IMPACT OF NUMBER OF POSITIVE LYMPH NODES AND LYMPH NODE RATIO ON SURVIVAL OF WOMEN WITH NODE-POSITIVE BREAST CANCER

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INTRODUCTION

Breast cancer is one of the most common malignancies, accounting for 23% of all cancers in women worldwide. In Brazil, 59.700 new breast cancer cases are expected in 2018 according to the Brazilian National Cancer Institute (INCA). Lymph node involvement has long been recognized as one of the most important prognostic factors in breast cancer. The presence of positive axillary lymph nodes is a predictor of increased risk of local and distant recurrence, directly affecting mortality. The association between lymph node involvement and survival has been previously demonstrated and it has been shown that overall survival rates are up to 40% lower in node-positive patients compared with node-negative ones.

OBJECTIVE

The study aimed to evaluate the effect of axillary positive lymph node(pN) and lymph node rate(LNR) on overall survival and disease-free survival of women with node-positive breast cancer.

MATERIAL AND METHODS

This is a retrospective cohort study of node-positive breast cancer patients (ICD-10, C50) diagnosed and treated between 2008 and 2009 at Cancer Hospital III, a reference center of the Brazilian National Cancer Institute (INCA), Brazil

Patients 18 years of age and older presenting with clinical stage II and III breast cancer were included. As per institutional routine, all patients underwent mastectomy or segmental resection + axillary lymphadenectomy(ALND) (Berg levels I, II or I, II and III) with or without previous axillary lymph node biopsy.

Patients without information on clinical stage (two patients) and number of positive lymph nodes (four patients) were excluded.

Patients were identified from the Hospital Cancer Registry (RHC). Data were collected directly from physical and electronic hospital records and medical charts. Socio-demographic, clinical and related to the oncological treatment variables were collected. Axillary lymph nodes were examined for the total number of lymph nodes removed, number of positive lymph nodes (pN), and lymph node ratio (LNR.).

Descriptive statistics were used for the calculation of measures of central tendency and dispersion for continuous variables and frequency distributions for categorical variables. Overall and disease-free survival curves for different pN and LNR risk groups were constructed using the Kaplan-Meier method and compared by the log-rank test at p < 0.05. Multivariate analysis was performed using stepwise forward Cox regression models, and all variables associated with the outcome variables at p < 0.20 on univariate analysis were included in multivariate models. A p value < 0.05 was considered statistically significant in the final model. The study was approved by the INCA Research Ethics Committee in accordance with resolution CNS n. 466/12 under protocol number 128/11.

All analyses were performed using SPSS version 21.0.0 (Statistical Package for the Social Sciences, São Paulo, Brazil).

RESULTS

During the study period, 628 women underwent surgery for invasive breast cancer with axillary lymph node involvement and no distant disease. The median age was 54 years (range: 23 91 years), most women were Caucasian (55%) (Table 1).

The median number of lymph nodes removed per patient was 19 (range: 6 77). Nearly all women (98%) had 10 or more lymph nodes removed, and the median number of positive lymph nodes was four (range: 1 77). Based on the AJCC/UICC staging system, 304 patients were classified as pN1 (48%), 186 (30%) as pN2, and 138 (22%) as pN3 according to the number of positive lymph nodes (Table 1).

Fifty-one percent of patients had lymph node ratio (LNR) < 0.20 (low-risk), 33% had LNR of 0.21 0.65 (intermediate-risk), and 16% of patients had LNR > 0.65 (high-risk). In the DFS model, the adjusted five-year risk of breast cancer recurrence of pN2 and pN3 patients was 2.47 and 2.42 times greater, respectively, than that of pN1 patients (p < 0.001). In addition, the five-year recurrence risk of intermediate- and high-risk LNR patients was 2.11 and 3.19 times greater, respectively, than that of low-risk LNR patients (p < 0.001Table2).

In the OS model, the adjusted risk of death was greater in pN2 (HR = 2.17, 95% CI: 1.42 3.30) and pN3 (HR = 2.41, 95% CI: 1.53 3.78) patients than in pN1 patients. In addition, the risk of death of intermediate- and high-risk LNR patients was 1.70 (p = 0.011) and 2.74 (p < 0.001) times greater, respectively, than that of low-risk LNR patient (Table2).

CONCLUSION

In women with node-positive breast cancer, the number of positive lymph nodes (pN) and lymph node ratio (LNR) are important prognostic factors of disease-free survival and overall

Table 1. Clinicopathologic characteristics of patients with node-positive breast cancer (n=628)

Variables	N	%
Age at diagnosis = 50 years	408	65.0
Median (min-max)	54 (23-91)	
Race/ethnicity White	348	55.4
Number of lymph nodes removed =10	616	98.1
Median (min-max)	19 (6 a 77)	
Number of positive lymph nodes		
Median (min-max)	4 (1 a 49)	
PN1 (1-3)	304	48.4
pN2 (4-9)	186	29.6
pN3 (=10)	138	22.0
Lymph node ratio		
Median (min-max)	0.20 (0.02-1.00)	
Low risk (= 0,20)	318	50.6
Intermediate risk (0,20 - 0,65)	208	33.1
High risk (> 0,65)	102	16.2

**Table 2.** Cox regression model (crude and adjusted) for risk of recurrence and death

Variables	N (%)		Univariate analysis		Multivariate analysis	
	Yes	No	HR (95% CI)	p value	HR (95% CI)	p value
Risk of Recurrence						
Number of lymph nodes positive*						
PN1 (1-3)	57 (28.1)	247 (58.3)	Reference		Reference	
pN2 (4-9)	82 (40.4)	103 (24.3)	2.70 (1.93-3.79)	<0.001	2.47 (1.72-3.56)	<0.001
pN3 (=10)	64 (31.5)	74 (17.5)	3.09 (2.16-4.42)	<0.001	2.42 (1.62-3.60)	<0.001
Lymph node ratio**						
Low risk (0.20)	63 (31.0)	255 (60.1)	Reference		Reference	
Intermediate risk (0.20 − 0.65)	88 (43.3)	120 (28.3)	2.41(1.74-3.32)	<0.001	2.11 (1.49-3.00)	<0.001
High risk (> 0.65)	52 (25.6)	49 (11.6)	3.38(2.34-4.88)	<0.001	3.19 (2.12-4.80)	<0.001
Risk of Death						
Number of lymph nodes positive***						
PN1 (1-3)	46 (30.9)	258 (53.9)	Reference		Reference	
pN2 (4-9)	55 (36.9)	131 (27.3)	2.10(1.42-3.12)	<0.001	2.17 (1.42-3.30)	<0.001
pN3 (=10)	48 (32.2)	90 (18.8)	2.71(1.81-4.07)	<0.001	2.41 (1.53-3.78)	<0.001
Lymph node ratio****						
Low risk (= 0.20)	51 (34.2)	267 (55.7)	Reference		Reference	
Intermediate risk (0.20 − 0.65)	58 (38.9)	150 (31.3)	1.85 (1.27-2.69)	0.001	1.70 (1.13-2.56)	0.011
High risk (> 0.65)	40 (26.8)	62 (12.9)	2.97 (1.96-4.49)	<0.001	2.74 (1.75-4.28)	<0.001

* Adjusted for clinical stage, hormone therapy, histological grade, and age.
** Adjusted for clinical stage, hormone therapy, histological grade, histological type, and age.
*** Adjusted for clinical stage, histological grade, hormone therapy, and radiotherapy.
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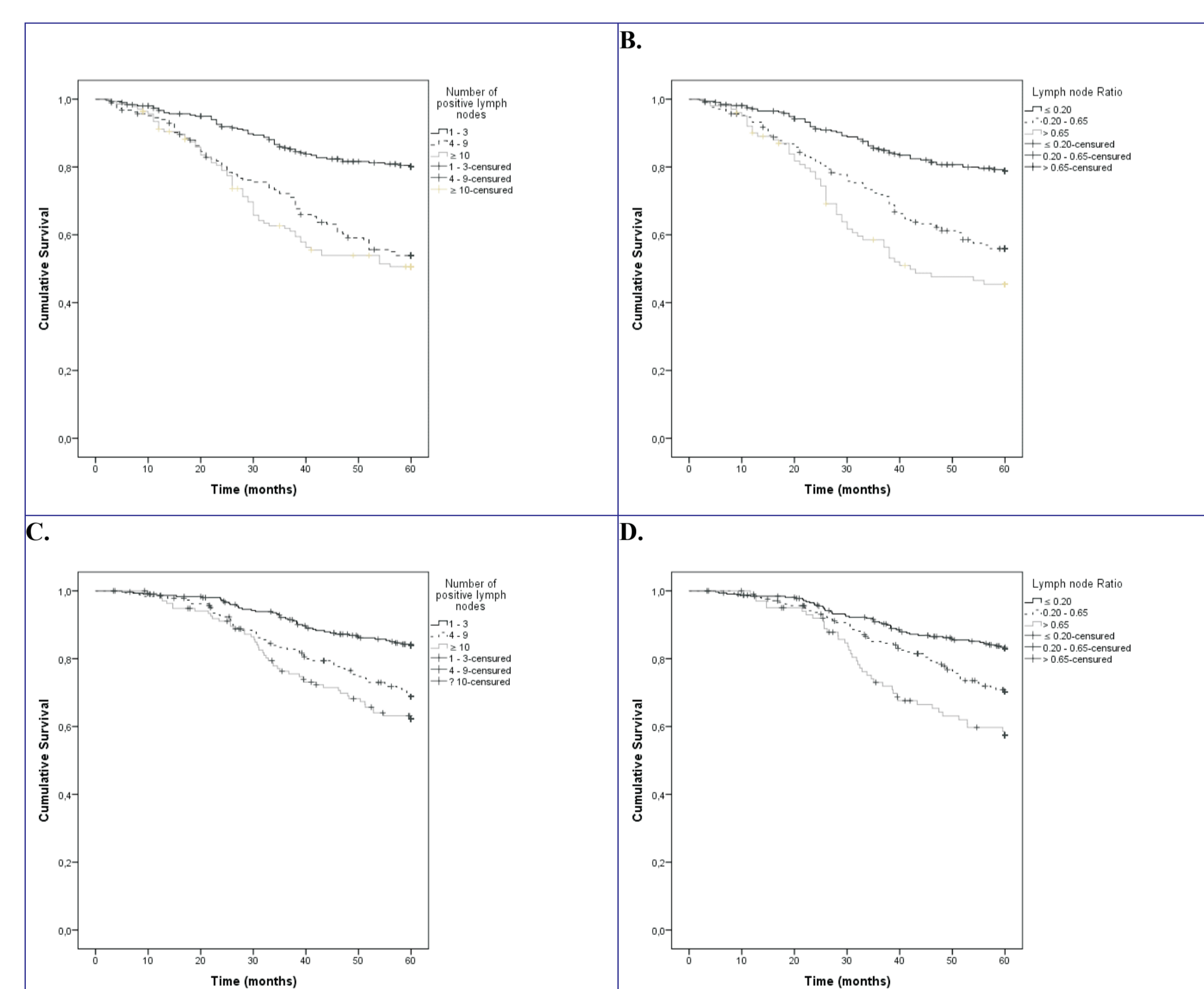
A and B = Disease Free Survival; C and D = Overall Survival
Figure 1. Kaplan-Meier survival estimates according to the number of positive lymph nodes (pN) and lymph node ratio (LNR) A and B = Disease Free Survival; C and D = Overall Survival

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