The Ratio Between Metastatic and Examined Lymph Nodes (N Ratio) Is an Independent Prognostic Factor in Gastric Cancer Regardless of the Type of Lymphadenectomy

Results From an Italian Multicentric Study in 1853 Patients

Alberto Marchet, MD, Simone Mocellin, MD,* Alessandro Ambrosi, PhD,*† Paolo Morgagni, MD,‡ Domenico Garcea, MD,‡ Daniele Marrelli, MD,§ Franco Roviello, MD,§ Giovanni de Manzoni, MD,‖ Annamaria Minicozzi, MD,‖ Giovanni Natalini, MD,¶ Francesco De Santis, MD# Luca Baiocchi, MD,** Arianna Coniglio, MD,** and Donato Nitti, MD* on behalf of the Italian Research Group for Gastric Cancer (IRGGC).*

Purpose: To investigate whether the ratio between metastatic and examined lymph nodes (N ratio) is a better prognostic factor as compared with traditional staging systems in patients with gastric cancer regardless of the extension of lymph node dissection.

Patients & Methods: We retrospectively reviewed the data of 1853 patients who underwent radical resection for gastric carcinoma at 6 Italian centers. Patients with >15 (group 1, n = 1421) and those with ≤15 (group 2, n = 432) lymph nodes examined were separately analyzed. N ratio categories (N ratio 0, 0%; N ratio 1, 1%–9%; N ratio 2, 10%–25%; N ratio 3, >25%) were determined by the best cut-off approach.

Results: After a median follow-up of 45.5 months (range, 4–182 months), the 5-year overall survival of N0, N1, and N2 patients of group 1 versus group 2 was 83.4% versus 74.2% ($P = 0.0026$), 54.3% versus 44.3% ($P = 0.018$), and 32.7% versus 14.7% ($P = 0.004$), respectively, suggesting that a low number of excised lymph nodes can lead to the understaging of patients. N ratio identified subsets of patients with significantly different survival rates within N1 and N2 stages in both groups. At multivariate analysis, the N ratio (but not N stage) was retained as an independent prognostic factor both in group 1 and group 2 (HR for N ratio 1, N ratio 2, and N ratio 3 = 1.67, 2.96, and 6.59, and 1.56, 2.68, and 4.28, respectively). In our series, the implementation of N ratio led to the identification of subgroups of patients prognostically more homogeneous than those classified by the TNM system.

Conclusion: N ratio is a simple and reproducible prognostic tool that can stratify patients with gastric cancer also in case of limited lymph node dissection. These data may represent the rational for improving the prognostic power of current UICC TNM staging system and ultimately the selection of patients who may most benefit from adjuvant treatments.

(*Ann Surg* 2007;245: 543–552)

The number of metastatic lymph nodes (N stage) and the depth of the primary tumor (T stage) are currently considered the most reliable prognostic indicators for patients with radically resected gastric cancer.[1–4] While T stage can be readily assessed by pathologic examination of the primary tumor, N stage assessment can be affected by the extension of lymph node dissection, which is classically termed D1, D2, and D3.[5,6] The UICC/AJCC classification, which is the most widely used for the staging of gastric cancer, suggests that at least 15 lymph nodes should be examined for a correct assessment of N stage.[7,8] This implies that D1 lymph node dissection, which is limited to the perigastric lymph nodes, might not guarantee an accurate staging.[9] Nevertheless, this type of lymphadenectomy is routinely performed in several Western countries,[10–12] which is supported by the fact that D2 lymphadenectomy is associated with higher rates of postoperative complications; moreover, its therapeutic efficacy has been questioned in 2 randomized clinical trials.[13–15]

When the AJCC/UICC N stage (which is based on the number of metastatic lymph nodes) is used, the phenomenon of "stage migration" has been observed in 10% to 15% of cases.[16–21] The ratio between metastatic and examined lymph nodes (N ratio) has been recently proposed by our group[22]

From the *Clinica Chirurgica Generale 2, University of Padova, Padova, Italy; †Statistics Center for Biomedical Sciences, San Raffaele University, Milan, Italy; ‡Department of General Surgery, Morgagni-Pierantoni Hospital, Forlì, Italy; §Surgical Oncology Unit, University of Siena, Siena, Italy; ‖First Division of General Surgery, University of Verona, Verona, Italy; ¶General Surgery Unit, General Hospital of Perugia, Perugia, Italy; #Department of Surgery, Todi-Marsciano General Hospital, Todi, Italy; and **Institute of Clinica Chirurgica, University of Brescia, Brescia, Italy.

Supported by the AIRC Regional Grant 2005.

Reprints: Donato Nitti, MD, Clinica Chirurgica Generale 2, Dipartimento di Scienze Oncologiche e Chirurgiche, Università di Padova, Via Giustiniani 2, 35128 Padova, Italy. E-mail: donato.nitti@unipd.it.

ISSN: 0003-4932/07/24504-0543
DOI: 10.1097/01.sla.0000250423.43436.e1

and others[1,19–21,23,24] as a novel prognostic factor that can identify prognostic subgroups among patients with N1 and N2 disease, and reduce the phenomenon of stage migration. In all these studies, an extended lymphadenectomy (D2), which is associated with a higher number of lymph nodes removed, was used as the standard surgical procedure: therefore, the issue of the prognostic value of the N ratio after D1 lymph node dissection has not been addressed yet.

In the light of these considerations, the aims of our present study were the following: 1) to validate the prognostic value of N ratio to efficiently stratify patients with different clinical outcome as compared with traditional prognostic systems in a large multi-institutional series; and 2) to investigate whether the N ratio maintains its prognostic power in patients with limited (D1) lymphadenectomy.

PATIENTS AND METHODS

In this retrospective multicentric study, data were collected from the medical records of 1853 patients who underwent radical resection (R0) for histologically confirmed gastric carcinoma from January 1988 through December 2001. Patients were operated at 6 Italian centers experienced in gastric cancer treatment: Clinica Chirurgica Generale 2, University of Padova (n = 331); First Division of General Surgery, University of Verona (n = 260), Institute of Surgical Sciences, University of Siena (n = 311), "Morgagni" Hospital of Forlì (n = 523); Institute of Clinica Chirurgica, University of Brescia (n = 184); Division of General Surgery, Hospital of Marsciano-Todi (n = 244).

Eligibility criteria included histologically confirmed R0 gastric resection (ie, negative resection margins, en bloc resection of adherent organs, and en bloc resection of greater and lesser omentum) and pathologic evaluation of the total number of resected lymph nodes as well as the number of metastatic lymph nodes. Patients with distant metastases (eg, hepatic, lung, peritoneal dissemination or extraregional lymph nodes [superior mesenteric artery, middle colic artery, and para-aortic lymph nodes] and tumors of the gastric stump after gastric resection for benign disease) were excluded from the analysis. Patients dead in the postoperative period were also excluded.

The resulting 1853 evaluable patients were divided into 2 groups according to the number of examined lymph nodes: group 1 consisted of 1,421 patients with more than 15 lymph nodes and group 2 consisted of 432 patients with 15 or less lymph nodes.

Following the Japanese Research Society for Gastric Cancer (JRSGC) guidelines,[5] lymphadenectomy was classified as D1, D2, and D3. To minimize the phenomenon of stage migration, the nodal dissection of the surgical specimen was performed by surgeons in a standardized fashion (ie, following the JRSGC classification system) on the bench of the operating room. In each center, node status was assessed by the same pathologist, who also reviewed the slides of all primary tumors. Lymph node involvement was classified according to both the 1997 UICC/AJCC TNM classification (N0 = no metastasis, N1 = 1 to 6 metastatic lymph nodes, N2 = 7–15 metastatic lymph nodes, N3 = more than 15 metastatic lymph nodes)[7] and the 1981 JRSGC classification (which is based on the anatomic level of involved lymph nodes according to the site of the primary tumor [upper, middle and lower third of the stomach]: n0 = no lymph node metastases; n1= metastasis to group N1 nodes; n2 = metastases to group N2 nodes; n3= metastases to group N3 nodes).[5]

N ratio intervals were determined by using the best cutoff approach (a method aimed at minimizing the identification of rare classes of patients) and considering patients' survival (log-rank statistic) as the dependent variable.[25] The functional form of the covariate under study was also evaluated by means of the martingale residual analysis.[25] Both analyses identified the following best-fit cutoff values: N ratio 0, 0%; N ratio 1, 1%–9%; N ratio 2, 10%–25%; N ratio 3, >25%. These cutoff values were used both in groups 1 and 2.

All patients had follow-up controls at 6-month intervals; the final date of follow-up was June 2004. The median follow-up after surgery was 45.5 months (range, 4–182 months) for all patients (n = 1853) and 68.9 months (range, 5–182 months) for survivors (n = 1044). In group 1, the median follow-up was 42.3 months (range 4–182 months) and 61.2 months (range, 5–182 months) for all patients (n = 1421) and for survivors (n = 818), respectively. In group 2, the median follow-up was 56.2 months (range, 4–181 months) and 90.3 months (range, 5–181.4 months) for all patients (n = 432) and for survivors (n = 226), respectively.

Overall survival (OS) rates and 95% confidence intervals (CI) were determined using the Kaplan-Meier estimator,[26] an event being defined as death for any cause. The log-rank test was used to identify differences between the survival curves of different patients' groups.[26] The following independent variables were analyzed: 1) age (<70 years versus >70 years); 2) sex (male versus female); 3) tumor site (cardias versus upper third versus middle third versus lower third versus diffuse); 4) type of surgical resection (subtotal gastric resection versus total gastrectomy versus extended total gastrectomy); 5) T stage (T1 [mucosa or submucosa infiltration] versus T2 [muscolaris propria or subserosa] versus T3 [sierosa] versus T4 [extension to other structures]); 6) grading (G1 versus G2 versus G3 versus G4 versus unknown); 7) Lauren type (intestinal versus diffuse versus unknown); 8) anatomic location of lymph node metastases (JGCA n0 versus n1 versus n2 versus n3); 9) number of metastatic lymph nodes (TNM N0 versus N1 versus N2 versus N3); 10) ratio between metastatic and examined lymph nodes (N ratio 0 versus N ratio 1 versus N ratio 2 versus N ratio 3). The number of lymph nodes examined, the number of metastatic lymph nodes, and their ratio were considered initially as continuous variables. However, for practical reasons, we ultimately reported the results after categorizing these variables: indeed, the clinical implementation of N ratio as a novel prognostic factor would require to group patients into prognostically homogeneous classes to make a therapeutic algorithm possible.

A constrained robust regression analysis was performed to evaluate the pattern of the number of metastatic lymph nodes as a function of the number of examined lymph nodes related to the different T categories.[27]

Multivariate survival analysis was performed by means of the Cox proportional hazards model, using the forward stepwise procedure for variable selection.[28] In this model, a key assumption is constant proportionality of hazard rates[29]; since we found some evidence of lack of proportionality ($P = 0.039$), we stratified the model according to the participating centers.

To compare the prognostic power of the TNM system (T stage combined with N stage) with that of a staging system based upon the T stage and the N ratio (TRM), we plotted the natural logarithm of the hazard risk (HR) against the 6 TNM classes (IA, IB, II, IIIA, IIIB, and IV) as well as against 6 novel TRM classes. These latter categories were selected by using k-means cluster analysis that grouped combinations of T stage and N ratio identifying prognostically homogeneous subsets of patients. For this analysis, all patients (n = 1853) were considered.

For all analyses, only P values <0.05 were considered significant.

Statistical analyses and graphics were performed in the "R" environment (www.R-project.org) and with the SPSS 12.0 statistical package (SPSS Inc., Chicago, IL).

RESULTS

Clinical and pathologic data of group 1 and group 2 and for the 5-year OS rates are summarized in Tables 1 and 2, respectively.

According to the JRSGC classification, D1, D2, and D3 lymphadenectomy was performed in group 1 in 159 (11.2%), 974 (68.5%), and 288 (20.3%) cases, respectively; in group 2, D1 and D2 lymphadenectomy was performed in 248 (57.4%) and 184 (42.6%) cases, respectively.

In group 1, a total of 46,713 lymph nodes (median, 30; mean, 32.9; range, 16–108) were removed and examined. Lymphadenectomy included 16 to 25 lymph nodes in 501 patients (35.2%), and more than 25 lymph nodes in the remaining 920 cases (64.8%). A total of 7070 lymph nodes (15.1%) were found to be metastatic (median, 1; range, 0–50).

In group 2, a total of 4588 lymph nodes (median, 11; range, 2–15) were removed and examined, and 760 (16.6%) resulted metastatic (median, 0; range, 0–13).

When applied to the whole set of patients (n = 1853), the constrained robust regression analysis showed that the number of metastatic lymph nodes increased with the number of examined nodes in patients with T2, T3, and T4 but not T1 tumors (slope coefficient: 0.00006, 0.13, 0.15, and 0.26, respectively).

We then evaluated the distribution of N ratio categories (1–3) across the N stage categories in group 1 (N1, N2, N3) and group 2 (N1, N2) patients, separately (Table 3).

In group 1, all 3 N ratio categories were represented in N1 tumors (49.1% N ratio 1, 44.6% N ratio 2, and 6.3% N ratio 3); N ratio 2 and 3 (but not N ratio 1) were represented in N2 tumors (35.4% N ratio 2 and 64.6% N ratio 3); and only N ratio 3 was represented in N3 tumors (Table 3, upper panel).

In group 2 patients, all 3 N ratio categories were represented in N1 tumors (14.7% N ratio 1, 40.6% N ratio 2, and 44.7% N ratio 3), whereas only N ratio 3 was represented in N2 tumors (Table 3, lower panel) (obviously N3 could not be evaluated in group 2).

As regards survival analysis, the 5-year OS rates were 59.2% (confidence interval [CI], 56.5%–62.0%) and 59.0% (CI, 54.4%–64.1%) in group 1 and group 2, respectively (Tables 1 and 2).

Survival differences (log-rank test) among group 1 and group 2 patients according to N stage and N ratio are reported in Table 4. Considering the N stage classification, the 5-year OS of N0, N1, and N2 patients was significantly longer when >15 lymph nodes (group 1) rather than ≤ 15 lymph nodes (group 2) had been removed (N0: 83.4% versus 74.3%, $P = 0.0026$; N1: 54.3% versus 44.3%, $P = 0.018$; N2: 32.7% versus 14.7%, $P = 0.004$, for group 1 and group 2, respectively). When the N ratio classification was applied, OS differences between group 1 and group 2 were maintained for N ratio 0 (which is identical to N0 stage), whereas no significant differences were observed for N ratio 1, N ratio 2, and N ratio 3 (Table 4).

As shown in Figure 1, in group 1 the use of N ratio allowed us to identify subsets of patients with significantly different 5-year OS both within the N1 stage (three subsets identified; P value <0.0001) and within the N2 stage (two subsets identified; $P = 0.003$). In group 2 patients, the N ratio classification did not identify subsets of patients, which is likely due to the low number of cases available.

When the OS rates of patients with different N ratio were compared across group 1 and group 2, no significant differences were found among N ratio 1, N ratio 2, and N ratio 3 of N1 stage and among N ratio 3 of N2 stage, which underscores the homogeneity of the prognostic classes identified by such a classification.

Stepwise regression analysis included all the prognostic factors considered at univariate analysis. In group 1 patients, the factors retained were the following: age (HR for patients older than 70 years = 1.78; CI, 1.502–2.097, $P < 0.0001$), T stage (HR for T2, T3, and T4: 1.59 [CI, 1.235–2.050], 1.69 [CI, 1.316–2.161], and 4.70 [CI, 2.863–7.719], respectively; $P < 0.0001$), type of resection (HR for total gastrectomy and extended total gastrectomy: 1.53 [CI, 0.655–3.557], 1.75 [CI, 1.0712–2.851], respectively, $P < 0.0001$), and N ratio (HR for N ratio 1, N ratio 2, and N ratio 3: 1.67 [CI, 1.246–2.242], 2.96 [CI, 2.303–3.811], and 6.59 [CI, 5.201–10.339], respectively; $P < 0.0001$) (Table 5, upper panel). On excluding the N ratio variable, the overall fit of the Cox model decreased (likelihood ratio test with and without N ratio: 517 and 488, respectively).

Considering group 2 patients (Table 5, lower panel), factors retained at stepwise analysis were the following: age (HR for patients older than 70 years: 1.05; CI, 1.037–1.067; $P < 0.0001$), sex (HR for men: 1.54; CI, 1.129–2.083; $P = 0.005$), tumor site (HR for diffuse, middle third, upper third, and cardias: 1.27 [CI, 0.730–2.192], 1.32 [CI, 0.931–1.881], 1.73 [CI, 1.062–2.814], and 2.39 [CI, 1.225–4.542], respectively; $P = 0.02$), T stage (HR for T2, T3, and T4: 1.84 [CI, 1.183–2.853], 1.33 [CI, 0.897–1.981], and 20.12 [CI, 8.633–46.885], respectively; $P < 0.0001$) and N ratio (HR for N

TABLE 1. Overall Survival (OS) Univariate Analysis According to Clinicopathologic Factors in 1421 Patients With >15 Lymph Nodes Resected Who Underwent Radical Resection for Gastric Cancer

Factor	No. Patients	5-Year OS Rate (%)	95% CI	*P*
All	1421	59.2	56.5–62.0	
Sex				0.299
Female	594	62.3	58.2–66.6	
Male	827	57.0	53.5–60.8	
Age (yr)				0.048
<70	832	64.9	61.5–68.4	
≥70	589	50.9	46.6–55.5	
Site				<0.001
Lower	649	64.1	60.2–68.3	
Middle	324	52.0	40.3–67.9	
Upper	229	31.0	18.6–52.4	
Cardias	87	37.0	20.6–65.2	
Diffuse	132	60.0		
Surgery				0.002
Gastric resection	942	63.0	59.2–73.5	
Total gastrectomy	447	40.0	29.6–54.3	
Extended total gastrectomy	32	36.0	16.6–79.5	
Grading				0.00127
Well differentiated (G1)	120	75.9	68.2–84.6	
Moderately differentiated (G2)	300	58.2	52.5–64.5	
Poorly differentiated (G3)	480	52.9	48.2–58.0	
Undifferentiated (G4)	23	56.5	37.2–85.7	
Unknown	498	61.9	57.4–66.6	
Lauren				0.802
Intestinal	738	62.0	58.3–66.0	
Diffuse	365	51.8	46.6–57.7	
Unknown	318	61.1	58.8–66.8	
T stage				<0.001
T1	458	82.6	78.9–86.5	
T2	458	46.6	41.7–52.1	
T3	477	45.5	41.1–50.4	
T4	28	22.3	10.7–46.4	
Anatomic location of metastatic nodes				<0.001
n0	607	83.1	79.9–86.4	
n1	386	48.7	43.6–54.5	
n2	368	35.1	30.2–40.8	
n3	60	15.2	9.0–35.0	
No. metastatic nodes				<0.001
N0	607	83.4	80.3–86.7	
N1	444	54.3	49.5–59.5	
N2	206	32.7	26.0–40.9	
N3	164	11.6	6.7–18.0	
Metastatic/examined nodes				<0.0001
N ratio 0	607	83.4	80.3–86.7	
N ratio 1	218	66.3	59.7–73.6	
N ratio 2	271	46.8	40.9–53.6	
N ratio 3	325	19.0	14.8–24.5	

ratio 1, N ratio 2, and N ratio 3: 1.56 [CI, 0.792–3.086], 2.68 [CI, 1.738–4.124], and 4.28 [CI, 3.028–6.049], respectively; $P < 0.0001$).

On excluding the N ratio variable, the overall fit of the Cox model decreased (likelihood ratio test with and without N ratio: 95 and 91, respectively).

TABLE 2. Overall Survival (OS) Univariate Analysis According to Clinicopathologic Factors in 432 Patients With <15 Lymph Nodes Resected Who Underwent Radical Resection for Gastric Cancer

Factor	No. Patients	5-Year OS Rate (%)	95% CI	*P*
All	432	59.0	54.4–64.1	
Sex				0.0434
Female	175	62.5	55.4–70.4	
Male	257	56.7	50.7–63.3	
Age (yr)				0.000181
<70	195	67.3	60.9–74.3	
≥70	237	51.7	45.3–58.9	
Site				0.00715
Lower	238	63.9	57.9–70.5	
Middle	109	61.7	52.8–72.0	
Upper	39	45.5	31.4–65.9	
Cardias	16	37.5	19.9–70.6	
Diffuse	30	40.3	25.5–63.5	
Surgery				0.002
Gastric resection	340	62.0	56.8–67.6	
Total gastrectomy	77	52.5	42.0–65.6	
Extended total gastrectomy	15	33.3	16.3–68.2	
Grading				0.361
Well differentiated (G1)	28	64.6	48.3–86.5	
Moderately differentiated (G2)	99	71.7	63.0–81.6	
Poorly differentiated (G3)	135	53.2	45.0–62.9	
Undifferentiated (G4)	3	66.7	30.0–100	
Unknown	167	54.3	47.1–62.6	
Lauren				0.415
Intestinal	322	62.3	57.0–68.0	
Diffuse	64	45.9	34.9–60.5	
Unknown	46	54.8	41.8–71.8	
T stage				<0.001
T1	127	75.6	67.0–83.1	
T2	85	45.6	35.9–58.0	
T3	211	43.8	37.4–50.2	
T4	9	0.0	0.0–0.0	
Anatomic location of metastatic nodes				<0.001
n0	250	74.2	68.7–80.1	
n1	138	39.6	31.9–59.0	
n2	44	31.7	19.7–51.0	
No. metastatic nodes				<0.001
N0	250	74.2	68.7–80.1	
N1	143	44.3	36.5–53.7	
N2	39	14.7	6.6–29.1	
Metastatic/examined nodes				<0.0001
N ratio 0	250	74.2	68.2–80.1	
N ratio 1	21	61.2	43.4–86.4	
N ratio 2	58	47.7	35.6–63.9	
N ratio 3	103	28.1	20.4–38.5	

Since N stage was not retained in the Cox model, we then tried to compare the prognostic power of the traditional TNM system with that of a hypothetical staging system based upon N stage and N ratio (TRM system). Using the survival data from our series (n = 1853), k-means cluster analysis identified 6 prognostically homogeneous TRM classes of patients (1: T1R0; 2: T2R0, T3R0, T1R1; 3: T4R0, T2R1, T3R1, T1R2; 4: T2R2, T3R2, T1R3; 5: T2R3, T3R3, T4R1; 6: T4R2, T4R3). When the 6 traditional TNM stages (IA, IB, II, IIIA, IIIB, and IV) were plotted against their respective HR ranges, significant overlapping was observed among all stages, with the exception of stage IA (Fig. 2, upper panel).

TABLE 3. Metastatic/Examined Nodes Ratio Distribution Among TNM Staging System N Categories in 1421 Patients With >15 Lymph Nodes Resected (Group 1) and 432 Patients With <15 Lymph Nodes Resected (Group 2)

	Metastatic/Examined Nodes (N ratio)				
	0 (0%)	1 (0%–9%)	2 (10%–25%)	3 (>25%)	Total
Group 1					
N0 (0)	607 (100%)				607 (100%)
N1 (1–6)		218 (49.1%)	198 (44.6%)	28 (6.3%)	444 (100%)
N2 (7–15)			73 (35.5%)	133 (64.5%)	206 (100%)
N3 (>15)				164 (100%)	164 (100%)
Group 2					
N0 (0)	250 (100%)				250 (100%)
N1 (1–6)		21 (14.7%)	58 (40.6%)	64 (44.8%)	143 (100%)
N2 (7–15)				39 (100%)	39 (100%)

TABLE 4. Overall Survival (OS) Rates Based Upon N Stage and N Ratio Classification, According to the Number of Lymph Nodes Removed (>15 vs. <15)

N Stage	5-Year OS Rate (%)	*P*	N Ratio	5-Year OS Rate (%)	*P*
N0	>15 (83.4)	0.0026	0	>15 (83.4)	0.0026
	<15 (74.3)			<15 (74.3)	
N1	>15 (54.3)	0.018	1	>15 (66.3)	0.591
	<15 (44.3)			<15 (61.2)	
N2	>15 (32.7)	0.004	2	>15 (46.8)	0.881
	<15 (14.7)			<15 (47.7)	
			3	>15 (19.0)	0.095
				<15 (28.1)	

By contrast, when the 6 TRM stages were plotted against their respective HR ranges, no overlapping was observed (Fig. 2, lower panel).

DISCUSSION

In the present retrospective study, we investigated the prognostic value of N ratio in a group of patients who underwent curative resection for gastric carcinoma. Multivariate analysis showed that a high N ratio has a prognostic value independent of both traditional prognostic factors and extent of lymphadenectomy (extended [more than 15 lymph nodes] versus limited [equal or less than 15 lymph nodes]).

The experience reported in this article comes from centers dedicated to gastric cancer surgery where D2 lymphadenectomy is considered the standard procedure, and thus the number of resected lymph nodes is usually ≥15. According to the constrained robust regression analysis and considering the whole set of patients (n = 1853), the number of metastatic nodes in patients with radically resected gastric cancer increased with the number of lymph nodes removed. Consequently, in patients with T2, T3, and T4 tumor, the number of metastatic lymph nodes may be underestimated if few lymph nodes are removed, which would lead to the understaging of patients. This consideration is supported by the observation that the 5-year OS rate of N0 patients is significantly better (83.4%) in group 1 patients than that observed in group 2 (74.3%). This finding could be due to the fact that some N0 patients from group 2 might turn out to be N+ if a more extended lymphadenectomy had been performed. Similarly, the OS of group 1 is significantly different from that of group 2, both in N1 (54.3% versus 44.3%, $P = 0.018$) and N2 stage patients (32.7% versus 14.7%, $P = 0.004$). Therefore, when a limited lymphadenectomy (D1) is performed, patients classified as N1 stage might instead turn out to be N2 or N3 stage if a D2 lymphadenectomy had been performed. Similar findings have been reported by others.[18–20] For instance, in a study on 650 gastric cancer patients who underwent curative D2 gastrectomy, Bando et al[20] estimated that 103 of 228 (45%) patients with lymph node metastasis would have been understaged as N0 if a D1 dissection had been carried out.

The ratio between positive and examined lymph nodes has been proposed as a simple, convenient and reproducible system that can be used to better identify subgroup of gastric, breast, and colon cancer patients with similar prognosis,[30–32] thus minimizing the stage migration phenomenon that can be observed using the current TNM staging system.

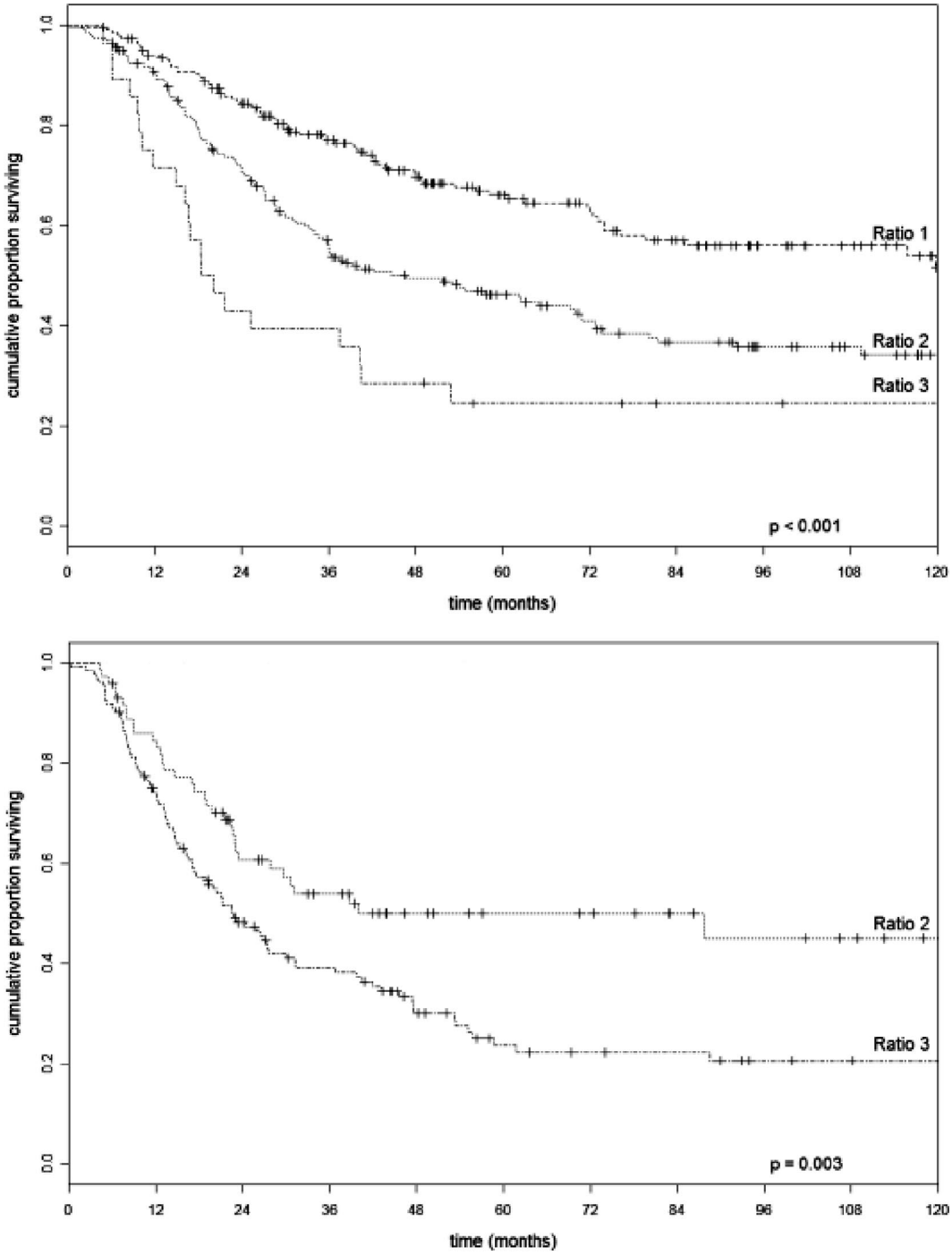

FIGURE 1. Overall survival curves for different N ratio among N1 (upper panel) and N2 (lower panel) patients with more than 15 lymph node resected.

As regards gastric cancer, different N ratio cutoffs have been proposed. In 474 patients treated with D2 lymphadenectomy, Inoue et al[21] adopted the following N ratio cutoffs: ≤25%, ≤50% and >50%; in 650 patients Bando et al[20] selected 4 different N ratio cutoff values: 0% (no lymph node involvement), 1% to 10%, 11% to 25%, and >25%. These authors did not describe a specific method for the selection of the reported cutoffs. Using the log-rank test and the Martingale residual analysis,[25] which avoids the identification of rare classes of patients, we found that the best-fit cutoff values were 0%, 1% to 9%, 10% to 25%, and >25%. These findings are similar to those we obtained in a previous study on 277 gastric cancer patients after D2 lymphadenectomy.[22]

TABLE 5. Prognostic Factors Retained at Multivariate Analysis in 1421 Patients With Gastric Cancer and >15 Lymph Nodes Resected (Group 1) and in 432 Patients With Gastric Cancer and <15 Lymph Nodes Resected (Group 2)

Factor	*P*	HR	>95% CI
Group 1			
Age (>70 yr)	<0.0001	1.78	1.502–2.097
Surgery	<0.0001		
Total gastrectomy	<0.0001	1.53	1.29–1.80
Extended total gastrectomy	0.02	1.75	1.072–2.851
T stage	<0.0001		
T2	0.0002	1.59	1.235–2.050
T3	<0.0001	1.69	1.316–2.161
T4	<0.0001	4.70	2.863–7.719
N ratio	<0.0001		
N ratio 1	0.0004	1.67	1.246–2.242
N ratio 2	<0.0001	2.96	2.303–3.811
N ratio 3	<0.0001	6.59	5.201–10.339
Group 2			
Age (>70 yr)	<0.0001	1.05	1.037–1.067
Sex (male)	0.005	1.54	1.129–2.083
Tumor site	0.02		
Diffuse	0.39	1.27	0.730–2.192
Middle	0.11	1.32	0.931–1.881
Upper	0.02	1.73	1.062–2.814
Cardias	0.006	2.39	1.255–4.542
T stage	<0.0001		
T2	0.005	1.84	1.183–2.853
T3	0.15	1.33	0.897–1.981
T4	<0.0001	20.12	8.633–46.885
N ratio	<0.0001		
N ratio 1	0.19	1.56	0.792–3.086
N ratio 2	<0.0001	2.68	1.738–4.124
N ratio 3	<0.0001	4.28	3.028–6.049

In different Western and Japanese series, the N ratio has been indicated as an effective prognostic tool after D2 or D3 lymphadenectomy.[1,19–24,33] In a study by Bando et al, at multivariate analysis the N ratio was retained as the only independent prognostic factor when the number and the side of metastatic lymph nodes were considered in the analysis.[20] Similarly, Kunisaki et al recently reported that the N ratio independently influenced the prognosis of 758 patients radically resected.[34]

The independent prognostic value of N ratio for patients after D2 lymphadenectomy was reported in our previous monoinstitutional study (n = 277).[22] In the present large multicentric series, we confirm that, when more than 15 lymph nodes are examined, the N ratio discriminates different prognostic categories among patients with N1 and N2 lymph node involvement. Moreover, the same finding was observed in patients with less than 15 lymph nodes examined. Thus far, all the published studies dealing with the prognostic value of N ratio in patients with gastric cancer have considered only patients who underwent extended lymphadenectomy (more than 15 lymph nodes removed): therefore, to our knowledge, the present study is the first report to evaluate and demonstrate the prognostic power of N ratio among patients with less extended lymph node dissection.

Unlike the N stage classification, whose prognostic power is significantly affected by the number of removed lymph nodes, the N ratio discriminated 3 subsets of patients (N ratio 1, 2, and 3) with similar prognosis both for group 1 and for group 2: 5-year OS of N ratio 1, 2, and 3 patients are 66.3% versus 61.2% ($P = 0.591$), 46.8% versus 47.7% ($P = 0.881$) and 19.0% versus 28.1% ($P = 0.095$) for group 1 and group 2, respectively. Moreover, when we considered only the N1 stage patients, no statistically significant differences in survival was observed between the group 1 and group 2 patients according to N ratio 1 ($P = 0.600$), N ratio 2 ($P = 0.944$) and N ratio 3 ($P = 0.317$). Overall, these findings underline the ability of N ratio classification to identify prognostically homogeneous subsets of patients.

Most importantly, at multivariate analysis, factors retained in group 1 patients were N ratio, age, type of resection, and T stage, and those retained in group 2 patients were N ratio, age, sex, tumor site, and T stage. Of note, the independent prognostic value of N ratio observed for patients with extended lymphadenectomy (HR for N ratio 1, 2, and 3: 1.67, 2.96, and 6.59, respectively) is similar to that reported in our previous study (HR for N ratio1, 2, and 3 were 1.60, 1.72, and 5.52, respectively).[22]

Although the multivariate survival analysis showed that N ratio does add prognostic power to the model in both groups 1 and 2, the question may arise up to which lower limit of examined lymph nodes the N ratio still works. Unfortunately, the number of patients in group 2 did not allow us to directly address this issue by means of survival analysis. From the statistical viewpoint, it should be considered that, simply by likelihood, the fewer nodes are examined, the lower the accuracy of the prognostic system. In addition, it is noteworthy that, while less than 16 nodes is per se a critical level for the N stage system (ie, no N3 class [>15 nodes] can be identified below this number), the critical limit to identify all 3 N ratio categories shifts down to 10 nodes (ie, no N ratio 1 [1%–9%] can be identified below this number).

Since N stage was not retained in the Cox model, our results strongly suggest that the ratio between metastatic and examined lymph nodes provides a model with a prognostic power greater than that obtained using the absolute number of metastatic lymph nodes (N stage). This observation is also supported by the better prognostic discrimination associated with the TRM system when compared with that associated with the TNM system (Fig. 2). Furthermore, for the first time, our findings, which are based on the largest series ever published, show that the N ratio is an independent prognostic factor both in patients with D1 and D2 lymphadenectomy. Taking into consideration that in many Western countries surgeons routinely perform D1 dissection, these results underscore the fact that N ratio might be implemented in the routine clinical practice independently of the type of lymphadenectomy.

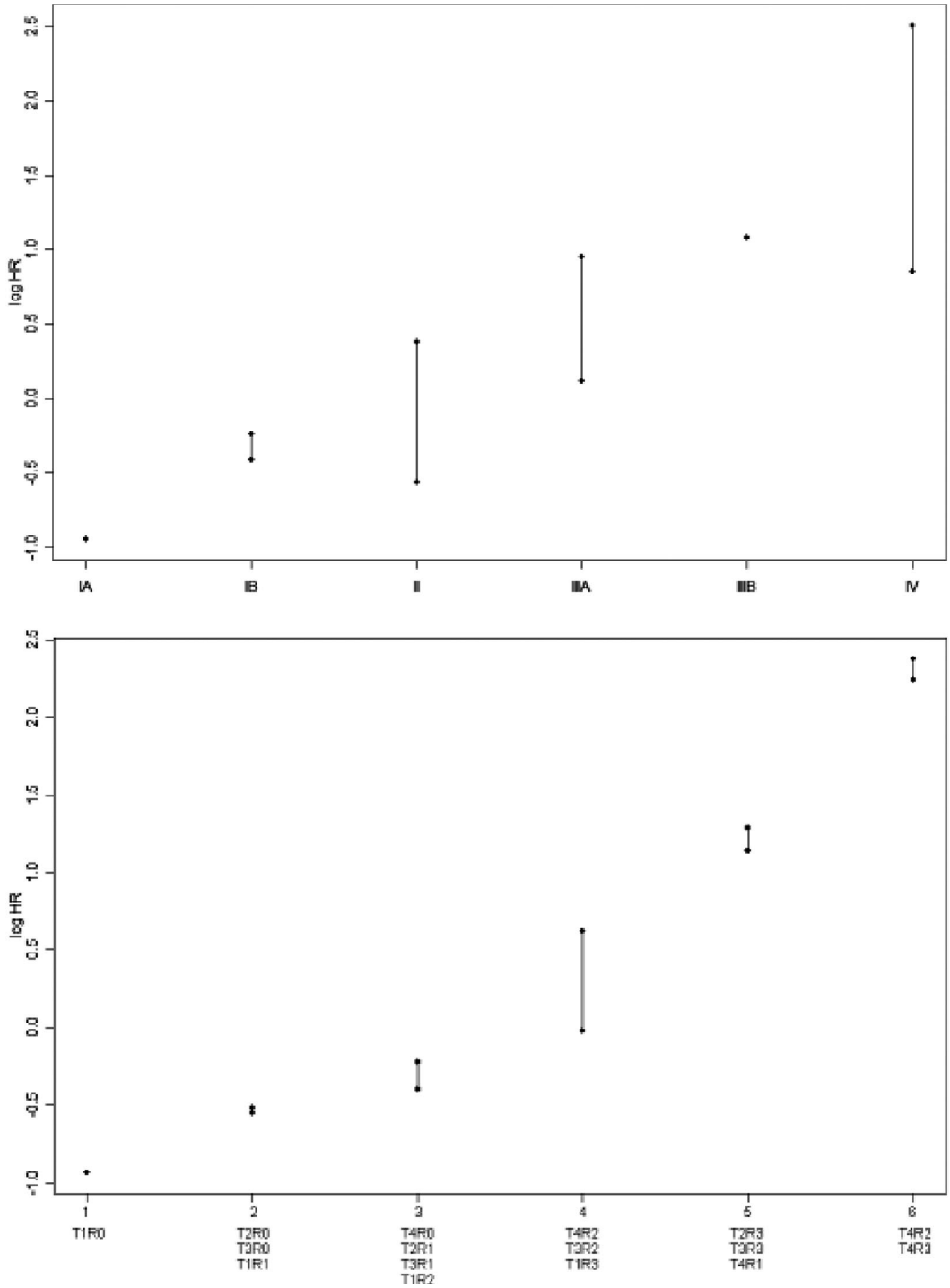

FIGURE 2. Comparison of prognostic discrimination power between the traditional (TNM) and N ratio based (TRM) staging systems. To this aim, we considered the overall survival data of all our patients (n = 1853). When the 6 TNM stages were plotted against their respective HR ranges, significant overlapping was observed among all stages, with the exception of stage IA (upper panel). K-means cluster analysis identified 6 prognostically homogeneous TRM classes: when the 6 TRM stages were plotted against their respective HR ranges, no overlapping was observed (lower panel).

CONCLUSION

We think that these data should draw the attention of the scientific community on the need and the possibility to improve the prognostic power of current staging systems, which would profoundly impact on the selection of patients who may most benefit from adjuvant treatments.

REFERENCES

1. Siewert JR, Bittcher K, Stein HJ, et al. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric cancer Study. *Ann Surg*. 1998;228:449–461.
2. Bozzetti F, Bonfanti G, Morabito T, et al. A multifactorial approach for the prognosis of patients with carcinoma of the stomach after curative resection. *Surg Gynecol Obstet.* 1986;162:229–234.
3. Hohenberger P, Gretschel S. Gastric cancer. *Lancet*. 2003;362:305–315.
4. Dicken BJ, Bigam DL, Cass C, et al. Gastric adenocarcinoma: review and considerations for future directions. *Ann Surg*. 2005;241:27–39.
5. Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study in surgery and pathology. I. *Jpn J Surg.* 1981;11: 127–139.
6. Japanese Gastric Cancer Association. *Japanese Classification of Gastric Carcinoma*, 2nd English ed. *Gastric Cancer.* Tokyo: Japanese Gastric Cancer Association, 1998:10–14.
7. Sobin LH, Wittekind CH. *International Union Against Cancer (UICC)*: *TNM Classification of Malignant Tumors*, 5th ed. New York: John Wiley & Sons, 1997.
8. Greene FL, Page DL, Fleming ID, et al. *AJCC Cancer Staging Manual*, 6th ed. New York: Springer-Verlag, 2002.
9. Bouvier AM, Haas O, Piard F, et al. How many nodes must be examined to accurately stage gastric adenocarcinomas? Results from a population based study. *Cancer*. 2002;94:2862–2866.
10. Wanebo HJ, Kennedy BJ, Chmiel J, et al. Cancer of the stomach: a patient care evaluation study by the American College of Surgeons. *Ann Surg*. 1993;218:583–592.
11. Hundal SA, Macdonald JS, Benedetti J, et al. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. *Ann Surg Oncol*. 2002;9:278–286.
12. Wanebo HJ, Kennedy BJ, Winchester DP, et al. Gastric carcinoma: does lymph node dissection alter the survival? *J Am Coll Surg*. 1996;183: 616–624.
13. Bonekamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. *N Engl J Med*. 1999;340:908–914.
14. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long term results of the MRC randomised surgical trial. *Br J Cancer*. 1999;79:1522–1530.
15. Jansen EP, Boot H, Verheij M, et al. Optimal locoregional treatment in gastric cancer. *J Clin Oncol*. 2005;23:4509–4517.
16. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med*. 1985;312:1604–1608.
17. Bonder BE. Will Rogers and gastric carcinoma [letter]. *Arch Surg*. 1988;123:1023–1024.
18. de Manzoni G, Verlato G, Roviello F, et al. The new TNM classification of lymph node metastasis minimises stage migration problems in gastric cancer patients. *Br J Cancer*. 2002;87:171–174.
19. Bunt AMG, Hermans J, Smit VTHBM, et al. Surgical/pathologic-stage migration confronts comparisons of gastric cancer survival rate between Japan and Western countries. *J Clin Oncol*. 1995;13:19–25.
20. Bando E, Yonemura Y, Taniguchi K, et al. Outcome of ratio of lymph node metastasis in gastric carcinoma. *Ann Surg Oncol*. 2002;9:775–784.
21. Inoue K, Nakane Y, Iiyama H, et al. The superiority of ratio-based lymph node staging in gastric carcinoma. *Ann Surg Oncol*. 2002;9:27–34.
22. Nitti D, Marchet A, Olivieri M, et al. Ratio between metastatic and examined lymph nodes is an independent prognostic factor after D2 resection for gastric cancer: analysis of a large European monoinstitutional experience. *Ann Surg Oncol*. 2003;10:1077–1085.
23. Hyung WJ, Noh SH, Yoo CH, et al. Prognostic significance of metastatic lymph node ratio in T3 gastric cancer. *World J Surg*. 2002;26:323–329.
24. Kodera Y, Yamamura Y, Shimizu Y, et al. Lymph node status assessment for gastric carcinoma: is the number of metastatic lymph nodes really practical as a parameter for N categories in the TNM classification? *J Surg Oncol*. 1998;69:15–20.
25. Therneau TM, Grambsh PM, Flemming TR. Martingale based residuals for survival models. *Biometrika*. 1990;77:147–160.
26. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457–481.
27. Hampel R, Ronchetti EM, Rousseew PJ, et al. *Robust Statistic*: *The Approach Based on Influence Functions*. New York: Wiley, 1986.
28. Cox DR. Regression models and life-tables. *J R Stat Soc B*. 1972;34: 187–220.
29. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–526.
30. Vinh-Hung V, Vershraegen C, Promish DI, et al. Ratios of involved nodes in early breast cancer. *Breast Cancer Res*. 2004;6:680–688.
31. Truong PT, Berthelet E, Lee L, et al. The prognostic significance of the percentage of positive/dissected axillary lymph nodes in breast cancer recurrence and survival in patients with one to three positive axillary lymph. *Cancer*. 2005;103:2006–2014.
32. Berger AC, Sigurdson ER, LeVoyer T, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. *J Clin Oncol*. 2005;23:8706–8712.
33. Cheong JH, Hyung WJ, Shen JG, et al. The N ratio predicts recurrence and poor prognosis in patients with node-positive early gastric cancer. *Ann Surg Oncol*. 2006;13:377–385.
34. Kunisaki C, Shimada H, Nomura M, et al. Clinical impact of metastatic lymph node ratio in advanced gastric cancer. *Anticancer Res*. 2005;25: 1369–1376.