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ORIGINAL ARTICLE – BREAST ONCOLOGY

Ratio Between Positive Lymph Nodes and Total Excised Axillary Lymph Nodes as an Independent Prognostic Factor for Overall Survival in Patients with Nonmetastatic Lymph Node-Positive Breast Cancer

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ABSTRACT

Background. The status of the axillary lymph nodes in nonmetastatic lymph node-positive breast cancer (BC) patients remains the single most important determinant of overall survival (OS). Although the absolute number of nodes involved with cancer is important for prognosis, the role of the total number of excised nodes has received less emphasis. Thus, several studies have focused on the utility of the axillary lymph node ratio (ALNR) as an independent prognostic indicator of OS. However, most studies suffered from shortcomings, such as including patients who received neoadjuvant therapy or failing to consider the use of adjuvant therapy and tumor receptor status in their analysis.

Methods. We conducted a single-center retrospective review of 669 patients with nonmetastatic lymph node-positive BC. Data collected included patient demographics; breast cancer risk factors; tumor size, histopathological, receptor, and lymph node status; and treatment modalities used. Patients were subdivided into four groups according to ALNR value (<.25, .25–.49, .50–.74, .75–1.00). Study parameters were compared at the univariate and multivariate levels for their effect on OS.

Results. On univariate analysis, both the absolute number of positive lymph nodes and the ALNR were significant predictors of OS. On multivariate analysis, only the ALNR remained an independent predictor of OS, with a 2.5-fold increased risk of dying at an ALNR of ≥.25.

Conclusions. Our study demonstrates that ALNR is a stronger factor in predicting OS than the absolute number of positive axillary lymph nodes.

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Breast cancer (BC) is the most common cancer in women and the second most common cause of female cancer death, with an estimated 182,460 new cases diagnosed and 40,480 deaths in the United States in 2008.[1] Despite the advent of sentinel node biopsy techniques and the dawning of the molecular era of BC staging, the status of the axillary lymph nodes (ALN) remains the single most important determinant of overall survival (OS).[2–6]

For patients with pathologically proven ALN involvement, the number of positive axillary lymph nodes (pALN)

correlates with the incidence of distant metastasis and OS, and more than three pALN is associated with a 13% to 24% locoregional recurrence rate.[7,8] The relationship between number of pALN and survival seems to be linear, with each additional pALN detected leading to a worsening of the prognosis.[9,10] The American Joint Committee on Cancer staging system was recently revised, grouping patients by the absolute number of pALN. This classification improved stratification in OS, but the confounding effect that the number of excised nodes may have on the yield of positive nodes and its effect on BC-specific survival prognostic accuracy and management decisions are problems that remain unresolved.[6,11] Thus, the ratio between the number of pALN and the total number of excised nodes, or the axillary lymph node ratio (ALNR), may be a more comprehensive approach to estimate prognosis because it takes into account the number of excised nodes and may accordingly adjust for differences in nodal staging.

Since 1999, several reports described the significance of ALNR as an independent prognostic factor for OS in nonmetastatic lymph node-positive BC.[12–18] Some studies included a heterogeneous group of patients recruited from different centers, which implies that patients were treated by different surgeons and different medical oncology teams.[14,18] Moreover, in many of these series, additional factors affecting OS, such as tumor receptor status (including *HER2*) and use of neoadjuvant or adjuvant treatment regimens, were not considered.[12–18] We thus report a single institutional experience with the prognostic significance of ALNR in nonmetastatic lymph node-positive BC patients treated by the same medical and surgical oncology team while attempting to address many of the shortcomings evident in some of the previous trials.

METHODS

We conducted a retrospective review of 1450 BC patients treated at the American University of Beirut Medical Center between the years 1983 and 2004. Data were retrieved from the medical records, tumor registry database, and the outpatient clinic charts of each patient. Of the 1450 patients, 1092 patients were diagnosed with stage I, II, or III (nonmetastatic) disease and were considered for further selection. Inclusion criteria included histologically proven invasive breast carcinoma with evidence of lymph node involvement at pathological staging; exclusion criteria included evidence of neoadjuvant chemotherapy. The tumor, node, and metastasis system of the American Joint Committee on Cancer (AJCC), 6th edition, was used for staging.[19]

Data collected included patients' demographics, medical history, history of benign breast disease, family history of breast malignancies, age at menarche, childbearing, use of oral contraceptive pills, menopause status, and use of hormone replacement therapy. Other retrieved data included age at diagnosis, type of surgery (partial vs. total mastectomy), ALN involvement, use of adjuvant chemotherapy, hormone therapy, and postoperative radiotherapy. Indications for postmastectomy radiotherapy included all T3 and T4 tumors, positive microscopic surgical margins, and/or any T stage with three or more ALN involved. Patients who underwent partial mastectomy were treated to the supraclavicular region including the axillary apex if they had $\geq$3 ALN involved.

Evaluated tumor characteristics included tumor size, histological type and grade, hormone receptor status, and *HER2* overexpression studies. *HER2* positivity was defined either immunohistochemically, where tumors show strong and complete circumferential membranous staining in at least 30% of cells, or by fluorescent in situ hybridization, where the currently used test does not include centromeric staining for chromosome 17, and the cutoff for *HER2* positivity is an average of 6-fold amplification of the *HER2* gene in the assessed (at least 20) tumor cells. In the 669 patients, ALNR (number of pALN divided by the total number of excised ALN) was calculated. Patients were subdivided into four groups according to ALNR value (<.25, .25–.49, .50–.74, .75–1.00); these mathematical quartiles were used to allow a fair chance for each quartile to represent itself and to try to delineate a practical cutoff for the clinical setting. The primary endpoint was OS, which was calculated as the length of time from diagnosis until death, irrespective of the cause. The institutional review board at our center approved this study.

Statistical Analysis

Abstracted data were coded and entered into SPSS version 16 statistical software (SPSS, Chicago, IL). Patients' general characteristics, tumor characteristics, and ALN description were summarized by frequencies and percentages. Five- and 10-year survival rates were carried out at the univariate level by Kaplan-Meier analysis, and *P* values from the log rank test were reported. Furthermore, variables that showed significance at the univariate level (tumor size, hormone receptor status, ALNR, number of pALN) were tested at the multivariate level by the Cox proportionate hazard model, with the exception of tumor stage, which was totally defined by tumor size and number of pALN, both of which were entered into the model. In this model, ALNR was used as a categorical variable to help compare different categories of ALNR; all the possible numbers of pALN were used as a continuous variable, allowing for maximal differentiation. Coefficients produced by the models were exponentiated, producing hazard ratios, and their respective standard errors were used to

TABLE 1 Patient demographics, medical history, and breast cancer risk-factor history for 699 patients

Parameter	*n* (%)
Age at diagnosis (y)	
<51	365 (54.2)
51–70	266 (39.8)
>70	38 (6)
Hypertension	
Yes	93 (14.2)
No	562 (85.8)
Missing	14
Diabetes	
Yes	49 (7.5)
No	606 (92.5)
Missing	14
Cardiac disease	
Yes	31 (4.7)
No	624 (95.3)
Missing	14
Family history of breast cancer	
Present	123 (18.7)
Absent	538 (81.3)
Previous malignancy	
Yes	29 (4.4)
No	628 (95.6)
Missing	12
Oral contraceptive pills	
Yes	92 (22.1)
No	325 (77.9)
Missing	252
Hormone replacement therapy	
Yes	23 (13.9)
No	146 (86.1)
Missing	500
Benign breast disease	
Yes	25 (3.8)
No	627 (96.2)
Missing	17
Smoking	
Yes	187 (36.1)
No	331 (63.9)
Missing	151
Pregnancy	
No previous pregnancy	105 (17)
Previous pregnancy	513 (83)
Missing	51
Menopause	
Post	356 (54.4)
Pre	299 (45.6)
Missing	14
Age at menarche (y)	
≤11	48 (9.4)
12–13	189 (37.1)
≥14	272 (53.7)
Missing	160

calculate the 95% confidence intervals. All analyses were carried out at the .05 level.

RESULTS

Patient Demographics and Disease Characteristics

Over the 21-year period, 1450 patients were diagnosed with BC. Among these, 669 patients had nonmetastatic node positive BC and were included in the analysis. The median age at diagnosis of the sample was 49 years (range, 24–86 years). Data on patient demographics, medical history, and BC risk factors are summarized in Table 1. Among 660 patients with available data on type of surgery, 559 (84.7%) had total mastectomy, while 101 (15.3%) had breast-conserving surgery. Adjuvant chemotherapy, hormone therapy, and radiotherapy were used in 81.4%, 29.6%, and 76% of patients, respectively. Chemotherapy regimens were mostly anthracycline based (56%), while hormone therapy mainly consisted of tamoxifen (95%). All patients were treated before 2005 so none of the patients received adjuvant trastuzumab.

Determinants of OS

The median follow-up for the entire cohort was 3.4 years (range, .08–17.42 years), and the median follow-up for all patients alive was 3.25 years (range, .08–17.42 years). In univariate analysis, tumor size (≤2 cm, 2.1–5, > 5 cm; $P = .037$), estrogen-progesterone receptor status ($P < .0001$), tumor stage ($P < .0001$), number of pALN (1–3, 4–9, ≥10; $P < .0001$), and ALNR (<.25, .25–.49, .50–.74, .75–1.00; $P < .0001$) were the only significant predictors of OS (Tables 2 and 3). Figures 1 and 2 display categorical survival for number of pALN and ALNR, respectively.

A multivariate model was obtained in which ALNR subgroups and all prognostic factors with univariate $P < .05$ (except tumor stage) were entered into the model. All factors were treated as simple categorical variables except number of pALN, which was used as a continuous variable. ALNR categories (<.25, .25–.49, .50–.74, .75–

TABLE 2 Disease parameters and effect on overall survival in 699 patients

Parameter	n (%)	5-year survival (%)	10-year survival (%)	*P* value
Age at diagnosis (y)				.325
<50	365 (54.7)	81 ± 3	69 ± 7	
51–70	265 (39.7)	73 ± 4	60 ± 8	
>70	37(4.6)	65 ± 15	0 ± –	
Missing	2			
Type of surgery				.173
Mastectomy	559 (84.7)	75 ± 3	60 ± 6	
Conservative	101 (15.3)	93 ± 3	93 ± 3	
Missing	9			
Tumor size (cm)				**.037**
≤2	167 (25.6)	82 ± 5	82 ± 5	
2.1–5	384 (58.9)	75 ± 4	53 ± 8	
>5	101 (15.5)	71 ± 7	61 ± 11	
Missing	17			
Tumor type				.616
Ductal	620 (93.8)	76 ± 3	62 ± 5	
Lobular	22 (3.3)	78 ± 15	78 ± 15	
Mixed	19 (2.2)	75 ± 22	80 ± 22	
Missing	8			
Estrogen-progesterone receptors				**<.0001**
Both positive	197 (44.7)	79 ± 5	61 ± 12	
One negative	103 (23.4)	83 ± 6	59 ± 15	
Both negative	141 (32)	63 ± 7	63 ± 7	
Missing	228			
HER2 positive				.09
Yes	59 (28.2)	63 ± 12	0 ± 0	
No	150 (71.8)	79 ± 6	72 ± 7	
Missing	460			
Tumor stage				**<.0001**
II	319 (47.7)	83 ± 4	69 ± 8	
III	350 (52.3)	71 ± 4	57 ± 7	
Tumor grade				.418
I	55 (8.2)	78 ± 1	78 ± 1	
II	338 (50.6)	78 ± 4	54 ± 8	
III	275 (41.8)	75 ± 4	70 ± 6	
Missing	1			
Chemotherapy				.902
Yes	542 (81.4)	76 ± 3	64 ± 5	
No	124 (18.6)	80 ± 6	54 ± 16	
Missing	3			
Hormone replacement therapy				.218
Yes	77 (29.6)	54 ± 8	32 ± 11	
No	183 (70.4)	66 ± 5	52 ± 10	
Missing	409			
Radiotherapy				.543
Yes	504 (76.6)	78 ± 3	61 ± 6	
No	154 (23.4)	72 ± 6	65 ± 9	
Missing	11			

Bold values indicate the significance at $P < 0.05$

TABLE 3 Axillary lymph node status and effect on overall survival in 699 patients

Parameter	*n* (%)	5-year survival (%)	10-year survival (%)	*P* value
No. of pALN				**<.0001**
1–3	325 (48.6)	82 ± 4	79 ± 4	
4–9	215 (32.1)	73 ± 7	62 ± 9	
≥10	129 (19.3)	60 ± 7	40 ± 12	
Total no. excised				.602
≤10	79 (11.8)	71 ± 9	39 ± 17	
>10	590 (88.2)	77 ± 3	66 ± 5	
ALNR				**<.0001**
<.25	343 (51.3)	84 ± 3	80 ± 5	
.25–.49	138 (20.6)	75 ± 6	53 ± 12	
.50–.74	88 (13.2)	72 ± 7	43 ± 16	
.75–1.00	100 (14.9)	55 ± 9	41 ± 14	

pALN, positive axillary lymph nodes; ALNR, axillary lymph node ratio

Bold values indicate the significance at $P < 0.05$

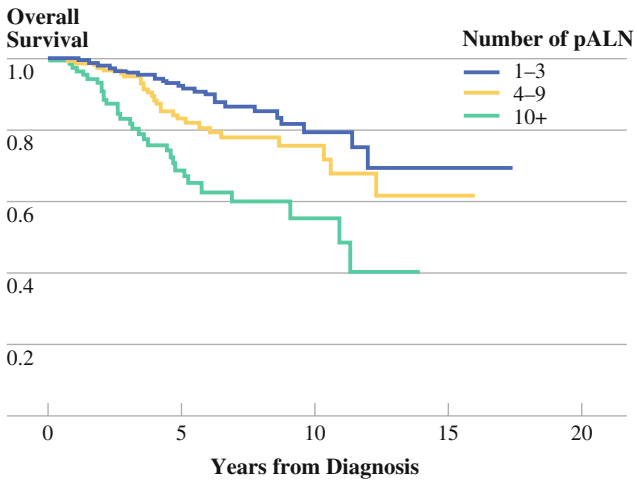

FIG. 1 Number of positive axillary lymph nodes (pALN) subcategories and effect on overall survival (OS) in patients with node-positive breast cancer ($P < .0001$)

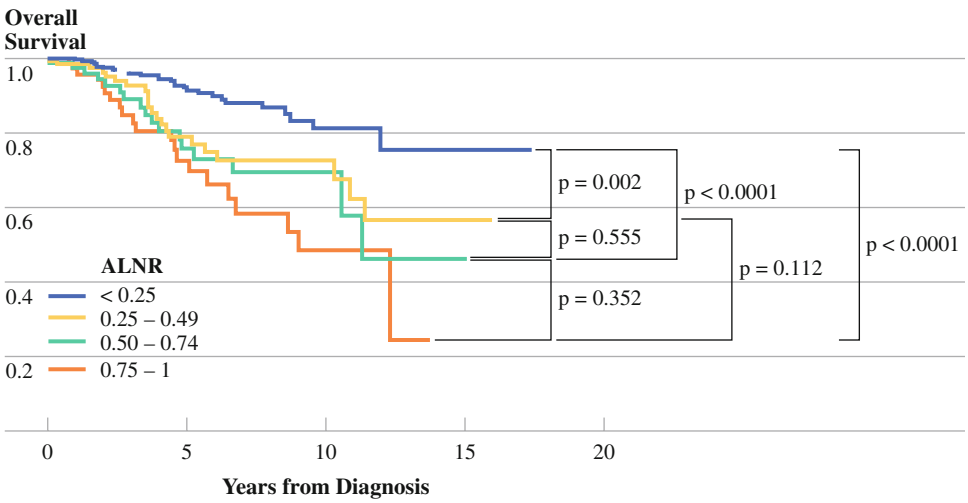

FIG. 2 Axillary lymph node ratio (ALNR) groups and effect on overall survival (OS) in patients with node-positive breast cancer. Significant difference in OS is only found as groups are compared with the <.25 subgroup. The most significant difference in OS is between ALNR < .25 vs. ≥.25 ($P < .0001$)

TABLE 4 Multivariate analysis for determinants of overall survival

Predictive factor	Hazard ratio[a]	95% confidence interval	*P* value
Estrogen-progesterone receptors			
Both positive	1.00		**.001**[b]
One negative	0.819	0.391–1.715	.597
Both negative	2.581	1.430–4.656	.002
Tumor size (cm)			
<2	1.00		.266[b]
2–5	1.761	0.889–3.489	.105
>5	1.651	0.660–4.127	.284
ALNR			
<.25[c]	1.00		**.043**[b]
.25–.49	2.418	1.170–5.000	.017
.50–.74	2.335	1.004–5.431	.049
.75–1.00	3.280	1.249–8.615	.016
No. of pALN[d]	1.020	0.976–1.066	.38

ALNR axillary lymph node ratio; *pALN* positive axillary lymph nodes

[a] Multivariate analyses performed by Cox proportional hazard models without interactions. Hazard ratios of <1.00 represent a decreased risk of death; hazard ratios of >1.00 represent an increased risk of death

[b] *P* value for global test

[c] Hazard ratio for ALNR ≥ .25 = 2.455 (95% confidence interval, 1.292–4.664; $P = .006$)

[d] Number of pALN was used as a continuous variable

Bold values indicate the significance at $P < 0.05$

1.00) and estrogen-progesterone receptor status were the only significant factors for OS ($P = .043$ and $P = .001$; respectively) (Table 4).

DISCUSSION

At the dawn of the molecular era, the status of the ALN remains the single most important determinant of OS in BC. Knowledge of this status is gained through pathologic examination of the ALN retrieved by full ALN dissection (ALND). Although the number of ALN involved with cancer has been demonstrated to be important for prognosis and is included in the 6th edition of the AJCC BC staging system, the role of the total number of ALN retrieved in an ALND specimen has received less emphasis.[20–24] This is despite data that clearly suggest that the likelihood of finding positive nodes in the axilla increases with the number of nodes dissected, and the likelihood of having residual disease in the axilla decreases with a more extensive dissection.[11,25] In an attempt to address the above, several studies have focused on the utility of the ALNR as an independent prognostic indicator of OS.[12–18]

Our study demonstrates a statistically significant negative correlation between ALNR and OS, thus supporting the findings of previous studies (Table 5).[12–18] The strength of the data in the present study draws on the following factors. First, it is a single-center experience, with the same team of medical and surgical oncologists managing all patients between 1983 and 2004. This standardized approach implies that the axillary surgery was performed consistently, using the comparative surgical approaches by the same group of surgeons, and that all patients received comparative postoperative adjuvant treatment protocols (according to the current practice guidelines of that moment). Second, data on the use of adjuvant hormone, chemotherapy, and radiotherapy were available and included into the analysis. These treatment modalities are established determinants of OS, and their inclusion into the analysis adds strength to the conclusions that will be drawn.[26,27] Third, patients who received neoadjuvant chemotherapy were identified and excluded from the study sample. This is relevant because neoadjuvant systemic treatments may modify the nodal yield in an axillary dissection.[28] Finally, our study is one of few to account for the

TABLE 5 Literature review on ALNR as a predictor of overall survival in breast cancer patients

Reference	No. of centers	No. of patients	No. with pALN	Variables studied	ALNR cutoff	HR[a]	ALNR vs. no. of pALN
van der Wal.[12]	1	453	157	Age, type of surgery, tumor size, histologic type, lymphovascular invasion, ER, tumor grade, tumor stage, adjuvant therapy	0.2	2.1	NS
Voordeckers.[13]	1	2073	741	Age, type of surgery, tumor size, histologic type, tumor grade, tumor stage, adjuvant therapy	0.5	2.32	Number of pALN lost significance with ALNR
Vinh-Hung.[14]	9	83,686	25,616	Age, type of surgery, tumor size, histologic type, lymphovascular invasion, ER, PR, tumor grade, tumor stage	Logistic association		NS
Truong.[15]	1	542	542	Age, histologic type, lymphovascular invasion, ER, tumor grade, tumor stage, adjuvant therapy	0.25	1.79	Number of pALN lost significance with ALNR
Kuru.[16]	1	801	801	Age, tumor size, histologic type, lymphovascular invasion, ER, tumor grade, tumor stage, adjuvant therapy	0.25	2.5	Number of pALN lost significance with ALNR
Lale Atahan.[17]	1	939	682	Age, tumor size, histologic type, lymphovascular invasion, surgical margin status, tumor grade, tumor stage, adjuvant therapy	0.26–0.50 >0.50	1.92 3.35	Number of pALN lost significance with ALNR
Vinh-Hung.[18]	Multiple	6,936	1,829	Age, year of diagnosis, socioeconomic class, tumor location, tumor grade, tumor size, adjuvant therapy	0.2 >0.65	1.78 3.21	ALNR predicts survival more accurately than pALN
This study	1	1,450	669	Age, type of surgery, tumor size, histologic type, ER, PR, *HER2,* tumor grade, tumor stage, adjuvant therapy	0.25	2.46	Number of pALN lost significance with ALNR

ALNR axillary lymph node ratio; *HR* hazard risk; *pALN* positive axillary lymph nodes; *ER* estrogen receptor; *PR* progesterone receptor; *NS* not studied

[a] Multivariate analyses performed by Cox proportional hazard models without interactions. Hazard ratios of <1.00 represent a decreased risk of death; hazard ratios of >1.00 represent an increased risk of death

status of estrogen and progesterone receptors as well as *HER2* overexpression, all of which are well-known predictors of OS.[29]

Our data support studies that suggest that ALNR is a stronger prognostic factor for OS than the absolute number of pALN.[13,16–18] In our multivariate model, when ALNR was included in the Cox analysis, the number of pALN lost its significance as an independent predictor of BC survival. Our data also show that among the initially assigned ALNR groups, statistically significant survival difference is only found when comparison was made with the <.25 subgroup, thus advocating the use of an ALNR of .25 as a cutoff. Interestingly, most studies had similar observations.[12,15–18] Thus, it may be interpreted that ALN involvement in >25% of the excised nodes is associated with a poor outcome. The outcome greatly worsens with increasing ALNR.

The question arises whether ALNR-based classification should replace classification based on number of pALN. If one assumes that all patients underwent the same extensive axillary dissection, the distinction between a number-based and a ratio-based staging would disappear, and there would be no advantage of replacing the number of pALN with an ALNR-based classification. However, heterogeneity of lymph node examination is commonly encountered in daily practice; thus, the ALNR can be useful to address that heterogeneity.[18] It is generally accepted that ≥10 nodes are needed for accurate assessment and staging of BC.[30] The recovery of too few ALN in an ALND may lead clinicians to understage patients, which in turn would lead to undertreatment.[31] The effect of understaging on OS and disease-free survival may be important, with some studies showing better 5-year OS for patients with >10 ALNs examined.[32–35]

For the same total absolute number of positive nodes, a variation in the total number of retrieved nodes in an ALND will lower the ALNR and thus help better differentiate patient subgroups in terms of OS. Moreover, variations in the methods of pathologic processing can affect the rates of detecting micrometastatic nodal involvement.[36] During the primary era of our study (1980 s and 1990 s), it is likely that most cases of micrometastatic disease were diagnosed by hematoxylin and eosin (H&E) staining, rather than immunohistochemistry (IHC) or molecular studies. Most centers have continued to use H&E staining as a minimum standard in nodal assessment. However, contemporary studies examining step sectioning and IHC protocols support the use of serial sectioning and IHC assessment to reduce the risk of false-negative results with H&E histological examination alone.[36–38] Thus, for the same number of positive nodes retrieved, a more extensive dissection may result in removing nodes that have positive micrometastatic disease undetected by conventional H&E examination. Furthermore, if < 10 ALN are retrieved after primary surgery, some have advocated axillary radiation to improve local control.[39] The addition of axillary radiation to ALND greatly increases the risk of lymphedema over ALND alone; thus, its use for the sole indication of <10 ALN retrieved may unnecessarily increase morbidity.[40] Thus, the usefulness of the ALNR in selecting patient subgroups for axillary radiation seems intuitive by the same rationale but would require confirmation in larger studies.

Our study demonstrates that the ALNR is a stronger factor in predicting OS than the absolute number of positive ALNs. It may aid in subdividing patients with positive ALNs into low-risk and high-risk groups, with potential implications for their subsequent adjuvant treatment. It may be suggested that in prospective adjuvant therapy trials, patients should be divided according to ALNR when the ALN status is a determinant of treatment choice.

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