■ Original Article

Prognostic Value of Metastatic Lymph Node Ratio in Locally Advanced Breast Cancer

Lokal İleri Meme Kanserinde Metastatik Lenf Nodu Oranının Prognostic Önemi

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ABSTRACT

Aim: In this study we evaluated the prognostic value of the lymph node ratio. (LNR: defined as the number of involved nodes divided by the number of the nodes examined).

Patients and Methods: In this retrospective study, patients underwent axillary dissection due to breast cancer were examined. We evaluated 348 women underwent axillary dissection for nonmetastatic breast cancer in 9 Eylül University Hospital between 2006 and 2016. LNR were divided into three groups as low, intermediate and high risk (low, ≤0.20; intermediate, 0.21-0.65; high, > 0.65). Overall survival of the patients was estimated by the Kaplan Meier method for LNR. Overall relative mortality risks associated with LNR and pN were calculated by Cox regression.

Results: The mean survival was 95.1 months LNR high-risk group, while it was 100 months in N3 group. Even though it was not statistically significant, a lower survival rate of less than 5 months was observed in the LNR high group (P <0.74). High LNR associated with poor disease specific survival rates with the mean 76.73 months of follow up. In the multivariate analysis, high LNR was an independent poor prognostic factor in breast cancer (LNR>0.65 HR 3.08; p=0.002).

Conclusion: LNR is highly significant in breast cancer and it provides more valuable information rather than TNM in terms of prognosis. Therefore, we think that, LNR can be used as a beneficial tool in breast cancer staging.

Keywords: breast cancer; lymph node ratio; survival.

ÖZ

Amaç: Bu çalışmada lenf nodu oranının prognostik değerini değerlendirdik. (LNR: ilgili düğümlerin sayısının incelenen düğümlerin sayısına bölümü olarak tanımlanır).

Hastalar ve Yöntem: Bu retrospektif çalışmada meme kanseri nedeniyle aksiller diseksiyon uygulanan hastalar incelendi. 9 Eylül Üniversitesi Hastanesinde 2006-2016 yılları arasında metastatik olmayan meme kanseri nedeniyle aksiller diseksiyon yapılan 348 kadın değerlendirildi. LNR düşük, orta ve yüksek riskli (düşük, ≤0,20; orta, 0,21-0,65; yüksek, > 0,65) olarak üç gruba ayrıldı. Hastaların genel sağkalımı, LNR için Kaplan Meier yöntemi ile tahmin edildi. LNR ve pN ile ilişkili genel göreceli ölüm riskleri Cox regresyonu ile hesaplandı.

Bulgular: Ortalama sağkalım LNR yüksek risk grubunda 95.1 ay iken, N3 grubunda 100 aydı. İstatistiksel olarak anlamlı olmasa da, LNR yüksek grupta 5 aydan daha düşük bir sağkalım oranı gözlendi (P <0.74). Ortalama 76.73 aylık takip süresinde LNR yüksek grupta hastalığa bağlı daha düşük sağkalım görüldü. Çok değişkenli analizde yüksek LNR, meme kanserinde bağımsız bir kötü prognostik faktör olarak görüldü. (LNR>0,65 HR 3,08; p=0,002).

Sonuç: LNR meme kanserinde oldukça önemlidir ve prognoz açısından TNM'den daha değerli bilgiler sağlar. Bu nedenle meme kanseri evrelemesinde LNR'nin faydalı bir araç olarak kullanılabileceğini düşünmekteyiz.

Anahtar Kelimeler: meme kanseri; lenf nodu oranı; sağkalım.

Introduction

Globally, breast cancer is the second most frequently diagnosed malignancy just behind lung cancer, accounting for over two million cases each year [1]. It is also the leading cause of cancer death among women worldwide. Axillary lymph node involvement and the number of metastatic axillary lymph nodes are the most important prognostic factors in breast cancer [2]. Currently, the TNM classification is used according to the staging system specified in the 8th edition of the AJCC (American Joint Committee on Cancer). TNM classification is divided into three groups based on the number of metastatic lymph nodes. These are pN1: 1-3 positive lymph nodes, pN2: 4-9 positive lymph nodes and pN3: ≥10 lymph nodes. However, the total number of lymph nodes dissected in the TNM staging is not taken into account. As it is known, the increase in the number of metastatic axillary lymph nodes is associated with a decrease in the average life expectancy and independent of the tumor diameter [3-5]. Results of recent studies suggest that all dissected lymph nodes rather than metastatic lymph nodes should be taken into account in terms of life expectancy [6-9]. Therefore, a new prognostic factor, lymph node ratio (LNR), is considered in the TNM stage. Lymph node ratio is the ratio of metastatic lymph nodes to all excised lymph nodes.

In this retrospective study, we compare the prognostic importance of the conventional AJCC N stage and the ratio based nodal staging system in breast cancer patients.

Material and Methods

Patient Selection

In this retrospective clinical study, patients who were operated breast disease between January 2006 and December 2016 at Department of General Surgery 9 Eylul University Medical Faculty Hospital. All procedures were performed by the same surgical team in tertiary center -University Teaching and Research Hospital- where the annual breast surgery procedures more than 400 cases and most of these are cancer procedures.

All parts of study and access to electronic medical records were approved by the Human Research Ethics Committee of 9 Eylul University, izmir, Turkey.

Patients' information was derived from hospital information management system data, and archives of pathology, radiology and general surgical departmants archives. A total of 3461 patients were found to be eligible for this study. Patients who were operated with benign causes (N: 712), received neoadjuvant therapy (N: 474) or with metastases at the time of diagnosis (N: 392), has pathologically negative lymph node (N: 1246) were exluded; furthermore, patients with absolute number of dissected lymph node less than 10 (N: 121) and patients whose information was not fully achieved were not included in the study (N: 168). Finally, remaining 348 patients were evaluated (Figure 1).
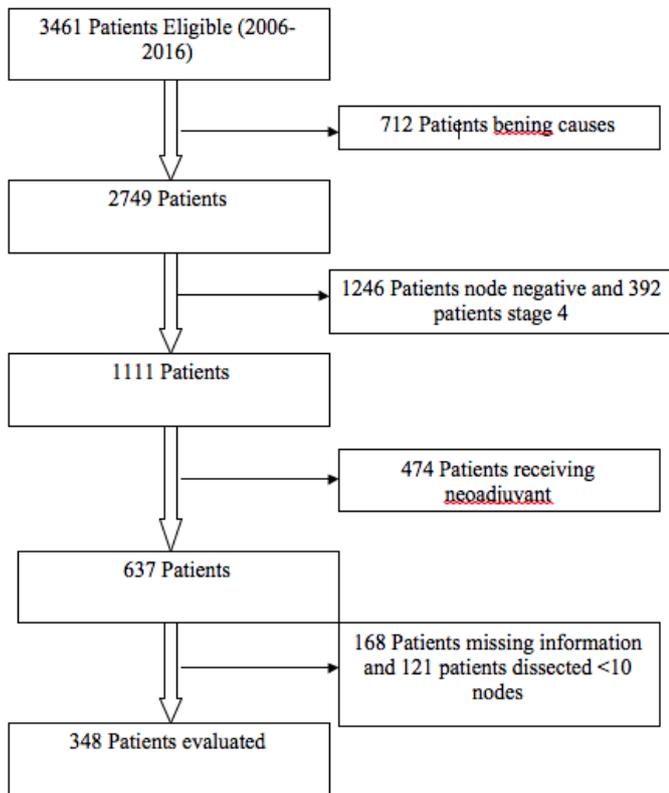
Figure 1: Flow Chart of the Study

Data Collection

The study focused on age, menopausal status, comorbidities, radiological finding, tumor localization, presence or absence of sentinel sampling, type of the surgery, pathological tumor characteristic, total number of dissected lymph nodes, number of metastatic lymph nodes, receptor status, HER2 status, Ki67 value and adjuvant treatment (chemotherapy, radiotherapy and hormone therapy) were recorded.

Postoperative follow-up was performed within 3 months interval during the first 3 years, and physical examination and laboratory examination was performed every 6 months in the 4th and 5th years. For the disease-free survival, the period from the date of operation to the occurrence of recurrence and metastasis was accepted. The last follow-up date of the patients was 2018 April. In the axillary dissection technique, level 1 and 2 lymph node dissection were applied to all patients. All specimens were evaluated by pathological examination and total number of dissected lymph nodes and number of metastatic lymph nodes were recorded. The number of metastatic lymph nodes were divided by total number of dissected lymph nodes and lymph node ratios were determined. All patient data and optimal lymph node

ratios were analyzed using IBM SPSS 22 version. Lymph node ratios were divided into three groups as low, intermediate and high risk (low, ≤0.20; intermediate, 0.21-0.65; and high, > 0.65). In addition, the number of lymph nodes was evaluated according to the TNM stage and divided into three groups. N1: 1-3 were recorded as metastatic nodes; N2: 4-9 were recorded as nodes; and N3: 10 and above were recorded as lymph nodes. Then, the survival rates of patients were compared according to lymph node ratios and TNM. In addition, low-risk N1 and intermediate -risk N2 and high-risk patients were compared separately with N3.

Statistical analyses

Chi-square test was performed in the comparisons of categorical variables. P values of Pearson Chi-Square coefficient are taken into consideration. Kaplan-Meier method was used to determine disease-free survival by evaluating the effect of positive lymph node number and lymph node ratio on survival. A Cox proportional hazards model was used to compare the parameters and to adjust for known prognostic clinical and pathological variables. In the primary analysis, we included age at diagnosis, tumor size, tumor grade, hormone-receptor status, Her2/Neu status, Ki 67 value and treatment modality. The prognostic value of LNR was evaluated, after adjusting for factors significantly associated with breast cancer recurrence and mortality. The 95% confidence interval was used to evaluate the effect of variable factors on survival. Statistical significance level (p) was considered as <0.05 for all comparisons. All statistical analyzes were calculated using IBM SPSS 22.0 software.

Results

The mean follow-up period of the patients was 76.73 months. 60.62 % of the patients were postmenopausal and 39.4% of the patients were premenopausal. In terms of the operation type, 100 patients underwent modified radical mastectomy (MRM), 74 patients underwent wide excision (WE) and axillary dissection (AD), and 174 patients underwent axillary dissection following wide excision sentinel sampling. The average survival rate depending on the operation type is as follows: 102.7 months in patients undergoing MRM; 116.9 months in WE and AD; and 118.4 months in patients who underwent axillary dissection after wide excision after sentinel sampling. There was no significant difference when the mean survival was evaluated according to the operation types (p= 0.094).

In the pathologically evaluated material, the tumor size ranged from 2 mm to 105 mm and was found to be 25 mm on

average. The tumors were grade 1 in 32 patients, grade 2 in 186 patients, and grade 3 in 119 patients. Estrogen receptor (ER) was negative in 17% of patients, 1+ in 10.7% of patients, 2+ in 18.9% of patients, and 3+ in 53.4% of patients. Progesterone Receptor (PR) was found to be negative in 29.9%, 1+ in 2%, 2+ in 15.5%, and 3+ in 52.6% of patients (Table 1).

Table 1: Clinicopathological features of node-positive breast cancer Patients

		No. of patients	%
Age (years)	Mean (Min-Max)	54 (24-87)	
Menopause status	Premenopouse	211	60.6
	Postmenapouse	137	39.4
Surgery	BCS	248	71.2
	MRM	100	28.8
Tumor size	<2 cm	128	36.7
	2-5 cm	186	53.6
	>5 cm	34	9.7
Tumor histology	Invasive ductal	130	37.4
	Invasive lobular	63	18.1
	Mixed	72	20.7
	Others	83	23.8
Histologic grade	Grade 1	33	9.2
	Grade 2	186	53.4
	Grade 3	119	34.2
Estrogen receptor	Positive	289	83
	Negative	59	17
Progesterone receptor	Positive	244	70.1
	Negative	104	29.9
Her-2	1+	39	11.2
	2+	47	13.5
	3+	36	10.3
	negative	226	64.9
Ki 67	0-20 %	107	30.7
	21-40 %	129	37
	41-60 %	70	20
	61-80 %	28	8
	81-100 %	14	4
Metastasis	Yes	53	15.2
	No	295	84.8

The overall mean survival (mean ± SD) of all patients in our study group was 75.5 ± 35.9 months (figure 2). Survival rates for 3, 5, 10 years were 93.7%, 86.6%, 73.6%, respectively. The survival rate was 116 ± 5.4 months in the group that underwent breast-conserving surgery, while it was 102.7 ± 4.1 months in the mastectomy group. There was no statistically significant difference between the two groups (p=0.094). When the patients were examined according to ER status in ER 1+, 2+,

3+, and negative group was 121.7, 120.6, 113.3, 107.8 months respectively. There were no statistically significant results for survival (p=0.255).
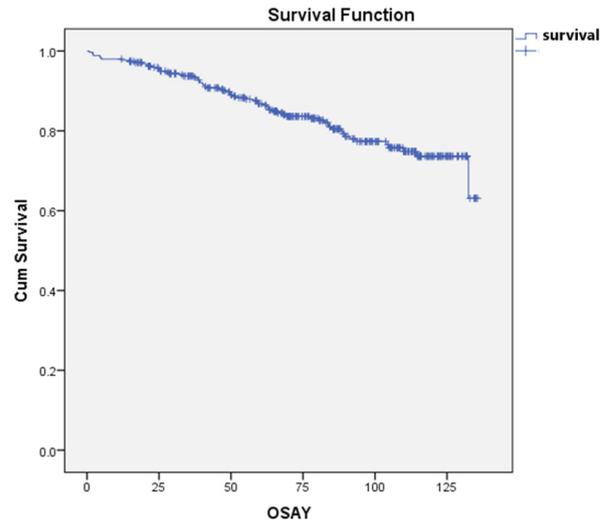

Figure 2: Survival analysis

The data in our study showed that the mean survival was 121 ± 2.6 (115-126) months in the N1 patient group, 112 ± 3.8 (105-120) months in the N2 patient group and 100 ± 2.2 (85-114) months in the N3 group. The 120-month survival rates for the N groups were 78.7%, 73.4%, 56.4%, respectively. The N3 group had significantly lower survival rates (p=0.001) (figure 3).
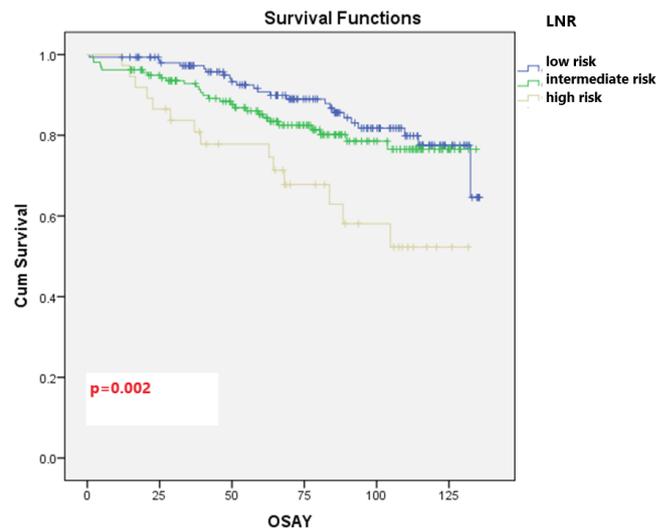

Figure 3: Kaplan – meier survival estimates according to risk groups by number of positive lymph nodes

To compare LNR subgroups and N1-2-3 groups in terms of survival rates: The mean survival in the LNR low-risk group was 120 ± 2.8 (115-126) months and 121 ± 2.6 (115-126) months in the N1 group respectively. There was no statistically

significant difference between the two groups in terms of survival (p<0.378).

The mean survival in the LNR intermediate risk group was 114 ± 3.4 (107-121) months and 112 ± 3.8 (105-120) months in the N2 group. There was no statistically significant difference in terms of survival (p<0.422).

Average life expectancy of LNR in low, intermediate and high groups are 84.9%, 82.3%, 62.2 % respectively. It is statistically significantly lower in the high group (p<0.001) (figure 4). In addition, the number of metastatic lymph nodes has an effect on the average life expectancy. According to the lymph node (N) category of TNM staging, the mean survival rates are 1-3, 4-9, 10 and above are 86.1%, 80.1%, 63.2% respectively (p<0.001).
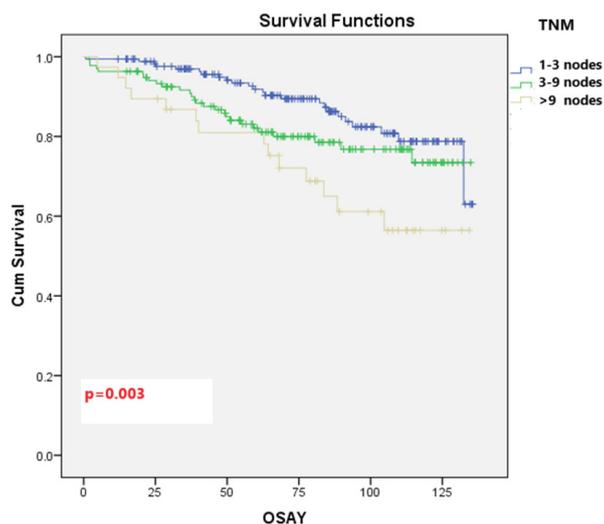

Figure 4: Kaplan – meier survival estimates according to risk groups by lymph node ratio (LNR) risk groups

When survival rates were compared according to LNR data, mean survival in LNR low risk group was 120 ± 2.8 (115-126) months, 114 ± 3.4 (107-121) months in LNR intermediate risk group, and 95.1 ± 7.7 (80-110) months in LNR high risk group (table 2). According to LNR groups, survival rates of 120

months were 78.1%, 73.2%, 46.6%, respectively. The LNR high-risk group had a significantly lower survival rate (p<0.003).

In 88.2% of patients, 10 or more lymph nodes were dissected. In 49.6% of the patients 1-3 metastatic nodes were detected. In 39.3% patients there were 4-9 metastatic nodes, and 11.1% of patients had 10 or more metastatic lymph nodes. In terms of lymph node ratio, 152 patients were in the low-risk group, 158 were in the intermediate risk group and 38 patients were in the high risk group.

During the follow-up period, metastasis was detected in 54 patients. In 294 patients, no metastasis was observed within the framework of clinical and radiological data. 35 of the patients with metastasis and 30 of those without metastasis died during follow-up. The mean survival was 81.2 months for patients with metastasis and 123.8 months for those without metastasis. The effect of metastasis on the mean survival was statistically significant (p<0.001) (figure 5).
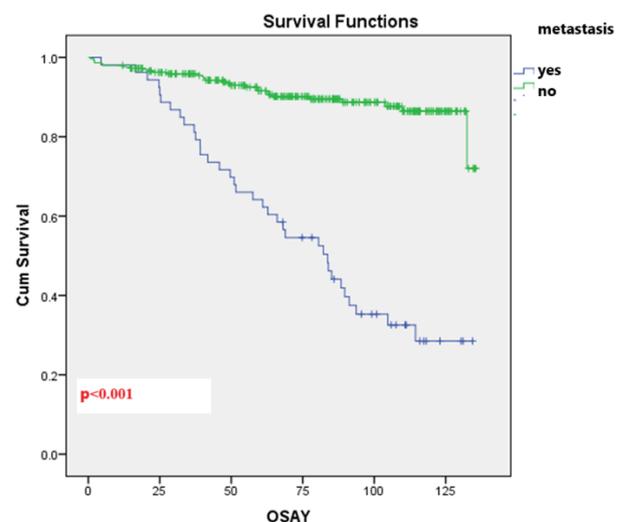

Figure 5: Survival analysis according to the metastasis

Lymph edema, bleeding and infection were evaluated as a morbidity. Lymph edema was detected in 14.7% of the patients.

Table 2: Overall survival in node-positive breast cancer patients (N = 348)							
		No. of patients	%	N of death	Overall survival (month)	5 years survival rate (%)	p-value
No. of positive LN	1-3	174	56.5	24	121.1	86.1	0.003
	4-9	136	31.3	27	112.6	80.1	
	≥10	38	13.2	14	100	60	
Lymph node ratio group	Low (0.2)	152	43.7	23	120.7	84.9	0.002
	Intermediate (0.2-0.65)	158	45.4	28	114	82.3	
	High (>0.65)	38	10.9	14	95.1	62.2	

Discussion

Breast cancer is the most common cancer in women. It is currently the second most common cause of cancer-related deaths. Although there are differences between the countries in terms of diagnostic evaluation, current radiological developments point out a global increase in the frequency of breast cancer. The number of metastatic lymph nodes is one of the most important prognostic factors in breast cancer. Correct evaluation and staging of the axillary region is of great importance in planning adjuvant treatment of patients. In recent years, several studies have shown that axillary lymph node ratio is superior to current TNM classification in evaluating tumor recurrence and survival [10]. In our study, too, the ratio of lymph nodes is an independent predictor of life expectancy in breast cancer patients.

In the AJCC statement, the average age of breast cancer is 62 years [11]. The mean age (mean, min-max) of the patients with breast cancer in our study consisted of 54.5, 24-87 years and patients younger than those in the literature.

The prognostic importance of lymph node ratio in breast cancer is increasing day by day. The prognostic significance of lymph node ratio has also been demonstrated in cancers of the esophagus, vulva, uterus, colon, stomach and pancreas [12-17].

There is no general consensus on the limits of lymph ratio in breast cancer. LNR is generally divided into 3 groups (low-intermediate -high risk) in all studies. In current studies, different rate values were used such as 0.10-0.50, 0.50-0.75, 0.33-0.67 0.17-0.43, 0.25-0.50, 0.10-0.50 [18-21]. However, there is no general consensus on which rate range is valuable, which means more studies are needed in larger patient groups.

In a wide array of studies, the LNR boundary ranges show variations. Some authors divide the ratio into two as low risk and high risk, while some others classify it as low, intermediate and high risk. In their study of node positive patients, Vinh-Hung et al. classified the patients lymph node ratio as low, intermediate and high risk. They classified the lymph node ratio as low risk <0.20, intermediate risk as 0.21-0.65, and high risk group> 0.65. However, they did not operate in large patient groups with wide limits of lymph node ratio. There is also a contradiction between some classifications. According to the cohort study reported by Ibrahim et al., the lymph node ratio of 0.21-0.65 and >0.65 did not affect the average life expectancy. However, in the study of Dings et al., and Ahn et al., the ratio of 0.21-0.65 and > 0.65 in lymph nodes shorten the average life expectancy. In another study by Chagpar et al., the lymph node ratio of 0.21-0.65 did not affect the mean life expectancy; whereas, >0.65 lymph node ratio decreased the mean life expectancy.

In our study, we used low/ intermediate /high risk scale (0.21, 0.21-0.65, 0.65) developed by Vinh-Hung et al. Their study also examined the relationship between age and lymph node ratio and showed that both factors were effective on the surgeon. They found that average life expectancy was 59.2% in women with low LNR and older than 50 years. They found that lymph node ratio was 32.6% in the group older than 50 years. When high lymph node ratio was combined with advanced age, the mortality increased threefold in breast cancer [22].

According to current opinion, although the axillary lymph node dissection limits are not clear, at least 10 lymph nodes should be dissected in the evaluation of the axillary region [23]. Kirucuta and Tausch showed that in the evaluation of axillary region removal of at least 10 lymph nodes indicated that 90% of the staging was performed correctly [24].

In our study, in support of the literature, an average of 17 LNs was excised. Moreover, the importance of total lymph node number was emphasized. The total number of axillary lymph nodes examined varies according to the experience of the surgeon, the experience of the pathologist and the patient's anatomy. In terms of postoperative treatment modalities, sufficient lymph node dissection is very important in evaluating the axillary region. Since the wider axillary dissection changes the number of positive lymph nodes, this may cause changes in the patient's stage. Axillary lymph node dissection provides not only prognostic data but also important information on locoregional control of disease and life expectancy.

In our study, we evaluated the N3 group with high risk group in terms of survival. We found the mean survival in the LNR group as 95.1 ± 7.7 (80-110) months and 100 ± 2.2 (110-119) months for N3. Although it was not statistically significant, we found lower survival in the LNR group up to 5 months (p<.074).

In evaluation of the overall survival of LNR groups with all N subgroups, we found HR: 3.028 (1.55-5.91) in the high-risk group of LNR. This gives about 3 times more valuable information for prognosis.

In recent years, there have been various limitations related to lymph node ratio. First, surgical technique and pathological evaluations of axillary dissection have not been studied sufficiently. Also, there may be differences between the centers

in terms of surgical techniques and pathological evaluations. In addition, as previously known, estrogen, progesterone, Ki67 index and HER2 status have an effect on prognosis; yet this has not been evaluated with lymph node ratio.

However, there are some limitations in our study as well. One of the most important constraints is that our study is single-centered. Extensive evaluations can be made with the LNR ratio by increasing the number of patients and the number of working centers. In spite of these, LNR is statistically significant and it is independent from the age of the patient, from the T stage, from the surgical form, and from pathological factors. The LNR ratio we used in our study was 0.21-0.65, which Vinh-Hung stated. Accurate data were obtained in survival studies. Our study also supports these ratios.

Conclusion

LNR is highly significant in breast cancer. It gives more valuable information than TNM in showing the prognosis. Therefore, we think that LNR can be used effectively in breast cancer staging.

Declaration of conflicting interests

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