Original Study

Role of Elective Nodal Irradiation in Patients With ypN0 After Neoadjuvant Chemotherapy Followed by Breast-Conserving Surgery (KROG 16-16)

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Abstract

This multi-institutional study aimed to investigate the role of elective nodal irradiation (ENI) in ypN0 patients following neoadjuvant chemotherapy and breast-conserving surgery according to subtype and primary tumor response. We analyzed 261 patients and found that ENI does not improve survival regardless of subtype or primary tumor response. Whole-breast irradiation might be sufficient in ypN0 patients.

Background: Given the lack of established indications for elective nodal irradiation (ENI) in ypN0 patients after neoadjuvant chemotherapy (NAC) and breast-conserving surgery (BCS), we set out to investigate the role of ENI in ypN0 patients according to subtype and pathologic complete remission (pCR) status. **Patients and Methods:** We analyzed 261 patients who received NAC followed by BCS and adjuvant radiotherapy in 13 institutions of the Korean Radiation Oncology Group from 2005 to 2011. The tumors were classified into one of 3 subtypes: luminal (estrogen receptor positive or progesterone receptor positive and HER2 negative), HER2 (HER2 positive), or triple negative (estrogen receptor, progesterone receptor, and HER2 negative). We compared locoregional control (LRC), disease-free survival (DFS), and overall survival (OS) according to ENI in different subgroups generated by the subtype and pCR statuses. **Results:** In all patients, the 5-year LRC, DFS, and OS rates were 96.0%, 91.0%, and 96.8%, respectively. In all patients, axillary lymph node dissection was found to be the only favorable factor for LRC ($P = .023$) and DFS ($P = .001$). Age $\geq$ 50 years ($P = .027$), negative resection margin ($P = .002$), and axillary lymph node dissection ($P = .002$) were all favorable factors for OS. ENI did not affect LRC, DFS, or OS. Subgroup analysis by tumor subtype and pCR showed that ENI was not associated with greater LRC or DFS in any subgroups. **Conclusion:** In ypN0 patients after NAC and BCS, ENI did not improve LRC or survival, regardless of subtype or primary tumor response. This result should be verified through larger prospective trials.

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Introduction

Neoadjuvant chemotherapy (NAC) before surgery in breast cancer increases the likelihood of breast-conserving surgery (BCS).[1-4] After NAC and BCS, the extent of adjuvant radiotherapy (RT) can be determined according to either the clinical stage at diagnosis or pathologic stage.[5] However, the discrepancy in clinical and pathologic stages due to a dramatic response to NAC complicates this decision in the RT field.

Breast cancer subtype is an essential predictor of disease progression in breast cancer patients.[6,7] Although tumor subtyping by multiple gene expression analyses is increasingly being used, immunohistochemistry (IHC)-based subtyping is still the most reliable and useful method for predicting prognosis in breast cancer.[8] Furthermore, the American Joint Committee on Cancer 8th edition staging system incorporated IHC subtypes into the stage grouping.[9] Tumor subtypes also predict responses to NAC in breast cancer, and the prognostic influence of the subtypes is somewhat complicated in NAC settings.[10,11]

The role of elective nodal irradiation (ENI) in patients who initially had nodal disease and who experienced ypN0 after NAC has been previously addressed in several retrospective studies.[3,12-14] Although most of these studies, including a previous one of ours, failed to confirm the benefits of ENI, the role of ENI according to different subtypes and residual primary tumor has yet to be investigated.[5] Unfortunately, our previous study investigating whether ENI is necessary in ypN0 patients was limited in exploring this issue because disease subtypes were unknown in 11.5% of cases, and HER2-targeted therapy was only delivered to 6% of HER2-positive patients.[14]

Thus, we conducted this multi-institutional study in the era of HER2-targeted therapy to evaluate the benefit of ENI in ypN0 patients after NAC and BCS according to disease subtype and primary tumor response.

Patients and Methods

Patients

Retrospective data of 450 patients who initially had suspicious axillary disease and experienced ypN0 after NAC were collected from 13 institutions of the Korean Radiation Oncology Group (KROG) from January 2005 to December 2011. Of these patients, 189 were treated with mastectomy, while 261 received BCS and whole-breast RT. Thus, we ultimately analyzed data of 261 patients, 36 of whom had participated in the KROG 12-05 study. All participating institutions obtained approval from their respective institutional review boards. We excluded patients who had a history of RT, previous or concurrent malignancy except for thyroid cancer at the time of diagnosis, distant metastases, clinically positive supraclavicular or internal mammary lymph nodes (LNs), or unclassified HER2 status.

Subtypes

In order to define the breast cancer disease subtypes, we identified the IHC expression of estrogen receptor, progesterone receptor, and HER2 status. We defined HER2 overexpression when the HER2 expression was detected as either grade 2 or 3 on IHC and confirmed by fluorescence in-situ hybridization or silver in-situ hybridization test, or when there was a history of HER2-targeted therapy. The tumors were classified into one of 3 subtypes: luminal (estrogen receptor positive or progesterone receptor positive and HER2 negative), HER2 (HER2 positive), or triple negative (estrogen receptor, progesterone receptor, and HER2 negative).

Treatment

All of the patients underwent NAC followed by BCS and whole-breast RT. The most frequent chemotherapeutic regimen for NAC was anthracycline plus taxane (n = 107, 41.0%), followed by anthracycline and cyclophosphamide combined with taxane (n = 84, 32.2%) and anthracycline and cyclophosphamide (30, 11.5%). The median number of NAC cycles was 4 (range, 2-12). Axillary LN confirmation with fine-needle aspiration before NAC was performed in 107 patients (41.0%). For the remaining 154 patients, axillary LN involvement was confirmed through either positron emission tomography–computed tomography (n = 79), magnetic resonance imaging (n = 50), computed tomography (n = 52), or ultrasound (n = 102).

Axillary LN dissection (ALND) was performed in 213 patients (81.6%), and 48 patients (18.4%) received sentinel LN biopsy (SLNB) alone. The median number of sampled LNs was 11 (range, 0-42). Additional adjuvant chemotherapy after surgery was provided to 133 patients (51.0%). The most common regimen in these cases was anthracycline plus taxane (n = 80, 30.7%), followed by anthracycline and cyclophosphamide (n = 24, 9.2%), then taxane only (n = 15, 5.7%). The median number of adjuvant chemotherapy cycles was 2 (range, 1-12). Adjuvant hormone treatment was administrated to 86 patients (33.0%). Among the HER2-type tumors (n = 95), HER2-targeted therapy was delivered to 48 patients (50.2%), of whom 27 (28.4%) received neoadjuvant HER2-targeted therapy.

The adjuvant RT dose to the whole breast was 45 to 54 Gy by 1.8 to 2.0 Gy per fraction. Boost RT to the primary tumor bed was delivered in 233 patients (89.3%), and the dose schedule for the boost was 6 to 18 Gy by 1.8 to 3.5 Gy per fraction. ENI including the supraclavicular region was performed in 102 patients (39.1%), of whom 20 (7.7%) received internal mammary irradiation. The RT dose to ENI was 45 to 54 Gy by 1.8 to 2.0 Gy per fraction.

Statistical Analysis

Pathologic complete remission (pCR) was defined as no residual tumor in dissected LNs and ductal carcinoma-in-situ or as no residual tumor in primary disease (pTis/0). The distributions of categorical variables between the groups were compared by the chi-square or Fisher exact tests, and continuous variables were compared by *t* test or Mann-Whitney test. Locoregional recurrence was defined as disease recurrence within the breast, chest wall, or regional lymphatic area (axillary, supraclavicular, or internal mammary LNs). Locoregional control (LRC) was defined as the time from initiation of NAC to locoregional recurrence or death. Disease-free survival (DFS) was defined as the time from the initiation of NAC to any recurrence or death. Overall survival (OS) was defined as the time from the initiation of chemotherapy to death from any cause.

Survival curves were estimated by the Kaplan-Meier method and compared by log-rank tests. Factors that showed a probability value of $< .1$ or that were thought to be otherwise relevant were entered into a Cox proportional hazards regression analysis in order to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to

Table 1 Characteristics of 261 Patients by ENI

Characteristic	All	No ENI (N = 159)	ENI (N = 102)	*P*
Histology				.615
IDC	253 (96.9)	155 (97.5)	98 (96.1)	
ILC	3 (1.1)	1 (0.6)	2 (2.0)	
Other	5 (1.9)	3 (1.9)	2 (2.0)	
Subtype				.613
Luminal	53 (20.3)	34 (21.4)	19 (18.6)	
HER2	95 (36.4)	60 (37.7)	35 (34.3)	
Triple negative	113 (43.3)	65 (40.9)	48 (47.1)	
Histologic Grade				.997
I	17 (6.5)	10 (6.3)	7 (6.9)	
II	68 (26.1)	42 (26.4)	26 (25.5)	
III	87 (33.3)	53 (33.3)	34 (33.3)	
Unknown	89 (34.1)	54 (34.0)	35 (34.3)	
cT Stage				.011
T1-2	203 (77.8)	132 (83.0)	71 (69.6)	
T3-4	58 (22.2)	27 (17.0)	31 (30.4)	
cN Stage				<.001
N1	188 (72.0)	127 (79.9)	61 (59.8)	
N2	73 (28.0)	32 (20.1)	41 (40.2)	
Axillary LN Confirmed				.064
No	154 (59.0)	101 (63.5)	53 (52.0)	
Yes	107 (41.0)	58 (36.5)	49 (48.0)	
Neoadjuvant Chemotherapy Regimen				.056
AC	30 (11.5)	25 (15.7)	5 (4.9)	
AT	107 (41.0)	63 (39.6)	44 (43.1)	
ACT	84 (32.2)	47 (29.6)	37 (36.3)	
Taxane	15 (5.7)	11 (6.9)	4 (3.9)	
Other	25 (9.6)	13 (8.2)	12 (11.8)	
ypT Stage				.409
T0-is	108 (41.4)	69 (43.4)	39 (38.2)	
T1-2	153 (58.6)	90 (56.6)	63 (61.8)	
Resection Margin				.244
Negative	246 (94.3)	147 (92.5)	99 (97.1)	
Close	13 (5.0)	10 (6.3)	3 (2.9)	
Positive	2 (0.8)	2 (1.3)	0	
Axillary Dissection				.395
SLNB only	48 (18.4)	31 (19.5)	17 (16.7)	
ALND	213 (81.6)	128 (80.5)	85 (83.3)	
No. of Dissected LNs[a]				.733
<10	68 (31.9)	42 (32.8)	26 (30.6)	
≥ 10	145 (68.1)	86 (67.2)	59 (69.4)	
LVI				.716
No	186 (82.3)	115 (82.1)	71 (82.6)	
Yes	32 (14.2)	19 (13.6)	13 (15.1)	
Unknown	8 (3.5)	6 (4.3)	2 (2.3)	
Tumor Bed Boost				.043
No	28 (10.7)	22 (13.8)	6 (5.9)	
Yes	233 (89.3)	137 (86.2)	96 (94.1)	

Data are presented as n (%).
Abbreviations: AC = anthracycline and cyclophosphamide; AC-T = anthracycline, cyclophosphamide, and taxane; ALND = axillary lymph node dissection; AT = anthracycline and taxane; ENI = elective nodal irradiation; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LN = lymph node; LVI = lymphovascular invasion; SLNB = sentinel lymph node biopsy.
[a]Number of dissected lymph nodes was analyzed in those who received ALND.

Table 2 Patterns of Failure

Failure Type	Total	ENI	No ENI	*P*
Locoregional Recurrence	8 (32.0%)	5 (41.7%)	3 (23.1%)	.311
Local	5	2	3	
Regional	2	2	0	
Both	1	1	0	
Distant recurrence	15 (60.0%)	7 (58.3%)	8 (61.5%)	
Both locoregional and distant recurrence	2 (8.0%)	0	2 (15.4%)	
Total	25	12	13	

Abbreviation: ENI = elective nodal irradiation.

Table 3 Prognostic Factors for LRC, DFS, and OS by Univariate Analysis

	5-y LRC		5-y DFS		5-y OS	
Characteristic	**%**	***P***	**%**	***P***	**%**	***P***
Age, y		.899		.101		.095
<50	95.9		89.3		95.4	
≥50	96.1		94.9		100	
Subtype		.874		.288		.188
Luminal	96.1		96.1		100	
HER2	96.6		92.5		98.9	
Triple negative	95.4		87.4		93.6	
Histologic Grade		.906		.053		.988
I-II	94.1		85.7		100	
III	94.5		90.8		95.4	
cT Stage		.386		.222		.128
cT1-2	95.4		92.4		97.4	
cT3-4	98.1		86.1		94.6	
cN Stage		.865		.160		.858
cN1	96.1		91.9		96.7	
cN2-3	95.5		88.9		97.1	
ypT Stage		.159		.077		.103
ypT0-is	98.0		94.2		99.0	
ypT1-3	94.5		88.8		95.3	
LVI		.672		.682		.820
No	96.0		90.7		96.6	
Yes	93.8		87.4		96.8	
Resection Margin		.001		.009		.002
Negative	96.6		73.3		97.0	
Close/positive	91.7		92.1		92.9	
Axillary Dissection		.006		<.001		.001
SLNB only	88.6		76.7		91.3	
ALND	97.6		94.3		98.0	
No. of Dissected LNs[a]		.018		.296		.263
<10	93.9		92.5		96.8	
≥ 10	99.3		95.1		98.6	
ENI		.367		.365		.448
No	96.7		92.3		98.0	
Yes	94.8		89.2		95.0	

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; DFS = disease-free survival; ENI = elective nodal irradiation; HR = hazard ratio; LN = lymph node; LRC = locoregional control; LVI = lymphovascular invasion; OS = overall survival; SLNB = sentinel lymph node biopsy.
[a]Number of dissected LNs was analyzed among those who received ALND.

Table 4 Prognostic Factors for LRC, DFS, and OS by Multivariate Analysis

Characteristic	LRC		DFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥50 vs. <50 y)					12.302 (1.334-113.407)	.027
Grade (III vs. I-II)			0.735 (0.312-1.732)	.481		
ypT stage (ypT1-3 vs. T0-is)			1.691 (0.479-5.973)	.415		
Resection margin (close/positive vs. negative)	3.391 (0.679-16.933)	.137	2.129 (0.678-6.682)	.195	12.377 (2.605-58.807)	.002
Axillary dissection (SLNB vs. ALND)	4.387 (1.222-15.754)	.023	4.022 (1.747-9.257)	.001	6.498 (2.030-20.805)	.002
ENI (no vs. yes)	0.310 (0.148-1.833)	.310	0.561 (0.249-1.264)	.163	0.350 (0.096-1.272)	.111

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; DFS = disease-free survival; ENI = elective nodal irradiation; LRC = locoregional control; OS = overall survival; SLNB = sentinel lymph node biopsy.

control other covariates. $P < .05$ was considered to be statistically significant. We conducted all analyses with SPSS 20 (IBM, Armonk, NY).

Results

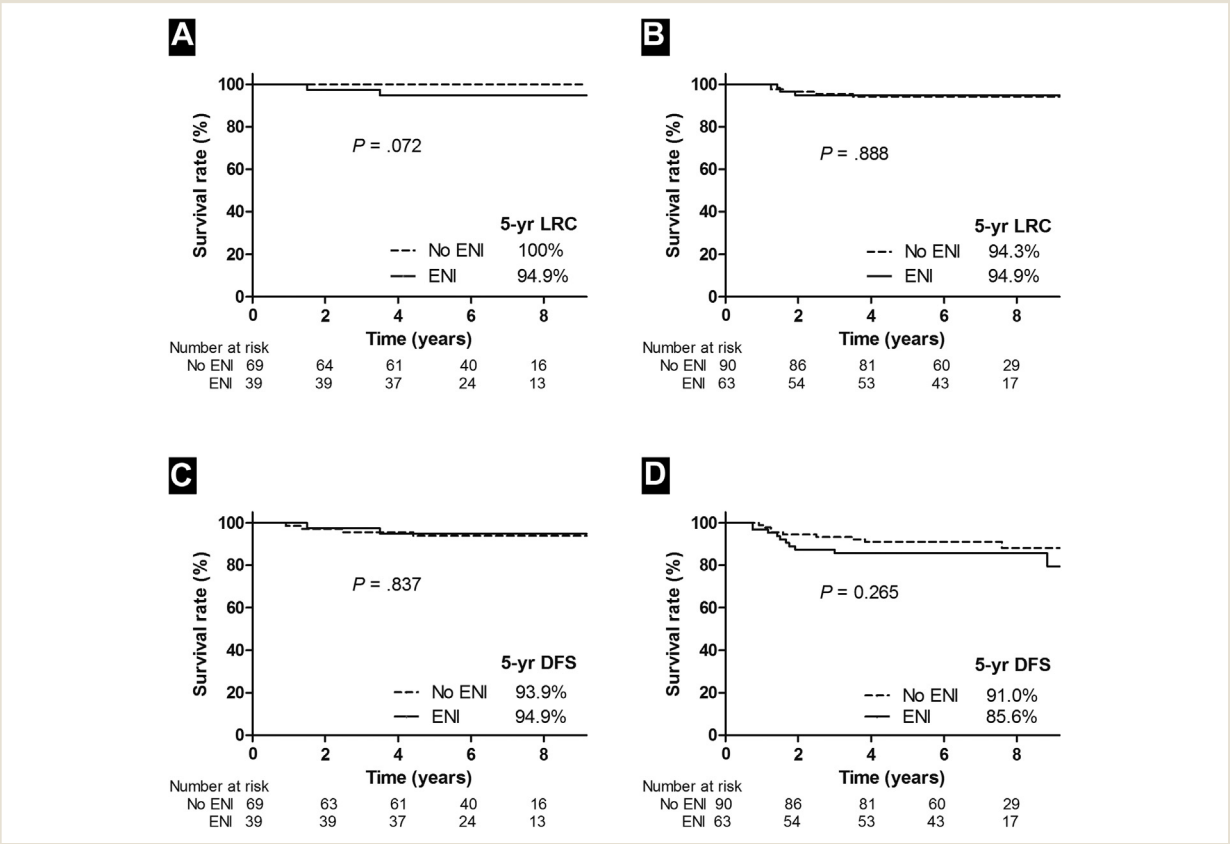
Patient Characteristics

Among all patients, the most frequent subtype was triple negative (n = 113, 43.3%), followed by HER2 (n = 95, 36.4%) and luminal (n = 53, 20.3%). Of all patients, 108 (41.4%) experienced ypCR, including ypT0 and ypTis. The patient and tumor characteristics according to ENI are listed in Table 1. Patients who were treated with ENI had more advanced clinical T stage ($P = .011$) and N stage ($P < .001$) disease. The tumor bed boost was more frequently delivered in the ENI group (94.1% vs. 86.2%, $P = .043$). The distributions of subtypes and pCR rates did not differ between the ENI groups.

Patterns of Failure and Prognostic Factors

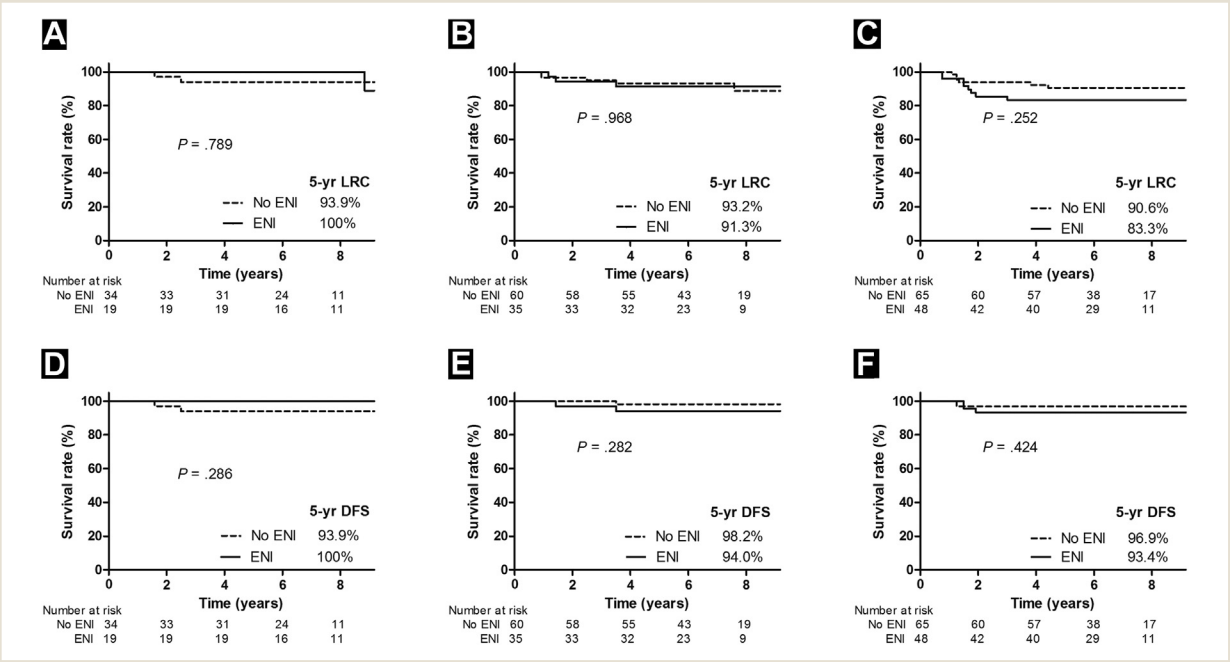
After a median follow-up of 79 months (range, 16-141 months), the 5-year LRC, DFS, and OS rates were 96.0%, 91.0%, and

Figure 1 Locoregional Control and Survival by Irradiation. Graph According to ENI in Patients Who Experienced (A) ypCR and (B) Non-CR. Disease-free Survival Graph According to ENI in Patients Who Experienced (C) ypCR and (D) Non-CR



Abbreviations: CR = complete response; ENI = elective nodal irradiation; ypCR = pathologic complete remission.

Figure 2 Locoregional Control and Survival by Disease Type. Locoregional Control Graph According to ENI in Patients With (A) Luminal Type (B) HER2 Type, and (C) Triple-negative Type. Disease-free Survival Graph According to ENI in Patients With (D) Luminal Type, (E) HER2 Type, and (F) Triple-negative Type



Abbreviation: ENI = elective nodal irradiation.

96.8%, respectively. Of 25 recurrences, distant recurrence (60.0%, n = 15) was the most frequent pattern of failure. Eight patients (32.0%) developed locoregional recurrences, and 2 patients (8.0%) experienced both locoregional and distant organ recurrence. The patterns of failure did not differ between the ENI and no-ENI groups (P = .311, Table 2). The prognostic factors for LRC, DFS, and OS were analyzed by univariate analyses, including age, subtype, histologic grade, cT stage, cN stage, ypT stage, lymphovascular invasion, resection margin, axillary dissection, number of dissected LNs, and ENI (Table 3). Unfavorable factors for LRC were close or positive resection margin (P = .001), SLNB only (P < .001), and < 10 dissected LNs (P = .018), while those for DFS were close or positive resection margin (P = .009) and SLNB only (P < .001). Significantly unfavorable factors for OS were close or positive resection margin (P = .002) and SLNB only (P = .001), while age 50 years or more was marginally significant (P = .095). LRC, DFS, and OS did not differ significantly between the patients who did and did not receive ENI (P = .367, P = .365, and P = .448, respectively). We entered the factors found to be significant by univariate analysis (P < .1) and ENI in multivariate analysis (Table 4). SLNB was found to be the only significant risk factor for LRC and DFS in multivariate analysis (HR, 95% CI = 4.387, 1.222-15.754 and 4.022, 1.747-9.257, respectively). For OS, age 50 years or older (HR, 95% CI = 12.302, 1.334-113.407), close or positive resection margin (HR, 95% CI = 12.377, 2.605-58.807), and SLNB (HR, 95% CI = 6.498, 2.030-20.805) were found to be unfavorable factors in multivariate analysis (Table 4).

Effect of ENI in Subgroups

We analyzed the effect of ENI on DFS in subgroups by primary tumor response. In both the pCR and non–complete response (CR) subgroups, ENI did not affect LRC and DFS (Figure 1). The effect of ENI was evaluated in different subtypes (Figure 2). LRC and DFS did not differ according to ENI in any tumor subtype.

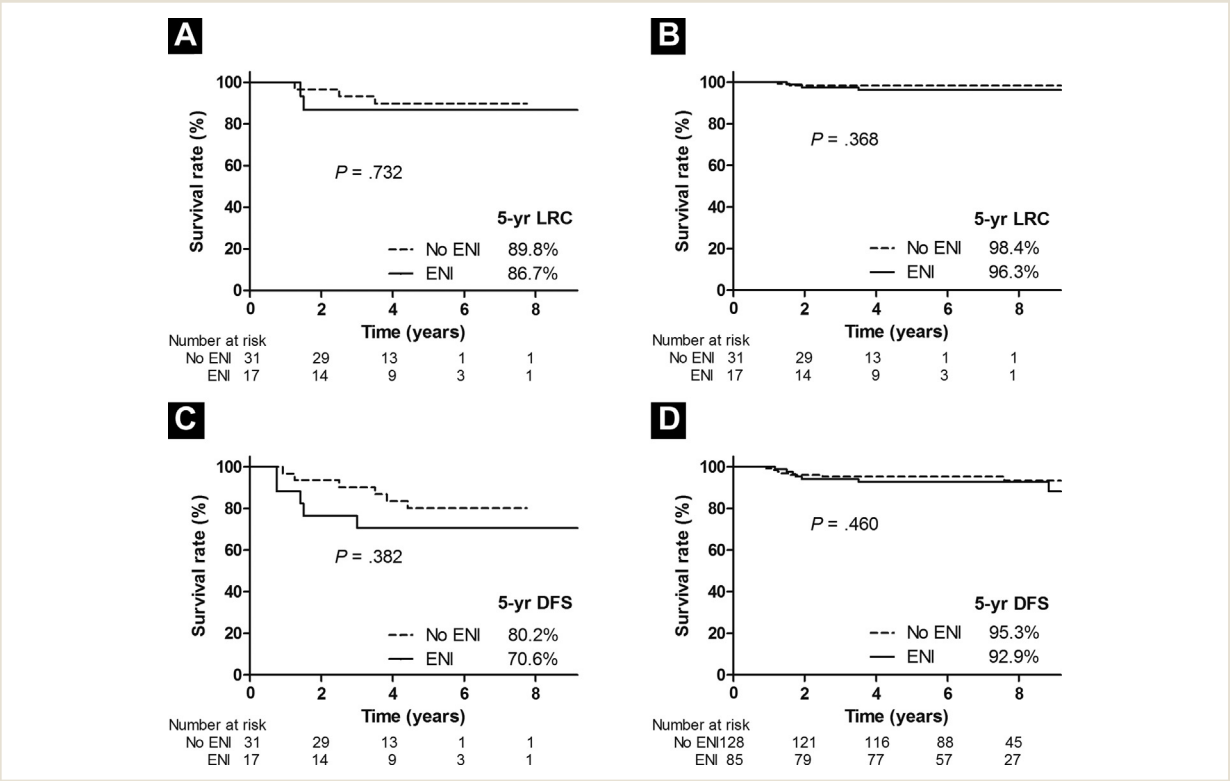
The benefit of ENI for LRC and DFS was further evaluated in those who received SLNB only versus ALND (Figure 3). ENI was not found to affect DFS in either group (P = .382 in SLNB-only group and P = .460 in ALND group)

We further divided the pCR and non-CR patients according to subtype and estimated the effect of ENI on LRC and DFS in each subgroup (Table 5). LRC and DFS were not found to differ between patients who did and did not undergo ENI in any subgroup.

Discussion

This study failed to identify any benefit from ENI in ypN0 patients in all patients as well as in any subgroups by tumor subtype and primary tumor response. Although trials by the National Cancer Institute of Canada Clinical Trials Group and European Organization for the Research and Treatment of Cancer 22922/10925 confirmed the benefit of ENI in initially resected tumors, the benefit of ENI in ypN0 patients after NAC remains to be established.[15,16] Daveau et al[17] evaluated the effect of ENI in ypN0 patients after NAC and BCS and showed that whole-breast RT alone was not associated with any worse outcomes than whole-breast RT plus ENI. Another retrospective study using the

Figure 3 Locoregional Control and Survival by Biopsy Type. Locoregional Control Graph According to ENI in Patients Who Received (A) SLNB Alone and (B) ALND. Disease-free Survival Graph According to ENI in Patients Who Received (C) SLNB Alone and (D) ALND



Abbreviations: ALND = axillary lymph node dissection; ENI = elective nodal irradiation; SLNB = sentinel lymph node biopsy.

National Cancer Data Base also indicated that the addition of ENI after BCS in ypN0 patients did not improve survival.[18]

This study further attempted to investigate the potential subgroups that would benefit ENI. Different effects of adjuvant RT according to tumor subtype have been reported in mastectomy cases, which revealed that RT benefit was the largest in luminal-type breast cancer.[19,20] However, in this study, we could not identify different effects of RT according to subtype. Furthermore, tumor subtypes were not a significant factor for tumor control and survivals. Although the ENI group more frequently had advanced cN stage and cT stage disease than did the no ENI group, advanced cT stage and cN stage were not significant factors for tumor control and survival in ypN0 patients after NAC. We further analyzed the effect of ENI in advanced clinical stage subgroups (cN2 and cT3-4); however, ENI was not found to affect DFS or OS in any group.

In the current study, axillary dissection was the most important factor for survival in multivariate analysis. For patients who had initially positive axillary disease and received NAC, ALND is the recommended treatment, while the feasibility of SLNB after NAC remains controversial.[21] An analysis of a trial by the American College of Surgeons Oncology Group Z1071 suggested that evaluation of $>$ 2 sentinel LNs, the use of dual agents, and clipping in biopsy-proven node at diagnosis were associated with lower false-negative rates of SLNB after NAC.[22,23] Unfortunately, we did not have details on SLNB, including the number of evaluated sentinel LNs. The worse clinical outcomes in SLNB subgroup might have been due to the falsely negative disease of LNs with insufficient SLNB. Nevertheless, the lack of a benefit of ENI in the SLNB subgroup implies that the administration of ENI appears not to offset the risk of insufficient axillary dissection. The ongoing A011202 trial (ClinicalTrials.gov, NCT01901094) will offer more evidence in regard to the optimal axillary management in ypN0 patients after NAC.

One of the limitations of this study is the heterogeneous NAC and RT regimens caused by the fact that the data were obtained retrospectively from multiple institutions. Second, axillary management is heterogeneous, and only 41% of patients underwent axillary evaluations with aspiration or biopsy before NAC. The misclassification of clinical nodal status limits the accurate identification of the patients who converted from positive to negative node status from those who were initially node negative. Third, the number of analyzed patients was not enough to draw conclusions, especially regarding subtypes.

In summary, the addition of ENI in patients who experience ypN0 after NAC and BCS did not improve DFS in any subgroup by subtype or primary tumor response. The results of this study

Table 5 ENI in Different Molecular Subtypes in pCR and Non-CR Patients

Characteristic	5-y LRC %	P	5-y DFS %	P
pCR (N = 108)				
Luminal (n = 11)	100		100	
HER2 (N = 49)		.212		.866
No ENI (n = 31)	100		93.4	
ENI (n = 18)	94.4		94.4	
TN (N = 48)		.171		.978
No ENI (n = 32)	100		93.3	
ENI (n = 16)	93.8		93.8	
Non-CR (N = 153)				
Luminal (n = 42)		.322		.849
No ENI (n = 28)	92.9		92.9	
ENI (n = 14)	100		100	
HER2 (N = 46)		.662		.791
No ENI (n = 29)	96.3		93.0	
ENI (n = 17)	93.8		88.2	
TN (N = 65)		.953		.302
No ENI (n = 33)	93.8		87.9	
ENI (n = 32)	93.1		78.1	

Abbreviations: CR = complete response; DFS = disease-free survival; ENI = elective nodal irradiation; pCR = pathologic complete remission; TN = triple negative.

need to be confirmed by the ongoing NSABP B-51/RTOG 1304 trial (ClinicalTrials.gov, NCT01872975) in order to serve as guidance for the optimal RT regimen for ypN0 patients.

Clinical Practice Points

- The role of ENI in ypN0 patients after NAC and BCS has yet to be established.
- This multi-institutional study aimed to investigate the role of ENI in ypN0 patients according to disease subtype and primary tumor response.
- In ypN0 patients after NAC and BCS, ENI does not improve DFS, regardless of subtype or primary tumor response.
- Whole-breast irradiation alone may be sufficient in ypN0 patients treated with NAC and BCS, without the need for ENI.

Disclosure

The authors have stated that they have no conflict of interest.

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