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ORIGINAL ARTICLE

The lymph node ratio as an independent prognostic factor for non-metastatic node-positive breast cancer recurrence and mortality

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Summary

Purpose: *To examine the prognostic value of lymph node ratio (LNR) in pathological nodal (pN) stage breast cancer patients. Also, to analyse additional clinical and pathologic prognostic factors and the impact of LNR among molecular subtypes.*

Methods: *Among a total of 3088 patients, 1004 women with non-metastatic lymph node-positive breast cancer were analysed. The patients were classified into low (≤0.20), intermediate (0.20 to 0.65) and high-risk (>0.65) LNR groups. Univariate and multivariate Cox proportional hazards regression model for disease-free survival (DFS), and overall survival (OS) were performed to evaluate the prognostic value of LNR.*

Results: *The median LNR was 0.17 (range 0.02-1.00). Of the patients, 55.7% were in low, 32.1% in intermediate, and 12.3% in high risk group. When compared with low risk group, high risk group had more often large tumor size and high grade tumor with lymphovascular invasion. The median follow-up period was 46.8 months. The 5-year breast cancer-specific OS and DFS rates for patients with low, intermediate, and high were 88%-67%, 65%-48% and 53%-24%, respectively (both $p_{log\text{-}rank} < 0.0001$). On multivariate analysis, pN stage and LNR were both independent predictors of survival, however, an overlapping between N1 (250 months, 95% confidence interval [CI] 88.15-413.21) and N2 (176 months, 95% CI 129.51-222.93) curves in pN staging was determined. We also observed clear prognostic separation for triple negative breast cancer with LNR survival over pN staging.*

Conclusion: *The LNR predicts survival more accurately than pN staging in node-positive breast cancer patients. The use of LNR may standardize the staging and guide decisions for adjuvant treatments.*

Key words: *breast cancer, lymph node ratio, non-metastatic, prognosis*

Introduction

Breast cancer is the most common cancer among women, with more than one million new cases occurring worldwide annually and the second most common cause of cancer mortality, accounting for 16% of cancer deaths in adult women [1]. Despite the advents in sentinel node biopsy techniques, genetic or molecular staging of breast cancer, the status of the axillary lymph nodes still remains one of the most important predictors of survival. The type of adjuvant systemic therapy and the decision for postmastectomy radiotherapy depend on axillary nodal involvement [2,3].

According to the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) staging system, breast cancer patients have been classified as pN0: node-negative, pN1: 1 to 3 positive nodes, pN2: 4 to 9 positive nodes and pN3: ≥ 10 positive nodes [4]. The involvement

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of more than 3 axillary lymph nodes is associated with a 13-24% locoregional recurrence rate [5]. The staging system grouping patients by the absolute number of axillary lymph nodes improved stratification in breast cancer-specific survival, however, in clinical practice, this process could be limited by such factors as case variances, pathological identification, surgical technique and experience [4,6]. Variation in these factors may result in a wide range of total number of lymph nodes dissected and identified among institutions, thereby influencing staging [6-8].

In recent years, the LNR defined as the absolute number of involved nodes divided by the number of lymph nodes examined, helps against this discrepancy [9-11]. Increasing evidence suggests that LNR is a superior prognostic indicator compared with the absolute number of involved nodes [6-14]. A systematic review of 32,299 patients reported that the LNR was superior to the number of involved nodes as a prognostic factor [10]. Vinh-Hung et al. conducted a population-based study and stratified the patients into those at low risk (0 to 0.20), moderate risk (0.2 to 0.65) and high risk (0.65 to 1). The survival rates of LNR groups were more accurate than pN staging [11]. Several other studies have supported that LNR is an alternative or an independent predictor of outcome in node-positive breast cancer patients [10-14]. On the other hand, some studies found a better prediction of LNR only in subgroups [9,15,16].

Despite the large number of studies that have addressed LNR, only few of them evaluated the additional clinico-pathological factors influencing survival such as age at diagnosis, tumor size, grade, hormone receptors status, HER-2 overexpression, lymphovascular invasion and treatment strategies [7-11].

The purpose of our study was to evaluate the prognostic value of LNR compared with pN stage in women with non-metastatic, lymph node-positive breast cancer. To overcome the variations, we only included patients treated by the same multidisciplinary team and, in order to address many of the shortcomings in the previous trials, we analysed additional clinical and pathologic prognostic factors as well. Moreover in the present study we analysed the prognostic effect of LNR among molecular subtypes.

Methods

Study population

A total of 3088 breast cancer patients who were treated and followed up in the Department of Medical Oncology, Hacettepe University, Institute of Oncology from January 2000 to June 2013 were retrospectively reviewed. Patients who received neoadjuvant chemotherapy (N=256), patients with absolute number of dissected lymph nodes less than 10 (N=104), patients with pathologically node negative (pN0) disease (N=1297), patients with missing information about the exact number of lymph nodes involved (N=178), and stage IV disease (N=249) were excluded.

The final number available was 1004 patients, representing the study population. All patients were subjected to breast-conserving surgery or mastectomy with axillary lymph node dissection. The tumor was completely dissected and surgical margins were negative in the whole study group. After surgery, all patients were administered adjuvant chemotherapy and/or radiotherapy and/or endocrine therapy according to NCCN guidelines [17].

Data collection

The sociodemographic data, clinicopathological factors and treatment modalities including types of surgery, adjuvant chemotherapy, radiotherapy, and hormone therapy were obtained from the medical records of each patient. Adjuvant treatments considered were radiotherapy (yes/no), chemotherapy (yes/no), and hormone therapy (yes/no).

Tumor characteristics included histopathology, tumor size (0- <2 cm, 2-5 cm, ≥5 cm, unknown), estrogen receptor (ER) and progesterone receptor (PR) status (positive, negative and unknown), HER-2 status (positive, negative and unknown), grade (good, moderate, poor, unknown) as well as presence of lymphovascular and perineural invasion (LVI, PNI). All this information was registered from the relevant diagnostic pathology reports.

ER and PR status was assessed by immunohistochemistry. Nuclear staining in at least 1% of tumor cells was considered as positive. Expression of HER-2 was also determined immunohistochemically. HER-2 positivity (a score of 3+) was defined as strong complete membrane staining in more than 10% of tumor cells; scores of 0 and 1 were considered negative, and fluorescence *in situ* hybridization was done for all 2+ tumors. Finally, tumor subtypes were classified as luminal A (ER positive and/or PR positive / HER-2 negative), luminal B (ER positive and/or PR positive / HER-2 positive), HER-2 overexpressing (ER negative / PR negative / HER-2 positive) and triple negative (ER negative / PR negative / HER-2 negative) [18].

The pN stages were determined as N1: metastasis to 1-3 lymph nodes; N2: metastasis to 4-9 lymph nodes; N3: metastasis to ≥10 lymph nodes [4]. The LNR was defined as the ratio of metastatic lymph nodes to the total of lymph nodes excised. The LNR groups were classified as low risk (0-0.20), intermediate risk (>0.20-0.65)

and high risk (>0.65-1.00), using the values determined in the study of Vinh-Hung et al. [11].

The primary endpoint of the study was DFS, which was defined as the interval from the date of diagnosis to the date of locoregional or distant recurrence. If recurrence was not evident, patients were censored on the last follow-up. The secondary endpoint was OS which was considered from the date of diagnosis to the date of breast cancer death. Data on mortality were obtained from the hospitals' medical records and the respective death registries.

Statistics

Pearson's x^2 test for frequencies and analysis of variance (ANOVA) for means were used to compare clinicopathological parameters among groups. Kaplan-Meier analysis with log-rank test was used to determine cumulative survival curves. Univariate and multivariate Cox proportional hazards regression model with 95% CI for DFS and OS were performed to evaluate the prognostic value of LNR, adjusting for covariates, such as age, tumor size, hormone receptor status, HER-2 overexpression and treatment modalities. To select those factors with independent significant influence on outcomes, multivariate analyses were carried out in a stepwise Cox regression. Prior to this application, univariate analyses were performed for a preliminary exploration of marked associations.

Statistical analyses were performed using SPSS 15.0 software (SPSS Inc., Chicago, Ill). All statistical assessments were two-sided and a p value of <0.05 was cosidered as statistically significant.

Results

The median patient age was 47.8 years (range 20-83). The median number of involved nodes was 3 (range 1-63), and the median number of dissected nodes was 21 (range 10-77). The median LNR was 0.17 (range 0.02-1.00). Of the 1004 patients in our cohort, 55.6% were in the low, 32.1% in the intermediate, and 12.3% in the high LNR group, respectively. Baseline characteristics of the study population is summarized in Table 1.

The clinicopathological characteristics of the LNR groups are given in Table 2. When compared with low risk group, high risk group more often had large tumor size (38.6 vs 14.0%; p< 0.0001) and high grade tumor (48.7 vs 41.3%; p=0.026) with LVI (61.0 vs 32.9%; p< 0.0001). There was no difference between LNR groups regarding age, menopausal status, histopathology, ER and PR. The percentage of patients with HER-2 overexpressing breast cancer (18.5 vs 7.2%; p<0.0001) was higher and the percentage of patients with triple negative breast cancer was lower (5.9 vs

Table 1. Characteristics of patients with node-positive breast cancer

Patient and tumor characteristics	*No. of patients*	*%*
Age at diagnosis (years)		
< 50	560	55.8
≥ 50	444	44.2
Menopausal status		
Premenopausal	561	55.9
Postmenopausal	432	43.0
Unknown	11	1.1
Histopathology		
Invasive ductal	766	76.3
Invasive lobular	47	4.7
Mixed	85	8.5
Others	106	10.5
Tumor size		
T1	246	24.5
T2	536	53.4
T3	196	19.5
Unknown	26	2.6
Lymph node involvement		
pN1	514	51.2
pN2	270	26.9
pN3	220	21.9
LNR classification		
Low risk (≤0.20)	559	55.6
Intermediate risk (0.20 to ≤0.65)	322	32.1
High risk (>0.65)	123	12.3
Grade		
I-II	503	50.1
III	416	41.4
Unknown	85	8.5
Lymphovascular invasion		
Yes	426	42.4
No	557	55.5
Unknown	21	2.1
Perineural invasion		
Yes	204	20.3
No	779	77.6
Unknown	21	2.1
Estrogen receptor		
Positive	715	71.2
Negative	266	26.5
Unknown	23	2.3
Progesterone receptor		
Positive	697	69.4
Negative	278	27.7
Unknown	29	2.9

Continued on next page

HER-2 overexpression		
Positive	250	24.9
Negative	700	69.7
Unknown	54	5.4
Subtypes of breast cancer		
Luminal	778	77.5
HER-2 overexpressing	96	9.6
Triple negative	108	10.8
Unknown	22	2.2
Surgery		
BCS	199	19.8
MRM	805	80.2
Adjuvant treatment		
Chemotherapy		
Yes	940	93.6
No	51	5.1
Unknown	13	1.3
Radiotherapy		
Yes	897	89.3
No	106	10.6
Unknown	1	0.1
Hormone therapy		
Yes	762	75.9
No	234	23.3
Unknown	8	0.8

LNR: lymph node ratio, BCS: breast conserving surgery, MRM: modified radical mastectomy

12.8%; p=0.001) among patients in the group of LNR >0.65 compared to low risk patients. Overall, the patients receiving adjuvant chemotherapy and adjuvant radiotherapy were significantly less in the group of LNR ≤ 0.20 than in the high risk group.

The median follow-up period after diagnosis was 46.8 months (range 3-377). Of 1004 patients 155 (15.4%) died and 274 (27.3%) had a breast cancer recurrence. The 5-year breast cancer-specific OS rates for patients with low-risk, intermediate-risk, and high-risk LNR were 88, 65, and 53%, respectively ($p_{log\text{-}rank}$ < 0.0001). On the other hand, the 5-year breast cancer-specific OS rates according to pN groups were 86% in pN1, 81% in pN2, and 51% in pN3, respectively ($p_{log\text{-}rank}$ < 0.0001) (Figures 1 and 2). The 5-year DFS rates were 67% in the low-risk, 48% in the intermediate-risk, and 24% in the high risk LNR group ($p_{log\text{-}rank}$ < 0.0001). The 5-year DFS rates for patients with pN1, pN2, and pN3 disease were 67, 55, and 32%, respectively ($p_{log\text{-}rank}$ < 0.0001) (Figures 3 and 4).

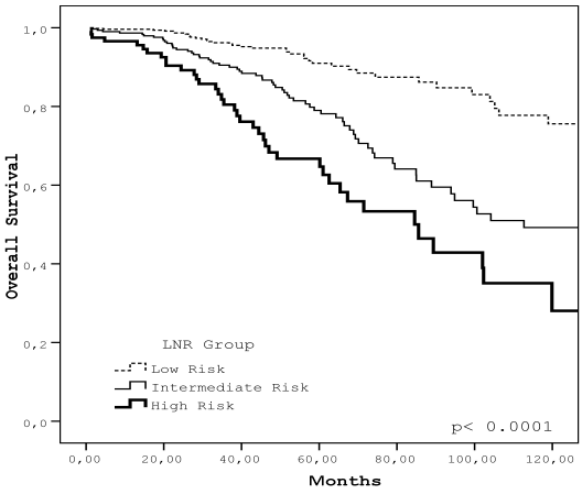

Figure 1. Overall survival according to LNR risk groups.

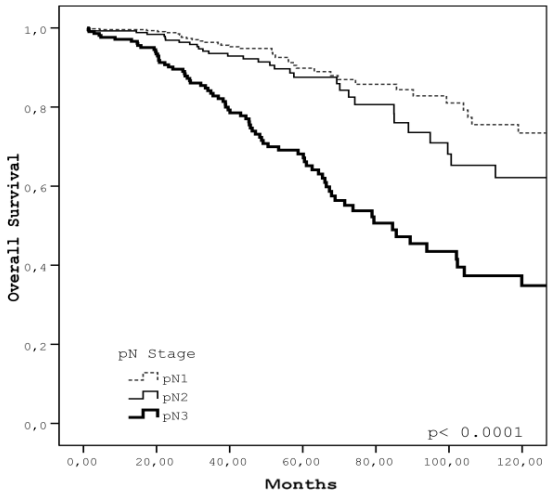

Figure 2. Overall survival according to pN stage.

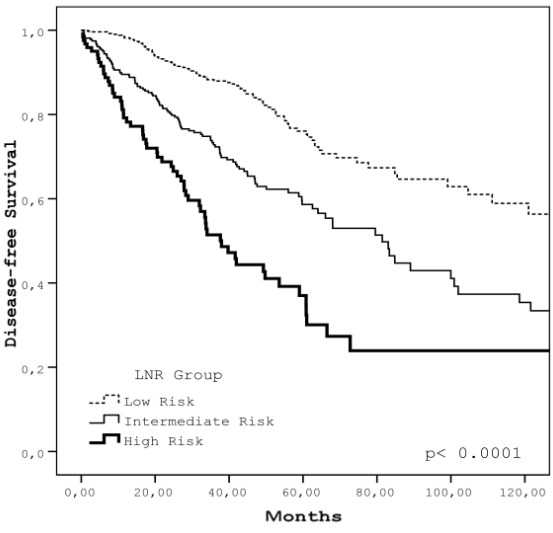

Figure 3. Disease-free survival according to LNR risk groups.

Table 2. Comparison of clinicopathologic characteristics of patients according to risk groups

Patient and tumor characteristics	*LNR ≤0.20* *No of patients (%)*	*0.20< LNR ≤0.65* *No of patients (%)*	*LNR >0.65* *No of patients (%)*	*p value*
Age at diagnosis (years)				0.774
< 50	313 (56.0)	182 (56.5)	65 (52.8)	
≥ 50	246 (44.0)	140 (43.5)	58 (47.2)	
Menopausal status				0.642
Premenopausal	318 (57.5)	179 (56.1)	64 (52.9)	
Postmenopausal	235 (42.5)	140 (43.9)	57 (47.1)	
Histopathology				0.132
Invasive ductal	427 (76.4)	251 (78.0)	88 (71.6)	
Invasive lobular	28 (5.0)	8 (2.5)	11 (8.9)	
Mixed	43 (7.7)	31 (9.6)	11 (8.9)	
Others	61 (10.9)	32 (9.9)	13 (10.6)	
Tumor size				<0.0001
T1	171 (31.3)	58 (18.6)	17 (14.3)	
T2	299 (54.7)	181 (58.0)	56 (47.1)	
T3	77 (14.0)	73 (23.4)	46 (38.6)	
Grade				0.026
I-II	297 (58.7)	148 (49.3)	58 (51.3)	
III	209 (41.3)	152 (50.7)	55 (48.7)	
Lymphovascular invasion				<0.0001
Yes	179 (32.9)	172 (54.4)	75 (61.0)	
No	365 (67.1)	144 (45.6)	48 (39.0)	
Perineural invasion				0.052
Yes	101 (18.6)	80 (25.3)	23 (18.7)	
No	443 (81.4)	236 (74.7)	100 (81.3)	
Estrogen receptor				0.372
Positive	401 (73.0)	234 (74.5)	80 (67.8)	
Negative	148 (27.0)	80 (25.5)	38 (32.2)	
Progesterone receptor				0.163
Positive	403 (73.5)	217 (70.2)	77 (65.3)	
Negative	145 (26.5)	92 (29.8)	41 (34.7)	
HER-2 overexpression				<0.0001
Positive	110 (20.7)	87 (28.7)	53 (46.1)	
Negative	422 (79.3)	216 (71.3)	62 (53.9)	
Subtypes of breast cancer				0.001
Luminal	439 (80.0)	249 (79.3)	90 (75.6)	
HER-2 overexpressing	40 (7.2)	34 (10.8)	22 (18.5)	
Triple negative	70 (12.8)	31 (9.9)	7 (5.9)	
Surgery				0.026
BCS	127 (22.7)	55 (17.1)	17 (13.8)	
MRM	432 (77.3)	267 (82.9)	106 (86.2)	
Adjuvant chemotherapy				0.001
Yes	475 (92.1)	300 (97.7)	114 (97.4)	
No	41 (7.9)	7 (2.3)	3 (2.6)	
Adjuvant radiotherapy				<0.0001
Yes	467 (83.7)	310 (96.6)	119 (96.7)	
No	91 (16.3)	11 (3.4)	4 (3.3)	
Adjuvant hormone therapy				0.411
Yes	436 (78.0)	239 (75.2)	87 (73.1)	
No	123 (22.0)	79 (24.8)	32 (26.9)	

For abbreviations see footnote of Table 1

In the subgroup analyses, the mean numbers of metastatic lymph nodes were 8.16 for patients with LVI and 5.03 for patients with no LVI (p<0.0001). The mean number of removed lymph nodes were similar (22.95 and 23.11; p=0.79). The mean LNR was 0.34 for patients with LVI and 0.22 for patients with no LVI (p<0.0001). The 5-year OS rates were 91% in the low-risk, 67% in the intermediate-risk, and 56% in the high risk LNR group with no LVI ($p_{log\text{-}rank}$ <0.0001), whereas they were 77, 62 and 51% in patients with LVI, respectively ($p_{log\text{-}rank}$ <0.0001) (Figures 5 and 6).

There was significant association between ER positivity (HR:0.63, 95%Cl 0.48-0.81; p=0.001), PR positivity (HR:0.77, 95%Cl 0.59-0.99; p=0.049), large tumor size (HR: 2.09, 95%Cl 1.43-3.04; p=0.001), high grade tumor (HR: 1.53, 95%Cl 1.19-1.97; p=0.001), presence of LVI (HR:1.38, 95%Cl 1.08-1.77; p=0.01) and breast cancer recurrence. In multivariate analysis, compared with the patients in the low LNR risk group, the adjusted hazard ratio for breast cancer recurrence risk was 2.01 (95%Cl 1.13-3.58; p=0.018) for patients in the intermediate LNR risk group and 3.06 (95%Cl 1.49-6.06; p=0.002) for patients in the high LNR risk group (Table 3). Other independent risk factors affecting breast cancer recurrence were pN stage (p=0.018), tumor grade (HR:1.44, 95%Cl 1.08-1.90; p=0.012), ER positivity (HR:0.58, 95%Cl 0.36-0.91; p=0.018), PR positivity (HR:0.64, 95%Cl 0.42-0.96; p=0.038), adjuvant chemotherapy (HR:0.64, 95%Cl 0.39-0.98; p=0.044) and adjuvant radiotherapy (HR:0.51, 95%Cl 0.32-0.82; p=0.005).

In univariate analysis, age at diagnosis (HR:1.47, 95%Cl 1.06-2.02; p=0.019), large tumor size (HR:2.58, 95%Cl 1.53-4.34; p=0.001), high grade (HR:2.26, 95%Cl 1.60-3.20; p<0.0001), ER positivity (HR:0.71, 95%Cl 0.49-0.96; p=0.034), PR positivity (HR:0.66, 95%Cl 0.47-0.93; p=0.017), presence of LVI (HR:1.96, 95%Cl 1.41-2.73; p<0.0001) and PNI (HR:1.64, 95%Cl 1.12-2.40; p=0.011) as well as pN and LNR were significantly associated with breast cancer mortality (Table 3). After adjustment for the prognostic factors (age, tumor size, grade, LVI and PNI, HER-2, hormonal status and adjuvant treatments), LNR and pN stage remained independent prognostic factors for node-positive breast cancer mortality. The patients with high grade tumor (HR:2.22, 95%Cl1.52-3.24; p<0.0001), HER-2 overexpressing breast cancer (HR:1.63, 95%Cl 1.07-2.49; p=0.022) and older women aged >50 years (HR:1.46, 95%Cl 1.02-2.11; p=0.04) had also independently increased risk of breast cancer mortality.

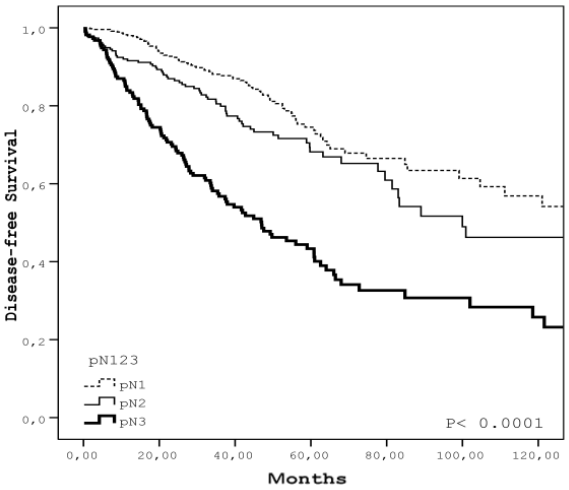

Figure 4. Disease-free survival according to pN stage.

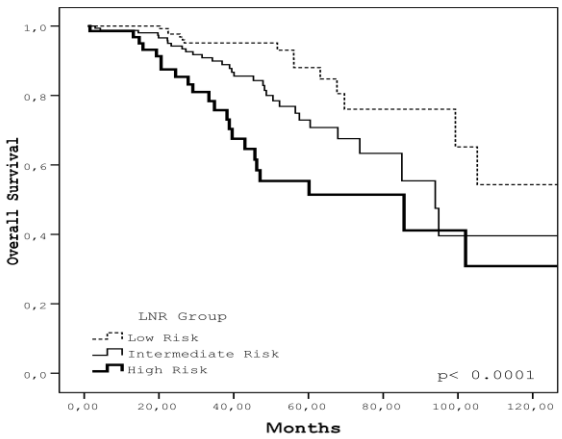

Figure 5. Overall survival in patients with lymphovascular invasion according to LNR risk groups.

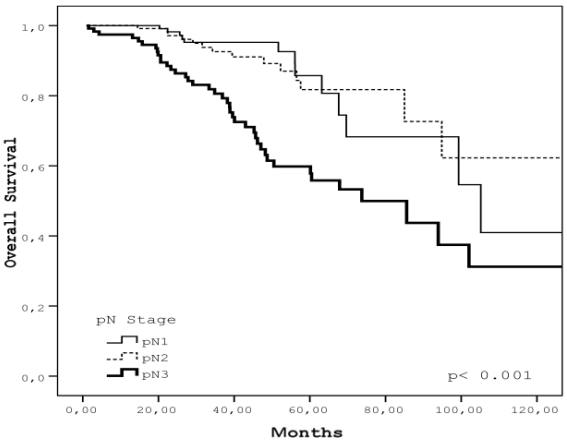

Figure 6. Overall survival in patients with lymphovascular invasion according to pN stage.

Table 3. The effect of the lymph node ratio and pN staging on disease-free survival and overall survival among patients with lymph node–positive breast cancer

Lymph node involvement	*Overall survival*		*Disease-free survival*	
	Univariate	*Multivariate*	*Univariate*	*Multivariate*
	HR (95% CI)	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
pN Stage				
pN1	1	1	1	1
pN2	1.32 (0.84-2.08)	1.35 (0.69-2.60)	1.45 (1.07-1.99)	1.06 (0.59-1.90)
pN3	3.93 (2.71-5.69)	2.36 (1.46-3.80)	3.32 (2.52-4.39)	1.87 (0.95-3.69)
	p <0.0001	p=0.002	p <0.0001	p=0.018
LNR classification				
≤0.20	1	1	1	1
0.20 to ≤0.65	2.62 (1.80-3.81)	3.73 (1.48-9.39)	2.23 (1.70-2.93)	2.01 (1.13-3.58)
>0.65	4.57 (2.98-7.02)	4.78 (1.67-13.59)	4.17 (3.02-5.75)	3.06 (1.49-6.06)
	p <0.0001	p= 0.008	p <0.0001	p= 0.005

LNR: lymph node ratio

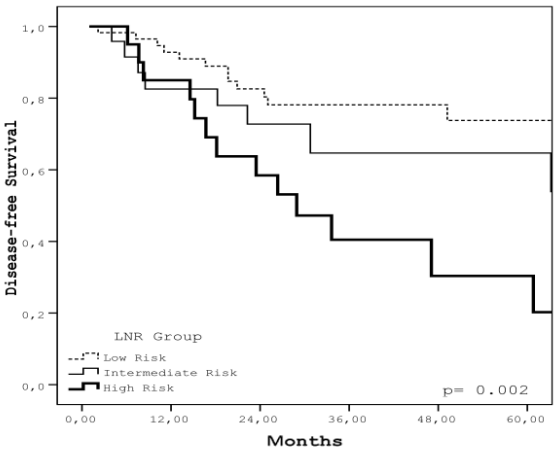

Figure 7. Disease-free survival according to LNR risk groups in triple negative breast cancer.

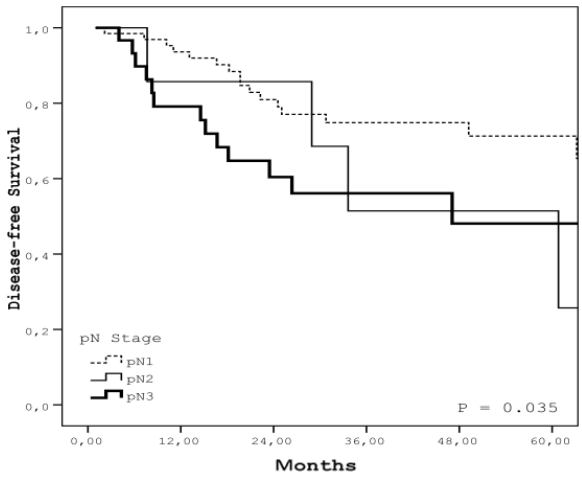

Figure 8. Disease-free survival according to pN stage in triple negative breast cancer.

When we stratified by the breast cancer molecular subtypes to analyse DFS, the pN classifications showed an imbalance in prognostic separation, the pN2 and pN3 survival curves overlapping in triple negative breast cancer. The median DFS was 60.8 months (95% CI 30.4-91.2) for pN2 disease and 47.1 months (95% CI 1.0-103.9) for pN3 triple negative breast cancer. In contrast, there were clear prognostic discrimination for the LNR survival curves (Figures 7 and 8). The survival curves for luminal and HER-2 overexpressing breast cancer were similar and significantly separated in both LNR and pN classification.

Discussion

In our study, patients with lower LNR had longer DFS and OS than those with higher LNR. Overall, pN stage and LNR were both independent prognostic factors for node-positive breast cancer recurrence and mortality. However, when examined more carefully, an overlapping between N1 and N2 curves in pN staging was determined and hazard ratios were as HR: 1 for N1, and HR: 1.35 (95% CI 0.69-2.60; p=0.37) for N2 disease in multivariate analysis. Therefore, our findings indicate that the predictive value of LNR might be superior to pN staging, especially in early-breast cancer. In a large study with 15,488 node-positive patients, the pN stage also showed an imbalance in prognostic separation, with the pN1 and pN2 survival curves overlapping in young women and women with HER-2 overexpressing and triple-negative breast cancer. In contrast, the authors reported clear prognostic separations for the LNR surviv-

al curves [15]. On the other hand, in the study of Ving-Hung et al. the classification according to the LNR provided non-overlapping risk groups, whereas, the pN2 and pN3 curves were crossed after 15-years follow-up, indicating a poorer separation between intermediate and high-risk groups [11].

Among the studies that have evaluated LNR as a prognostic indicator, the thresholds were not uniform. Most of the studies used the cut-off value of 0.20 to 0.65 [6,11,16,19-21], whereas some used 0.15 [22] and others used 0.25 [12,23]. The cut-off values for LNR were selected according to the outcomes and the level of statistical significance [10]. Recently, there is no clear consensus about the most reliable cut-off values of LNR for a staging classification. A population-based study by Vinh-Hung et al. obtained optimal cut-off values of <0.20, 0.20 to 0.65, and >0.65, which were more accurate in predicting survival than pN staging system [11]. A meta-analysis of 23 LNR studies reported that, the cut-off values 0.2 and 0.65 could be suitable to predict OS, DFS, and mortality of breast cancer [24]. These findings were supported in many studies around the world [10-15]. Therefore, we categorized the patients into LNR risk groups with the cut-offs of 0.20 and 0.65 in the current study.

Our findings were consistent with previous studies reporting that the prognostic value of LNR in breast cancer is superior to that of pN stage [6-8,10,14,15,21,22]. Moreover, we determined the independent predictive effect of LNR when adjusted for clinical and pathologic features as well as treatment modalities. The well-known prognostic factors for breast cancer (ie. ER, PR and HER-2 status, LVI, histopathology, adjuvant treatment, tumor subtype) were not available totally in some of the studies evaluating the prognostic impact of LNR [7-9,11,12,15,21].

In our view, this is the only study incorporating the data of LVI into LNR risk groups. The International Breast Cancer Study Group randomized 1,275 women with node-negative breast cancer and demonstrated that the presence of LVI was associated with a 15% increase in the 5-year recurrence risk, and this effect was independent [25]. In a meta-analysis of 20 studies comprising 40,417 breast cancer patients, LVI was associated with similarly detrimental OS regardless of lymph node or ER status [26]. We found that LVI was accociated significantly with high LNR and poor prognosis.

There were no data of HER-2 status in most of the studies evaluating the prognostic value of LNR [8,9,11,13,16,23]. HER-2 overexpression is associated with increased tumor aggressiveness, and increased rates of recurrence and mortality in breast cancer patients [27]. We also analysed the LNR risk groups according to molecular subtypes and found the superior impact of LNR in triple negative breast cancer patients. Similary, Ahn et al. found superiority of LNR over pN staging in triple negative and HER-2 positive breast cancer [15]. There is need for more studies evaluating LNR according to molecular subtypes.

Removal of at least 10 axillary lymph nodes is considered adequate for accurate assessment and staging of breast cancer [17]. In the present study we only included patients with more than 10 dissected and examined axillary lymph nodes for more accurate comparison of pN staging and LNR. Wang et al. [28] reported that the superiority of LNR and pN as prognostic predictors was dependent on whether less or more than 10 lymph nodes were dissected. However, the studies which included patients with less than 10 nodes removed, reported significantly better predictive value only in subgroups. Saxena et al. found additional prognostic information of LNR over pN staging in the subgroups of older women with ER negative and high grade disease. In their study, 17% of the patients had less than 10 nodes removed during axillary dissection [16]. In another study, Ahn et al. showed a better survival prediction of LNR over pN stage in younger women and women with HER-2 overexpressing or triple negative tumors. The number of dissected lymph nodes was <10 in 10% of their cohort [15]. Taush et al. conducted an analysis on 7052 endocrine-responsive breast cancer patients and reported that only the subgroup with pN1 stage disease and mastectomy could benefit from identifying the LNR. The percentage of the patients with less than 10 removed axillary nodes was approximately 20% in their study [9].

In conclusion, LNR is an independent factor for breast cancer recurrence and mortality with a more accurate staging over pN classification. The number of lymph nodes retrieved and examined is highly dependent on the surgeons' and pathologists' experience. Heterogeneity of lymph node examination is commonly encountered in clinical practice. Thus, LNR is more comprehensive and reliable prognostic factor for patients with node-positive breast cancer and it may function as standardisation factor against the variability of nodal assessment.

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