

# Impact of Regional Nodal Irradiation for Breast Cancer Patients with Supraclavicular and/or Internal Mammary Lymph Node Involvement: A Multicenter, Retrospective Study (KROG 16-14)

**Kyubo Kim, MD, PhD<sup>1</sup>**  
**Yuri Jeong, MD<sup>2</sup>**  
**Kyung Hwan Shin, MD, PhD<sup>3</sup>**  
**Jin Ho Kim, MD, PhD<sup>3</sup>**  
**Seung Do Ahn, MD, PhD<sup>4</sup>**  
**Su Ssan Kim, MD, PhD<sup>4</sup>**  
**Chang-Ok Suh, MD, PhD<sup>5</sup>**  
**Yong Bae Kim, MD, PhD<sup>5</sup>**  
**Doo Ho Choi, MD, PhD<sup>6</sup>**  
**Won Park, MD, PhD<sup>6</sup>**  
**Jihye Cha, MD, PhD<sup>7</sup>**  
**Mison Chun, MD, PhD<sup>8</sup>**  
**Dong Soo Lee, MD<sup>9</sup>**  
**Sun Young Lee, MD, PhD<sup>10</sup>**  
**Jin Hee Kim, MD, PhD<sup>11</sup>**  
**Hae Jin Park, MD, PhD<sup>12</sup>**  
**Wonguen Jung, MD, PhD<sup>1</sup>**

\*A list of author's affiliations appears at the end of the paper.

Correspondence: Kyung Hwan Shin, MD, PhD  
Department of Radiation Oncology,  
Seoul National University College of Medicine,  
101 Daehak-ro, Jongno-gu, Seoul 03080, Korea  
Tel: 82-2-2072-2524  
Fax: 82-2-765-3317  
E-mail: radiat@snu.ac.kr

Co-correspondence: Su Ssan Kim, MD, PhD  
Department of Radiation Oncology,  
Asan Medical Center, University of Ulsan  
College of Medicine, 88 Olympic-ro 43-gil,  
Songpa-gu, Seoul 05505, Korea  
Tel: 82-2-3010-5680  
Fax: 82-2-3010-6950  
E-mail: watermountain@hanmail.net

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\*Kyubo Kim and Yuri Jeong contributed equally to this work.

## Purpose

The purpose of this study was to evaluate the treatment outcomes of radiotherapy (RT) for breast cancer with ipsilateral supraclavicular (SCL) and/or internal mammary (IMN) lymph node involvement.

## Materials and Methods

A total of 353 patients from 11 institutions were included. One hundred and thirty-six patients had SCL involvement, 148 had IMN involvement, and 69 had both. All patients received neoadjuvant systemic therapy followed by breast-conserving surgery or mastectomy, and postoperative RT to whole breast/chest wall. As for regional lymph node irradiation, SCL RT was given to 344 patients, and IMN RT to 236 patients. The median RT dose was 50.4 Gy.

## Results

The median follow-up duration was 61 months (range, 7 to 173 months). In-field progression was present in SCL (n=20) and/or IMN (n=7). The 5-year disease-free survival (DFS) and overall survival rates were 57.8% and 75.1%, respectively. On multivariate analysis, both SCL/IMN involvement, number of axillary lymph node  $\geq 4$ , triple-negative subtype, and mastectomy were significant adverse prognosticators for DFS ( $p=0.022$ ,  $p=0.001$ ,  $p=0.001$ , and  $p=0.004$ , respectively). Regarding the impact of regional nodal irradiation, SCL RT dose  $\geq 54$  Gy was not associated with DFS (5-year rate, 52.9% vs. 50.9%;  $p=0.696$ ) in SCL-involved patients, and the receipt of IMN RT was not associated with DFS (5-year rate, 56.1% vs. 78.1%;  $p=0.099$ ) in IMN-involved patients.

## Conclusion

Neoadjuvant chemotherapy followed by surgery and postoperative RT achieved an acceptable in-field regional control rate in patients with SCL and/or IMN involvement. However, a higher RT dose to SCL or IMN RT was not associated with the improved DFS in these patients.

## Key words

Breast neoplasms, Supraclavicular lymph node, Internal mammary lymph node, Radiotherapy

## Introduction

Since the recent publication of randomized controlled trials [1,2], elective regional nodal radiotherapy (RT) including supraclavicular lymph nodes (SCL) and internal mammary lymph nodes (IMN) has become the standard treatment in the adjuvant RT for node-positive breast cancer. In the meanwhile, neoadjuvant systemic therapy (NST) followed by surgery and postoperative RT is a widely accepted treatment for breast cancer with clinically apparent SCL or IMN [3-5]. Initially involved nodal areas are usually included in the RT field, but there are little data on the impact of regional nodal RT in this setting.

Historically, SCL involvement presented as palpable disease, and the IMN involvement was confirmed after surgical excision such as extended radical mastectomy. With the development of imaging technologies such as positron emission tomography-computed tomography (PET-CT), however, extra-axillary regional lymph nodes in locally advanced breast cancer have been increasingly detected [6-8]. Despite the possibility of over-diagnosis, non-palpable SCL and/or clinically detected IMN involvement is becoming more and more common, and more data on the treatment outcome in this setting is needed.

In this study, we evaluated the treatment outcomes of NST followed by surgery and postoperative RT for breast cancer with SCL and/or IMN involvement and investigated the impact of regional nodal RT on the outcomes in these patients.

## Materials and Methods

### 1. Study population

After institutional review board approval, a total of 353 patients with involved SCL and/or IMN but without distant metastases were included from 11 institutions between January 2000 and December 2013. SCL and/or IMN metastases were defined as involvement on imaging studies including PET-CT, magnetic resonance imaging (MRI) of the breast, chest CT, and/or breast ultrasonography (US).

Overall, PET-CT was performed in 325 patients (92.1%), MRI in 274 (77.6%), CT in 119 (33.7%), and US in 342 (96.9%). Among patients with SCL involvement (n=205), SCL was observed in PET-CT (173 of 189), MRI (71 of 141), CT (41 of 76), and US (146 of 198). Meanwhile, IMN was observed in PET-CT (184 of 205), MRI (134 of 187), CT (37 of 69), and US (127 of 213) among 217 patients with IMN involvement.

According to the number of imaging modalities, all four modalities identified SCL in three patients, three modalities in 71, two modalities in 75, and a single modality in 56, while IMN was identified by all four modalities in three patients, three modalities in 95, two modalities in 67, and a single modality in 52. Pathological confirmation was done in 99 patients for SCL and 59 patients for IMN.

### 2. Treatment

All patients received NST. Chemotherapeutic regimen was adriamycin-based chemotherapy (n=60), taxane-based chemotherapy (n=268), and others (n=18). Seven patients received hormonal therapy and/or anti-human epidermal growth factor receptor 2 (HER2) therapy without cytotoxic chemotherapy.

With regard to surgical treatment for breast, mastectomy was performed in 224 patients, breast-conserving surgery in 127, and no breast surgery in two due to occult breast cancer. Axillary lymph node dissection was performed in 304 patients and sentinel lymph node biopsy in 49. Fifty-nine patients underwent SCL excision and 14 patients underwent IMN excision.

Postoperative RT was given to breast/chest wall up to a median dose of 50.4 Gy (range, 43.2 to 70 Gy). SCL RT was given in 344 patients, and IMN RT in 236. The median dose to SCL and IMN was 50.4 Gy (range, 45 to 70.4 Gy) and 50.4 Gy (range, 43.2 to 66 Gy), respectively.

One hundred and fifty patients received adjuvant chemotherapy: adriamycin-based chemotherapy in 22 patients, taxane-based chemotherapy in 100, and others in 28. One hundred and ninety-one patients received hormonal therapy, and 111 patients received anti-HER2 therapy.

### 3. Statistical analysis

Local recurrences were defined as disease recurrences in the ipsilateral breast or chest wall, and regional recurrences as those in the ipsilateral axillary lymph node, SCL, and/or IMN. Disease recurrences other than local and/or regional recurrences were defined as distant metastases. The time between initial treatment and recurrence or last follow-up was measured as disease-free survival (DFS). Overall survival (OS) was defined from the date of initial treatment to the date of death from any cause or last follow-up. The actuarial survival rates were calculated by the Kaplan-Meier method and compared using the log-rank test. On multivariate analysis, Cox proportional-hazards model was applied. Factors with p-value < 0.05 on univariate analysis were included in the multivariate analysis. A p < 0.05 was considered statistically significant. Differences in categorical variables were compared using the standard chi-square test or

**Table 1.** Patient and tumor characteristics

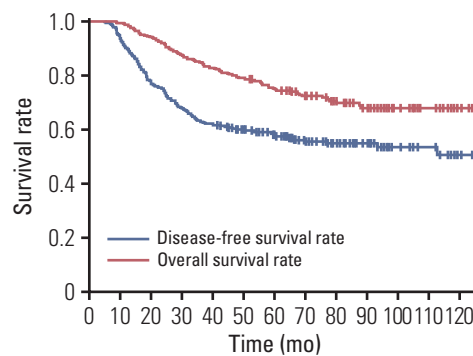
Variable	No. (%) (n=353)
Age (yr)	47 (23-84)
<b>Clinical T category</b>	
cT1-2	188 (53.3)
cT3-4	161 (45.6)
cTx	4 (1.1)
<b>Nodal involvement</b>	
IMN only	148 (41.9)
SCL only	136 (38.5)
SCL+IMN	69 (19.5)
<b>Pathologic T category</b>	
ypT0	47 (13.3)
ypTis	19 (5.4)
ypT1	129 (36.5)
ypT2	87 (24.6)
ypT3-4	71 (20.1)
<b>No. of positive axillary nodes</b>	
0	103 (29.2)
1-3	98 (27.8)
4-9	90 (25.5)
≥ 10	62 (17.6)
<b>Hormonal receptor status</b>	
Positive	187 (53.0)
Negative	166 (47.0)
<b>HER2 status</b>	
Positive	132 (37.4)
Negative	207 (58.6)
Equivocal	14 (4.0)
<b>SCL response to NST</b>	
Clinical CR	267 (75.6)
Clinical non-CR	72 (20.4)
Unknown	14 (4.0)
<b>IMN response to NST</b>	
Clinical CR	268 (75.9)
Clinical non-CR	66 (18.7)
Unknown	19 (5.4)

Values are presented as median (range) or number (%). IMN, internal mammary lymph node; SCL, supraclavicular lymph node; HER2, human epidermal growth factor receptor 2; NST, neoadjuvant systemic therapy; CR, complete remission.

Fisher exact test. All statistical analyses were performed using SPSS software (release 18.0.1. SPSS Inc., Chicago, IL).

#### 4. Ethical statement

The institutional review board approved this study (approval number: H-1612-095-815 at Seoul National University



**Fig. 1.** Disease-free and overall survival curves among all the patients (n=353).

Hospital), and waived the requirement for obtaining informed consent.

## Results

### 1. Characteristics

The patient and tumor characteristics are summarized in Table 1. The median age was 47 years (range, 23 to 84 years). As for clinical T category, 188 patients had cT1-2, and 161 had cT3-4 disease. One hundred and thirty-six patients had SCL involvement, 148 had IMN involvement, and 69 had both. After NST, pathologic T categories were as follows: ypT0-is in 66 patients, ypT1-2 in 216, and ypT3-4 in 71. The number of involved axillary lymph nodes was 0 in 103 patients, 1-3 in 98, 4-9 in 90, and ≥ 10 in 62. Regarding the response of SCL and IMN to NST, each 75.9% of patients showed clinical complete remission (CR) on imaging. Hormonal receptor was positive in 53.0% of patients, and HER2 positivity was observed in 37.4% of patients.

### 2. Outcomes and prognostic factors

The median duration of follow-up was 61 months (range, 7 to 173 months). There were 67 patients with loco-regional recurrences and 140 patients with distant metastases. Among loco-regional recurrences, 20 patients had isolated local recurrences, 23 isolated regional recurrences, and 24 local and regional recurrences. The 5-year DFS and OS were 57.8% and 75.1%, respectively (Fig. 1).

On univariate analysis, ypT category, extent of SCL and/or IMN involvement, number of involved axillary lymph nodes, histologic grade, lymphovascular invasion, molecular

**Table 2.** Univariate and multivariate analyses for DFS and OS

Variable	DFS				OS			
	5-Year rate	p-value (univariate)	HR (95% CI)	p-value (multivariate)	5-Year rate	p-value (univariate)	HR (95% CI)	p-value (multivariate)
<b>Age (yr)</b>								
< 40	50.9	0.089			74.7	0.290		
≥ 40	60.3				75.3			
<b>ypT category</b>								
0-1	64.1	0.002	1	0.543	80.1	0.004	1	0.065
2-4	50.0		1.126 (0.768-1.652)		68.9		1.534 (0.974-2.414)	
<b>Nodal involvement</b>								
Both SCL/IMN	47.8	0.046	1.568 (1.066-2.304)	0.022	63.4	0.019	1.818 (1.145-2.887)	0.011
Others	60.3		1		78.0		1	
<b>No. of axillary lymph nodes</b>								
0-3	72.1	< 0.001	1	0.001	80.5	0.001	1	0.354
≥ 4	49.1		1.950 (1.323-2.875)		68.0		1.235 (0.791-1.928)	
<b>Histologic grade</b>								
1 or 2	61.8	0.007	1	0.081	81.4	0.001	1	0.025
3	50.0		1.362 (0.963-1.928)		64.8		1.647 (1.065-2.548)	
<b>Lymphovascular invasion</b>								
Absent	64.0	< 0.001	1	0.108	73.7	0.570		
Present	49.1		1.363 (0.934-1.989)		76.5			
<b>Molecular subtype</b>								
Triple-negative	39.0	< 0.001	2.626 (1.482-4.653)	0.001	58.6	< 0.001	3.311 (2.121-5.170)	< 0.001
Others	63.9		1		80.8		1	
<b>Breast surgery</b>								
BCS	71.7	< 0.001	1	0.004	85.4	0.001	1	0.002
Mastectomy	49.8		1.911 (1.224-2.984)		69.2		2.421 (1.393-4.207)	
<b>Postoperative chemotherapy</b>								
No	57.6	0.802			73.7	0.189		
Yes	57.7				77.0			
<b>Hormonal therapy</b>								
No	49.2	< 0.001	1	0.620	65.8	< 0.001	1	0.350
Yes	65.1		0.884 (0.542-1.441)		83.0		0.760 (0.427-1.352)	
<b>Herceptin</b>								
No	54.2	0.042	1	0.867	72.3	0.032	1	0.270
Yes	65.5		0.960 (0.595-1.549)		81.0		0.687 (0.352-1.338)	

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; SCL, supraclavicular lymph node; IMN, internal mammary lymph node; BCS, breast-conserving surgery.

subtype, type of breast surgery, hormonal therapy, and anti-HER2 therapy were significantly associated with DFS. On multivariate analysis, both SCL and IMN involvement (hazard ratio [HR], 1.568; 95% confidence interval [CI], 1.066 to 2.304;  $p=0.022$ ), four or more involved axillary lymph nodes (HR, 1.950; 95% CI, 1.323 to 2.875;  $p=0.001$ ), triple-negative subtype (HR, 2.626; 95% CI, 1.482 to 4.653;  $p=0.001$ ), and mastectomy (HR, 1.911; 95% CI, 1.224 to 2.984;  $p=0.004$ ) were

adverse prognostic factors for DFS (Table 2).

With regard to OS, ypT category, extent of SCL and/or IMN involvement, number of involved axillary lymph nodes, histologic grade, molecular subtype, type of breast surgery, hormonal therapy, and anti-HER2 therapy were significant prognostic factors on univariate analysis. Among these, both SCL and IMN involvement (HR, 1.818; 95% CI, 1.145 to 2.887;  $p=0.011$ ), histologic grade 3 (HR, 1.647; 95%

**Table 3.** Patterns of SCL failure among 201 SCL-involved patients receiving SCL RT

	Recurrence in SCL/Total		Total	p-value
	SCL RT $\geq$ 54 Gy	SCL RT < 54 Gy		
CR to NST <sup>a)</sup>	3/45 (6.7)	6/70 (8.6)	9/115 (7.8)	> 0.990
Non-CR to NST <sup>a)</sup>	7/28 (25.0)	1/44 (2.3)	8/72 (11.1)	0.005
CR to NST <sup>b)</sup>	3/41 (7.3)	6/62 (9.7)	9/103 (8.7)	> 0.990
Non-CR to NST <sup>b)</sup>	3/14 (21.4)	0/11 (0)	3/25 (12.0)	0.230
Total	11/79 (13.9)	9/122 (7.4)	20/201 (10.0)	0.130

Values are presented as number (%). SCL, supraclavicular lymph node; RT, radiotherapy; CR, complete remission; NST, neoadjuvant systemic therapy. <sup>a)</sup>14 patients, whose response to NST was unavailable, were excluded, <sup>b)</sup>73 patients, whose response to NST was unavailable and who underwent SCL excision, were excluded.

**Table 4.** Patterns of IMN failure among 217 IMN-involved patients

	Recurrence in IMN/Total		Total	p-value
	IMN RT (+)	IMN RT (-)		
CR to NST <sup>a)</sup>	3/109 (2.8)	3/23 (13.0)	6/132 (4.5)	0.065
Non-CR to NST <sup>a)</sup>	4/60 (6.7)	0/6 (0)	4/66 (6.1)	> 0.990
CR to NST <sup>b)</sup>	3/107 (2.8)	3/23 (13.0)	6/130 (4.6)	0.068
Non-CR to NST <sup>b)</sup>	4/48 (8.3)	0/6 (0)	4/54 (7.4)	> 0.990
Total	7/185 (3.8)	3/32 (9.4)	10/217 (4.6)	0.169

Values are presented as number (%). IMN, internal mammary lymph node; RT, radiotherapy; CR, complete remission; NST, neoadjuvant systemic therapy. <sup>a)</sup>19 patients, whose response to NST was unavailable, were excluded, <sup>b)</sup>33 patients, whose response to NST was unavailable and who underwent IMN excision, were excluded.

CI, 1.065 to 2.548;  $p=0.025$ ), triple-negative subtype (HR, 3.311; 95% CI, 2.121 to 5.170;  $p < 0.001$ ), and mastectomy (HR, 2.421; 95% CI, 1.393 to 4.207;  $p=0.002$ ) were independently correlated with a worse OS on multivariate analysis (Table 2).

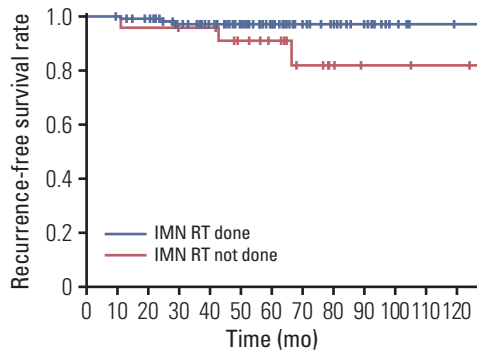
### 3. Patterns of SCL and IMN failure according to the treatments

Among 205 patients with SCL involvement, 201 patients received SCL RT. More patients failed in the SCL with the higher RT dose to SCL  $\geq$  54 Gy, but the difference was not statistically significant (13.9% vs. 7.4%,  $p=0.130$ ). According to the response of SCL to NST, significantly more SCL failures were observed with  $\geq$  54 Gy in patients failing to achieve CR to NST (25.0% vs. 2.3%,  $p=0.005$ ). When 59 patients undergoing SCL excision were excluded, there were no differences in the crude SCL failure rates according to the dose to the SCL (Table 3). Among those patients who underwent SCL excision, 12 patients achieved CR to NST and 47 did not, and five patients who failed to achieve CR experienced SCL failures. Regarding four patients who did not receive SCL

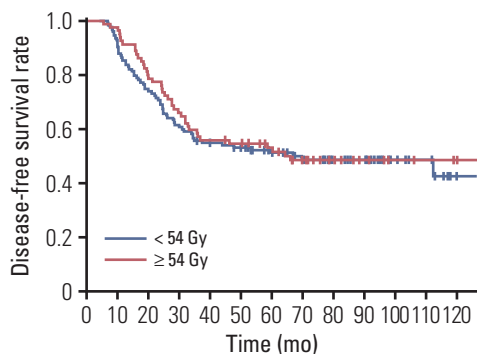
RT, they achieved CR to NST and did not undergo SCL excision, and there were no SCL failures during follow-up.

One hundred and eighty-five of 217 patients with IMN involvement received IMN RT. As for IMN failure, there was no significant difference according to the receipt of IMN RT in patients with IMN involvement (3.8% vs. 9.4%,  $p=0.139$ ). Patients achieving CR to NST had more IMN failures when IMN RT was not given, but the difference did not reach a statistical significance (13.0% vs. 2.8%,  $p=0.065$ ). When 14 patients undergoing IMN excision were excluded, a similar finding was observed (Table 4). Among those patients who underwent IMN excision, two patients achieved CR to NST and 12 did not, and no patient experienced IMN failure. When a log-rank test was performed in 184 patients who did not undergo IMN excision and whose response to NST was available, the 5-year IMN failure-free survival rates were 96.9% and 90.9% in patients with and without IMN RT, respectively ( $p=0.064$ ) (Fig. 2).





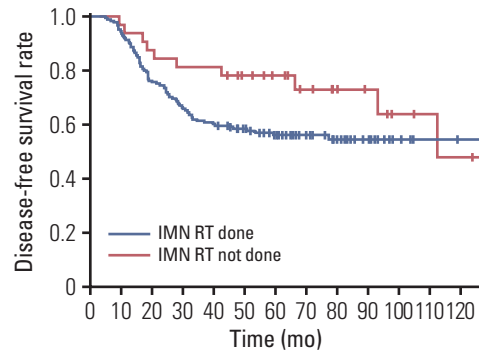
**Fig. 2.** Internal mammary lymph node (IMN) failure-free survival curves in patients with IMN involvement who did not undergo IMN excision and whose response to neoadjuvant systemic therapy was available (n=184). RT, radiotherapy.



**Fig. 3.** Disease-free survival curves according to the dose to the supraclavicular lymph node (SCL) among those patients with SCL involvement (n=201). Four patients not receiving radiation to the SCL were excluded.

#### 4. Subgroup analysis according to the involvement of SCL or IMN

Within patients with SCL involvement (n=205), higher ypT category, four or more involved axillary lymph nodes, histologic grade 3, triple-negative subtype, clinical non-CR of SCL to NST, mastectomy, and SCL excision were associated with an inferior DFS on univariate analysis. However, the SCL RT dose  $\geq 54$  Gy did not improve DFS (5-year rate, 52.9% vs. 50.9%;  $p=0.696$ ) (Fig. 3). On multivariate analysis, four or more involved axillary lymph nodes (HR, 1.636; 95% CI, 1.020 to 2.621;  $p=0.041$ ), histologic grade 3 (HR, 1.665; 95% CI, 1.085 to 2.555;  $p=0.020$ ), triple-negative subtype (HR, 2.181; 95% CI, 1.369 to 3.473;  $p=0.001$ ), and mastectomy (HR, 1.867; 95% CI, 1.036 to 3.365;  $p=0.038$ ) were significant prog-



**Fig. 4.** Disease-free survival curves according to the receipt of internal mammary lymph node (IMN) irradiation among those patients with IMN involvement (n=217). RT, radiotherapy.

nosticators predicting a worse DFS.

With regard to those patients with IMN involvement (n=217), additional SCL involvement, four or more involved axillary lymph nodes, lymphovascular invasion, triple-negative subtype, mastectomy, and no hormonal therapy were correlated with an inferior DFS on univariate analysis. However, the receipt of IMN RT did not impact on DFS (5-year rate, 56.1% with IMN RT vs. 78.1% without IMN RT;  $p=0.099$ ) (Fig. 4). On multivariate analysis, additional SCL involvement (HR, 1.663; 95% CI, 1.070 to 2.587;  $p=0.024$ ), four or more involved axillary lymph nodes (HR, 1.814; 95% CI, 1.098 to 2.998;  $p=0.020$ ), triple-negative subtype (HR, 3.995; 95% CI, 2.106 to 7.579;  $p < 0.001$ ), and mastectomy (HR, 2.409; 95% CI, 1.405 to 4.129;  $p=0.001$ ) were significant adverse prognosticators for DFS.

#### 5. Impact of SCL or IMN excision on the outcomes

Among 205 patients with SCL involvement, 59 patients underwent SCL excision along with the breast and axillary surgery. Among these, the response to NST was clinical CR in 12 and non-CR in 47. All of them received SCL RT, and the median dose was 50.4 Gy (range, 45 to 66 Gy). Regarding the patterns of failure, there were 10 patients with local recurrences, nine with regional recurrences including five with SCL recurrences, and 35 with distant metastases. The 5-year DFS was 38.1%, significantly inferior to those without SCL excision (57.5%,  $p=0.026$ ). As mentioned earlier, however, the significance of SCL excision disappeared on multivariate analysis.

Fourteen of 217 patients with IMN involvement had IMN excision. Among these, the response to NST was clinical CR in two and non-CR in 12. All of them received IMN RT. There were two patients with local recurrences, two with regional

recurrences (one in axillary lymph node and the other in the SCL), and five with distant metastases. The 5-year DFS was 56.3%, which was not significantly different from those without IMN excision (59.6%,  $p=0.901$ ).

## Discussion

In our study, the outcomes of NST followed by surgery and postoperative RT were analyzed in 353 breast cancer patients with SCL and/or IMN involvement which was detected on imaging studies. The SCL and/or IMN failures were rare, and a higher SCL RT dose as well as the receipt of IMN RT was not associated with a better control rate. DFS and OS were comparable with the contemporary results, but were not improved by a higher dose SCL RT and IMN RT.

As for the treatment for extra-axillary regional lymph nodes in breast cancer, especially IMN, there have been a number of historical reports to date [9]. However, extended radical mastectomy has rarely been performed since several randomized trials noted no survival benefit of such an aggressive treatment [10,11]. With regard to the management for SCL, some institutions reported the outcomes of SCL excision along with breast surgery, but its benefit is not evident until now [12,13]. Therefore, the involved SCL and/or IMN is usually diagnosed clinically and treated by regional nodal RT combined with systemic therapy.

Recently, especially with the development of imaging studies, more data on the multidisciplinary treatment in this setting are becoming available. Among these, Zhang et al. [5] reviewed 809 patients with cN2-3 patients, and found that 112 patients (13.8%) had IMN involvement on PET-CT, MRI, CT and/or US [5]. They also analyzed the outcomes of NST followed by surgery and postoperative RT in these patients, and 72.1% of IMN-involved patients achieved clinical CR on imaging after NST. In the present study, SCL and/or IMN involvement was determined via the same imaging studies, and each 75.9% of patients with SCL and IMN involvement achieved clinical CR to NST. The treatment outcomes were also very similar, and the 5-year DFS and OS were 56% and 76% in the Zhang et al.'s study [5], and 57.8% and 75.1% in our study, respectively. In addition, Noh et al. [14] also reported the treatment outcomes of SCL- and/or IMN-involved breast cancer which was detected on imaging studies including PET-CT and MRI. When treated with NST followed by surgery and postoperative RT, the 5-year DFS and OS were 60.2% and 75.5%, respectively. These observations suggest that despite of the advanced nodal disease, favorable DFS and OS can be achieved when multimodality treatments are given. However, these data should be interpreted with

caution, because the involvement of SCL and/or IMN might be overestimated on imaging and those patients with occult distant metastases could be excluded after more meticulous imaging studies such as PET-CT compared with historical controls. Compared with aforementioned studies, Huang et al. [4] reported the relatively inferior DFS and OS, that is, 30% and 47%, respectively, in SCL-involved breast cancer patients receiving multimodality treatments. In this study, SCL involvement was presented as palpable disease in 77.5% of patients, and clinical CR rate to NST was only 49%. These findings suggest that their population might have a higher tumor burden. In addition, pathologic confirmation of IMN involvement on fine-needle aspiration biopsy was reported to be associated with an inferior progression-free survival compared to those of clinically involved IMN on PET-CT [15].

Regarding the impact of regional nodal RT for SCL and/or IMN, Park et al. [3] analyzed 55 patients with PET-detected cN3 breast cancer who were treated with NST followed by surgery and postoperative RT. The 5-year locoregional relapse-free survival, DFS, and OS were 80%, 60%, and 79%, respectively. And, both the higher RT dose to SCL  $\geq 55$  Gy and the receipt of IMN RT was not associated with better outcomes. We also observed similar findings among 353 patients from 11 institutions, that is, DFS was not improved by a higher dose SCL RT or IMN RT. Although the receipt of IMN RT was associated with a lower IMN failure rate even in patients achieving clinical CR to NST, the difference did not reach statistical significance. Rather, more SCL failures were observed with a higher SCL RT dose in patients failing to achieve clinical CR to NST. The paradoxical dose-response relationship could be explained that a higher RT dose might be prescribed to a larger residual lesion after NST. However, the major patterns of failure were distant metastases, and therefore this finding might not be translated into a meaningful DFS difference. In the aforementioned study by Huang et al. [4], a higher SCL RT dose was prescribed to patients with non-CR to NST and was not associated with a better SCL control. However, non-CR to NST was the independent prognostic factor associated with an inferior DFS [4]. Considering the increase of treatment failures in those patients with non-CR to NST (S1 and S2 Tables), more intensified systemic therapy should be incorporated to these patients.

The limitations of this study are as follows. First, there might be potential biases which are the typical shortcomings of retrospective studies. Performance of mastectomy was associated with an inferior DFS, which suggests that patients with more advanced disease underwent mastectomy. Second, the involvement of SCL and/or IMN was determined on imaging studies, and therefore might be overestimated. In some patients undergoing SCL and/or IMN excision or biopsy, the pathologic confirmation was done, but it was not a routine procedure in most institutions. However, the diag-

nostic accuracy of SCL and/or IMN involvement by PET-CT or US was reported to be about 80%-90% [7,8], and our patients showed positive findings on multiple imaging studies in 72.2% for SCL involvement and 76.0% for IMN involvement. Lastly, the extent of SCL and/or IMN involvement was not specified. As mentioned earlier, the paradoxical dose-response relationship between SCL RT dose and SCL failure might be resulted from a higher tumor burden unavailable from the retrospective chart review. Despite these limitations, our study represents one of the largest series on the outcomes of multidisciplinary treatment for breast cancer patients with SCL and/or IMN involvement.

In conclusion, NST followed by surgery and postoperative RT achieved an acceptable in-field regional control rate in patients with SCL and/or IMN involvement. However, a higher SCL RT dose or IMN RT was not associated with the improved DFS in these patients. SCL and/or IMN excision, which was more frequently performed in patients with non-CR to NST, achieved acceptable local control but did not improve DFS, either. Given the major patterns of failure were distant metastases, more intensified systemic therapy should be incorporated especially in those patients with non-CR to NST.

#### Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (<https://www.e-crt.org>).

#### Conflicts of Interest

Conflict of interest relevant to this article was not reported.

#### Author Details

<sup>1</sup>Department of Radiation Oncology, Ewha Womans University College of Medicine, Seoul, <sup>2</sup>Department of Radiation Oncology, Wonkwang University Hospital, Wonkwang University School of Medicine, Iksan, <sup>3</sup>Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, <sup>4</sup>Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, <sup>5</sup>Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, <sup>6</sup>Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, <sup>7</sup>Department of Radiation Oncology, Wonju Severance Christian Hospital, Wonju, <sup>8</sup>Department of Radiation Oncology, Ajou University School of Medicine, Suwon, <sup>9</sup>Department of Radiation Oncology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, <sup>10</sup>Department of Radiation Oncology, Chonbuk National University Hospital, Jeonju, <sup>11</sup>Department of Radiation Oncology, Keimyung University Dongsan Medical Center, Keimyung University School of Medicine, Daegu, <sup>12</sup>Department of Radiation Oncology, Hanyang University College of Medicine, Seoul, Korea

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