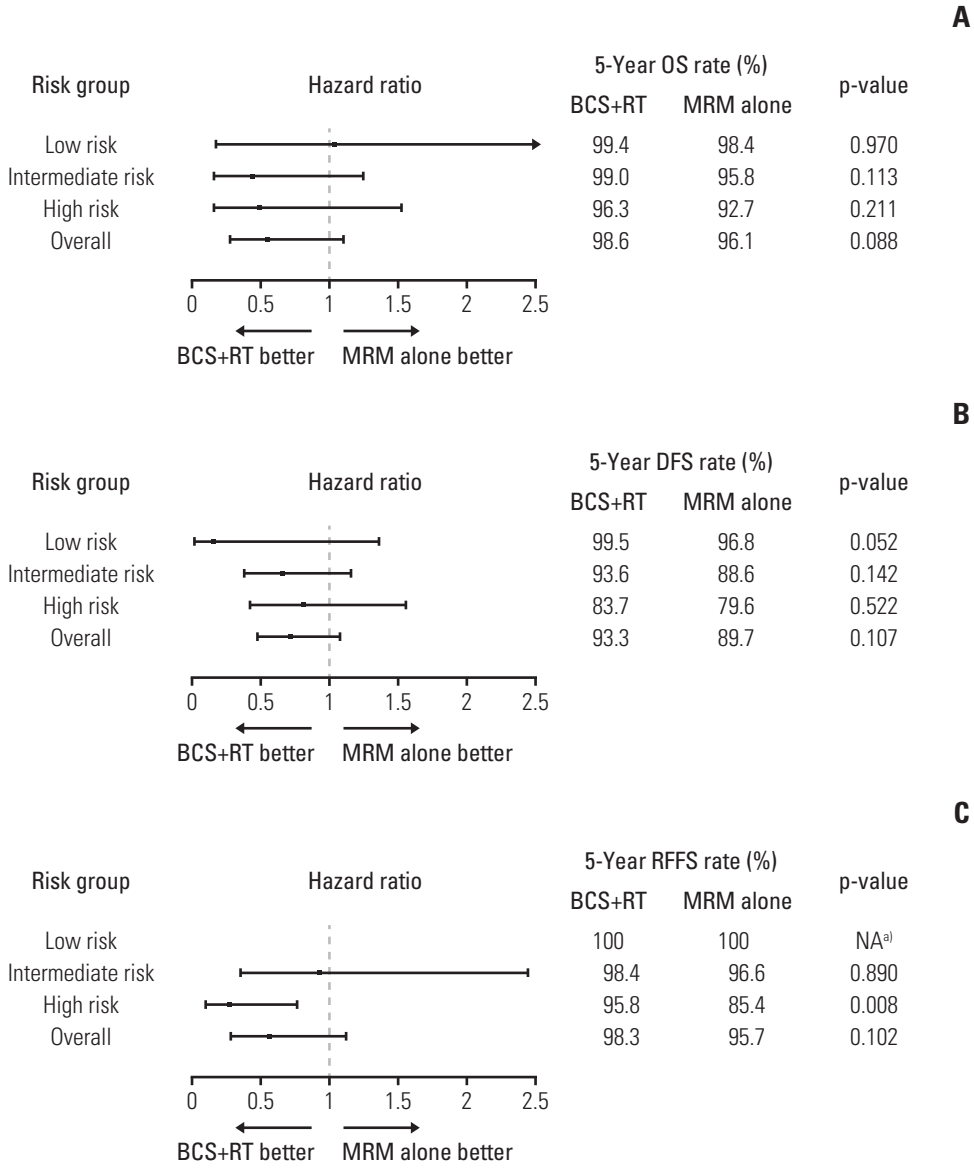

Fig. 2. Subgroup analyses according to risk group for overall survival (OS) (A), disease-free survival (DFS) (B), and regional failure-free survival (RFFS) (C). BCS+RT, breast conserving surgery plus radiation therapy; MRM, modified radical mastectomy; NA, not applicable, [a)]Hazard ratio was not calculated for RFFS in the low risk group because there was no regional failure in that subgroup.

Table 6. Treatment-related toxicities

Morbidity	BCS+RT (n=676)			MRM alone (n=398)			p-value
	Grade 1	Grade ≥ 2	Total	Grade 1	Grade ≥ 2	Total	
Lymphedema	69 (10.2)	22 (3.3)	91 (13.5)	26 (6.5)	6 (1.5)	32 (8.0)	0.007
Pneumonitis	8 (1.2)	1 (0.1)	9 (1.3)	0	0	0	0.031

Values are presented as number (%). BCS, breast conserving surgery; RT, radiation therapy; MRM, modified radical mastectomy.

ber of risk factors (positive LVI and HG of III) identified in multivariate analysis for DFS and RFFS: the low risk group (n=346) had no risk factors, the intermediate risk group (n=512) had one risk factor, and the high risk group (n=216) had two risk factors. For the high risk group, BCS+RT showed significantly superior RFFS (99.5% vs. 96.8%, p=0.008) (Fig. 2). Although there was also a tendency for BCS+RT to have better DFS for all risk groups, there were no statistically significant differences (Fig. 2).

3. Toxicity

Lymphedema and radiation pneumonitis occurred more frequently in the BCS+RT group than in the MRM-alone group (Table 6). A total of 8.0% of patients in the MRM-alone group showed lymphedema, while 13.5% of patients presented with lymphedema after BCS+RT (p=0.007). Radiation pneumonitis was present in 1.3% of patients in the BCS+RT group, whereas no patient in the MRM group showed radiation pneumonitis (p=0.031).

Discussion

Randomized trials comparing BCS+RT with mastectomy in early-stage breast cancer have shown comparable oncologic outcomes by long-term follow-up data [1-6]. However, several recent population-based studies reported that BCS+RT resulted in superior oncologic outcomes compared to mastectomy [7-11]. There are several reasons for this inconsistency in results between historic randomized trials and population-based studies. Those randomized trials were conducted in the 1980s with outdated diagnostic and therapeutic procedures; therefore, local recurrence was much higher [11,22]. Differences in study designs and patient populations may be additional reasons for inconsistent results between randomized trials and population-based studies [23]. The evolution of chemotherapy for early breast cancer may also deviate from the results of historic randomized trials [18,19]. Therefore, special caution is required in interpreting those randomized trials in current practice. Those population-based studies also have some limitations. The chemotherapy regimens were not standard. In addition, comparisons between treatment modalities were stratified only according to pathologic T or N category, not according to any other histologic or molecular subtype-based characteristics. To our knowledge, the current research is the first study to compare treatment outcomes between BCS+RT and MRM alone under a modern and homogeneous chemotherapy regimen. In addition, the treatment outcomes were compared according to subgroups stratified with various pathological variables for pN1 breast cancer. The inhomogeneity of the demographic and histologic properties was amended by propensity score matching.

The oncologic outcomes were not significantly different between treatment modalities. Among population-based studies, two reported the outcome of the pN1 subgroup. Chen et al. [8] used the National Cancer Database and reported the adjusted hazard ratio of mastectomy alone as 1.44 (range, 2.31 to 1.53; $p < 0.001$) over BCS+RT in patients with pN1 breast cancer. van Maaren et al. [11] analyzed patients selected from the Netherlands Cancer Registry and reported a higher mortality risk rate in the mastectomy compared with the BCS+RT. However, in those studies, mastectomy groups contained higher proportions of patients with large and multi-centric tumors, which are known prognostic factors associated with inferior LRFFS and OS. In addition, information regarding detailed chemotherapy regimen was not clarified, and a considerable proportion of patients treated with chemotherapy were included in the study population. In the modern chemotherapy era, the outcome of mastectomy alone has improved [18,19]. In particular, some studies have specifically reported that patients with 1-3 positive LNs showed improvement in oncologic outcomes [20,24,25]. Therefore, the results are inconsistent, with the current study showing better outcomes for the mastectomy group than those studies.

The role of PMRT is also a controversial issue for pN1 non-metastatic breast cancer. The DBCG 82 B&C trial and EBCTCG revealed that PMRT reduced mortality rates regardless of the number of LN metastases [6,13,14]. On the other hand, recent retrospective studies showed that addition of PMRT in patients with pN1 breast cancer seems to have no significant impact on oncologic outcomes in the modern chemotherapy era [20,24,25]. In the current study, the benefit of PMRT was not evaluated because patients who received PMRT were excluded from analyses. However, in the high-risk subgroup with LVI and HG 3, which were identified as independent factors associated with poor DFS, the BCS+RT group showed significantly better RFFS than the MRM-alone group. This implied that there might be a role of adjuvant RT in reducing regional recurrence for patients with LVI and HG 3, which are well-known risk factors related to poor locoregional control and LN metastasis [20,26-28]. Therefore, PMRT is a consideration for patients with LVI and HG III even in the modern chemotherapy era. Further large scale randomized trials with stratification according to detailed risk groups are necessary to identify the role of PMRT in pN1 non-metastatic breast cancer.

There are several limitations in the current study. First, there is inevitable selection bias due to its retrospective nature. Although the propensity score matching method was

utilized to balance treatment groups, some variables that were excluded from score matching might have been unevenly distributed. The pathologic data were collected from several different institutions, so bias regarding pathologic information also could not be excluded. Finally, the relatively short follow-up duration of the current study is also a limitation. The median follow-up duration of the total cohort was 69 months, which is not enough to detect late recurrence and treatment-related sequelae [29]. Therefore, further follow-up is required to compare long-term oncologic outcomes and adverse effects between treatment groups.

In conclusion, there are no differences in OS, DFS, LRFFS, and RFFS between BCS+RT and MRM alone under the AT chemotherapy regimen for patients with pN1 non-breast cancer. However, BCS+RT showed superior RFFS in patients with LVI and HG III, implying that adjuvant RT potentially has a role in reducing regional recurrence. Therefore, PMRT might be considerable for patients with LVI and HG 3.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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