의학석사 학위논문

병리적 병기 N1 유방암에서 최적의 방사선 치료범위

Optimal radiation treatment field for pathological N1 (pN1) breast cancer

울산대학교 대학원

의 학 과

조 지 환

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이 논문을 의학석사 학위 논문으로 제출함

2020년 2월

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조지환의 의학석사학위 논문을 인준함

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Abstract

Purpose: To evaluate the treatment outcomes and recurrence pattern of clinical N0 (cN0) breast cancer patients who were assessed as pathological N1 (pN1) after breast-conserving surgery and to determine the appropriate radiation treatment field accordingly.

Materials and Methods: We retrospectively analyzed pN1M0 breast cancer patients who were treated with breast-conserving surgery and adjuvant radiation therapy (RT) between January 2012 and July 2015. We divided the patients into two groups, the SNB group and the ALND group. To compare treatment outcomes and complications, 40 patients treated with third field RT (whole breast RT + regional nodal irradiation) in the ALND group were excluded. A total of 289 breast cancer patients were included in this study. Among these patients, 130 patients underwent axillary lymph node dissection (ALND) and 159 patients underwent sentinel lymph node biopsy (SNB) only. In the SNB group, 81 patients (51%) received whole breast RT and 55 patients received High-tangents RT (35%). Only 14% (n=23) of patients in the SNB group treated with third field RT. The dose to the whole breast was usually 50 Gy at 2Gy per fraction and all patients received an electron boost to the tumor bed (10-15 Gy in 4-6 fractions). Adjuvant chemotherapy was given to 81% of patients. All patients with positive hormone receptor received hormone therapy. The primary end point was regional recurrence free survival (RRFS). Secondary end points were overall

survival (OS), disease-free survival (DFS), and breast cancer-related lymphedema (BCRL).

Results: The median patient age was 50 years (range, 27-78 years). The proportion of patients with positive estrogen receptor (ER) and those with Ki-67 less than 14% in the SNB group were significantly lower than that in the ALND group. And the proportion of pN1mic patients was higher in the SNB group. Patients included in SNB group were analyzed according to radiation treatment field. Compared to patients who treated with other types of RT (whole breast RT, high-tangents RT), patients treated with third field RT had more high risk features. At the median follow-up of 73 months, there were 6 cases of IBTR and 3 cases of regional recurrence (axillary and supraclavicular lymph nodes). There were 10 cases of distant recurrences. Among the regional failure cases, 1 patient underwent SNB and 2 patients underwent ALND. In SNB group, regional recurrence was observed in one patient treated with standard tangential field RT. Regional recurrence was not observed in the patients who underwent high-tangents RT or third field RT. The 5yr RRFS were 99.2% in the SNB group and 98.2% in the ALND group (p=0.590). There was no significant difference in 5yr RRFS according to type of radiation treatment field or molecular subtype. The 5yr OS and the 5yr DFS were also not statistically different (OS 99.4% vs. 99.2%, DFS 94.1% vs. 93.4%). Patients in the ALND group had significantly higher rates of BCRL (1.9% vs. 15.1%, p<0.001).

Conclusion: In cN0/pN1 breast cancer patients, ALND did not improve OS or DFS but

increased the rate of BCRL. Risk-adapted axillary coverage for cN0/pN1 patients who underwent BCS and SNB was helpful in maintaining excellent regional control rate without increasing treatment associated lymphedema.

Keywords: Breast cancer, Regional recurrence, Overall survival, Disease-free survival, Radiotherapy, Retrospective studies

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Introduction

Currently, in early breast cancer patients, breast-conserving therapy that uses radiation therapy (RT) to remove the residual microscopic cancer after breast-conserving surgery is recognized as standard treatment. Breast-conserving therapy can preserve breasts with an equivalent survival rate compared with the case of mastectomy [1-6].

Although the standard treatment for sentinel node-positive breast cancer patients is completion ALND, in some studies, omission of completion ALND did not show any difference in treatment outcomes even with positive sentinel node in cN0 patients [7-9]. If additional ALND is performed in cN0/sentinel node biopsy (SNB) positive patients, the chance of additional axillary lymph node metastasis is reported as 27-53% [9,10]. The reason for no difference in regional recurrence was reported to be the role of axillary RT in addition to the role of systemic therapy [7,8].

However, there is still controversy over how to establish the extent of the radiation field if positive lymph node has been identified in breast cancer patients who have not undergone ALND. There are some randomized trials that reported regional nodal irradiation (RNI) improved overall survival and distant metastases free survival [11,12], and many patients have now only a SNB, even if case of positive sentinel lymph node. Nevertheless, it is still

unclear whether the addition of RNI to whole-breast irradiation after breast-conserving surgery (BCS) is necessary. And the usefulness of the high-tangents RT is not yet apparent.

So in this study, we evaluate the treatment outcomes of breast cancer patients who were assessed as N1 in the pathological stage after BCS and to determine the appropriate radiation treatment field accordingly.

Materials and Methods

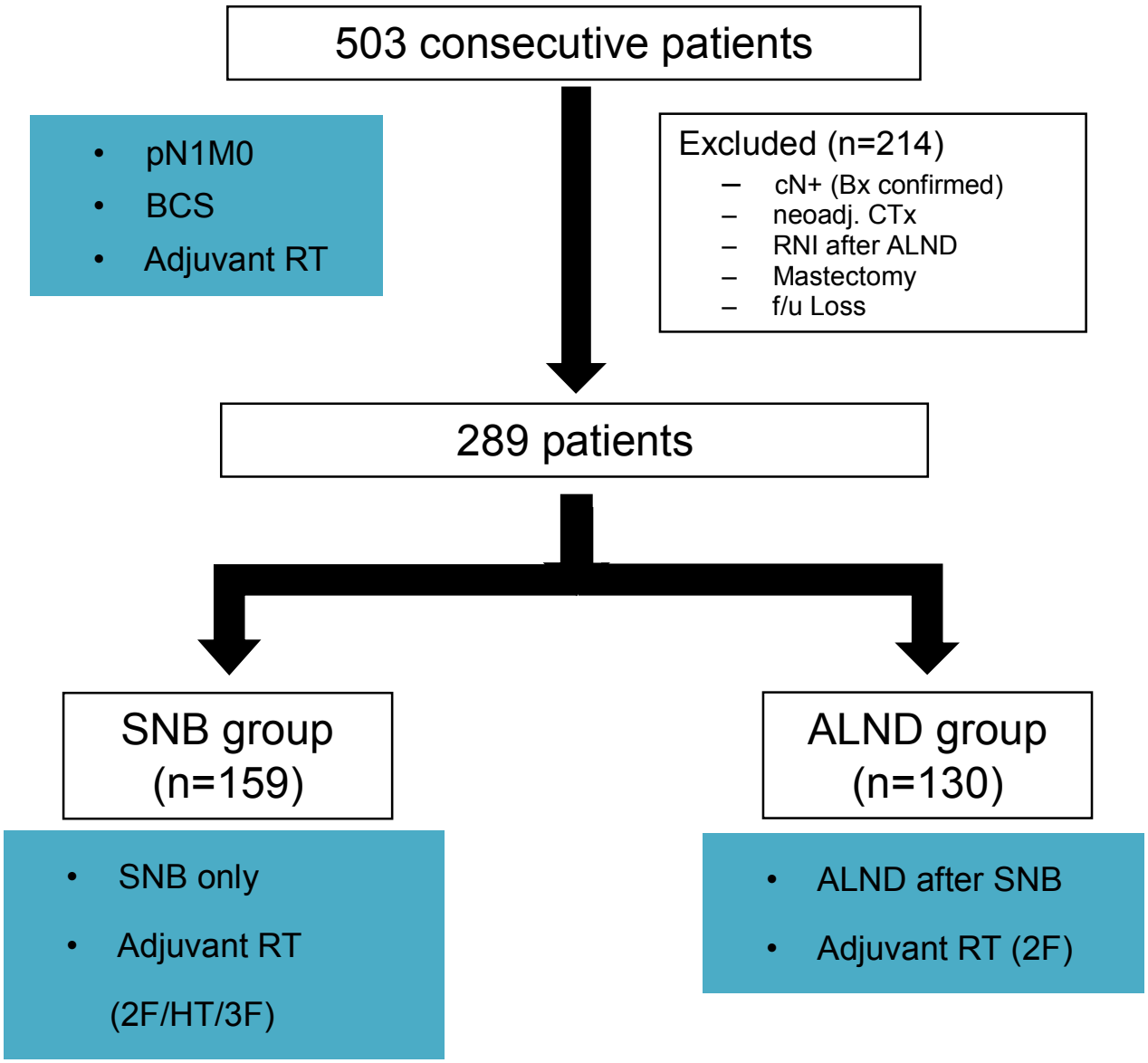
We retrospectively analyzed cN0/pN1 breast cancer patients who were treated with breast-conserving surgery and adjuvant RT between January 2012 and July 2015. Patients with pathologically confirmed lymph node metastasis before surgery, or who underwent neoadjuvant chemotherapy were excluded from this study (Fig 1).

Imaging studies were used to identify clinical lymph node metastasis, and fine-needle aspiration biopsy was performed if lymph node metastasis was suspected.

Patients underwent whole breast irradiation or high-tangents RT or whole breast irradiation plus regional nodal irradiation (including axillary and supraclavicular nodes). The type of radiation treatment field was determined according to the preference of individual physician considering following the following high-risk features; age, status of hormone receptor, tumor grade, proliferative index, lymphovascular invasion, extranodal extension) patient have. CT-based planning was used for treatment planning. The dose to the whole breast was usually 50 Gy at 2Gy per fraction and all patients received an electron boost to the tumor bed (10-15 Gy in 4-6 fractions).

In our institution, high-tangential field was used for treat more of the axillary level I and II

Figure 1.Enrollment of study patients



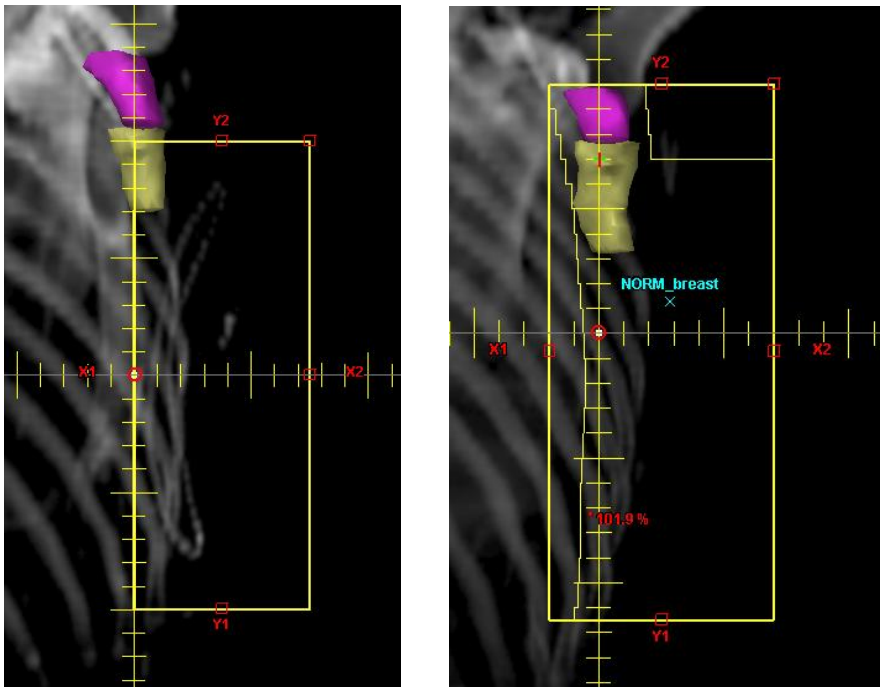
lymph nodes. We contoured axillary level I and II lymph nodes for adequate coverage and adjusted caudal border to cover 1cm superior to axillary vessel (Fig 2). The field-in-field technique was applied to improve the homogeneity index. High-tangential fields were modified with multileaf collimators (MLCs) to reduce the radiation dose irradiate to pectoralis major muscle and to obtain adequate coverage of axillary lymph nodes. More than 90% ($\geq$45Gy) of the prescribed dose was irradiated in the axillary area.

Patients who underwent breast conserving surgery were included in this study and patients who underwent mastectomy were excluded. The extent of ALND varied according to the preference of the individual surgeon, but in most patients, level I and level II lymph nodes were dissected (n=82, 63%).

Adjuvant chemotherapy was given to 234 of 289 patients (81%). Various regimens have been used for chemotherapy, but regimens containing doxorubicin, cyclophosphamide and taxane drugs were most used. All patients with positive hormone receptor received hormonal therapy.

We evaluated regional recurrence-free survival (RRFS), overall survival (OS), disease-free survival (DFS), and the recurrence pattern (i.e., locoregional, contralateral breast, distant metastasis). Regional recurrence was defined as disease recurrence in the ipsilateral regional

Figure 2.High tangential field



Standard field High-tangential field

lymph nodes (axillary, supraclavicular). RRFS was defined as the time from the initiation of RT to regional recurrence or death of any cause. OS was defined as the time from the first diagnosis of disease to the date of the last follow-up or the date of death. DFS was defined as the time from the initiation of RT to disease recurrence or death of any cause.

Lymphedema was assessed by limb volume measurement (Circumference at wrist and 5cm below/above elbow). And breast cancer-related lymphedema (BCRL) was defined as the difference in circumference between the affected arm and unaffected arm of 2cm or more.

The statistical analysis was performed using SPSS, version 23.0.

Results

We found 503 patients with pathological stage N1 breast cancer. Of these, 289 patients were included in this study. We divided the patients into two groups, the SNB group and the ALND group. 130 patients underwent axillary lymph node dissection and 159 patients underwent only a sentinel lymph node biopsy (Fig 1).

Patient characteristics are summarized in Table 1. The median age of all patients was 50 years (range 27- 78). Invasive ductal carcinoma was the most common histologic type. In the SNB group, 156 patients had T1-2 tumors (98%), and 3 had T3-4 tumors (2%). 149 patients (94%) had intermediate to high histologic grade tumor. 43 (27%) had EIC-positive tumors, and 112 (70%) had EIC-negative tumors. 93 (58%) were LVI-positive, and 66 (42%) were LVI-negative. In ALND group, all patients had T1-T2 tumors. 126 patients (97%) had intermediate to high histologic grade tumor. 27 (21%) had EIC-positive tumors, and 102 (78%) had EIC-negative tumors. 55 (42%) were LVI-positive, and 74 (57%) were LVI-negative. The proportion of patients with positive estrogen receptor (ER) and those with Ki-67 less than 14% in the SNB group were significantly lower than that in the ALND group. And the proportion of pN1mic patients was higher in the SNB group.

The characteristics of patients in the SNB group were summarized according to the

Table 1. Patient Characteristics

Variables	**SNB (n=159)**	**ALND (n=130)**	**p-value**
Age (yr)			0.182
Median	50	51	
Range	27-76	33-78	
BMI			0.021
Median	23	24	
Range	16.6-32.6	16.3-33.3	
Pathology			
IDC	141 (89)	120 (92)	
ILC	7 (4)	4 (3)	
Mixed IDC & ILC	1 (1)	2 (2)	
Other	10 (6)	4 (3)	
Pathological T			0.060
pTmi	1 (1)	3 (2)	
pT1a	3 (2)	1 (1)	
pT1b	18 (11)	4 (3)	
pT1c	81 (51)	69 (53)	
pT2	53 (33)	53 (41)	
pT3	2 (1)	0 (0)	
pT4	1 (1)	0 (0)	
Pathological N			0.000
1mic	86 (54)	16 (12)	
1	73 (46)	114 (88)	
Resection margin			0.558

Involved	7 (4)	4 (3)	
Not involved	152 (96)	126 (97)	
ENE			0.018
Positive	3 (2)	10 (8)	
Negative	156 (98)	120 (92)	
Histologic grade			0.285
Low	10 (6)	4 (3)	
Intermediate	111 (70)	100 (77)	
High	38 (24)	26 (20)	
LVI			0.977
Positive	93 (58)	55 (42)	
Negative	66 (42)	74 (57)	
NA	0 (0)	1 (1)	
EIC			0.218
Positive	43 (27)	27 (21)	
Negative	112 (70)	102 (78)	
NA	4 (3)	1 (1)	
ER status			0.003
Positive	122 (77)	117 (90)	
Negative	37 (23)	13 (10)	
PR status			0.112
Positive	113 (71)	103 (79)	
Negative	46 (29)	27 (21)	
Her-2			0.145
Positive	30 (19)	15 (12)	

Negative	129 (81)	115 (88)	
Ki-67			0.001
< 14%	50 (31)	65 (50)	
14% ≥	109 (69)	65 (50)	

Abbreviations: ENE=extranodal extension; LVI: lymphovascular invasion EIC=extensive intraductal component

Table 2. Patient characteristics according to radiation treatment field (SNB group)

Variables	**Whole breast (n=81)**	**High-tangential (n=55)**	**Whole breast + RNI (n=23)**	**p-value**
Age (yr)				0.634
50 ≥	49 (60)	29 (53)	14 (61)	
50 <	32 (40)	26 (47)	9 (39)	
Pathological T				0.002
pT1mi	1 (1)	0 (0)	0 (0)	
pT1a	0 (0)	3 (6)	0 (0)	
pT1b	8 (10)	10 (18)	0 (0)	
pT1c	46 (57)	25 (45)	10 (43)	
pT2	26 (32)	17 (31)	10 (43)	
pT3 or pT4	0 (0)	0 (0)	3 (13)	
Pathological N				0.119
1mic	42 (52)	35 (64)	9 (39)	
1	39 (48)	20 (36)	14 (61)	
ENE				0.625
Positive	1 (1)	1 (2)	1 (4)	
Negative	80 (99)	54 (98)	22 (96)	
Histologic grade				0.030
Low	7 (9)	3 (5)	0 (0)	
Intermediate	56 (69)	43 (78)	12 (52)	
High	18 (22)	9 (17)	11 (48)	
LVI				0.939
Positive	35 (43)	23 (42)	9 (39)	

Negative	46 (57)	32 (58)	14 (61)	
ER status				0.609
Positive	62 (77)	44 (80)	16 (70)	
Negative	19 (23)	11 (20)	7 (30)	
PR status				0.791
Positive	58 (72)	40 (73)	15 (65)	
Negative	23 (28)	15 (27)	8 (35)	
Her-2				0.464
Positive	16 (20)	10 (18)	2 (9)	
Negative	65 (80)	45 (82)	21 (91)	
Ki-67				0.037
< 14%	22 (27)	24 (44)	4 (17)	
14% ≥	59 (73)	31 (56)	19 (83)	

Abbreviations: ENE=extranodal extension; LVI=lymphovascular invasion

radiation treatment field (Table 2). There were significant differences in three items (pathological T, histologic grade, Ki-67). Patients included in SNB group were also analyzed according to the molecular subtype (Table 3). Proportion of Luminal A was significantly higher in patients treated with high-tangents RT.

The high-risk features of patients in the SNB group are summarized according to the radiation treatment field (Table 4). The proportion of patients with two or more high risk features was 44% in patients who treated with whole breast RT (36/81) and 42% in patients who treated with high-tangents RT (23/55). Compared to these two groups, patients treated with third field RT (whole breast + RNI) had more high risk features (Table 5).

Characteristics of treatments are listed in Table 6. R0 resection of primary tumor was achieved most of patients (276 of 289 patients, 96%). Involvement of resection margin (R1 resection) was identified in 13 patients (4%), but none of these patients experienced disease recurrence. All patients received adjuvant RT after BCS. The median RT dose was 60 Gy in both groups. In the SNB group, 81 patients (51%) received whole breast RT and 55 patients received High-tangents RT (35%). In ALND group, all patients received whole breast RT. Adjuvant chemotherapy was given to 111 patients (70%) in the SNB group and 123 patients (95%) in the ALND group. Adjuvant hormone therapy was administered to 125 patients (79%) in the SNB group and 118 patients (91%) in the ALND group.

Table 3. Molecular subtype according to radiation treatment field

Variables	**Whole breast (n=81)**	**High-tangential (n=55)**	**Whole breast + RNI (n=23)**	**p-value**
Molecular subtype				0.044
Luminal A	18 (22)	23 (42)	4 (17)	
Luminal B	44 (54)	21 (38)	12 (52)	
Her-2 enriched	8 (10)	7 (13)	4 (4)	
Triple-negative	11 (14)	4 (7)	6 (26)	

Table 4. High risk features according to radiation treatment field (SNB group)

Variables	**Whole breast (n=81)**	**High-tangential (n=55)**	**Whole breast + RNI (n=23)**
Age < 40	9 (11)	4 (7)	2 (9)
Hormone receptor (-)	19 (23)	11 (20)	7 (30)
High tumor grade	18 (22)	9 (16)	11 (48)
High ki-67	39 (48)	19 (35)	11 (48)
LVI (+)	35 (43)	23 (42)	9 (39)

Abbreviations: LVI= lymphovasuclar invasion; ENE=extranodal extension

Table 5. Number of high risk features according to radiation treatment field

No. of High risk features	**Whole breast (n=81)**	**High-tangential (n=55)**	**Whole breast + RNI (n=23)**
0	17 (21)	16 (29)	5 (22)
1	28 (35)	16 (29)	5 (22)
2	17 (21)	15 (27)	3 (13)
3	10 (12)	6 (11)	8 (35)
4	9 (11)	1 (2)	2 (9)
5	0 (0)	1 (2)	0 (0)

Table 6. Treatment characteristics

Recurrence type	**SNB (n=159)**	**ALND (n=130)**
Radiation therapy		
Type of RT		
- Whole breast	81 (51%)	130 (100%)
- High tangential	55 (35%)	0 (0%)
- Whole breast + RNI	23 (14%)	0 (0%)
Dose (Gy/fx)	51.6/20, 60-65/29-31	60, 65/29-31
Adjuvant chemotherapy		
Yes	111 (70%)	123 (95%)
No	48 (30%)	7 (5%)
Hormone therapy		
Yes	125 (79%)	118 (91%)
No	34 (21%)	12 (9%)

Abbreviations: fx=fraction

At the median follow-up of 73 months, there were 6 cases of ipsilateral breast tumor recurrence (IBTR) and 2 relapsed in the contralateral breast. There were 3 cases of regional recurrence (axillary and supraclavicular lymph nodes) and 10 cases of distant recurrences. Among the regional failure cases, 1 patient underwent SNB and 2 patients underwent ALND. The details of the sites of recurrence are shown in Table 7.

The 5yr RRFS were 99.2% in the SNB group and 98.2% in the ALND group (p=0.590). (Fig 3) The 5yr OS of SNB group and ALND group were 99.4% and 99.2% respectively (p=0.568). The 5yr DFS were 94.1 % in the SNB group and 93.4 % in the ALND group (p=0.689). (Fig 4) We also subdivided the patients in the SNB group according to the molecular subtype (i.e., Luminal A, Luminal B, Triple-negative, Her-2 enriched) or radiation treatment field (i.e., Whole breast, High-tangential, Whole breast + RNI), but no significant differences were observed in RRFS (Fig 5, 6), OS or DFS. Patients in the ALND group had significantly higher rates of BCRL. 5yr cumulative incidence of BCRL was 1.9% in the SNB group and 15.1% in the ALND group (Fig 7). The median time to develop BCRL was 13 months in SNB group and 7.5 months in ALND group.

Table 7. Patterns of recurrence according to treatment group

Recurrence type	**SNB (n=159)**	**ALND (n=130)**
Locoregional		
IBTR	3 (2%)	3 (2%)
Regional LN	1 (1%)	2 (2%)
Distant metastasis	5 (3%)	5 (4%)
Contralateral breast	1 (1%)	1 (1%)

Abbreviations: IBTR= ipsilateral breast tumor recurrence; LN=lymph node

Figure 3. Regional recurrence-free survival

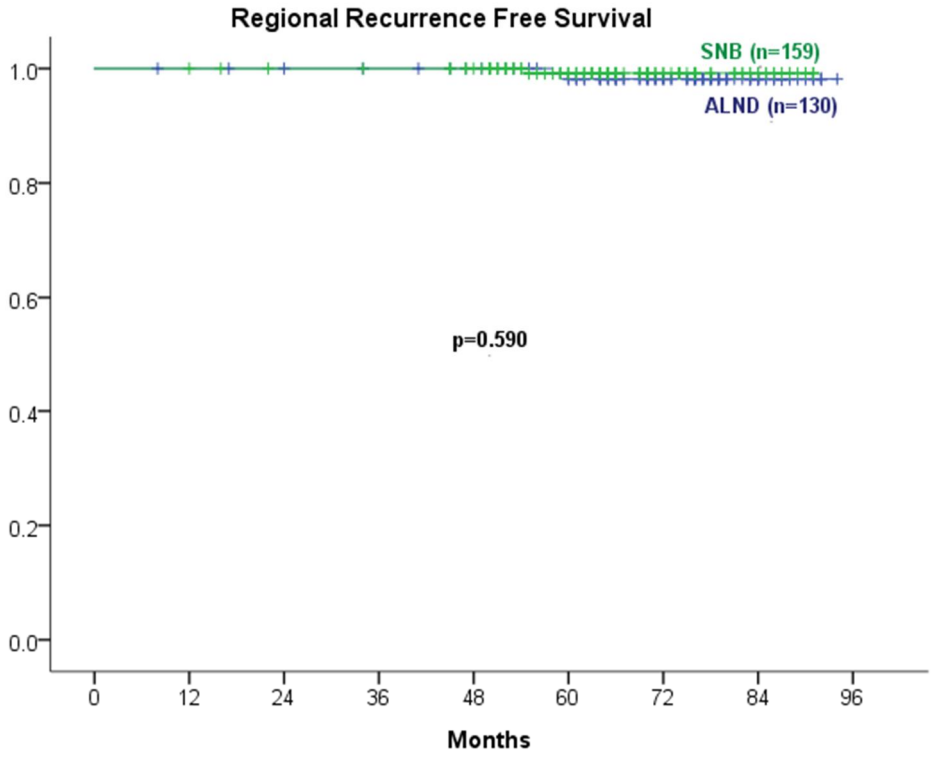
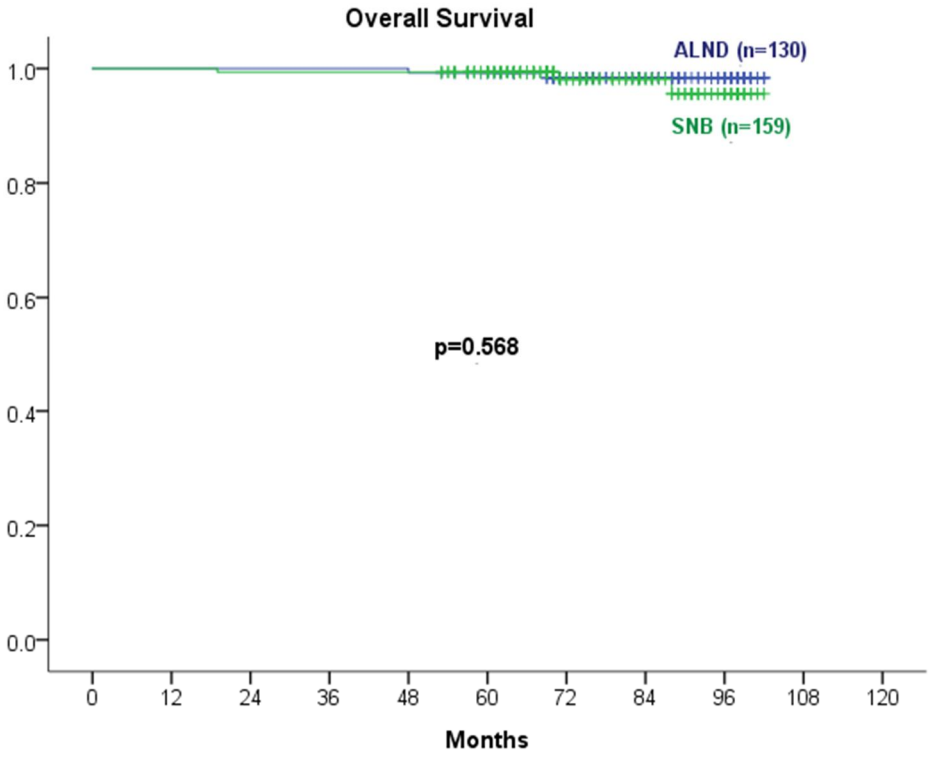


Figure 4. Overall survival (A) and disease-free survival (B)

(A)



(B)

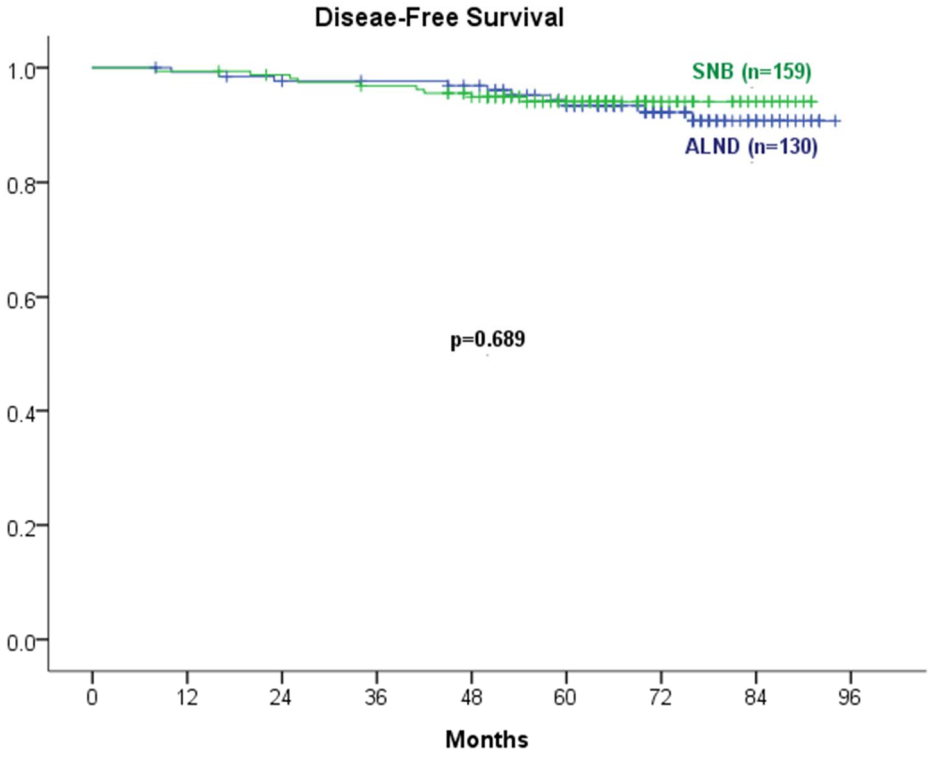


Figure 5. Regional recurrence-free survival according to radiation treatment field

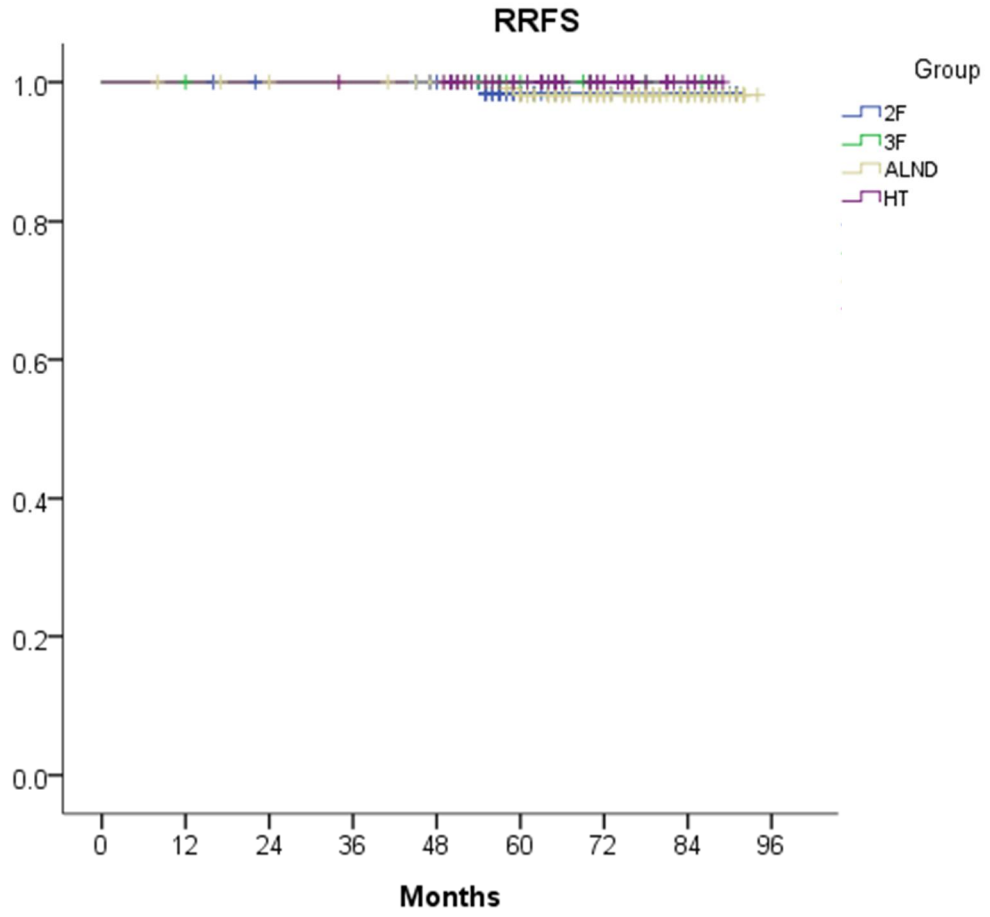
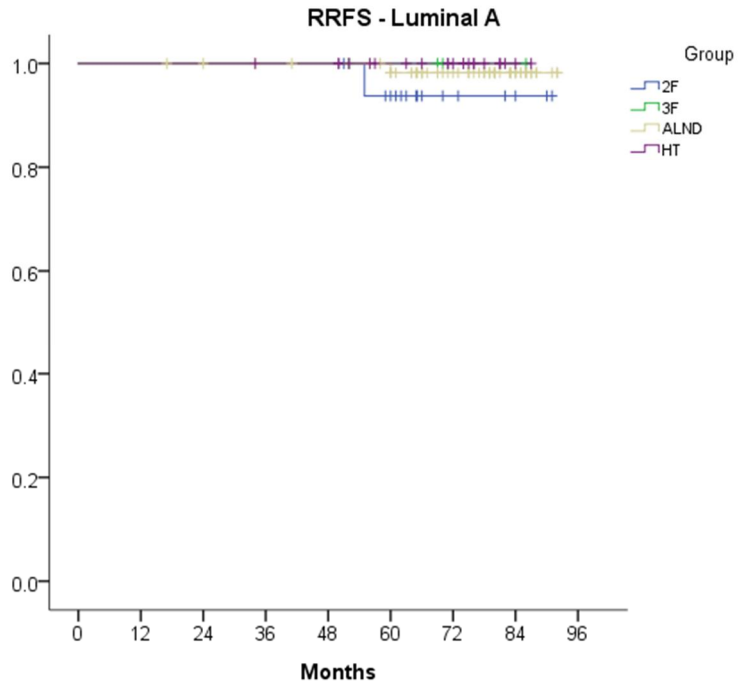


Figure 6. Regional recurrence-free survival according to molecular subtype. Luminal A (A), Luminal B (B)

(A)



(B)

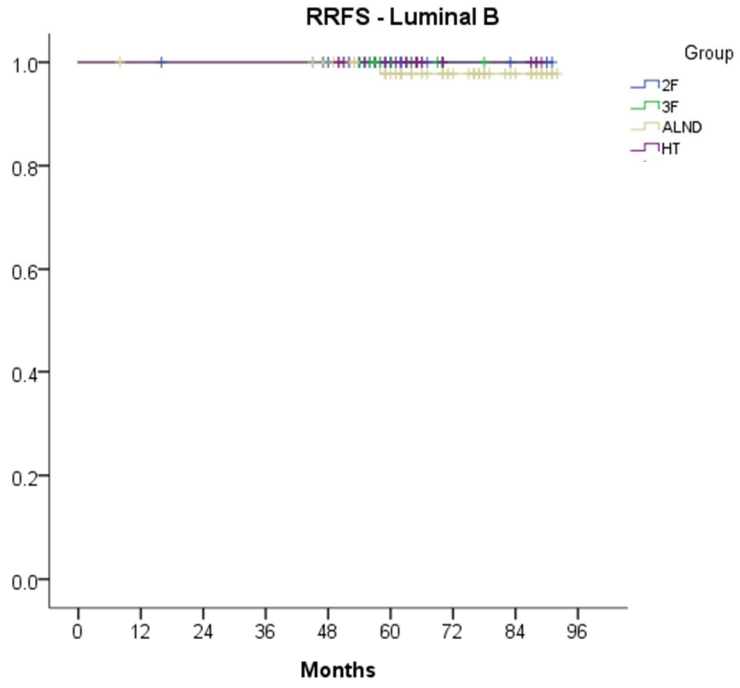
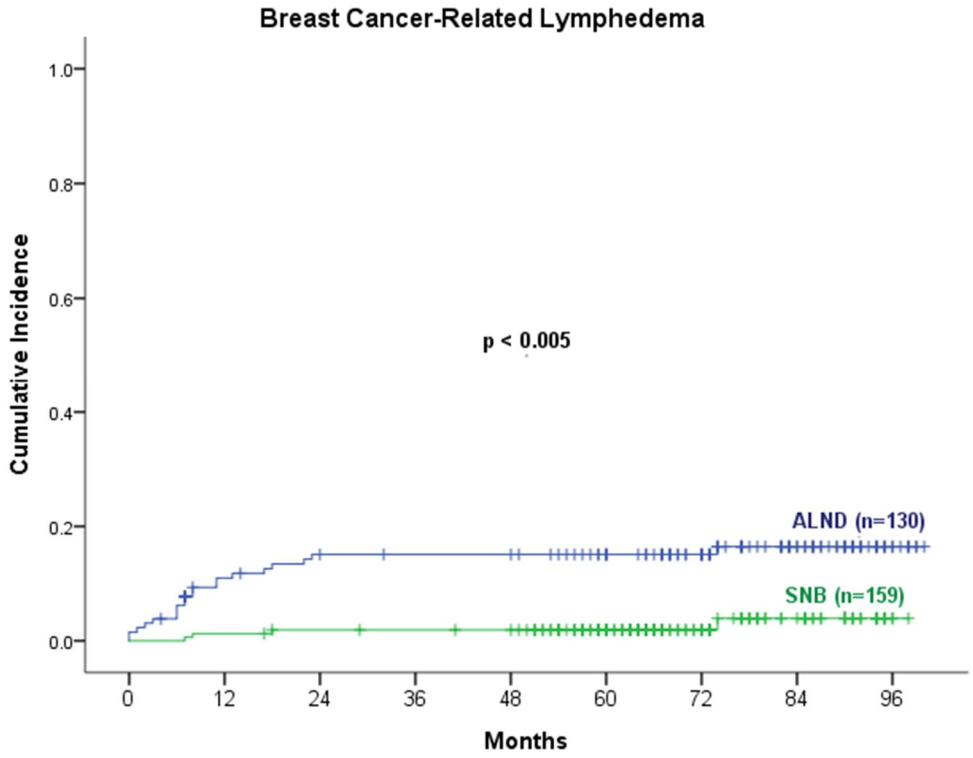


Figure 7. Cumulative incidence of breast cancer-related lymphedema



Discussion

Traditionally, the standard treatment for sentinel node-positive breast cancer patients was completion ALND. However, there are several studies examined the necessity of ALND in case of positive sentinel lymph node. In the ACOSOG Z0011 trial [9], patients with 1-2 positive sentinel lymph nodes and no extranodal extension were included. Patients were randomly assigned to two groups, ALND versus no ALND. There was no statistically significant difference in OS, locoregional recurrence, or DFS between two groups. In the IBCSG 23-01 trial [8], patients with micrometastases were included and they were divided into two groups, ALND versus no ALND. Most of patients received adjuvant RT without RNI. There was no significant difference in OS or DFS and incidence of lymphedema was significantly higher in ALND group. In the EORTC AMAROS trial [7], cT1-2N0M0 patients were enrolled. Patients were randomized between ALND and axillary RT in case of positive sentinel lymph node. The primary endpoint was axillary recurrence rate. Axillary and supraclavicular area were included in radiation treatment field. The axillary recurrence rate was 0.43% in ALND arm and 1.19 % in axillary RT arm. There was no significant difference in OS or DFS, but higher rate of lymphedema was observed in ALND arm (23% at 5 years). In this background, the proportion of patients who do not undergo ALND is increasing, even though the sentinel lymph node is positive. However, the optimal radiation treatment field for these patients is still not clear.

In this study, there were 1 regional lymph node recurrence in the SNB group and 2 in the ALND group. There was no significant difference in RRFS, OS, and DFS between the ALND group and SNB group. Furthermore, there was no significant difference in treatment outcomes when compared with the results of patients who treated with whole breast RT only or high-tangents RT after SNB. However, BCRL was significantly higher in ALND group. This result is consistent with the results of other studies comparing ALND and adjuvant RT in patients with positive sentinel lymph nodes [8,9]. Thus in patients identified as pN1 after SNB, It is thought that completion ALND is unnecessary. In positive sentinel lymph node cases, the probability of having non-sentinel lymph node involvement is not low [9,10,13-15]. Nevertheless, regional recurrence, as well as overall survival, did not differ between the SNB group and ALND group. It is thought that the following factors may have influenced these outcomes. Not only third field RT which include supraclavicular and axillary area, whole breast RT and High-tangents RT also may include the considerable component of the axillary area [16-18]. And adjuvant systemic therapy may have affected this outcome. Adjuvant chemotherapy was given to 81% of patients (n=234), according to risk factors (e.g., tumor size, histologic grade, extranodal extension, lymphovascular invasion) patients have. Hormone therapy was also administered to a large portion of patients (n=243, 84%). These factors may have contributed to achieving equivalent regional controls in the SNB group.

In the SNB group, there was no significant difference in treatment outcomes (RRFS, OS, DFS, BCRL) according to the radiation treatment field. There was only one case of regional lymph node recurrence (axillary lymph node), and this patient was treated with standard tangential field RT. BCRL occurred in 4 patients, 3 of whom were treated with high-tangents RT and 1 with whole breast RT. Most of BCRLs in the SNB group occurred in patients receiving High-tangents RT (75%), although it was not statistically significant. But still, the Incidence of BCRL was significantly lower than that of ALND group (5 year incidence rate 5.5% vs. 15.1%, p=0.045).

Currently, if it is evaluated as low risk in the results of genomic tests such as MammaPrint or Oncotpye Dx, chemotherapy is not performed even if positive sentinel lymph node. Although these patients are classified as low risk, given that chemotherapy may affect regional control [19], it may be helpful to cover the axillary area through RT. In these patients, high-tangents RT can provide better coverage of axillary area than standard tangential RT [20,21]. In current study, regional recurrence was not observed in the patients who underwent high-tangents RT or RNI. The treatment outcomes of patients who underwent high-tangents RT were not worse than those of patients who underwent ALND or whole breast RT. Furthermore, high-tangents RT did not increased the incidence of BCRL and it was significantly lower than that ALND group. Since there are few regional recurrences, to clarifying the conclusion, longer follow up period and larger studies are

needed.

This study has several limitations. First of all, this is a retrospective study. And due to relatively small number of patients and short follow-up period, the statistical power was insufficient. Small numbers of recurrence and death cases were observed, and when dividing the patients into subgroups according to radiation treatment field, the number of patients included in each group was not large. It makes challenging to confirm whether there was a significant difference in treatment outcomes according to radiation treatment field and draw firm conclusion. Despite these drawbacks, this study has some advantages. This study was conducted in a single institution and, if nodal lymph node involvement is suspected before treatment, biopsy confirmation was performed. Since the clinical lymph node metastasis was judged according to the strict standard in a single institution, it is thought that more homogeneous cN0 patients were included in this study and we could obtained the good therapeutic outcomes. And the absence of regional recurrence in patients treated with high-tangents RT or RNI suggests that axillary coverage through RT can be helpful in patients who have not undergone ALND.

Conclusions

In conclusion, among pN1 breast cancer patients, ALND did not improve overall survival or disease-free survival but increased the rate of BCRL. RT could replace ALND in patients with low burden of axillary disease. Risk-adapted axillary coverage for cN0/pN1 patients who underwent BCS and SNB was helpful in maintaining excellent regional control rate without increasing treatment associated lymphedema, but there is still insufficient data supporting this. Further study is needed to clarify which type of radiation treatment is adequate for pN1 breast cancer patients who had not undergone ALND.

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국문요약

목적: 임상적 병기 N0 (cN0) 로 평가되었던 유방암 환자들 중에서, 유방보존수술 후에 병리적 병기가 N1 (pN1)으로 확인된 환자들의 치료성적 및 재발양상을 확인하고, 이에 따른 적절한 방사선 치료범위를 확인하고자 하였다.

대상 및 방법: 2012 년 1 월부터 2015 년 7 월까지 유방보존수술 후 방사선 치료를 시행한 환자들 중에서 병리적 병기가 N1M0 로 평가된 환자들을 후향적으로 분석하였다. 우리는 환자들을 감시림프절생검 시행군과 액와림프절 곽청술 시행군으로 나누었다. 그리고 치료 성적과 합병증을 비교하기 위하여, 액와림프절 곽청술을 시행받은 환자들 중 영역 림프절 방사선 치료 (regional nodal irradiation) 을 시행 받은 환자 40 명은 제외하였다. 총 289 명의 환자들이 이 연구에 포함되었다. . 이 환자들 중 130 명은 액와림프절 곽청술을 시행 받았으며, 159 명은 감시림프절 생검만을 시행 받았다. 감시림프절 생검만을 시행한 환자들 중에서 81 명은 표준 접사면 방사선 치료 (standard tangential field radiation therapy), 55 명은 고접사면 방사선 치료 (high-tangents radiation therapy), 23 명은 유방 전체와 영역 림프절 방사선 치료를 함께 시행 받았다. 방사선 치료 선량은 대부분의 경우 전 유방에 1 회 선량 2Gy 씩, 총 50 Gy 까지 조사되었으며, 전자선(electron)으로 종양 바닥 (tumor bed) 에 10-15Gy 가 추가 조사되었다. 보조 항암화학요법은 81%의 환자들에서 시행되었다. 그리고 모든 호르몬 수용체 양성 환자에서 호르몬 치료가 시행되었다. 본 연구의 일차 평가 변수 (primary endpoint) 는 국소무재발

생존율 (regional recurrence-free survival) 이었으며, 이차 평가 변수 (secondary endpoint)는 전체생존율, 무재발생존율 및 유방암 관련 림프부종 (breast cancer-related lymphedema) 이었다.

결과: 연구에 포함된 환자들의 나이의 중앙값은 50 세였다. 감시림프절 생검을 시행 받은 환자들에서 액와림프절 곽청술을 시행 받은 환자들에 비해 에스트로겐 수용체 양성 및 Ki-67 발현율이 14% 미만인 환자의 비율이 유의하게 낮았다. 그리고 병리적 병기가 N1mic 인 환자의 비율은 감시림프절 생검만을 시행한 환자들에서 유의하게 높았다. 추적 관찰기간의 중앙값은 73 개월 이었으며, 6 건의 동측 유방 내 재발과 (ipsilateral breast tumor recurrence) 3 건의 국소 재발이 발생하였다. 원격 재발은 10 건이 발생하였다. 국소 재발 3 건 중 1 건은 감시림프절 생검만 시행 받은 환자에서 발생하였으며, 2 건은 액와림프절 곽청술을 시행받은 환자에서 발생하였다. 감시림프절 생검만 시행한 환자군에서, 국소 재발은 (regional recurrence) 표준 접사면 방사선 치료로 치료받은 환자에서만 1 건 발생하였으며, 고접사면 방사선 치료나 영역 림프절 방사선 치료를 시행 받은 환자들에서는 발생하지 않았다. 5 년 국소무재발 생존율은 감시림프절 생검만을 시행 받은 환자군에서 99.2% 였으며, 액와 림프절 곽청술을 시행 받은 환자군에서는 98.2% 였다 (p=0.590). 방사선치료의 종류나 분자 아형(molecular subtype) 에 따른 5 년 국소무재발 생존율은 차이가 없었다. 또한 5 년 전체 생존율, 국소무재발생존율 은 두 군간에 유의한 차이가 없었다(각각 99.4% vs. 99.2%, 94.1% vs. 93.4%). 유방암 관련 림프부종의 발생률은 액와림프절 곽청술을 시행 받은 환자들에

서 유의하게 높았다 (1.9% vs 15.1%, p<0.001).

결론: cN0/pN1 유방암 환자들에서 액와림프절 곽청술은 전체생존율 및 무재발생존율 기간을 향상시키지 않았으나, 유방암 관련 림프부종의 발생을 증가시켰다. 환자가 가지고 있는 위험요소들에 따라 액와부를 방사선 치료범위에 포함 하는 것이 cN0/pN1 유방암 환자들에서 치료 관련 림프부종의 발생을 증가시키지 않으면서 좋은 국소재발율을 유지하는데 도움이 될 것으로 생각된다.

핵심용어: 유방암, 국소재발, 전체 생존율, 무재발생존율, 방사선치료, 후향적 연구