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The Prognostic Value of Axillary Lymph Node Ratio for Non-Metastatic Node Positive Breast Cancers

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Abstract: ***Introduction:*** *Breast cancer is the most common female cancer worldwide representing nearly a quarter (25%) of all cancers with an estimated 1.67 million new cancer cases diagnosed in 2012. Women from less developed regions (883 000 cases) have slightly more number of cases compared to more developed (794 000) regions.*

Materials and Methods: *Our study is a retrospective case control study where we had analyzed the medical records of all the cases of breast cancers who had undergone surgery (Modified Radical Mastectomy, MRM; with axillary lymph node dissection, ALND) and post-operative adjuvant therapy (chemotherapy, radiotherapy or hormonal) during January, 2018 and December, 2018. From the information recorded and retrieved from the Hospital Information system (HIS) of the Mahatma Gandhi Institute of Medical Sciences and the District Cancer Registry, a total of 353 number of cases had met with the criteria for the study (n=353). The study was approved by the Ethics Committee of the institution where the study was held.*

Results: *ata from 353 patients were evaluated and 213 met the inclusion criteria. The mean age was 46 years and most patientswere premenopausal (Table 1). The majority of patients (84.0%) had T1-2 stage cancer and received modified radical surgery (96.3%). The median number of axillary lymph nodes removed was 14 and the median LNR was 0.18. About half the patients' tumors were positive for estrogen or progesterone receptor expression and about a quarter expressed HER2 (Table 1). All patients received chemotherapy most of which included a regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), or a taxane, anthracycline regimen (Table 1). Approximately one fourth of the patients had radiotherapy and over half received adjuvant endocrine therapy (Table 1).*

Conclusion: *In conclusion, our findings support the use of LNR as a predictor of survival in patients with breast cancer, and that LNR is superior to pN staging in determining disease prognosis. These findings, as well as others, indicate that cancer staging should not be confined to the TNM staging system and should at least include LNR assessment.*

Key Words: *breast cancer, chemotherapy, cyclophosphamide, methotrexate, and 5-fluorouracil*

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I. Introduction

Breast cancer is the most common female cancer worldwide representing nearly a quarter (25%) of all cancers with an estimated 1.67 million new cancer cases diagnosed in 2012. Women from less developed regions (883 000 cases) have slightly more number of cases compared to more developed (794 000) regions.[1] In India, although age adjusted incidence rate of breast cancer is lower (25.8 per 100 000) than United Kingdom (95 per 100 000) but mortality is at par (12.7 *vs* 17.1 per 100 000) with United Kingdom.[2]Earlier cervical cancer was most common cancer in Indian woman but now the incidence of breast cancer has surpassed cervical cancer and is leading cause of cancer death, although cervical cancer still remains most common in rural India.[3]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.[4] 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.[5] The Lymph Node Ratio (LNR) is defined as the absolute number of involved nodes divided by the number of lymph nodes examined on histopathology.[6] Increasing evidence suggests that LNR is a superior prognostic indicator compared with the absolute number of involved nodes.In recent years, several studies have identified that LNR was better at predicting breast cancer specific mortality

than the traditional pN staging as a way to account for the variability in the nodal count, for various levels of dissection and number of positive lymph nodes.[6-8]

In the current TNM classification system, nodal status is based on the absolute number of involved lymph nodes and does not take into account the total number of lymph nodes removed and assumes that all lymph node dissections are the same. Although TNM classification remains the basis of LS.

II. Aims and Objectives

1. To assess the significance of lymph node ratio for prognosis of patients with non-metastatic node positive breast cancer
2. To compare the significance of number of positive lymph nodes and lymph node ratio

III. Materials And Methods

Patient Selection

Our study is a retrospective case control study where we had analyzed the medical records of all the cases of breast cancers who had undergone surgery (Modified Radical Mastectomy, MRM; with axillary lymph node dissection, ALND) and post-operative adjuvant therapy (chemotherapy, radiotherapy or hormonal) during January, 2018 and December, 2018. From the information recorded and retrieved from the Hospital Information system (HIS) of the Mahatma Gandhi Institute of Medical Sciences and the District Cancer Registry, a total of 353 number of cases had met with the criteria for the study (n=353).

The socio-demographic data, clinic-pathological factors and treatment modalities including types of surgery, adjuvant chemotherapy, radiotherapy, and hormone therapy were obtained from the medical records of each patient.Selected patients were women of age <80 years who presented with non-metastatic non-inflammatory invasive breast carcinoma who had undergone surgery with lymph nodes positive for metastatic deposits and had received adjuvant therapy including hormonal therapy. Adjuvant treatments considered were radiotherapy, chemotherapy, and hormone therapy. Estrogen receptor (ER), progesterone receptor (PR) and Her2-neu status were assessed by immune histochemistry, the pN Stage of the patients were assessed and staged according to AJCC Staging (pN1: metastasis to 1-3 lymph nodes; pN2: metastasis to 4-9 lymph nodes; pN3: metastasis to ≥10 lymph nodes). The Lymph Node Ratio (LNR) was defined as the ratio of metastatic lymph nodes to the total of lymph nodes excised. All the patients were categorized as Low Risk of Grade I (LNR = 0.01–0.20), Intermediate Risk of Grade II (LNR =0.21–0.65) and High Risk or Grade III (LNR > 0.65).Tumor characteristics including histopathological grade (good, moderate, poor, unknown), 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), as well as presence of lymphovascular and perineural invasion (LVI, PNI) were included in the study.

Follow-up of patients was done through telephone call and direct interaction and survival end event was defined as death from breast cancer.

Statistical Analysis:

Statistical analysis was done by univariate and multivariate analysis using descriptive and inferential statistics using Chi-square test and Multiple Regression Analysis and software used in the analysis were SPSS17.0 version and GraphPad Prism 5.0. *P* value <0.05 is regarded as being statistically significant. Survival Outcomes were estimated using a Kaplan-Meier method.

IV. Results

In our study, Data from 353 patients were evaluated and 213 met the inclusion criteria. The mean age in the study was 46 years and most patientswere premenopausal status (Table 1). The majority of patients (83.0%) had T1–2 stage cancer and received modified radical surgery (85.3%). The median number of axillary lymph nodes removed was 14 and the median LNR was 0.18. About half the patients' tumors were positive for estrogen or progesterone receptor expression and about a quarter expressed HER2 (Table 1). All patients received chemotherapy most of which included a regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), or a taxane, anthracycline regimen (Table 1).

In followup, 338 patients died. The median follow up time was 66.9 months (range 5 to 168 months). The 5-year and 10-year overall survival rates were 89.3% and 78.8%, respectively (Figure 1A). The 5-year disease-free survival was 81.6% (Figure 1B), and distant metastasis-free survival was 83.5% (Figure 1C).

S.No	Demographic characteristics	N (Percentage)
1	T1-2	176(83%)
2	T3-4	17(8.0%)
3	Unknown	16(7.8%)
4	LN positive	99(46.5%)
5	Median number of axillary LN dissected (range)	14(1-73)
6	Median lymph node ratio (range) operation	0.19(0.03-1.00)
7	Modified radical surgery	181(85.3%)
8	Breast conserving surgery	31(14.7%)
9	chemotherapy	
10	CMF	33(15.7%)
11	Taxane anthracycline-based regimen	173(81.04%)
12	Unknown	6(3.2%)
13	Radiotherapy	53(25.2%)
14	Adjuvant Endocrine Therapy	137(64.7%)
15	Estrogen receptor positive	110(51.8%)
16	Progesterone receptor positive	120(56.4%)
17	HER-2 positive	59(27.8%)

Table 1: Patients' demographics and basic characteristics (n=213)

S.No	**Characteristic**	**Distant metastasis-free survival**		**Disease-free survival**		**Overall survival**	
		HR (95%CI)	P-Value	HR (95%CI)	P-Value	HR (95%CI)	P-Value
1	Age (years)	0.99 (0.98, 1.00)	0.057	0.99 (0.98, 1.00)	0.106	1.00 (0.99, 1.01)	0.887
2	Menopausal status						
3	Post vs pre	1.08 (0.88, 1.32)	0.449	1.13 (0.93, 1.36)	0.211	1.20 (0.96, 1.51)	0.113
4	T Stage						
5	N1 vs N0	1.91 (1.53, 2.38)	<0.001	1.93 (1.57, 2.38)	<0.001	2.04 (1.57, 2.65)	<0.001
6	N2 vs N0	2.93 (2.14, 4.00)	<0.001	2.68 (1.98, 3.63)	<0.001	3.05 (2.10, 4.42)	<0.001
7	N3 vs N0	6.12 (4.69, 7.97)	<0.001	5.97 (4.64, 7.69)	<0.001	7.00 (5.17, 9.46)	<0.001
8	Lymph node ratio						
9	≤0.20 vs 0	1.71 (1.34, 2.17)	1.72 (1.38, 2.16)	1.72 (1.38, 2.16)	<0.001	1.78 (1.33, 2.37)	<0.001
10	0.21-0.65 vs 0	2.93 (2.28, 3.76)	<0.001	2.84 (2.24, 3.60)	<0.001	3.12 (2.33, 4.19)	<0.001
11	>0.65 vs 0	6.20 (4.74, 8.12)	<0.001	6.04 (4.67, 7.81)	<0.001	7.06 (5.20, 9.58)	<0.001
12	ER Status						
13	Positive vs Negative	0.62 (0.51, 0.75)	<0.001	0.61 (0.51, 0.72)	<0.001	0.52 (0.41, 0.64)	<0.001
14	PR Status						
15	Positive vs Negative	0.70 (0.58, 0.85)	<0.001	0.65 (0.54, 0.78)	<0.001	0.54 (0.43, 0.67)	<0.001
16	HER-2-neu status						
17	Positive vs Negative	1.44 (1.18, 1.76)	<0.001	1.45 (1.02, 1.76)	<0.001	1.39 (1.10, 1.72)	0.006

Table 2: The results of univariate Cox proportional hazards regression analysis of potential prognostic factors.

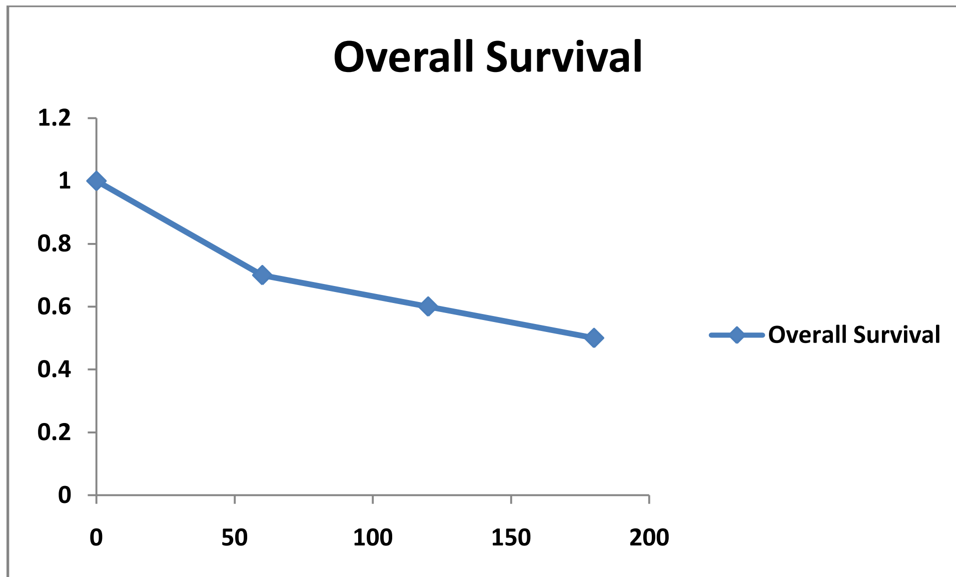

Figure 1A: Overall Survival

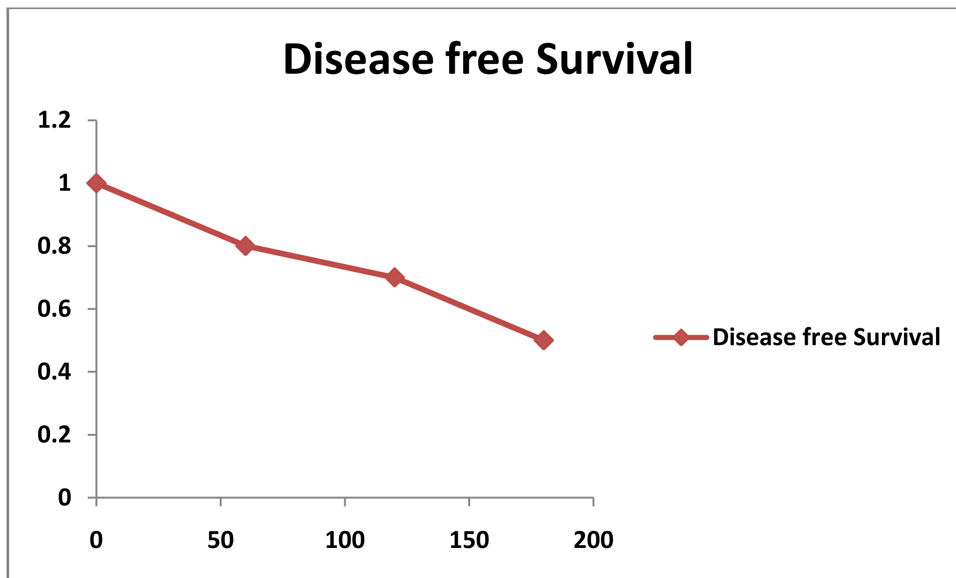

Figure 1B: Disease free Survival

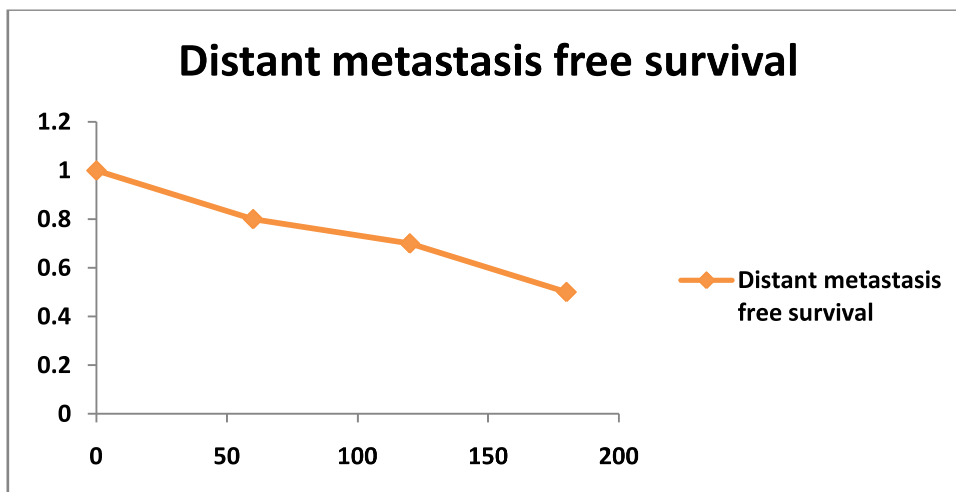

Figure 1C: distant metastasis-free survival

V. Discussion

In this study, we found that breast cancer patients with lower LNR had longer overall survival, disease-free survival, and distant metastasis-free survival than patients with higher LNR values. Mutlivariate analysis found pN stage and LNR were independent predictors of overall, disease-free, and distant metastasis-free survival. If pN stage and LNR were included together in a single multivariate model, LNR was still an independent prognostic factor for overall, disease-free, and distant metastasis-free survival. These findings support the use of LNR as a prognostic factor for Chinese breast cancer patients. It also indicates that the predictive value of LNR might be superior to pN staging.[9]

Our findings are consistent with others who have investigated the prognostic value of LNR compared to pN in breast cancer and found that the prognostic value of LNR in breast cancer is superior to that of pN stage. Most of these studies evaluated the relationship of LNR with survival and found that the greater the LNR the poorer the prognosis including shorter overall and disease-free survival, as well as distant metastasis-free survival time.[10] Patients with LNR of >15 or >25% had a higher rate of distant-metastasis and reduced overall survival time than those with lower LNR. In one study, in univariate and multivariate analyses LNR correlated significantly with overall and disease-free survival only in a subgroup of patients who had a mastectomy and with 1–3 lymph nodes. Although, our findings are consistent with these prior studies direct comparison is difficult due to difference in study design and patient populations.

LNR classification showed superiority to pN staging for the prognosis of breast cancer in current and previous studies, this superiority was also related with total number of dissected lymph nodes. Wang and his colleague reported that the superiority of LNR and pN as prognostic predictor was dependent on whether less or more than 10 lymph nodes were dissected. The median number of axillary LN dissected in this study was 14. Saxena et al. reported that in combination with other factors (i.e. age, treatment, grade, tumor size and receptor status) LNR did not provide any added prognostic value for south east Asian breast cancer patients in comparison to pN except for ≥60 year old women with ER negative or grade 3 tumors. In current study, both LNR and pN status were associated with overall survival, disease-free survival, and distant metastasis-free survival in the multivariate analysis with LRN or pN separately (model 1 and model 2). It seems LNR was not superior to pN for the prognosis of breast cancer. But, in the analysis with LNR and pN together (model 3), LNR, but not pN, showed significant association with overall survival, disease-free survival, and distant metastasis-free survival. Our study confirmed that LNR might be better than pN for the prognosis of breast cancer.

Many of the prior studies have used diverse patient groups, and in most, the cutoffs for the nodal ratios were not determined independently or validated in alternative data sets. In contrast, we used cutoffs (≤0.20, 0.2 to 0.65, and >0.65) for the categories of LNR that had previously been tested and validated via bootstrap resampling of a population-based cohort of women with lymph-positive breast cancer. In addition, we evaluated a fairly homogenous population of patients with no indications of disease metastasis at diagnosis (out of 2591 patients, 2495 underwent modified radical surgery and 96 received breast conserving surgery), all of which received adjuvant chemotherapy. Our findings support the value of these cutoffs and indicate that they are applicable to Chinese breast cancer patients. The International Nodal Ratio Working Group is investigating the prognostic value of LNR in breast cancer. Additional studies are needed to further evaluate the use of LNR as a prognostic indicator in breast cancer.[11]

VI. CONCLUSION

In conclusion, our findings support the use of LNR as a predictor of survival in patients with breast cancer, and that LNR is superior to pN staging in determining disease prognosis. These findings, as well as others, indicate that cancer staging should not be confined to the TNM staging system and should at least include LNR assessment.

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