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Impact of lymph node ratio on survival of colorectal cancer patients

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ABSTRACT

Background and Purpose: This study analyzed the prognostic significance of the staging system based on the metastatic Node Ratio (NR) compared with the TNM staging system in patients with colorectal cancer.
Methods: We reviewed the data of 444 patients who underwent colorectal resection for cancer between January 2005 and December 2011. NR categories NR0 (0%), NR1 (1–19%) and NR2 (⩾20%) were determined by the best cut-off approach at log-rank test. To compare the prognostic power of the NR versus pN, we plotted these different factors against the mortality estimates. Additionally, we evaluated the relationship between these variables and the extent of lymphadenectomy.
Results: Both the NR and the pN classification significantly stratified patient outcomes ($p < 0.0001$), but the NR system seems to better discriminate prognostic subgroups than the pN. Furthermore, NR is less dependent on the extent of lymphadenectomy than pN.
Conclusions: NR is a simple and reliable tool to stratify survival of colorectal cancer patients and it seems to have a higher prognostic power than the current pN system, because it is less dependent on the extent of lymphadenectomy.

1. Introduction

The Tumour, Nodes, and Metastasis (TNM) staging system is a worldwide benchmark for reporting the extent of malignant disease and it is a major prognostic factor for predicting the outcome of patients with cancer. [1]

For colorectal cancer, the optimal staging system still represents a matter of intense debate because in all the TNM editions, the definition of lymph node status (N) has always been affected by the extent of lymph node dissection or node retrieval by pathologists. [2–5]

With these premises, a pragmatic approach could be represented by a lymph node staging system based on a classification that does not depend strictly on the extent of lymph node dissection. Recently, several authors have discussed the possible significance of the metastatic Node Ratio (NR, the number of metastatic lymph nodes related to the total number of dissected lymph nodes). NR has been indicated as an optimal classification criterion in predicting patient survival and avoiding stage migration errors. [6]

The oncological value of NR as a prognostic factor in colorectal cancer survival seems to overcome the dependence of the lymph node number on anatomical features, surgical technique, surgeon skills, and pathological analyses. [7–17]

In the present study, more than 400 patients with colorectal cancer were reviewed and the prognostic significance of the NR was evaluated in comparison with conventional N classification according to the TNM staging system. [1]

2. Patients and methods

A total of 492 consecutive patients with colorectal carcinoma underwent surgery between January 2005 and December 2011. Eighteen patients (3.7%) were lost to follow up and 30 (6.1%) were excluded because of incomplete data. The study is based on 444 patients (90.2%): 204 females (45.9%) and 240 males (54.1%) with a mean±SD age of 67±11 years (median age: 65 years). Data were collected from clinical charts and pathological exams: the factors considered are specified in Table 1.

Pretreatment tumor stage was determined in all cases by conventional imaging techniques, such as colonoscopy and chest and abdominal CT scan. The colonic resections were performed via conventional open or laparoscopic approach by different surgeons with high experience in colorectal surgery.

2.1. Statistical analysis

The survival analysis was obtained from data collected during a 5-year follow-up program. The end-point of our study was cancer-related death. Survival was considered from surgery to the last patient

Table 1
Clinical and pathological data of the 444 patients with results of the univariate survival analysis

Variable	No. of patients	% of patients	5-year survival (%)	p-value [a]
Gender				0.091
M	240	54.1	65.0	
F	204	45.9	75.8	
Age (years)				0.007
<65	193	80.0	79.9	
⩾ 65	251	20.0	62.2	
Comorbidities [b]				N.S.
Yes	401	91.8	72.3	
No	36	8.2	69.1	
BMI (kg/m^2) [b]				N.S.
<27	145	67.4	69.8	
⩾27	70	32.6	77.9	
Symptoms				0.080
Yes	337	75.9	68.4	
No	107	24.1	72.3	
CEA (U/l) [b]				<0.001
<5 ng/dl	70	63.0	93.1	
⩾5 ng/dl	41	34.0	22.5	
Surgical approach				0.011
Laparoscopic	228	51.4	79.2	
Conversion	18	4.5	50.8	
Open	198	44.6	79.2	
pT				<0.001
T1	19	4.3	66.3	
T2	66	14.9	94.6	
T3	321	72.3	69.4	
T4	38	8.5	49.5	
pN				<0.001
N0	233	52.5	83.3	
N1	117	26.3	68.0	
N2	94	21.2	42.3	
NR				<0.001
NR0	233	52.5	83.3	
NR1	134	30.2	63.7	
NR2	77	17.3	43.3	
Total nodes				0.100
<21	234	52.7	65.2	
⩾21	210	47.3	74.5	
M				<0.001
M0	374	84.2	80.2	
M1	70	15.8	21.0	
Grading				<0.001
G1/ G2	368	82.9	76.3	
G3	76	17.1	51.4	
Lymphoinvasion [b]				<0.001
Yes	142	32.6	56.1	
No	293	67.2	78.6	
Neuroinvasion [b]				0.004
Yes	51	11.6	51.8	
No	386	88.1	72.0	
Angioinvasion [b]				<0.001
Yes	60	13.8	44.5	
No	375	86.0	75.3	
Postoperative complications				0.025
Yes	59	13.3	59.8	
No	385	86.7	71.4	
Adjuvant therapy				0.002
Yes	312	70.2	81.2	
No	132	29.8	66.1	

[a] Only p values ⩽0.1 are listed explicitly. N.S., not significant.
[b] Variable with missing data.

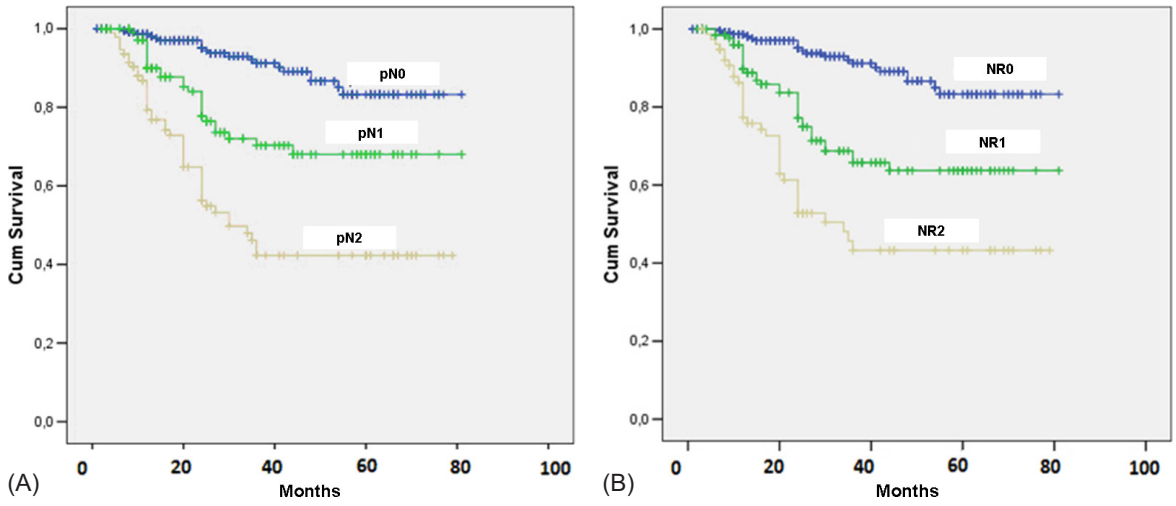

Fig. 1. (A) Survival curve according to pN. (B) Survival curve according to NR.

follow up or death (with patients censored for non cancer-related death).

All variables were expressed as mean ± standard deviation (SD) or median and range, as appropriate. Correlations between two continuous variables were analyzed by the Pearson test. For some tests continuous variables have been categorized according to the median value or the literature suggestions. Five-year survival rates were calculated according to the Kaplan–Meier method; the log-rank test was used to assess the statistical difference between groups. Multivariate analysis was performed using the Cox proportional hazard model selected in backward stepwise regression, including only the variables with $p < 0.1$ at log-rank test. For all the variables the hazard ratio (HR) and the 95% confidence interval (95% CI) were calculated. The regression model was controlled by the goodness of fit tests.

In order to stratify the NR based prognosis, we used a cut-off of 20% (NR0 = 0%, NR1 = 1–19%, NR2 $\geqslant$ 20%): this value derives from the best discrimination obtained by the log-rank test applied to different levels of NR. Values of $p < 0.05$ were considered significant. The statistical analysis was performed via SPSS (16th edition) software for Windows©.

3. Results

After a median follow up of 26 months (31.5±20.8 months), 355 patients (80%) were alive; 89 had died, of whom 69 (69/89, 77.5%) from colorectal cancer. The 5-year (cancer-related) survival rate was 70.2±5.8%.

We observed 162 (36.5%) right colon cancers, 27 (6.1%) transverse colon, 59 (13.3%) left colon, 98 (22.1%) sigmoid colon, 49 (11.0%) rectum–sigmoid junction and 54 (12.2%) rectum. Only 6 patients (1.4%) presented multifocal localization.

Laparoscopic resections were performed in 228 cases (51.4%); 18 patients (4.5%) required conversion to open resection; 198 patients (44.6%) underwent conventional open resection. The mean number of positive nodes was 2.1±4.0 and the mean number of total removed nodes was 22.9±12.5.

Clinical and pathological data of the 444 patients with results of the univariate survival analysis are shown in Table 1.

Figure 1 graphically demonstrates survival differences related to the variables associated with lymph node staging (pN, NR).

Tables 2 and 3 show the results of multivariate analysis: in order to overcome the multi-colinearity problem and to obtain an estimate of reliability for pN and NR, we designed two different models of multivariate analysis in which the lymph node status was included separately as pN or NR.

Table 2
Results of multivariate analysis by Cox regression for NR

Variable	p-value	Hazard ratio	95% CI	
			LL	UL
Node Ratio				
N2	<0.001	5.16	2.72	9.77
N1	0.003	2.63	1.39	4.99
N0	–	1	–	–
Angioinvasion				
Yes	0.011	1.92	1.16	3.17
No	–	1	–	–
Neuroinvasion				
Yes	0.04	1.88	1.03	3.42
No	–	1	–	–
Lymphoinvasion				
Yes	0.016	1.79	1.12	2.88
No	–	1	–	–

LL, lower limit; UL, upper limit.

Table 3
Results of multivariate analysis by Cox regression for pN

Variable	p-value	Hazard ratio	95% CI	
			LL	UL
pN				
N2	<0.001	5.07	2.72	9.46
N1	0.013	2.34	1.2	4.58
N0	–	1	–	–
Angioinvasion				
Yes	0.014	1.90	1.14	3.15
No	–	1	–	–
Grading				
G3	0.05	1.67	1.0	2.78
G1/G2	–	1	–	–
Lymphoinvasion				
Yes	0.041	1.63	1.02	2.62
No	–	1	–	–

LL, lower limit; UL, upper limit.

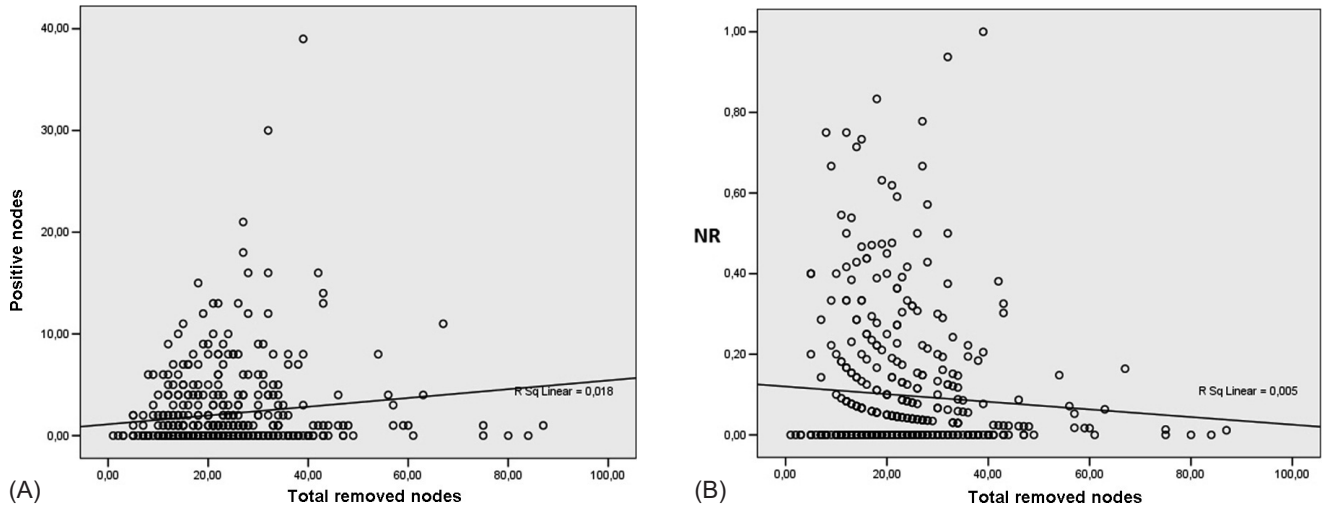

Fig. 2. (A) Scatter plot for correlations between positive nodes and total number of nodes removed. (B) Scatter plot for correlations between NR and total number of nodes removed.

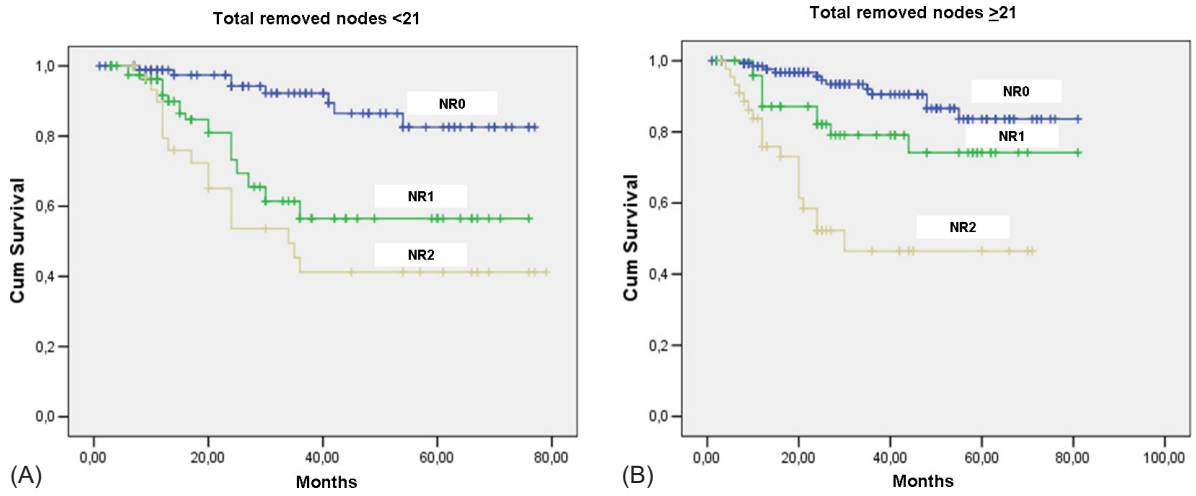

Fig. 3. (A) Survival curve of patients with <21 removed nodes, stratified according to NR. (B) Survival curve of patients with ⩾21 removed nodes, stratified according to NR.

Moreover, we tested the relationship between lymphadenectomy (numerically evaluated, as suggested by the TNM system) and number of lymph node metastases and NR, respectively: we verified a significant strong direct correlation ($r = 0.134$, $p = 0.005$) between number of lymph node metastases and total number of nodes retrieved, without any evidence of significant association ($r = -0.069$, $p = 0.150$) between NR and number of lymph nodes removed (Fig. 2).

To further confirm the independence between the NR and lymphadenectomy (evaluated this time according to a numeric cut-off, as suggested for clinical practice), we stratified patients with < or ⩾21 removed lymph nodes (our median value) for NR subgroups: NR is able to significantly stratify survivals of both groups (Fig. 3). A similar result was obtained using the cut-off of 12 nodes as minimum number of lymph nodes to remove established by TNM staging system (5-year survival rates in patients with <12 total nodes: 64.5% in NR1 cases and 41.2% in NR2 cases, $p < 0.001$; 5-year survival rate in patients with ⩾12 total nodes: 59.1% in NR1 cases and 55.4% in NR2 cases, $p = 0.004$). [1]

4. Discussion

The last editions of UICC-TNM codified the minimum number of lymph nodes to remove (12 in total) in order to accurately stage the nodal involvement in colorectal cancer patients. [1] It is clear that surgeons are not able to count the nodes during their procedure and the number of removed nodes is necessarily a postoperative datum. Hence, an ideal staging criterion for N status should not be affected by the extent of lymphadenectomy. Node ratio has been proposed as a solution to this problem. [6–17]

Firstly, our study confirmed that nodal involvement is among the strongest prognostic factors for colorectal cancer patients: pN and NR significantly stratified patient survival (Fig. 1) and multivariate analysis showed that these indicators were both independent prognostic factors. Actually, the hazard ratios for NR better discriminated different groups than the HRs for pN (Tables 2, 3).

Secondly, we aimed to verify the relationship between NR and extent of lymphadenectomy. Given that the current TNM staging system categorizes patients with less than 12 examined nodes as unclassifiable, [11,12] we investigated the potential independence of NR from the number of removed nodes, possibly in order to stage these patients. In our study, we demonstrated that NR is not entirely

independent from the lymphadenectomy evaluated with numerical criteria: in fact, NR has a decreasing trend (though not significantly) when the number of removed lymph nodes increases (Fig. 2). However, this dependence is not significant compared with the direct dependence calculated for the pN staging: in fact, we significantly stratified according to NR categories also patients with a limited lymphadenectomy (with <21 or <12 total nodes). This is a further demonstration that the NR differs from pN: the number of positive lymph nodes is the numerator of a ratio in which the denominator is the total number of removed lymph nodes; thus, the NR can work as a "reliever" of the factors that influence the number of lymph nodes examined.[18–21] However, also the node ratio is not immune to the stage migration phenomenon. Graphically, this risk could find a demonstration in Fig. 3a, where the survival curves of patients with less than 21 lymph nodes examined are similar for the NR1 and NR2 groups; this is not the case for patients with more than 21 nodes removed, where the NR1 survival curve is closer to the NR0 one. Specifically, the NR1 group of patients with less than 21 lymph nodes examined might include patients who with a more extended lymphadenectomy would be classified in the group with worse prognosis (NR2).

Finally, although this study has non-negligible limitations related to its retrospective design and actuarial survival, our results are consistent with the literature about the relevant prognostic impact of NR (even though expressed with different cut-offs). However, an open problem is the correlation between NR and lymphadenectomy: if this correlation will never be demonstrated, NR could appear as the best prognostic factor for lymph node status because not susceptible of stage migration. *On the contrary, if this correlation will be proven beyond doubt and a more extended lymphadenectomy (with a potentially higher number of lymph nodes to be examined) will be performed reducing the NR value (by increasing the denominator), NR could appear as the best measure of lymphadenectomy.*

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Disclosure statement
The authors have no conflicts of interest to declare.

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