Original Article

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Lymph Node Ratio (LNR): Predicting Prognosis after Neoadjuvant Chemotherapy (NAC) in Breast Cancer Patients

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ABSTRACT

Objective: Axillary lymph node status is an important prognostic factor in breast cancer (BC). Residual nodal disease burden after neoadjuvant chemotherapy (NAC) is one of the important prognostic factors to determine the prognosis and in the treatment of BC. Lymph node ratio (LNR) defined as the ratio of the number of positive lymph nodes to total excised axillary lymph nodes, may be a stronger determinant of prognosis than pN in axillary nodal staging, although there is very limited data evaluating its prognostic value in the setting of NAC. In this cohort of patients, we studied the utility of LNR in predicting recurrence and overall survival (OS) after NAC.

Materials and Methods: An Institutional cancer registry was queried from 2009 to 2014 for women with axillary node-positive BC with no evidence of distant metastasis, and who received NAC followed by surgery for loco-regional treatment (axillary dissection with breast conserving surgery or total mastectomy). Patients with axillary complete response were excluded. Locoregional recurrence (LRR), distant recurrence (DR) and overall survival (OS) rates were reviewed regarding pN and LNR.

Results: A total of 179 patients were analyzed. Median follow up time was 24 [25%, 75%: 13-42] months. Patients with pN1 in comparison to pN2 and pN3 had lower rate of LRR (9% vs. 15% and 14%, respectively; p=0.41), lower rate of DR (14% vs. 25% and 27%, respectively, p=0.16) and increased rate of OS (89% vs. 79% and 78%, respectively, p=0.04). In comparison to patients with LNR >20%, patients with LNR ≤20% had lower LRR (9% vs. 14%, p=0.25), lower DR (13% vs. 27%, p=0.01) and improved OS (89% vs. 79%, p=0.02) rates. In the pN1 group, patients who had a LNR >20% had higher DR (22% vs. 14%, p=0.48) rates in comparison to patients with LNR ≤20%. In ER/PR (+) patients who had LNR ≤20% DR was 6% compared with 23% in patient who had LNR >20% (p=0.02), and in triple negative patients' OS rate was significantly better compared the LNR less/equal or more than 20% (71% vs 33%, p=0.001).

Conclusion: Our study demonstrated that LNR adds valuable information for the prognosis after NAC and this additional information should be considered when deciding further treatment and follow-up for patients who had residual tumor burden on the axilla. This observation should be tested in a larger study.

Keywords: Breast cancer, lymph node, neoadjuvant chemotherapy, prognosis

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Introduction

Axillary lymph node status is one of the most important prognostic factors in patients with breast cancer (BC) (1-3). Advanced nodal disease is associated with increased locoregional recurrence (LRR) and poor overall survival (OS) (1, 4-6). The total count of involved lymph nodes has been the determinant of nodal staging (pN) in the current AJCC staging system (6, 7). However, excluding the total number of removed lymph nodes could possibly under stage the axilla, leading to inadequate treatment and an overall improper prediction of prognosis (3, 8). Lymph node ratio (LNR) of total number of positive nodes to the total number of removed lymph nodes has been introduced as an alternative prognostic factor by some studies (3, 9-12): authors have argued that LNR predicts OS and LRR more accurately than pN staging.

Neoadjuvant Chemotherapy (NAC) is a standard treatment modality in locally advanced BC, and is being increasingly used for triple negative and Her 2 neu (+) patients in early stage breast cancer (13-15). Residual nodal cancer burden after neoadjuvant chemotherapy (NAC) is one of the important prognostic factors for determining the prognosis (16). It is well known that NAC is as effective in downstaging the axilla

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as treating the primary tumor (13, 17, 18). On the other hand, it has been reported that the total count of lymph nodes excised during axillary dissection is decreased in most cases following NAC as compared to patient with no NAC (13, 17, 18). As a result, traditional pN staging may underestimate true residual nodal disease in patients who have completed NAC. Alternatively, LNR may be a stronger determinant in axillary nodal staging and has only been evaluated by a few studies in the NAC setting (19). The aim of this study was to evaluate the importance of LNR in predicting LRR, distant recurrence (DR) and OS after NAC.

Materials and Methods

After obtaining Institutional Review Board approval, our institutional breast cancer registry was queried from 2009 to 2014 for women with a node positive axilla and no evidence of distant metastasis, who sequentially received NAC and local treatment (segmental or total mastectomy with axillary lymph node dissection [ALND]). Patients with a complete pathologic response in the axilla to NAC were excluded from the study. Also, patients who were lost to follow up, or died because of a non-breast cancer related reason, were excluded from the study. Electronic medical records were reviewed for age and menopausal status at time of diagnosis, histology, histological grade, TNM staging, type of surgery, total count of excised lymph nodes, adjuvant therapies, date of last follow up visit, local/distant recurrence and death.

Hematoxylin and eosin staining or immunohistochemical (IHC) staining were used, and microscopic or macroscopic diseases were accepted to be positive for nodal involvement. LNR was calculated by dividing the number of positive lymph nodes to total number of lymph nodes excised then multiplied by 100. In prior studies LNR was categorized as 1-20%, 21-60% and >61% (20). We categorized into two groups: patients with LNR £20% and patients with LNR >20% based on literature and considering LNR ≤20% is less tumor burden. LRR, DR and OS rates were assessed regarding pN and LNR.

Student's t-test was used for continuous variables, and chi-square test was used for categorical variables. Linear regression test was used for multivariate analysis. Overall survival (OS) was compared using Kaplan-Meier log-rank tests. Univariate and multivariate Cox models were used to estimate hazard ratios. Statistical package for social sciences (SPSS) software (version 20.0) was used for analysis. P values of less than 0.05 were considered as statistically significant.

Results

A total of 179 BC patients who underwent ALND after NAC were included in the study. Median follow up time was 24 [25%, 75%: 13-42] months. The mean age of the cohort was 53.7±11.7 years with 65% (n=116) of the cohort being 50 years of age or older. 58% (n=103) of the patients were postmenopausal (Table 1).

At initial presentation, 47% (n=65) of the patients had a clinical stage 3 disease and 63% (n=110) underwent segmental mastectomy. Adjuvant radiation treatment was given to 75% (n=130) of the cohort (85% WBRT, 15% PMRT), (Table 1). The majority had a tumor histology of invasive ductal carcinoma (90%, n=160), while 7% (n=12) had invasive lobular carcinoma. ER /PR+ and Her2/neu (–), triple positive, Her2/neu + and triple negative tumors comprised 53% (n=94), 16% (n=29), 16% (n=9), and 22% (n=39), respectively.

The mean count of lymph nodes excised during ALND was 17.1 ±5.4 [10-39]. Rates of pN1, pN2 and pN3 diseases were 59% (n=105), 29% (n=52) and 12% (n=22), respectively. Fifty-seven percent (n=102) of the cohort has a LNR ≤20%. Lymphovascular invasion was seen in 45% (n=79) of the patients, and 44% (n=78) of the patients with axillary metastases had extracapsular invasion in the metastasized lymph node (Table 1).

Twenty patients (11%) had a LRR in the cohort. Patients with LNR ≤20% had lower LRR rate compared with LNR >20% (9% vs. 14%, p=0.25) (Table 2). Patients with pN1 disease had lower LRR rate (9%) in comparison to pN2 and pN3 disease (15% and 14%, respectively, p=0.41). Among patients with pN1 disease, patients with LNR ≤20% had lower LRR rate compared with LNR >20% (8% vs. 11%,

Table 1. Descriptive characteristics of the patient group (n=179)

Age (y)		53.7±11.7
Median [%25, 75%]		54 [46.61]
Follow up (months) (median (25%, 75%)		24 [13.42]
Postmenopausal patients		103 (58)
Stage	1	13 (9)
	2	61 (44)
	3	65 (47)
Mastectomy	Segmental	110 (63)
	Total	65 (37)
Lymph nodes examined		17.3±5.5
Median [%25, 75%]		16 [13-20]
Adjuvant radiotherapy		130 (75)
Tumor histology	Ductal	160 (90)
	Lobular	12 (7)
	Other	6 (3)
Tumor grade	1	100 (62)
	2	59 (37)
	3	2 (1)
Hormonal receptor status	ER and/or PR (+),	
	Her-2 (-)	94 (53)
	Triple positive	29 (16)
	HER 2 type	16 (9)
	Triple negative	39 (22)
pN stage	1	105 (59)
	2	52 (29)
	3	22 (12)
Lymph node ratio (%)	≤20	102 (57)
	>20	77 (43)
Lymphovascular invasion (%)		79 (45)
Extracapsular invasion in the lymph node (%)		78 (44)

Categorical data were presented as n (%)
Continuous data were presented as (mean ±SD [range]) unless stated otherwise

Table 2. Comparison of pN staging and LNR with LRR

Locoregional Recurrence		No (%)	Yes (%)	p
Lymph node ratio	≤20%	93 (91)	9 (9)	0.25
	>20%	66 (86)	11 (14)	
pN	1	96 (91)	9 (9)	0.41
	2	44 (85)	8 (15)	
	3	19 (86)	3 (14)	
pN1	≤20%	88 (92)	8 (8)	0.78
	>20%	8 (89)	1 (11)	
Lymph node ratio ≤20%	pN1	88 (92)	8 (8)	0.49
	pN2	5 (80)	1 (20)	
	PN3	0 (0)	0 (0)	
ER/PR (-), ≤20%	20 (83)	4 (17)	0.23	
Her 2 (-)	>20%	10 (67)	5 (33)	
ER/PR (-),	≤20%	11 (92)	1 (8)	0.38
Her 2 (+)	>20%	3 (75)	1 (25)	
ER/PR (+),	≤20%	45 (96)	2 (4)	0.40
Her 2 (-)	>20%	43 (91)	4 (9)	
ER/PR (+),	≤20%	17 (89)	2 (11)	0.97
Her 2 (+)	>20%	9 (90)	1 (10)	

Categorical data were presented as n (%)
Continuous data were presented as (mean ±SD [range]) unless stated otherwise

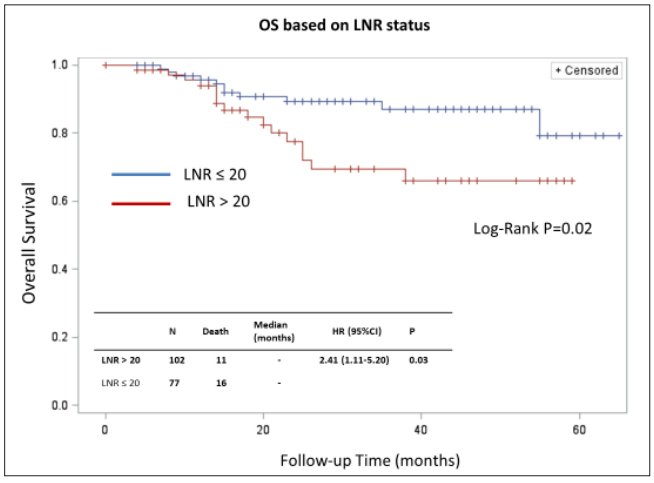

Figure 1. KM survival curve based on LNR

p=0.78). Among patients with LNR ≤20%, patients with pN1 disease had lower LRR rate (8%) in comparison to patients with pN2 disease (20%) (p=0.49).

We then evaluated the data for distant recurrence; 34 patients (19%) had a DR in entire cohort. Patients with a pN1 disease had a lower DR rate (14%) in comparison to patients with pN2 and pN3 diseases (25% and 27%, respectively, p=0.16) as projected. After we combined the pN2 and pN3 patients and compared it to the pN1 patients the p value for DR approached significance (p=0.056). In our study, LNR >20% increased DR rate by 2.57-fold (27% vs. 13%, p=0.01, OR 2.57 [1.19-5.54]). Among patients with pN1 disease, patients with LNR ≤20% had lower DR rate compared with LNR >20% (14% vs. 22%, p=0.48). Patients with pN2 disease and LNR ≤20% had a DR rate of 0% while it is 25% (n=13) in all pN2 patient without considering the LNR; all pN2 patients with DR had LNR>20% (Table 3). In ER/PR (+) and Her 2/neu (-) patients who had LNR ≤20% DR was 6% compared with 23% in patient who had LNR >20% (p=0.02).

Overall survival rate was 85% in our cohort and 27 patients (15%) died because of BC during follow up. OS rate was higher among patients with LNR ≤20% compared with LNR >20% (89% vs. 79%, p=0.02) (Table 4). Hazard of death was significantly higher in the LNR >20% compared with LNR ≤20% with a HR of 2.41 (95%CI: 1.11-5.20; p=0.03) (Figure 1). OS rate was higher among pN1 patients (89%) in comparison to pN2 (79%) and pN3 patients (78%) (p=0.04). After we combined the pN2 and pN3 and compared with pN1 for OS p value was statistically significant; mortality rate was 10.4% in the pN1 group vs 21.6%, in the pN2/3 patients; p=0.04). Among patients with pN1 disease, OS rate was similar between patients with LNR ≤20% and LNR >20% (90% vs. 89%, respectively, p=0.89). In triple negative patients, OS rate was significantly better among patients with a LNR ≤20% compared with LNR > 20% (71% vs 33%, p=0.001). Crude and adjusted for age, ER, PR and Her2/neu status multivariate Cox regression analysis showed that hazard of death was significantly high in >20% LNR and pN2-3 patients (Table 5).

Table 3. Comparison of pN staging and LNR with DR

Distant Recurrence (DR)		No (%)	Yes (%)	p
Lymph node ratio	≤20%	89 (87)	13 (13)	0.01
	>20%	56 (73)	21 (27)	
pN	1	90 (86)	15 (14)	0.16
	2	39 (75)	13 (25)	
	3	16 (73)	6 (27)	
pN1	≤20%	83 (86)	13 (14)	0.48
	>20%	7 (78)	2 (22)	
Lymph node ratio ≤20%	pN1	83 (86)	13 (14)	0.33
	pN2	6 (100)	0 (0)	
	PN3	0 (0)	0 (0)	
Lymph node ratio >20%	pN1	7 (78)	2 (22)	0.93
	pN2	33 (72)	13 (28)	
	PN3	16 (73)	6 (27)	
ER/PR (-),	≤20%	16 (67)	8 (33)	0.41
Her 2 (-)	>20%	8 (53)	7 (47)	
ER/PR (-),	≤20%	12 (100)	0 (0)	0.07
Her 2 (+)	>20%	3 (75)	1 (25)	
ER/PR (+),	≤20%	44 (94)	3 (6)	0.02
Her 2 (-)	>20%	36 (77)	11 (23)	
ER/PR (+),	≤20%	17 (89)	2 (11)	0.48
Her 2 (+)	>20%	8 (80)	2 (20)	

Categorical data were presented as n (%)
Continuous data were presented as (mean ±SD [range]) unless stated otherwise

Discussion and Conclusion

It is well documented that axillary lymph node metastasis and the extent of axillary disease is one of the most important prognostic factors in the care of the BC patient (3). The number of lymph nodes obtained during ALND can however be affected by several factors. These may include inadequate surgical experience, increased patient age, patient's co-morbidities and improper handling of the specimen. The latter can therefore lead to under-staging of the disease, improper prediction of prognosis and inadequate treatment (4, 8, 9). LNR has been suggested as an alternative or complementary method to AJCC staging (1, 11-14, 21-25). It aims to improve the prognostication of BC by reducing the effect of heterogeneity of axillary procedures on staging the axilla. Recently, there has been increasing evidence demonstrating the superiority of LNR to traditional pN staging as an indicator of axillary tumor burden. In addition, a ratio based staging system, which confers additional information on the total number of lymph nodes dissected, can be a powerful predictor of prognosis in patients with axillary disease (25-30). In our study DR rate was significantly higher in patient who had LNR>%20 compared with LNR ≤20%, but pN was not a discriminator for DR. On the other hand, patients who had ER/PR + and Her2/neu (–) phenotype tumor DR was almost 4 times higher when LNR was greater than 20%.

Vinh-Hugh et al. (25) and Kuru et al. (27) have emphasized the improvement in survival as the numbers of total lymph nodes and negative lymph nodes increased and reported the LNR as a significant independent predictor for survival in patients with axillary involvement. In our study, LNR and pN were both good discriminators to predict the OS rate, but LNR was a better predictor for DR than pN. Patients with a diagnosis of triple negative phenotype and LNR >20% had more than 2 times risk of death compared with the same phenotype with LNR ≤20% (p=0.001).

Studies have shown that quantity of lymph nodes retrieved during ALND in patients who have received NAC is significantly lower than the patient, who did not receive NAC (6-9). This can lead to understaging the disease and predicting the prognosis incorrectly. Although LNR has been repeatedly studied in patients undergoing upfront surgery, very few studies examined its efficacy in NAC setting (10, 19, 31). Tsai et al. (19) studied on 165 node positive patients and found that lymph node categories were inversely associated with disease free survival. They picked a LNR single value of 15% and found that LNR<15% was significantly associated with disease free survival in ER/PR+ (p=0.04) and triple negative patients (p=0.001). In another study Kim et al. (10) studied LNR in patents with 1-3 positive LNS and found in the multivariate analysis that >18% of LNR had HR=1.81 (95%CI, 1.34-2.45, p=0.0001), and the estimated survival

Table 4. Survival rate regarding pN staging and LNR

		Alive (%)	Dead (%)	LogRank P
Lymph node ratio	≤20%	91 (89)	11 (11)	0.02
	>20%	61 (79)	16 (21)	
pN	1	94 (89)	11 (11)	0.04
	2	41 (79)	11 (21)	
	3	17 (77)	5 (23)	
pN1	≤20%	86 (90)	10 (10)	0.89
	>20%	8 (89)	1 (11)	
Lymph node ratio ≤20%	pN1	86 (90)	10 (10)	0.84
	pN2	5 (83)	1 (17)	
	PN3	0 (0)	0 (0)	
ER/PR (-),	≤20%	17 (71)	7(29)	0.001
Her 2 (-)	>20%	5 (33)	10 (67)	
ER/PR (-),	≤20%	12 (100)	0 (0)	0.01
Her 2 (+)	>20%	3 (75)	1 (25)	
ER/PR (+),	≤20%	44 (94)	3 (6)	0.48
Her 2 (-)	>20%	43 (91)	4 (9)	
ER/PR (+),	≤20%	18 (95)	1 (5)	0.73
Her 2 (+)	>20%	9 (90)	1 (10)	

Categorical data were presented as n (%)
Continuous data were presented as (mean ±SD [range]) unless stated otherwise

Table 5. Crude and adjusted Cox models for overall survival

	Univariate		Multivariate[a]	
	HR (95%CI)	P	HR (95%CI)	p
Lymph node ratio				
≤20%	Reference		Reference	
>20	2.41 (1.12-5.20)	0.02	4.22 (1.85-9.63)	0.0006
pN				
pN1	Reference		Reference	
pN2	2.53 (1.09-5.85)	0.03	4.07 (1.68-9.84)	0.002
pN3	2.85 (1.00-8.21	0.05	5.89 (1.84-18.88)	0.003

[a]Adjusted for Age
Estrogen receptor, progesterone receptor, and Her2 status

was 76.7% in the LNR<18% and it was 61.4% in the LNR>18%. In addition to the overall survival they found that postmastectomy radiation therapy increased the estimated survival rate at 10 years around 30% in the group that had LNR>18% compared with low LNR.

The number of required LNs for ALND is also controversial and there is a potential possibility of down staging the axilla by examining low number of LNs (10, 21, 28, 32). While the AJCC recommends removing and examining a minimum of 6 LNs, Fisher et al. (33) has demonstrated that nodal involvement can most reliably be evaluated if at least 10 LNs are evaluated. The predictability of the prognoses by LNR and pN has also been shown to depend on evaluation of at least 10 or more LNs (34). In this study, we utilized the previously validated cutoffs (≤20%; 20-65%; ≥65%) for LNR categories, however we simplified the cutoffs to ≤20% vs >20%. These were tested via bootstrap resampling of a population-based cohort of women with lymph-node positive BC (8).

pN staging classification tends to accept all axillary dissections as homogenous. It is therefore, important to keep in mind that when

heterogeneity in the number of excised and examined lymph nodes is encountered (i.e. patients, who received NAC), LNR-based classification as defined by ≤20% vs >20% can give additional information in predicting prognoses of the disease and this knowledge should be considered when deciding further treatment and follow-up patients who had residual tumor burden on the axilla.

This study has a limited number of NAC patients, but the accumulation of data from large prospective studies with longer follow up periods, will solidify the LNR-based classification system.

In conclusion residual nodal tumor burden after NAC is a sign of poor prognosis, however, how much residual tumor is left is important to predict the prognosis and it also affects the decision of the further treatment. Notwithstanding, LNR-based classification is not widely used it is a useful additional tool that can be implemented in the clinic practice to better predicting prognosis and planning the further treatment after NAC inpatient with BC.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Magee Womens Hospital of University of Pittsburgh Medical Center.

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

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