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CORRESPONDENCE

Lymph Node Ratio Better Predicts Disease-Free Survival in Node-Positive Breast Cancer Than the Number of Positive Lymph Nodes

Vinh-Hung et al[1] proposed a ratio of the number of positive versus the number of removed lymph nodes to stage node-positive breast cancer. The authors start with the construction of a multivariate survival model with breast cancer death as primary outcome and conclude on the significance of the prognostic value of the lymph node ratio (LNR). In a second step, two cutoffs were sought to categorize the LNR such that the difference in maximal partial likelihood between the continuous and the categorized model is minimized. Vinh-Hung et al claim that the LNR is a significant prognostic indicator in the multivariate model, and that after categorizing the LNR with cutoffs at 0.20 and 0.65, the LNR is a good alternative to pN staging.

Using data from a different population, we tested whether these two hypotheses were valid for disease-free survival rather than overall survival. A database of primary operable breast cancers diagnosed between 2000 and 2005 in the University Hospital Leuven was used. A total of 2,064 patients were admitted in this period, 1,852 without sentinel node procedure, which was introduced in June 2003. The pathological report of 35 patients did not contain the number of removed or positive lymph nodes (1.9%). In the remaining sample of 1,817 patients, 696 patients had positive lymph nodes (38.3%). Seven patients were removed because of missing values in the treatment variables or the size of the tumor (1.0%). The median age of the patients was 54 years. The median number of positive nodes was 2 (range, 1 to 42). The median LNR was 0.13 (range, 0.03 to 1.00; Table 1).

Table 1. Characteristics of Patients With Lymph Node Positive Breast Cancer in the Leuven Dataset

Characteristic	Patients (N = 689)	
	No.	%
Age, years		
Median	54	
Lower-upper quartiles	47-65	
< 50	230	33.4
≥ 50	459	66.6
Year of diagnosis		
2000	122	17.7
2001	133	19.3
2002	137	19.9
2003	126	18.3
2004	112	16.3
2005	59	8.6
High histologic grade	343	49.8
Tumor size, cm		
Median	32	
Lower-upper quartiles	20-46	
≤ 2	183	26.6
> 2	506	73.4
No. of lymph nodes removed		
Median	18	
Lower-upper quartiles	14-22	
1-3	4	0.6
4-6	5	0.7
6-9	47	6.8
≥ 10	633	91.9
No. of positive lymph nodes		
Median	2	
Lower-upper quartiles	1-5	
1-3, pN1	452	65.6
4-9, pN2	159	23.1
≥ 10, pN3	78	11.3
Lymph node ratio		
Median	0.13	
Lower-upper quartiles	0.07-0.29	
≤ 0.20	464	67.3
> 0.20 and ≤ 0.65	173	25.1
> 0.65	52	7.6
Adjuvant treatment		
None	8	1.2
Radiotherapy	626	90.9
Chemotherapy	420	61.0
Endocrine therapy	561	81.4

A multivariate Cox regression[2] model including age at diagnosis, the year of diagnosis, high histologic grade, the logarithm of the tumor size, radiotherapy, chemotherapy, endocrine therapy, and LNR confirmed the significant prognostic value of the LNR (hazard ratio = 9.46, 95% CI, 5.03 to 17.79). The discriminative ability of the LNR and the number of positive lymph nodes was compared by means of the time dependent receiver operating characteristic curve.[3] Figure 1A shows that LNR was superior to the number of positive lymph nodes to discriminate relapsing from nonrelapsing patients.

Vinh-Hung et al[1] proposed two cutoff values to categorize the LNR to obtain three different groups with respect to overall survival. Since our goal is to test the LNR as a prognostic measure for disease-free survival, the cutoff values may need to be adapted. The multivariate model discussed above was used to identify a pair of cutoff values to categorize the LNR. Both cutoffs were varied between 0.05 and 0.95 in steps of 0.05. Optimal cutoff values were defined as the pair of cutoffs leading to the minimal negative change in maximal partial likelihood in comparison with the continuous LNR on 5,000 bootstrap iterations. However, this analysis suggested three possible pairs of cutoffs. In a second analysis, the concordance index as introduced by Harrell et al[4] was used to select the optimal cutoff values. This led to a single peak in the distribution of the optimal cutoffs (Fig 2). The optimal cutoffs (LNR = 0.10 and LNR = 0.40) were used to categorize the LNR and the discriminative ability was compared with the continuous LNR and the pN classification in Figure 1B. Obviously, the categorization of LNR leads to a decrease in performance, but the performance is still better than that of the pN classification.[5]

We tested the LNR as a prognostic factor for disease-free survival rather than overall survival. In our sample the continuous LNR was a

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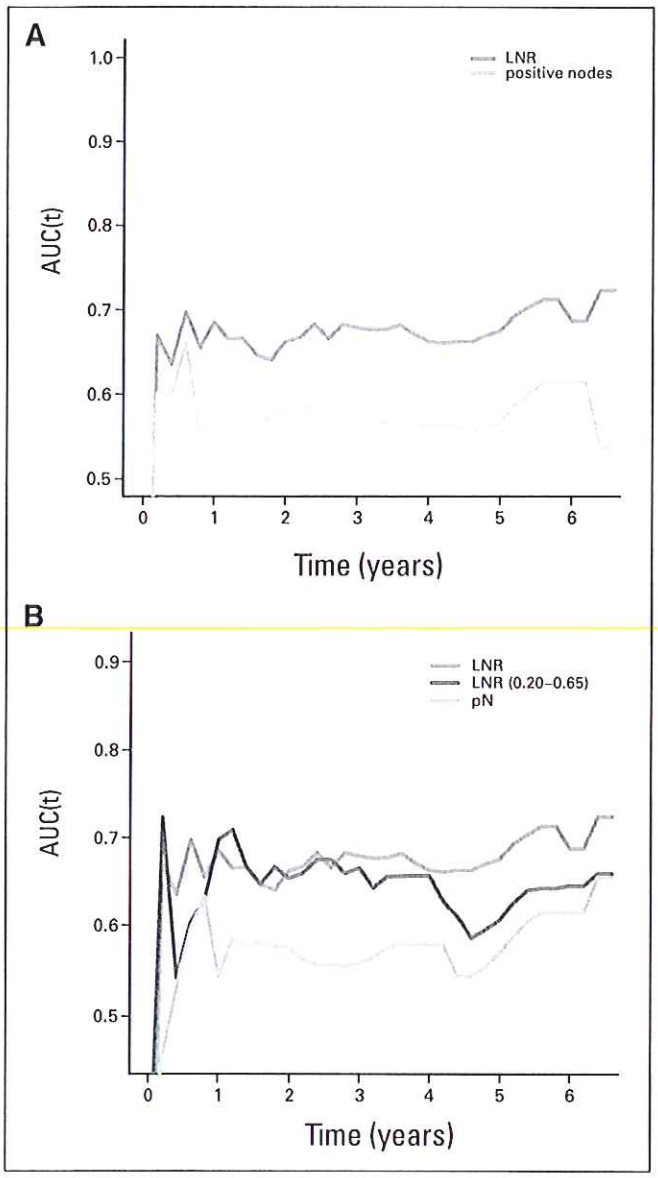


Fig 1. Time-dependent receiver operating characteristic. (A) Lymph node ratio (LNR; blue line) and the number of positive lymph nodes (gold line) as continuous variables. (B) Comparison of the discriminating ability for the continuous LNR (blue line) and the optimal categorization by maximizing the concordance index (gray line). The categorization based on the number of positive nodes (pN; gold line) is performing less than the categorized LNR.

strong predictor of breast cancer relapse. Cutoff values to categorize the LNR in prognostic risk groups (low, LNR ≤ 0.10; intermediate, $0.10 < \text{LNR} \leq 0.40$; and high, $0.40 < \text{LNR}$) were identified using the concordance index based on 5,000 bootstrap samples. LNR categorization was a better predictor for breast cancer relapse than categorization based on the number of positive lymph nodes.

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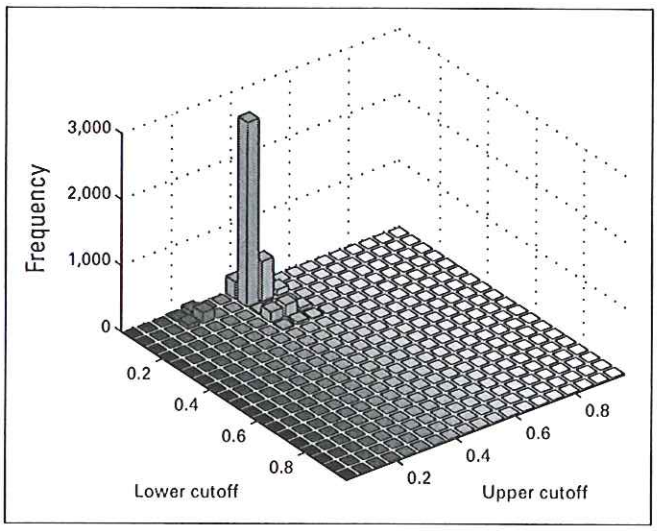


Fig 2. Distribution of bootstrap lymph node ratio cutoff points. The concordance index was used to select the optimal cutoff values in 5,000 bootstrap iterations.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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