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의학석사 학위논문

Prognostic Value of the Nodal Ratio and Ki-67 Expression in Breast Cancer Patients Treated with Postmastectomy Radiotherapy

유방절제술 후 방사선치료를 받은 유방암 환자에서 림프절 전이비율과 Ki-67 발현의 예후적 가치

2014년 2월

서울대학교 대학원

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지도 교수 김 인 아

이 논문을 의학 석사 학위논문으로 제출함

2013 년 10 월

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Prognostic Value of the Nodal Ratio and Ki-67 Expression in Breast Cancer Patients Treated with Postmastectomy Radiotherapy

by

Tae Ryool Koo

A thesis submitted to the Department of Clinical Medical Sciences, Graduate School in partial fulfillment of the requirements for the Master of Science in Clinical Medical Sciences at Seoul National University College of Medicine

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Professor Hong-Gyun Wu Chairman

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ABSTRACT

Introduction: We performed this study to evaluate prognostic factors of postmastectomy radiotherapy for breast cancer patients undergoing systemic therapy in either preoperative or postoperative setting, in order to identify patients at high risk of disease relapse and survival.

Methods: Between 2003 and 2009, 113 patients received postmastectomy radiotherapy in Seoul National University Bundang Hospital: 61 underwent preoperative systemic therapy and 52 received postoperative systemic therapy. The most common chemotherapy regimen was six cycles of docetaxel and doxorubicin in patients with preoperative systemic therapy; and four cycles of doxorubicin, cyclophosphamide, and paclitaxel in patients with postoperative systemic therapy. Hormonal therapy was administered in patients with a positive hormone receptor status; and trastuzumab was recommended for patients with a tumor exhibiting c-erbB-2 overexpression (3+) or HER2 gene amplification. For radiotherapy, the chest wall and supraclavicular fossa were irradiated with up to 50.4 Gy at 1.8 Gy per fraction with 5 fractions per week. Following histopathologic parameters were evaluated by immunohistochemical analysis: the status of hormone receptor and the expression of c-erbB-2, p53, Ki-67, and COX-2. The positive cut-off values were immunohistochemical staining in ≥1% for hormone receptor, in >10% for p53, in >20% for Ki-67, and a 3+ staining score for COX-2 and c-erbB-2. The analysis of HER2 gene amplification was performed with Fluorescence *in situ* hybridization. Lymph node status was evaluated by hematoxylin and

eosin staining. The nodal ratio was defined as the number of axillary lymph nodes with cancer involvement divided by the total number of excised axillary lymph nodes. The cut-off value was 0.2, after comparing survival rates by using the maximal chi-square method in the R program version 2.13.0.

Results: The median follow-up time was 72.3 months (range, 34.0-109.4 months) for surviving patients. In univariate analysis of all patients, disease-free survival (DFS) was associated with age, nodal ratio, and Ki-67 expression; overall survival (OS) was associated with nodal ratio and Ki-67 expression. Pathologic N stage and HER2 expression were marginally associated with DFS and OS. In patients with postoperative systemic therapy, DFS was associated with age, nodal ratio, venous invasion, and Ki-67 expression; OS was associated with age. In patients with preoperative systemic therapy, DFS was associated with ypN stage and nodal ratio; OS was associated with ypN stage, histologic grade, HER2 expression, and p53 expression. In multivariate analysis of all patients, DFS and OS were significantly associated with nodal ratio ($p = 0.003$ and $p = 0.019$, respectively) and Ki-67 expression ($p = 0.002$ and $p = 0.015$, respectively). Patients were classified into low-risk (nodal ratio $\leq$0.2 and Ki-67 $\leq$20%; n=34), intermediate-risk (nodal ratio >0.2 or Ki-67 >20%; n=63), and high-risk (nodal ratio >0.2 and Ki-67 >20%; n=16) subgroups. All low-risk patients were alive at the time of analysis. High-risk ($p < 0.001$ and $p = 0.001$, respectively) and intermediate-risk ($p = 0.022$ and $p = 0.008$, respectively) patients had significantly shorter DFS and OS than low-risk patients. This prognostic model was statistically significant for DFS when applied to

patients with preoperative systemic therapy (p = 0.001) and with postoperative systemic therapy (p = 0.016) separately. We classified patients into three intrinsic subtypes: luminal A (hormone receptor positive and HER2 negative; n=55), luminal B (hormone receptor positive and HER2 positive; n=12), HER2 overexpression (hormone receptor negative and HER2 positive; n=16), and basal-like (hormone receptor negative and HER2 negative; n=30). DFS and OS had no association with intrinsic subtypes (p = 0.249 and p = 0.202, respectively). When our prognostic model was applied to luminal A subtype, there was a marginal association in DFS (p = 0.078), while not in OS (p = 0.173).

Conclusions: For breast cancer patients undergoing postmastectomy radiotherapy, nodal ratio and Ki-67 are potential prognostic factors. A model using these factors might help predict a poor prognosis. Whether nodal ratio and Ki-67 are also prognostic for different setting of systemic therapy, preoperative or postoperative, warrants further study to develop a more sophisticated prognostic model.

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Keywords: Breast neoplasms, Ki-67 antigen, Lymph nodes, Mastectomy,

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INTRODUCTION

1. Background

For patients with locally advanced breast cancer, even after mastectomy and systemic therapy, the possibility of occult disease cannot be excluded. Postmastectomy radiotherapy is performed to improve locoregional control and survival, a strategy supported by the findings of a number of randomized trials [1-3].

Axillary lymph node status is an important prognostic factor for locoregional control and survival in patients with breast cancer, and the seventh American Joint Committee on Cancer (AJCC) staging system for breast cancer is based on the absolute number of pathologically positive axillary lymph nodes [4]. Recently, several studies have reported that the nodal ratio, the proportion of involved axillary lymph nodes amongst all excised axillary lymph nodes, is of equal prognostic importance [5-10].

In addition, both gross pathologic and biomolecular parameters can be useful prognostic factors for breast cancer. In this regard, hormone receptor status and c-erbB-2/HER2 status are markers of specific intrinsic subtypes of breast cancer. The Ki-67 index, a marker of cell proliferation, is likewise a marker of a specific intrinsic subtype [11,12] and is also associated with breast cancer recurrence and death [13-16].

2. Purpose

Conventionally, postmastectomy radiotherapy was performed following postoperative systemic therapy in locally advanced breast cancer patients. Recently however, preoperative systemic therapy has been widely used in order to facilitate conservation of breast tissue. We performed this study to identify prognostic or predictive factors for patients with locally advanced breast cancer who undergo postmastectomy radiotherapy in either preoperative or postoperative setting of systemic therapy, in order to identify patients at high risk of disease relapse and survival.

MATERIALS AND METHODS

With the approval of the Institutional Review Board of Seoul National University Bundang Hospital (B-1205/153-107), we retrospectively reviewed the medical records of 113 patients with locally advanced breast cancer who underwent mastectomy followed by postmastectomy radiotherapy between March 2003 and December 2009 (Figure 1). Patients who had synchronous metastases at diagnosis, a history of malignancy, or incomplete radiotherapy were excluded from the present study. The pathologic stage was graded according to the seventh edition of the AJCC cancer staging system [4]. Patient and tumor characteristics are listed in Tables 1 and 2.

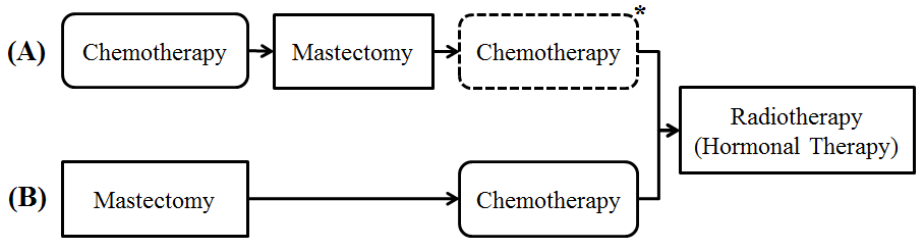


Figure 1. A flow sheet on treatment of breast cancer: patients with preoperative systemic therapy (A) and patients with adjuvant systemic therapy (B). Preoperative systemic therapy was considered in patients with advanced clinical T stage or axillary lymph node involvement.

*Chemotherapy was administered before and after mastectomy; or additional chemotherapy was given in patients with adverse pathologic features.

Table 1. Patient characteristics

Variable		Value	(%)
Age (years)	Median (range)	47	(27–77)
Excised Lymph Nodes	Median (range)	22	(1–55)
Menopausal Status	Pre	74	(65)
	Post	39	(35)
Clinical T*	cT1	3	(5)
	cT2	11	(18)
	cT3	29	(48)
	cT4	18	(30)
Clinical N*	cN0	4	(7)
	cN1	31	(51)
	cN2	18	(30)
	cN3	8	(13)
Clinical Stage*	II	11	(18)
	III	50	(82)
Pathologic T	(y)pT0	9	(8)
	(y)pT1	32	(28)
	(y)pT2	52	(46)
	(y)pT3	16	(14)
	(y)pT4	4	(4)
Pathologic N	(y)pN0	24	(21)
	(y)pN1	25	(22)
	(y)pN2	34	(30)
	(y)pN3	30	(27)
Pathologic Stage	0	7	(6)

I	8	(7)
II	29	(26)
III	69	(61)

* The patients with preoperative systemic therapy are included only.

Table 2. Tumor characteristics

Variable		Value	(%)
Histology	IDC	94	(83)
	Others	19	(17)
Histologic Grade	I	4	(4)
	II	51	(45)
	III	47	(42)
Extracapsular Extension	Negative	28	(25)
	Positive	49	(43)
Lymphatic Invasion	Negative	41	(36)
	Positive	72	(64)
Venous Invasion	Negative	94	(83)
	Positive	19	(17)
Baseline Hormone Receptor	Negative	46	(41)
	Positive	67	(59)
Baseline c-erbB-2	0–2+	80	(71)
	3+	33	(29)
Baseline HER2	Negative	85	(75)
	Positive	28	(25)
Baseline p53 (%)	≤ 10	83	(73)
	> 10	30	(27)
Baseline Ki-67 (%)	≤ 20	72	(64)
	> 20	41	(36)

IDC = infiltrating ductal carcinoma.

1. Surgery

All the patients underwent mastectomy. Axillary lymph node dissection (level I and II) was performed in 110 cases (97%), with sentinel lymph node biopsy alone performed in the remaining 3 cases (3%). Of the patients undergoing axillary lymph node dissection, 70 underwent axillary lymph node dissection alone and 40 underwent sentinel lymph node biopsy followed by axillary lymph node dissection (Table 3).

2. Chemotherapy

The most common preoperative systemic therapy regimen was DA (docetaxel and doxorubicin) followed by ACT (doxorubicin, cyclophosphamide, and paclitaxel). After completion of preoperative systemic therapy, the patients underwent mastectomy with axillary lymph node dissection. ACT was the most common adjuvant chemotherapy regimen. Adjuvant hormonal therapy was administered in patients with a positive hormone receptor status and consisted of 5 years of tamoxifen for premenopausal women and initial aromatase inhibitor therapy or a switch from tamoxifen to aromatase inhibitor therapy for postmenopausal women. Trastuzumab was recommended for all patients with a tumor exhibiting c-erbB-2 overexpression (3+) or HER2 gene amplification (Table 3).

Table 3. Treatment regimens

Variable		Value	(%)
Chemotherapy	Preoperative		
	DA×3 cycles+DA×3 cycles*	20	(33)
	DA×6 cycles	19	(31)
	DA×3 cycles→DAC×3 cycles	4	(7)
	AC×4 cycles+T×4 cycles*	10	(16)
	Postoperative		
	AC×4 cycles→T×4 cycles	43	(83)
Hormone Therapy	Tamoxifen	33	(29)
	AI	13	(12)
	Tamoxifen → AI	15	(13)
Targeted Therapy	Herceptin	24	(21)
LN Dissection	SLNBx	3	(3)
	ALND	110	(97)
Radiotherapy	Median Dose (Gy)	50.4	(46.8–59.4)
	Regional Node Irradiation	106	(94)
	Tumor Bed Boost	3	(3)

DA = docetaxel and doxorubicin; AC = doxorubicin and cyclophosphamide; T = docetaxel; AI = aromatase inhibitor; LN = lymph node; SLNBx = sentinel lymph node biopsy; ALND = axillary lymph node dissection.

* Chemotherapy was performed before and after surgery.

3. Radiotherapy

For radiotherapy, the chest wall and supraclavicular fossa were irradiated with up to 50.4 Gy at 1.8 Gy per fraction with 5 fractions per week; for a scar boost, 9 Gy at 1.8 Gy per fraction with electrons was administered. Two opposing tangential and one anterior photon beam were used for chest wall and supraclavicular fossa radiotherapy, respectively (Table 3). Postmastectomy radiotherapy was started after the completion of adjuvant chemotherapy. When capecitabine was used as the adjuvant chemotherapeutic agent, the patient received postmastectomy radiotherapy concurrently (n=4).

4. Biomarkers

We reviewed the following histopathologic parameters: estrogen receptor status; progesterone receptor status; and the expression of c-erbB-2, p53, Ki-67, and COX-2. Baseline histopathologic parameters were evaluated by immunohistochemical analysis using pre-chemotherapy biopsy specimens (patients with preoperative systemic therapy) or surgical specimens (patients with postoperative systemic therapy). Immunohistochemical staining was performed using a BenchMark XT auto¬stainer (Ventana Medical Systems, Tucson, USA) and an i-View detection kit (Ventana Medical Systems) as previously described [17]. The positive cut-off values were immunohistochemical staining in ≥1% for hormone receptor [18], in >10% for p53, and a 3+ staining score for COX-2 and c-erbB-2. The nodal ratio was defined as the number of axillary lymph nodes with cancer involvement

divided by the total number of excised axillary lymph nodes. Lymph node status was evaluated by hematoxylin and eosin staining. Fluorescence *in situ* hybridization was performed for the analysis of HER2 gene amplification as reported previously [17].

5. Follow-up

The base follow-up duration was defined from the date when the first treatment was initiated. In cases of treatment failure, we analyzed the first site of relapse. Locoregional recurrence included recurrences in the ipsilateral chest wall or ipsilateral regional lymph nodes (axillary, supra/infraclavicular, and internal mammary). Relapses in the contralateral chest wall, axillary lymph nodes, supra/infraclavicular lymph nodes, internal mammary lymph nodes, cervical lymph nodes, or other organs were defined as distant metastases.

6. Statistics

Using the Kaplan-Meier method and the log-rank test, survival curves and differences between subgroups were estimated. For multivariate analysis, the Cox proportional hazards method was used. To compare proportions between subgroups, Pearson chi-square and Fisher exact test were used. SPSS version 18.0 (SPSS, Chicago, USA) was used for statistical analyses. A *p*-value less than 0.05 was deemed to be statistically significant.

Generally, a value above 10% to 20% of the Ki-67 index was defined

as a high level [12-14,16]. We compared survival curves using 3 hypothetical cut-off values, 10%, 15%, and 20% of the baseline Ki-67 index, and found that the latter gave the most significant differences.

The nodal ratio cut-off value used in previous studies varied from 0.15 to 0.25 [5,7-10]. We used 6 candidates for the cut-off value of the nodal ratio, ranging from 0.05 to 0.3 with intervals of 0.05. The maximal chi-square method in the R program version 2.13.0 (R Development Core Team, Vienna, Austria; available from http://www.R-project.org) was used to obtain the optimal cut-off value of the nodal ratio, which was 0.2.

RESULTS

A total of 61 patients with an advanced clinical T stage tumor (T3 and T4) or axillary lymph node involvement received preoperative systemic therapy. In these patients, 7 patients received additional chemotherapy because of adverse pathologic features such as advanced stage or negative hormone receptor status. The other 52 patients received postoperative systemic therapy. Chest wall and supraclavicular fossa irradiation was administered in 106 patients, and chest wall irradiation only in 7 patients. A total of 3 patients received a scar boost. The median number of excised axillary lymph nodes was 22 (range, 1-55) in the whole cohort and 23 (range, 1-55) and 21 (range, 5-50) in patients with postoperative and preoperative systemic therapy, respectively. The median nodal ratio was 0.19 (range, 0-1) in the whole cohort, including patients with pathologically noninvolved axillary lymph nodes (pN0), and 0.26 (range, 0.03-1.0) in patients with pathologically involved axillary lymph nodes (pN+). We used the nodal ratio of 0.2 as a cut-off value to classify patients into high and low nodal ratio groups.

1. Follow-up and failure analysis

The median follow-up duration was 72.3 months (range, 34.0-109.4 months) for surviving patients. In the entire cohort, the 5-year survival rates were 87.2%, 78.9%, 77.3%, and 85.3% for locoregional progression-free

survival (LRPFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS), respectively.

With respect to the type of initial disease relapse, locoregional recurrence occurred in 4 patients (preoperative systemic therapy, 4), distant metastasis in 14 patients (postoperative systemic therapy, 7; preoperative systemic therapy, 7), and both locoregional recurrence and distant metastasis in 10 patients (postoperative systemic therapy, 3; preoperative systemic therapy, 7). One of the patients with initial locoregional recurrence underwent resection and the other 3 underwent systemic therapy. Of those patients with initial locoregional recurrence and distant metastasis, 1 patient underwent resection and systemic therapy, 1 patient underwent chemotherapy and whole brain irradiation, and 6 patients were treated using systemic therapy only.

2. Univariate analysis

Univariate analysis revealed that patients with a nodal ratio of >0.2 had a significantly lower DMFS (p = 0.003), DFS (p = 0.006), and OS (p = 0.032) than those with a nodal ratio of ≤0.2. Patients with a baseline Ki-67 index of >20% had a significantly lower LRPFS (p = 0.032), DMFS (p = 0.013), DFS (p = 0.007), and OS (p = 0.030) than those with a baseline Ki-67 index of ≤20%. The baseline hormone receptor status was associated with LRPFS (p = 0.025) but not with DMFS (p = 0.379), DFS (p = 0.236), and OS (p = 0.253). The pathologic nodal stage (pN0-1 vs. pN2-3) was marginally

associated with DMFS (p = 0.064), DFS (p = 0.087), and OS (p = 0.084). These results are detailed in Table 4, Figures 2 and 3.

We also performed subgroup analysis for patients with postoperative and preoperative systemic therapy, separately. In the former, age (p = 0.010), nodal ratio (p = 0.030), venous invasion (p = 0.035), and the baseline Ki-67 index (p = 0.037) were associated with DFS, although only age (p = 0.048) was associated with OS. In patients with preoperative systemic therapy, cN stage (cN0-1 vs. cN2-3; p = 0.047), ypN stage (ypN0-1 vs. ypN2-3; p = 0.048) and nodal ratio (p = 0.028) were associated with DFS and cN stage (cN0-1 vs. cN2-3; p = 0.026), ypN stage (ypN0-1 vs. ypN2-3; p = 0.030), histologic grade (p < 0.001), baseline HER2 expression (p = 0.048), and baseline p53 expression (p = 0.026) were associated with OS (Table 5).

Table 4. Univariate analysis for entire patients

Variable		n	5-year LRPFS (%)	*p*	5-year DMFS (%)	*p*	5-year DFS (%)	*p*	5-year OS (%)	*p*
Age (years)	> 35	100	88.6	0.240	80.1	0.041	79.4	0.049	86.3	0.471
	≤ 35	13	76.2		69.2		61.5		76.9	
cT*	cT1-2	14	92.9	0.200	77.9	0.561	77.9	0.473	73.5	0.700
	cT3-4	47	78.2		72.9		69.2		86.2	
cN*	cN0	4	75.0	0.988	75.0	0.696	75.0	0.689	75.0	0.999
	cN1-3	57	82.3		74.4		67.1		81.8	
	cN0-1	35	87.6	0.152	82.3	0.102	82.3	0.047	94.3	0.026
	cN2-3	26	73.1		62.9		56.6		68.0	
pT	pT1-2	93	89.1	0.129	78.9	0.553	78.1	0.649	83.4	0.347
	pT3-4	20	78.9		78.9		73.8		95.0	
pN	pN0	24	87.5	0.914	87.5	0.198	87.5	0.156	95.7	0.105
	pN1-3	89	87.2		76.8		74.8		82.9	
	pN0-1	49	89.8	0.778	86.5	0.064	84.7	0.087	89.6	0.084

	pN2-3	64	85.3		73.2		71.7		82.0	
Nodal Ratio	≤ 0.2	59	89.8	0.644	89.2	0.003	87.9	0.006	89.7	0.032
	> 0.2	54	84.3		68.0		66.1		80.6	
ECE	Negative	64	83.9	0.432	80.0	0.334	77.0	0.423	87.4	0.324
	Positive	49	91.7		77.4		77.6		82.6	
Histologic Grade	I/II	66	95.3	0.001	81.4	0.211	81.4	0.118	88.5	0.145
	III	47	75.6		75.4		71.7		80.3	
Venous Invasion	Negative	98	86.4	0.500	80.8	0.076	78.9	0.097	87.4	0.066
	Positive	15	93.3		66.7		66.7		72.0	
Lymphatic Invasion	Negative	41	90.2	0.383	84.6	0.208	82.4	0.300	91.0	0.149
	Positive	72	85.4		75.8		74.6		82.0	
Baseline HR	Negative	46	77.9	0.025	75.3	0.379	71.5	0.236	78.9	0.253
	Positive	67	93.6		81.4		81.4		89.8	
Baseline c-erbB-2	0–2+	80	89.4	0.269	83.1	0.263	80.7	0.282	86.9	0.206
	3+	33	81.7		68.6		68.9		81.5	
Baseline HER2	Negative	85	90.1	0.099	84.1	0.069	81.8	0.071	87.6	0.050
	Positive	28	78.4		63.4		63.6		78.2	

Baseline p53	≤ 10%	83	92.5	0.008	81.5	0.148	79.1	0.171	86.5	0.431
	> 10%	30	72.2		71.3		72.2		82.5	
Baseline Ki-67	≤ 20%	72	92.6	0.032	85.8	0.013	85.8	0.007	92.4	0.030
	> 20%	41	77.7		67.1		62.8		73.5	

LRPFS = locoregional progression-free survival; DMFS = distant metastasis-free survival; DFS = disease-free survival; OS = overall survival; ECE = extracapsular extension; HR = hormone receptor.

* The patients with preoperative systemic therapy are included only.

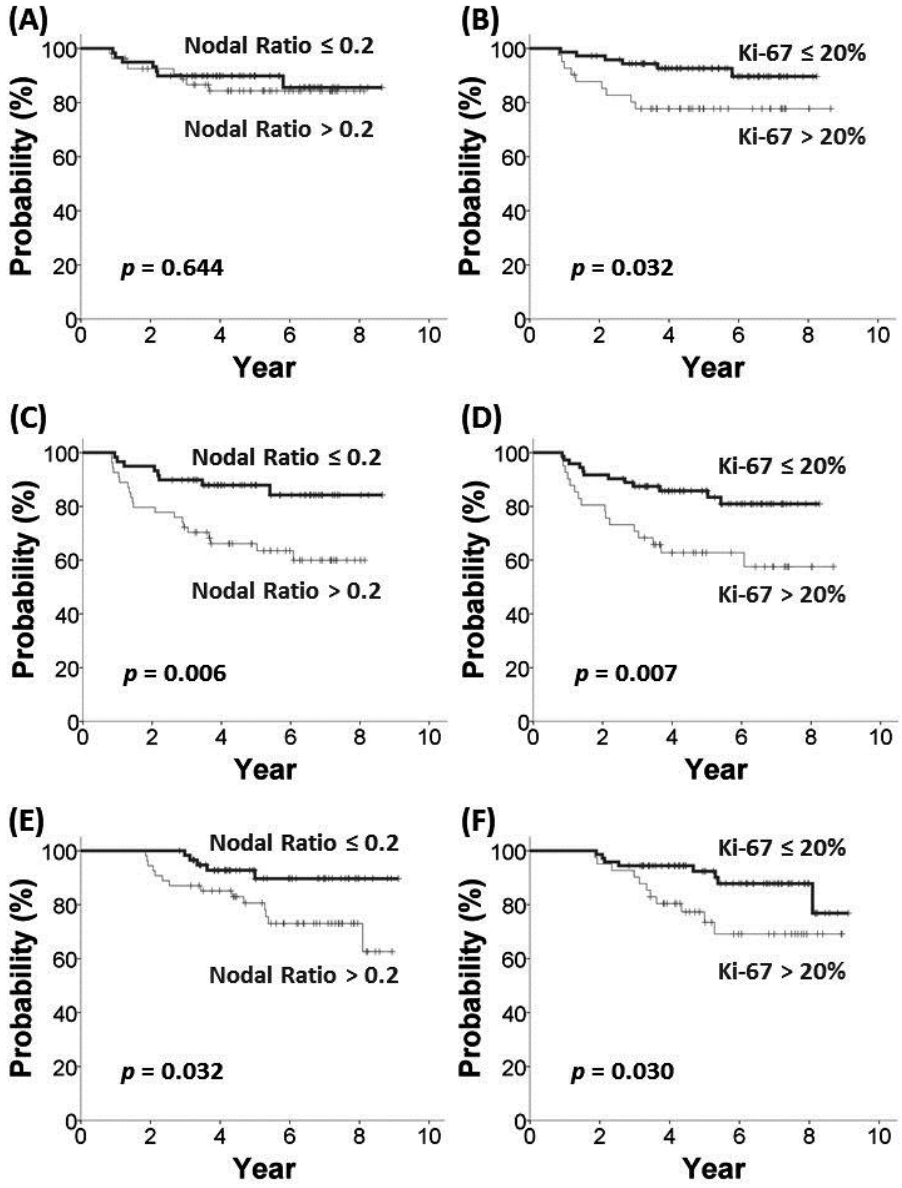


Figure 2. Survival curves in the patients with breast cancer having postmastectomy radiotherapy: locoregional progression-free survival according to the nodal ratio (A) and the baseline Ki-67 (B); disease-free survival according to the nodal ratio (C) and the baseline Ki-67 (D); overall survival according to the nodal ratio (E) and the baseline Ki-67 (F).

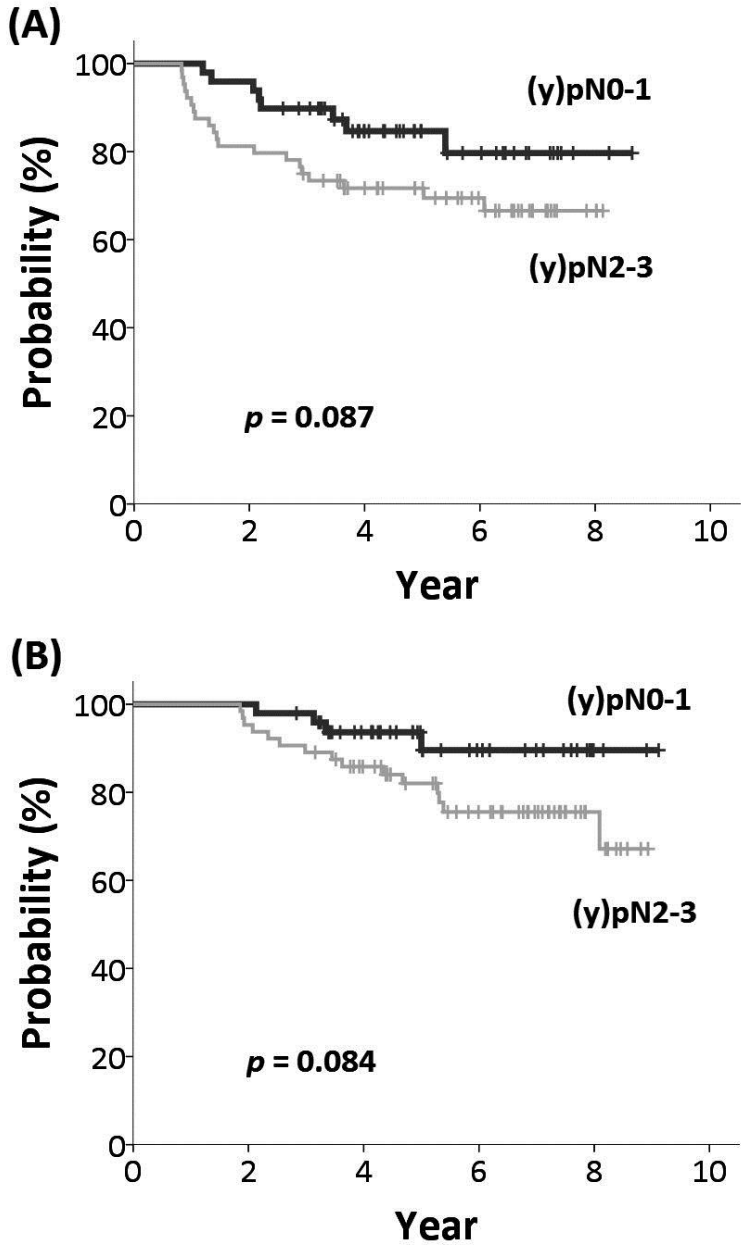


Figure 3. Survival curves in the patients with breast cancer having postmastectomy radiotherapy according to pathologic nodal stage: (A) disease-free survival, and (B) overall survival.

Table 5. Univariate analysis according to sequence of systemic therapy

Variable		Postoperative systemic therapy subgroup					Preoperative systemic therapy subgroup				
		n	5Y DFS (%)	*p*	5Y OS (%)	*p*	n	5Y DFS (%)	*p*	5Y OS (%)	*p*
Age (years)	> 35	47	87.0	0.010	90.4	0.048	53	72.5	0.617	82.4	0.651
	≤ 35	5	60.0		60.0		8	62.5		87.5	
cT*	cT1-2						14	77.9	0.473	73.5	0.700
	cT3-4						47	69.2		86.2	
cN*	cN0						4	75.0	0.689	75.0	0.999
	cN1-3						57	67.1		81.8	
	cN0-1						35	82.3	0.047	94.3	0.026
	cN2-3						26	56.6		68.0	
pT	pT1-2	44	84.0	0.583	87.7	0.720	49	73.0	0.382	79.4	0.372
	pT3-4	8	87.5		87.5		12	62.5		100	

pN	pN0	5	100	0.328	100	0.456	19	84.2	0.128	94.7	0.096
	pN1-3	47	82.9		86.4		42	65.5		78.3	
	pN0-1	15	93.3	0.247	93.3	0.578	34	81.6	0.048	89.1	0.030
	pN2-3	37	81.1		86.1		27	58.5		75.9	
Nodal Ratio	≤ 0.2	23	95.7	0.030	95.5	0.114	36	83.1	0.028	86.2	0.100
	> 0.2	29	75.9		82.2		25	53.7		78.7	
ECE	Negative	24	91.7	0.080	95.8	0.121	40	68.5	0.982	82.5	0.834
	Positive	28	78.6		80.9		21	76.2		85.7	
HG	I/II	31	77.2	0.117	85.3	0.309	30	73.0	0.978	92.6	<0.001
	III	21	95.2		90.5		31	69.5		64.2	
Venous Inv	Negative	43	88.1	0.035	89.1	0.156	55	71.9	0.634	85.8	0.161
	Positive	9	66.7		77.8		6	66.7		55.6	
Lymphatic Inv	Negative	15	93.3	0.621	100	0.386	26	76.7	0.225	86.5	0.169

	Positive	37	80.9		82.8		35	67.7		80.9	
Baseline HR	Negative	15	80.0	0.467	86.2	0.730	31	67.4	0.518	73.9	0.266
	Positive	37	86.3		87.6		30	75.6		92.5	
Baseline c-erbB-2	0–2+	39	84.3	0.693	85.6	0.902	41	77.3	0.128	87.9	0.070
	3+	12	84.6		92.3		20	58.5		74.3	
Baseline HER2	Negative	42	85.4	0.877	86.8	0.677	43	78.2	0.064	88.0	0.048
	Positive	10	80.0		90.0		18	55.0		71.8	
Baseline p53	≤ 10%	38	81.4	0.914	85.5	0.338	45	77.1	0.069	87.2	0.026
	> 10%	14	92.9		92.9		16	53.6		73.9	
Baseline Ki-67	≤ 20%	40	89.9	0.037	91.2	0.087	32	80.7	0.134	93.8	0.163
	> 20%	12	66.7		75.0		29	60.7		70.7	

Y = year; DFS = disease-free survival; OS = overall survival; ECE = extracapsular extension; HG = histologic grade; Inv = invasion; HR = hormone receptor.

3. Multivariate analysis

We performed multivariate analysis incorporating the nodal ratio, baseline Ki-67 index, age, histologic grade, and baseline p53 expression, all of which were found to be significantly associated with DFS or OS in univariate analysis of the entire cohort. A high nodal ratio was associated with poor DMFS (relative risk [RR], 4.063; 95% confidence interval [CI], 1.701-9.701; $p = 0.002$), DFS (RR, 3.589; 95% CI, 1.567-8.220; $p = 0.003$), and OS (RR, 3.444; 95% CI, 1.227-9.669; $p = 0.019$). A high baseline Ki-67 index was associated with poor DMFS (RR, 3.125; 95% CI, 1.450-6.731; $p = 0.004$), DFS (RR, 3.274; 95% CI, 1.536-6.979; $p = 0.002$), and OS (RR, 3.133; 95% CI, 1.249-7.856; $p = 0.015$). Results of the multivariate analysis are detailed in Table 6.

Table 6. Multivariate analysis

Variable	LRPFS	DMFS	DFS	OS
	p RR (95% CI)	*p* RR (95% CI)	*p* RR (95% CI)	*p* RR (95% CI)
Young Age (≤35 years)	-	-	-	-
Histologic Grade (III)	0.004 6.308 (1.778–22.373)	-	-	-
High Nodal Ratio (>0.2)	-	0.002 4.063 (1.701–9.701)	0.003 3.589 (1.567– 8.220)	0.019 3.444 (1.227– 9.669)
Baseline Ki67 (>20%)	-	0.004 3.125 (1.450–6.731)	0.002 3.274 (1.536– 6.979)	0.015 3.133 (1.249– 7.856)
Baseline Hormone Receptor (+)	-	-	-	-
Baseline p53 (>10%)	-	-		-

LRPFS = locoregional progression-free survival; DMFS = distant metastasis-free survival; DFS = disease-free survival; OS = overall survival; RR = relative risk; CI = confidence interval.

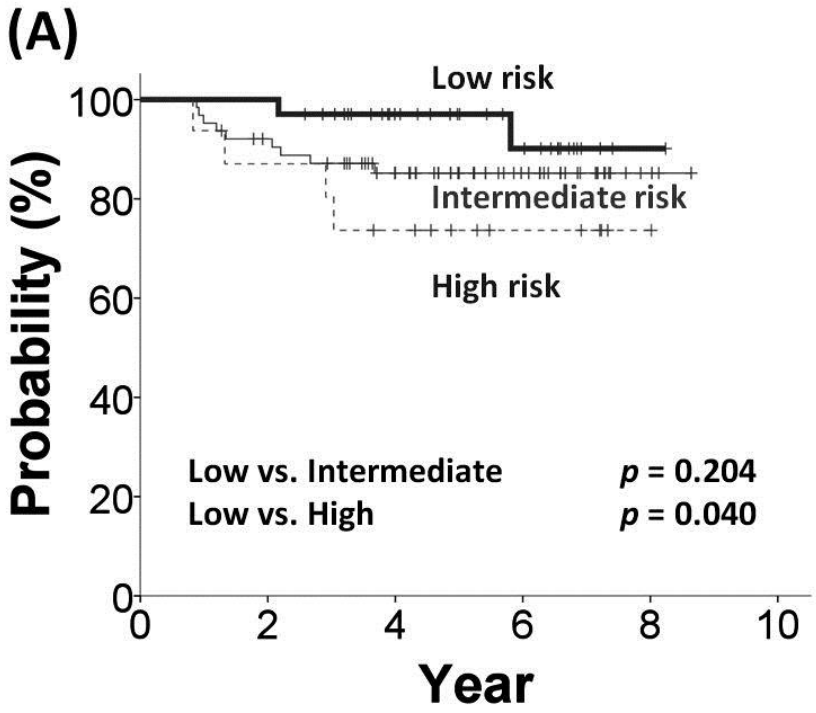
4. Prognostic model

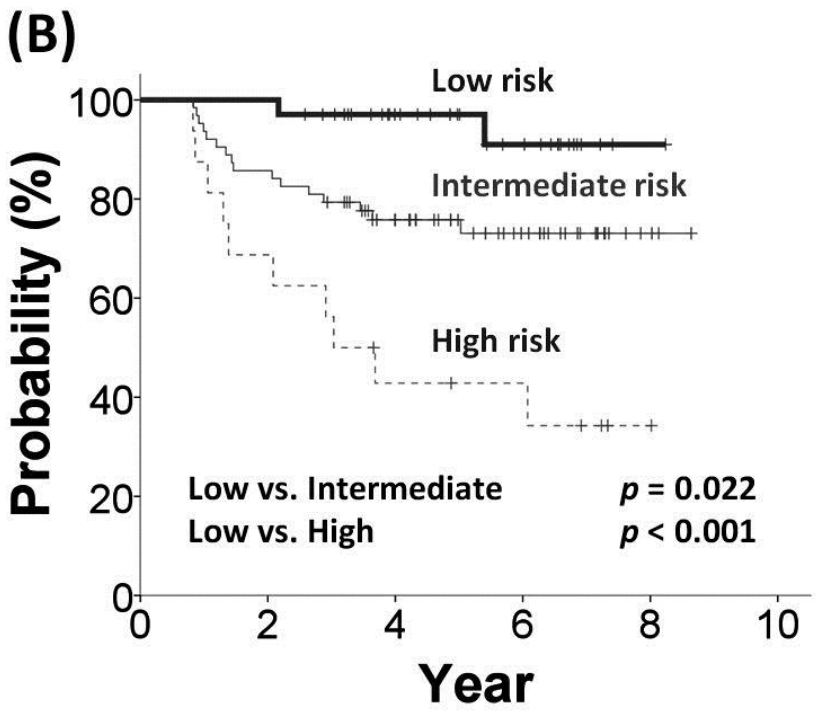
We devised a prognostic model using the nodal ratio and baseline Ki-67 index, with a score of zero points for a nodal ratio of ≤0.2 or a baseline Ki-67 index of ≤20% and 1 point for a nodal ratio of >0.2 or a baseline Ki-67 index of >20%. Patients were classified into 3 subgroups according to their total score: low risk (0 point, n=34), intermediate risk (1 point, n=63), and high risk (2 points, n=16). No deaths occurred in the low-risk group, whereas 13 patients in the intermediate-risk group and 6 patients in the high-risk group had died at the time of the last follow-up. When comparing the high- and low-risk patients, a significant difference was found in LRPFS ($p = 0.040$), DMFS ($p < 0.001$), DFS ($p < 0.001$), and OS ($p < 0.001$). A significant difference was also observed between the intermediate- and low-risk groups with respect to DMFS ($p = 0.031$), DFS ($p = 0.022$), and OS ($p = 0.008$), but not LRPFS ($p = 0.204$) (Figure 4).

We used the Cox proportional hazards method in order to evaluate the RR among the different risk groups. For LRPFS, the high- and intermediate-risk groups demonstrated RRs of 4.898 (95% CI, 0.897-26.753; $p = 0.067$) and 2.599 (95% CI, 0.562-12.032; $p = 0.222$), respectively, and for DMFS, the RRs of the high- and intermediate-risk groups were 14.110 (95% CI, 3.089-64.448; $p = 0.001$) and 4.400 (95% CI, 1.006-19.241; $p = 0.049$), respectively. With respect to DFS, the high- and intermediate-risk patients showed RRs of 14.264 (95% CI, 3.122-65.165; $p = 0.001$) and 4.785 (95% CI, 1.100-20.814; $p = 0.037$), respectively.

We applied this prognostic model to patients with postoperative and preoperative systemic therapy. There was a significant difference in DMFS (p = 0.016 and p < 0.001) and DFS (p = 0.016 and p < 0.001) in patients with postoperative and preoperative systemic therapy, respectively. There was no significant difference in the LRPFS (p = 0.364 and p = 0.224) in patients with postoperative and preoperative systemic therapy, respectively. There was a significant difference with respect to OS in patients with preoperative systemic therapy (p = 0.045) but not with postoperative systemic therapy (p = 0.074).

We classified patients into three intrinsic subtypes: luminal A (hormone receptor positive and HER2 negative; n=55), luminal B (hormone receptor positive and HER2 positive; n=12), HER2 overexpression (hormone receptor negative and HER2 positive; n=16), and basal-like (hormone receptor negative and HER2 negative; n=30). There was no significant difference in DFS (p = 0.249) and OS (p = 0.202) according to intrinsic subtypes. When our prognostic model was applied to intrinsic subtypes, HER2 overexpression and basal-like subtypes showed significantly different DFS (p = 0.034 and p = 0.027, respectively) among the risk groups, and luminal A subtype had a marginally different DFS (p = 0.078) among the risk groups. Only HER2 overexpression subtype had a significantly different OS (p = 0.046), while other subtypes did not, among the risk groups (Table 7).


(A)
Low risk
Intermediate risk
High risk
Probability (%)
100
80
60
40
20
0
0
2
4
6
8
10
Year
Low vs. Intermediate
p = 0.204
Low vs. High
p = 0.040


(B)
Low risk
Intermediate risk
High risk
Probability (%)
100
80
60
40
20
0
0
2
4
6
8
10
Year
Low vs. Intermediate
p = 0.022
Low vs. High
p < 0.001

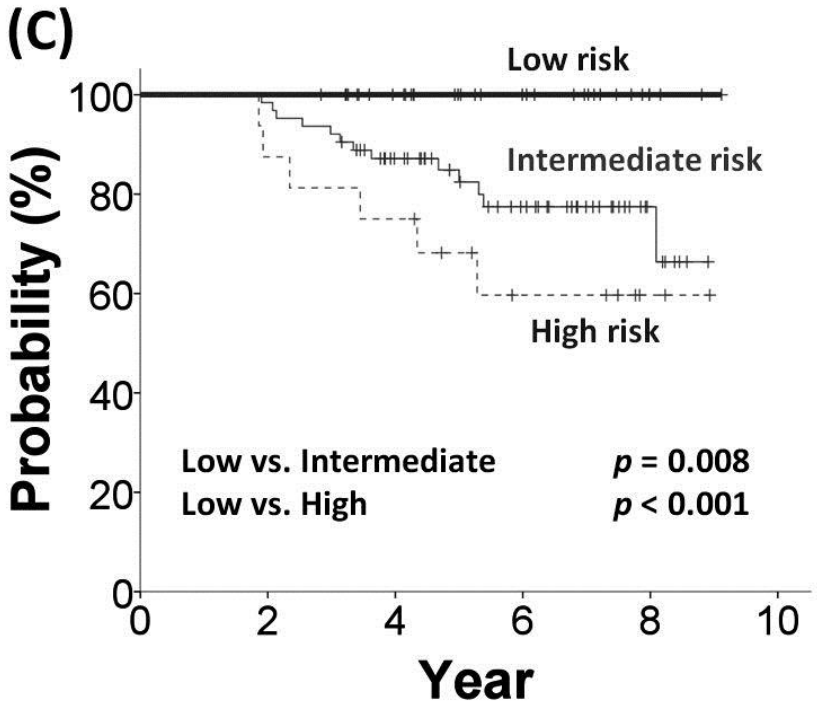


Figure 4. Survival curves in the patients with breast cancer having postmastectomy radiotherapy according to the risk group: (A) locoregional progression-free survival, (B) disease-free survival, and (C) overall survival.

Table 7. Comparisons among the intrinsic subtypes of breast cancer

Variable	n	5Y DFS (%)	*p*	5Y OS (%)	*p*
Luminal A	55	85.0	0.249	91.1	0.202
Low-risk	21	100	0.078	100	0.173
Intermediate-risk	29	78.6		88.2	
High-risk	5	60.0		75.0	
Luminal B	12	65.6		83.3	
Low-risk	3	100	0.355	100	0.434
Intermediate-risk	8	62.5		75.0	
High-risk	1	0.0		100	
HER2 overexpression	16	62.5		73.9	
Low-risk	5	80.0	0.034	100	0.046
Intermediate-risk	9	66.7		66.7	
High-risk	2	0.0		50.0	
Basal-like	30	76.4		81.9	
Low-risk	5	100	0.027	100	0.152
Intermediate-risk	17	81.9		83.7	
High-risk	8	50.0		62.5	

Y = year; DFS = disease-free survival; OS = overall survival.

DISCUSSION

Several large, randomized studies have shown that postmastectomy radiotherapy improves locoregional control and survival in breast cancer patients, particularly those with more than 3 involved axillary lymph nodes [1-3]. To date though, the role of postmastectomy radiotherapy in breast cancer patients with fewer than 4 metastatic axillary lymph nodes has not been evaluated. Overgaard et al. [19] conducted a reanalysis of Danish trials and found that postmastectomy radiotherapy benefited patients with 1 to 3 positive axillary lymph nodes. Recently, the number of excised axillary lymph nodes was shown to be as important as the number of involved axillary lymph nodes, suggesting that the nodal ratio is an important prognostic factor [5-10]. In a study by the Surveillance, Epidemiology and End Results program, the nodal ratio was found to be better at predicting disease-specific survival than the number of involved axillary lymph nodes [7]. Truong et al. [8] reported that a nodal ratio of 0.25 was associated with a poor prognosis with respect to locoregional recurrence, distant metastasis, and OS in patients with 1 to 3 involved axillary lymph nodes. Ahn et al. [10] analyzed a nationwide registry of pN+ patients and concluded that the nodal ratio was a better prognostic factor than pN stage, particularly in patients with high-risk factors such as young age, a HER2/*neu*-enriched tumor, or a triple-negative tumor.

In the study we report here, the pN stage showed only a borderline association with recurrence or survival in univariate analysis. A possible reason for this finding may be the heterogeneity in the sequence of systemic

therapy. After preoperative systemic therapy, more patients could have a lower N stage as a result of chemotherapy. This finding might also be explained by the relatively small size and short follow-up period of our study. As shown in Figure 2, the DFS and OS curves differed between patients with pN0-1 and pN2-3, and it is possible that with a greater number of patients and a longer follow-up period, a statistically significant relationship might be found between survival and pN stage.

Although this study included patients with different pN stages, the nodal ratio (cut-off value of 0.2) was associated with a high risk of metastasis and short survival in locally advanced breast cancer patients. Because the nodal ratio reflects the absolute number of excised axillary lymph nodes, it might have a higher prognostic value than pN stage [20]. In the current cancer staging system [4], the usefulness of the absolute number of involved nodes for predicting disease burden in the axilla is confounded by the number of nodes removed [21]. When additional axillary lymph nodes are excised, less residual occult disease may be expected. In Canada, axillary lymph node dissection, including all level I and II axillary lymph nodes, is recommended for accurate staging and reducing the risk of recurrence in the axilla [22].

Although several studies have reported a possible prognostic role for the nodal ratio in locoregional control [8,23,24], we could not establish a relationship between the nodal ratio and locoregional control in this study. This may have been because of the relatively short follow-up duration (approximately 6 years). Improved locoregional control as a result of regional radiotherapy [25,26] might also account for the lack of any significant

difference in LRPFS between the high nodal ratio and low nodal ratio patient groups. We suggest therefore that a randomized controlled study focusing specifically on the prognostic role of nodal ratio be conducted.

In addition to the nodal ratio, biomolecular markers might also have prognostic value for locally advanced breast cancer patients. It is generally accepted that biomolecular markers of cell proliferation, such as the baseline Ki-67 index used in our study, are associated with the response to systemic therapy [27]. Our study showed that a high baseline Ki-67 index was associated with a high risk of mortality. Furthermore, a relationship between a high Ki-67 index and other indicators of a poor prognosis has been previously reported [28]. This negative relationship would explain the prognostic value of Ki-67 index. In the present study, a Ki-67 index in excess of 20% was associated with baseline negative hormone receptor expression ($p < 0.001$).

Consistent with our findings, the Ki-67 index has been shown to be a possible prognostic marker in several other studies. Cheang et al. [12] classified invasive breast cancer into luminal A, luminal B, and HER2-positive intrinsic subtypes on the basis of hormone receptor status, HER2 status, and the Ki-67 index, as determined using immunohistochemical analysis. The Ki-67 index was used to distinguish luminal B from luminal A, using a cut-value of 14%. The luminal B and luminal HER2 subtypes were found to have a poor prognosis with respect to breast cancer recurrence-free and disease-specific survival. The 10-year breast cancer-specific survival rates were 92%, 79%, and 78% in luminal A, luminal B, and HER2 positive cancer, respectively ($p < 0.001$). In a meta-analysis study of early breast cancer, Ki-

67 positivity (cut-off points were defined by the authors of the studies being included) was associated with increased relapse (RR, 1.93; 95% CI, 1.74-2.14; $p < 0.001$) and shorter survival (RR, 1.95; 95% CI, 1.70-2.24; $p < 0.001$) in all patients. The authors of that study suggested that Ki-67 positivity was a prognostic marker in patients with early breast cancer [14].

Despite these studies, in general, the association between specific biomolecular markers and locoregional control remains unclear. Two previous studies found that the Ki-67 index was a possible prognostic factor of locoregional control [13,16]. Voduc et al. [13] defined the luminal B subtype as being hormone receptor positive and HER2 negative and having a Ki-67 index of ≥14% in patients who had undergone mastectomy. The luminal B subgroup was associated with a high risk of local and regional recurrences. Selz et al. [16] reported that a Ki-67 index of >20% was prognostic for LRPFS (RR, 4.18; 95% CI, 1.11-15.77; $p = 0.0215$) in breast cancer patients with pN0 after modified radical mastectomy.

In addition to HER2 status, the Ki-67 index, representing tumor aggressiveness, may also be a means of identifying high-risk groups among breast cancer patients. However, controversy still exists regarding the optimal cut-off point for Ki-67; a level of Ki-67 above 10% to 20% has been suggested to define a high-risk group in several studies [12-14,16]. In our study, the baseline Ki-67 index was used to determine the risk groups, using a cut-off point of 20%. The 2011 St. Gallen Consensus [11] recommended a Ki-67 labeling index of 14% as the cut-off point to classify the intrinsic subtype

of breast cancer; however, these guidelines have not been clarified. It therefore remains necessary to develop a standardized approach to using the Ki-67 index, including a single cut-off value and a reproducible way of determining the index.

Here, we propose a prognostic model using 2 parameters, the nodal ratio and baseline Ki-67 index, both of which are significantly associated with disease relapse, reflecting the probability of residual tumor on a macroscopic scale and the possibility of disease relapse on a microscopic scale, respectively. Our prognostic model is simple to apply and can identify the poor prognostic group amongst a heterogeneous population with disparate pN stages or sequences of systemic therapy. Using our prognostic model, patients with a high risk of disease relapse can be identified, and intensified adjuvant treatment can be considered to improve their survival. With respect to locoregional control, however, the high-risk group tended to have a worse prognosis than the low-risk group ($p = 0.067$), and the intermediate-risk group showed no association. We expect that this prognostic model would be more useful to identify the high-risk group among locally advanced breast cancer patients with an increased long-term follow-up period.

Our study has several limitations. The patients needed to be analyzed independently according to the use of preoperative systemic therapy because the nodal ratio has a prognostic value in patients with preoperative systemic therapy [6]. However, subgroup multivariate analysis was not performed because of an insufficient number of patients. In addition, the relatively short follow-up duration was a hindrance to comparing OS. These limitations may

have made it more difficult to identify a relationship between treatment outcomes and well-known prognostic factors, such as T/N stage and hormone receptor status. Furthermore, the study included patients with a range of different N stages and 21% of patients had pN0 tumors, whereas the other studies on the prognostic value of nodal ratio discussed here only involved node-positive patients. Therefore, a further study is needed with a more homogenous patient group with respect to the sequence of systemic therapy and pN stage. Additionally, for a more precise prognostic model, the change in biomarker status before and after preoperative systemic therapy [15,29] should be considered.

In conclusion, we found that the nodal ratio and baseline Ki-67 index were potential prognostic markers in locally advanced breast cancer patients who underwent postmastectomy radiotherapy. Our prognostic model, using these 2 factors, might be able to identify patients at high risk of disease relapse. Improved prognostic models will help to individualize treatment regimens for breast cancer patients.

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국문 초록

서론: 본 연구의 목적은 유방절제술 후 방사선치료를 시행 받은 유방암환자의 예후에 영향을 미치는 인자를 찾고자 함이며, 이를 기반으로 하여 유방암의 재발 및 사망의 위험도가 높은 환자군을 찾고자 하였다.

방법: 2003년부터 2009년까지 분당서울대학교병원에서 유방절제술 후 방사선치료를 받은 유방암환자 113 명을 대상으로 하였다. 이 중 61명의 환자는 수술 전 항암화학요법을 시행 받았고, 52명의 환자는 수술 후 항암화학요법을 시행 받았다. 수술 전 항암화학요법으로는 6차에 걸친 docetaxel, doxorubicin 병용요법이 가장 많이 사용되었으며, 수술 후 항암화학요법으로는 4차에 걸친 doxorubicin, cyclophosphamide, paclitaxel 병용요법이 가장 많이 사용되었다. 호르몬 수용체 양성인 경우 호르몬 치료가 시행되었으며, c-erbB-2 과발현(3+)이나 HER2 유전자 증폭이 있는 경우 trastuzumab이 추천되었다. 방사선치료는 흉벽 및 빗장위림프절에 대하여 시행되었으며 50.4 Gy를 28회에 걸쳐 조사하였다. 면역조직화학염색법을 이용하여 호르몬 수용체 양성 여부와 c-erbB-2, p53, Ki-67, COX-2 유전자의 발현 여부를 분석하였다. 양성 판정 기준은 면역조직화학염색 상 호르몬 수용체의 경우 1% 이상, p53의 경우 10% 초과, Ki-67의 경우 20% 초과, COX-2와 c-erbB-2의 경우 3+이었다. HER2 유전자 증폭 여부는 형광제자리부합법을 이용하여 확인하였다. 림프절 전이 여부는 헤마톡실린과 에오신 염색으로 확인하였고, 림프절 전이비율은 전이된 림프절 개수를 절제된 림프절 개수로 나누어

구하였다. 림프절 전이비율의 절단값은 R 프로그램(2.13.0 버전)의 maximal chi-square method를 이용하여 생존율 차이가 가장 크게 나타나는 0.2로 정하였다.

결과: 연구 기간 동안 생존한 환자들의 중앙 추적관찰 기간은 72.3개월(범위, 34.0-109.4개월)이었다. 전체 환자에 대한 단변량 분석에서 무병생존기간은 연령, 림프절 전이비율, Ki-67 발현과 연관성이 있었으며, 전체생존기간은 림프절 전이비율, Ki-67 발현과 연관성이 있었다. pN stage 및 HER2 발현 여부는 무병생존기간 및 전체생존기간에 대하여 통계학적으로 미약한 연관성을 보였다. 수술 후 항암화학요법을 시행 받은 환자에서 무병생존기간은 연령, 림프절 전이비율, 정맥침범, Ki-67 발현과 연관성이 있었고, 전체생존기간은 연령과 연관성이 있었다. 수술 전 항암화학요법을 시행 받은 환자에서 무병생존기간은 ypN stage와 림프절 전이비율이 연관성이 있었고, 전체생존기간은 ypN stage, 조직학적 분화도, HER2, p53 발현과 연관성이 있었다. 전체 환자에 대한 다변량분석에서 무병생존기간과 전체생존율은 각각 림프절 전이비율(p = 0.003, p = 0.019), Ki-67 발현(p = 0.002, p = 0.015)과 통계학적 유의성을 보였다. 림프절 전이비율과 Ki-67 발현을 조합한 예후 모델을 이용하여 저위험도(림프절 전이비율 0.2 이하, 그리고 Ki-67 발현 20% 이하), 중간위험도(림프절 전이비율 0.2 초과, 혹은 Ki-67 발현 20% 초과), 고위험도(림프절 전이비율 0.2 초과, 그리고 Ki-67 발현 20% 초과) 환자군으로 나누었다. 저위험도 환자군은 고위험도 및 중간위험도 환자군에 비해 긴 무병생존기간(p < 0.001, p = 0.022)과 전체생존기간(p = 0.001, p = 0.008)을 보였다. 예후 모델을 수술 전 항암화학요법을 시행 받은 환자와 수술 후 항암화학요법을 시행 받은 환자에 적용했을 때 무병생존기간에서

통계학적 유의성을 보였다(p = 0.001, p = 0.016). 전체 환자를 세 분류의 intrinsic subtype으로 나눌 수 있었다. 55명의 환자는 호르몬 수용체 양성이며 HER2 음성인 luminal A, 12명의 환자는 호르몬 수용체 양성이며 HER2 양성인 luminal B, 16명의 환자는 호르몬 수용체 음성이며 HER2 양성인 HER2 overexpression, 30명의 환자는 호르몬 수용체 음성이며 HER2 음성인 basal-like이었다. Intrinsic subtype에 따른 무병생존율(p = 0.249) 및 전체생존율(p = 0.202)의 차이는 없었다. 예후 모델을 luminal A 환자들에 적용하였을 때 위험도에 따라 무병생존율(p = 0.078)은 차이가 나는 경향성을 보였으나 전체생존율(p = 0.173)은 통계학적으로 유의한 차이를 보이지 않았다.

결론: 유방절제술 후 방사선치료를 받은 유방암환자에서 림프절 전이비율과 Ki-67 발현은 유용한 예후 인자임이 확인되었다. 두 인자를 조합한 모델은 유방절제술 후 방사선치료를 받은 유방암 환자의 위험집단을 나누는데 사용할 수 있겠다.

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주요어: 림프절, 방사선치료, 유방암, 유방절제술, ki-67

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