

EVALUATION OF N-RATIO IN SELECTING PATIENTS FOR ADJUVANT CHEMORADIOTHERAPY AFTER D2-GASTRECTOMY

Wilson Luiz da COSTA JUNIOR¹, Felipe José Fernández COIMBRA¹, Thales Paulo BATISTA², Héber Salvador de Castro RIBEIRO¹, Alessandro Landskron DINIZ¹

ABSTRACT - Context - Whether adjuvant chemoradiotherapy may contribute to improve survival outcomes after D2-gastrectomy remains controversial. **Objective** - To explore the clinical utility of N-Ratio in selecting gastric cancer patients for adjuvant chemoradiotherapy after D2-gastrectomy. **Methods** - A retrospective cohort study was carried out on gastric cancer patients who underwent D2-gastrectomy alone or D2-gastrectomy plus adjuvant chemoradiotherapy (INT-0116 protocol) at the Hospital A. C. Camargo from September 1998 to December 2008. Statistical analysis were performed using multiple conventional methods, such as c-statistic, adjusted Cox's regression and stratified survival analysis. **Results** - Our analysis involved 128 patients. According to c-statistic, the N-Ratio (i.e., as a continuous variable) presented "area under ROC curve" (AUC) of 0.713, while the number of metastatic nodes presented AUC of 0.705. After categorization, the cut-offs provide by Marchet et al. displayed the highest discriminating power – AUC value of 0.702. This N-Ratio categorization was confirmed as an independent predictor of survival using multivariate analyses. There also was a trend of better survival by adding of adjuvant chemoradiotherapy only for patients with milder degrees of lymphatic spread – 5-year survival of 23.1% vs 66.9%, respectively (HR = 0.426, 95% CI 0.150–1.202; $P = 0.092$). **Conclusions** - This study confirms the N-Ratio as a tool to improve the lymph node metastasis staging in gastric cancer and suggests the cut-offs provided by Marchet et al. as the best way for its categorization after a D2-gastrectomy. In these settings, the N-Ratio appears a useful tool to select patients for adjuvant chemoradiotherapy, and the benefit of adding this type of adjuvancy to D2-gastrectomy is suggested to be limited to patients with milder degrees of lymphatic spread (i.e., NR2, 10%–25%).

HEADINGS - Stomach Neoplasms. Lymph Node Excision. Adjuvant Chemotherapy. Adjuvant Radiotherapy.

INTRODUCTION

Gastric cancer patients are usually faced with a poor prognosis due to diagnosis at later stages^(8,24). In these settings, combination therapy has become an established treatment for patients with locally advanced gastric cancer, whereas the high risk of locoregional relapses has favored the inclusion of radiotherapy as a perioperative component of its comprehensive therapeutic strategy. Herein, major changes in adjuvant therapy for gastric cancer favoring the use of chemoradiotherapy followed the results of the INT-0116 trial^(15, 19). However, a well-known weakness of this trial was that only 10% of patients included in the analysis had undergone a formal D2-lymphadenectomy while most of patients (54%) had undergone less than a complete dissection of the N1 nodes. Thus, some questions remain unanswered about whether

chemoradiotherapy might contribute to improve outcomes after an adequate D2-gastrectomy.

The current UICC/AJCC N-staging system (pN) is based on the number of metastatic lymph nodes for the assessment of each N-category. Nevertheless, the identified number of involved lymph nodes depends on the number of lymph nodes removed and examined, which might not guarantee an accurate staging due to effect of the stage migration phenomenon (also called 'Will Rogers' phenomenon). In these settings, the N-Ratio system (i.e., the ratio between metastatic and examined lymph nodes) could be a better option to compensate for this effect and may predict survival more accurately, especially for patients undergoing a limited lymph node dissection^(12, 20, 21). Based on the superiority of N-Ratio for gastric cancer staging^(21, 22) and the potential benefit from chemoradiotherapy for patients with positive pathologic lymph nodes

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¹ Departamento de Cirurgia Abdominal, Hospital Antônio Cândido de Camargo (A. C. Camargo), São Paulo, SP, Brasil; ² Departamento de Cirurgia/Oncologia, Faculdade Pernambucana de Saúde, Instituto de Medicina Integral Professor Fernando Figueira (FPM/IMP), Recife, PE, Brasil.

Correspondence: Thales Paulo Batista. Av. Boa Viagem, 5212. Ed. Transatlântico, ap. 1515 – Boa Viagem - 51030-000 - Recife, PE, Brasil. E-mail: t.paulo@bol.com.br

after an extended lymphadenectomy^(3, 10, 13, 23), we explore the clinical utility of N-Ratio in selecting candidates for adjuvant chemoradiotherapy using our sample of patients who underwent a D2-gastrectomy.

METHODS

Study Design

A retrospective cohort study was carried out on gastric cancer patients treated at Hospital A.C. Camargo from September 1998 to December 2008. Using our own database, we selected patients with pathologically confirmed adenocarcinoma who underwent D2-gastrectomy for treatment of staged IB to IIIC tumors TNM 7th ed. We limited our study to patients with complete data in their medical records that were treated with surgery-only or surgery plus adjuvant chemoradiotherapy according to the INT-0116 protocol. Patients with tumors of the gastric stump or who died postoperatively were also excluded. All procedures complied with the standards of the Declaration of Helsinki and current ethical guidelines.

Analytic Approach

We explored our sample using four consecutive statistical steps. First, we applied the c-statistic, equivalent to the area under the ROC curve (AUC), to establish the overall prognostic accuracy of the N-Ratio for predicting survival as a continuous variable. Second, we evaluated the prognostic value of N-Ratio in predicting survival when categorized according to clinically relevant cutoffs. Herein, the N-Ratio was categorized as described in previous studies^(9, 16, 18, 20, 22). Third, we confirm the categorized N-Ratio (i.e., the categorization method with higher AUC value in the previous step) as an independent predictor of survival using multivariate analyses to control the effect of other clinical/pathologic prognostic factors. In this approach, factors whose association with survival showed a *P*-value <0.20 were used in a multivariate analysis adjusted for the type of treatment (surgery-only group vs. surgery plus adjuvant chemoradiotherapy group). Thus, separate Cox's proportional-hazards models were first fit to each group of treatment and the log-likelihoods for those models were summed up. This log-likelihood was then compared to that of the overall model (collapsed across groups). Finally, we performed stratified survival analysis comparing survival outcomes of the treatment groups among the N-Ratio categories.

Descriptive statistics were summarized as medians (interquartile range) or frequencies (percentages). The Mann-Whitney U test or chi-square tests were performed to analyze the descriptive statistics and relapse rates, which included Yates's correction or Fischer's exact test, as appropriate. The Kaplan-Meier method was applied to survival estimation. Cancer-specific survival was explored as a function of time after surgical treatment until the date of cancer-related death or end of the study. Data on those patients alive or dead due to other reasons at the time of analysis were "censored" for survival estimation. All patients were usually followed up

with clinical exams, lab tests and imaging exams every 3-6 months in the first two years postoperative, every 6-12 months up to 5 years postoperative, and annually thereafter. Annually, upper endoscopy had also been performed.

Statistical analyses were performed using the MedCalc statistical package, Version 12.4 (MedCalc Software, Mariakerke, Belgium) and the STATISTICA Data Analysis Software System, Version 8.0 (Statsoft, Inc., Tulsa, OK, USA), considering a two-tailed *P*-value of 0.05 as statistically significant.

Sample Characteristics

Three hundred twenty-seven patients with confirmed gastric cancer were surgically treated at our center from September 1998 to December 2008. Among these patients, 69 had M1 disease, 50 had T1a-bN0 tumors, 19 presented gastric stump tumors, 34 received a different multimodality treatment, 10 were lost to follow-up, and there were 3 postoperative deaths. These patients were not included to analysis. Additionally, we excluded 14 patients who underwent D1-gastrectomy.

Most patients were consecutively treated with surgery-only before 2005, whereas adjuvant chemoradiotherapy including 3D conformal therapy was usually considered at our institution after 2004. Applying the INT-0116 protocol, patients received two cycles of 5-FU and leucovorin followed by concurrent chemoradiotherapy with 45 Gy of radiation administered using fields encompassing the entire gastric bed, regional nodes, and 2 cm proximal and distal margin. Treatment was completed as planned by about 77% of patients. Resection included a distal or total gastrectomy and D2-lymphadenectomy, as routinely recommended at our center. Pancreatectomy and/or splenectomy were only performed when deemed necessary so that negative margins could be obtained. Platinum- or taxane-based chemotherapy, and best support care were offered after disease recurrence, as appropriate.

RESULTS

Our analysis involved 128 patients who underwent surgery-only (*n* = 83; 64.8%), or surgery plus adjuvant chemoradiotherapy (*n* = 45; 35.1%) for treatment of gastric cancer. Their baseline characteristics and descriptive statistics are summarized in Table 1. Over the 13.8-year follow-up period, 70 (54.7%) patients were alive with a median follow-up of 70 months (Q25 = 47 – Q75 = 89), and disease recurrence were observed in 44 (34.4%) patients. Patterns of these relapses are presented in the Table 2. Most deaths resulted from disease recurrence (*n* = 41), but three patients were alive with relapses at the time of this analysis, while 17 patients died because of non-oncological reasons. Overall, our cumulative 5-year cancer-specific survival was 64.3%.

According to c-statistic, the prognostic accuracy of N-Ratio (i.e., as a continuous variable) for predicting cancer-specific survival was 0.713 (95% CI 0.626 – 0.789). Similarly, the number of metastatic nodes presented an AUC value of

TABLE 1. Baseline characteristics and descriptive statistics

Variable	Overall ¹	Treatment Groups ¹		P-value ²
		Surgery-only	Chemoradiation	
Age	63 (51 – 70)	66 (55 – 73)	54 (50 – 65)	<0.001
Gender				0.566
Male	71 (55.5)	44 (53)	27 (60)	
Female	57 (44.5)	39 (47)	18 (40)	
Gastrectomy				0.120
Total	75 (58.6)	44 (53)	31 (68.9)	
Subtotal	53 (41.4)	39 (47)	14 (31.1)	
No. of Dissected Nodes	35 (25 – 46.5)	34 (23 – 42)	40 (31 – 47)	0.059
No. of Metastatic Nodes	3 (0 – 6)	2 (0 – 6)	4 (2 – 7)	0.008
N-Ratio (%)	8 (0 – 18)	6 (0 – 18)	11 (6 – 18)	0.033
pT-Category (7th ed.)				0.733
T1	10 (7.8)	4 (4.8)	6 (13.3)	
T2	24 (18.8)	17 (20.5)	7 (15.6)	
T3	10 (7.8)	5 (6)	5 (11.1)	
T4	84 (65.6)	57 (68.7)	27 (60)	
pN-Category (7th ed.)				0.070
N0	39 (30.5)	34 (41)	5 (11.1)	
N1	20 (15.6)	12 (14.4)	8 (17.8)	
N2	38 (29.7)	19 (22.9)	19 (42.2)	
N3	31 (24.2)	18 (21.7)	13 (28.9)	
Tumor Location				0.942
Cardia	20 (15.6)	11 (13.2)	9 (20)	
Body	53 (41.4)	33 (39.8)	20 (44.5)	
Antrum	53 (41.4)	38 (45.8)	15 (33.3)	
Linitis	2 (1.6)	1 (1.2)	1 (2.2)	
Extended Resection				0.768
Yes	26 (20.3)	18 (21.7)	8 (17.8)	
No	102 (79.7)	65 (78.3)	37 (82.2)	
Lauren Histology				0.470
Intestinal	61 (47.7)	42 (50.6)	19 (42.2)	
Diffuse	67 (52.3)	41 (49.4)	26 (57.8)	
Lymphatic Vessel Invasion				0.351
Yes	54 (42.2)	38 (45.8)	16 (35.6)	
No	74 (57.8)	45 (54.2)	29 (64.4)	
Perineural Invasion				0.383
Yes	65 (50.8)	45 (54.2)	20 (44.4)	
No	63 (49.2)	38 (45.8)	25 (55.6)	

¹Median (interquartile range) or n (%); ²Comparisons between groups using the Mann-Whitney U test or chi-square tests, which included the Yates's correction or the Fischer's exact test, as appropriated.

TABLE 2. Descriptive statistics according to the recurrence rates

Pattern of Recurrence	Overall – n (%)	Treatment Groups – n (%)		P-value ¹
		Surgery-Only	Chemoradiation	
Total	44 (34.4)	29 (34.9)	15 (33.3)	0.990
Distant	31 (24.2)	21 (25.3)	10 (22.2)	0.863
Locoregional	10 (7.8)	7 (8.4)	3 (6.7)	1.000
Not Recorded	3 (2.3)	1 (1.2)	2 (4.4)	0.282

¹Comparisons between groups using chi-square tests, which included the Yates's correction or the Fischer's exact test, as appropriate.

0.705 (95% CI 0.618 – 0.782) (Figure 1A). After categorization, the cutoff intervals provide by Marchet et al.⁽¹⁶⁾ (i.e.: NR0 = 0%, NR1 = 1%-9%, N2 = 10%-25%, N3≥25%) displayed N-Ratio categories with the highest discriminating power – AUC value of 0.702 (95% CI 0.615–0.780), while the overall accuracy of N-Ratio categories according to Inoue et al.⁽⁹⁾, Siewert et al.⁽¹⁸⁾, Sun et al.⁽²⁰⁾, and Xiao et al.⁽²²⁾ demonstrated AUC values of 0.673 (95% CI 0.584–0.753), 0.684 (95% CI 0.596–0.764), 0.691 (95% CI 0.604–0.770), and 0.670

(95% CI 0.58 –0.750); respectively. Applying categorization according to the TNM 7th edition, we found AUC = 0.667 (95% CI 0.578–0.748) (Figure 1B).

Using adjusted multivariate analyses, we confirm the N-Ratio categorized according to Marchet et al.⁽¹⁶⁾ as an independent predictor of cancer-specific survival. Others independent predictors of survival in our analysis were the number of metastatic nodes and presence of perineural invasion. Summary of this approach is presented in Table 3.

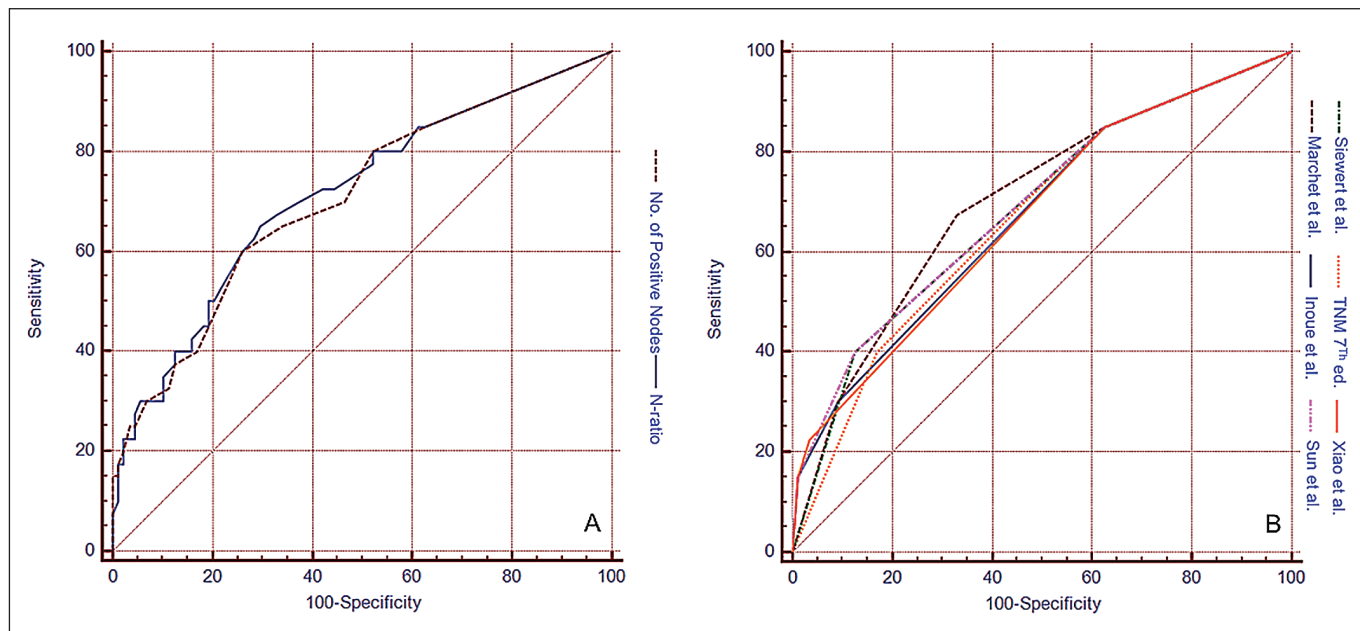


FIGURE 1. Receiver operating characteristic (ROC) curve for the overall discriminatory power of N-Ratio in predicting 5-year cancer-specific survival A. The ROC curve for the prognostic value of N-Ratio and the number of metastatic nodes as continuous variables; B. The ROC curve for the prognostic value of the N-Ratio after categorization using clinically relevant cutoff intervals.

TABLE 3. Survival analysis using adjusted regression

Variable	Univariate ¹	Multivariate Analysis ²	
		Nonadjusted	Adjusted
Age	0.080	0.377	0.457
Gender	0.789	–	–
Gastrectomy	0.077	0.901	0.932
No. of Dissected Nodes	0.617	–	–
No. of Metastatic Nodes	<0.001	0.008	0.008
N-Ratio (Marchet et al.)	0.001	0.007	0.008
pT-Category	0.074	0.411	0.405
Extended Resection	0.002	0.055	0.072
Lauren Histology	0.347	–	–
Tumor Location	0.063	0.178	0.180
Lymphatic Vessel Invasion	0.049	0.956	0.906
Perineural Invasion	0.009	0.043	0.043

¹ Univariate analysis using the log rank test (categorical data) or the Cox-proportional hazards model (continuous data); ² Multivariate analysis using the Cox-proportional hazards model. This analysis was also adjusted to treatment groups (surgery-only vs. surgery plus adjuvant chemoradiotherapy).

Figure 2 shows the survival curves in regards to treatment groups and to N-Ratio categorization provided by Marchet et al.⁽¹⁶⁾

Patient's survival analyses for treatment groups stratified according to the N-Ratio categorization described by Marchet et al.⁽¹⁶⁾ are presented in Figure 3. In the NR1 category,

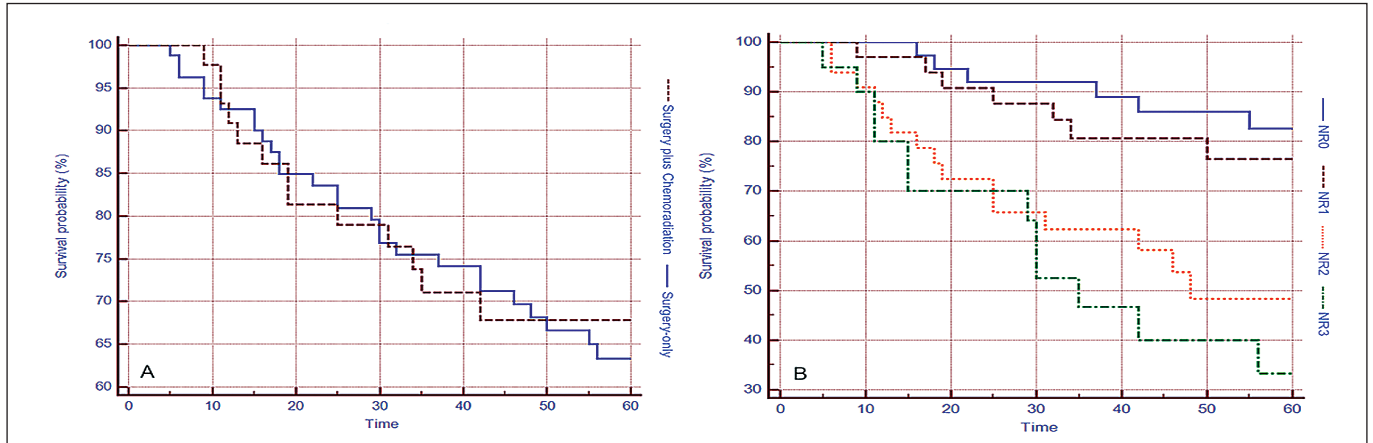


FIGURE 2. Kaplan–Meier cancer-specific survival

A. Survival analysis of patients according to treatment groups. Five-year survivals were 63.4% vs 67.8%, for the surgery-only vs surgery plus adjuvant chemoradiotherapy groups, respectively (HR = 0.525, 95% CI 0.494–1.835; $P = 0.884$); B. Survival analysis of patients according to N-Ratio categorization provided by Marchet et al.⁽¹⁶⁾ The correspondent 5-year survival for NR0, NR1, NR2 and NR3 categories were 82.6%, 76.4%, 48.3% and 33.3%, respectively ($P = 0.001$).

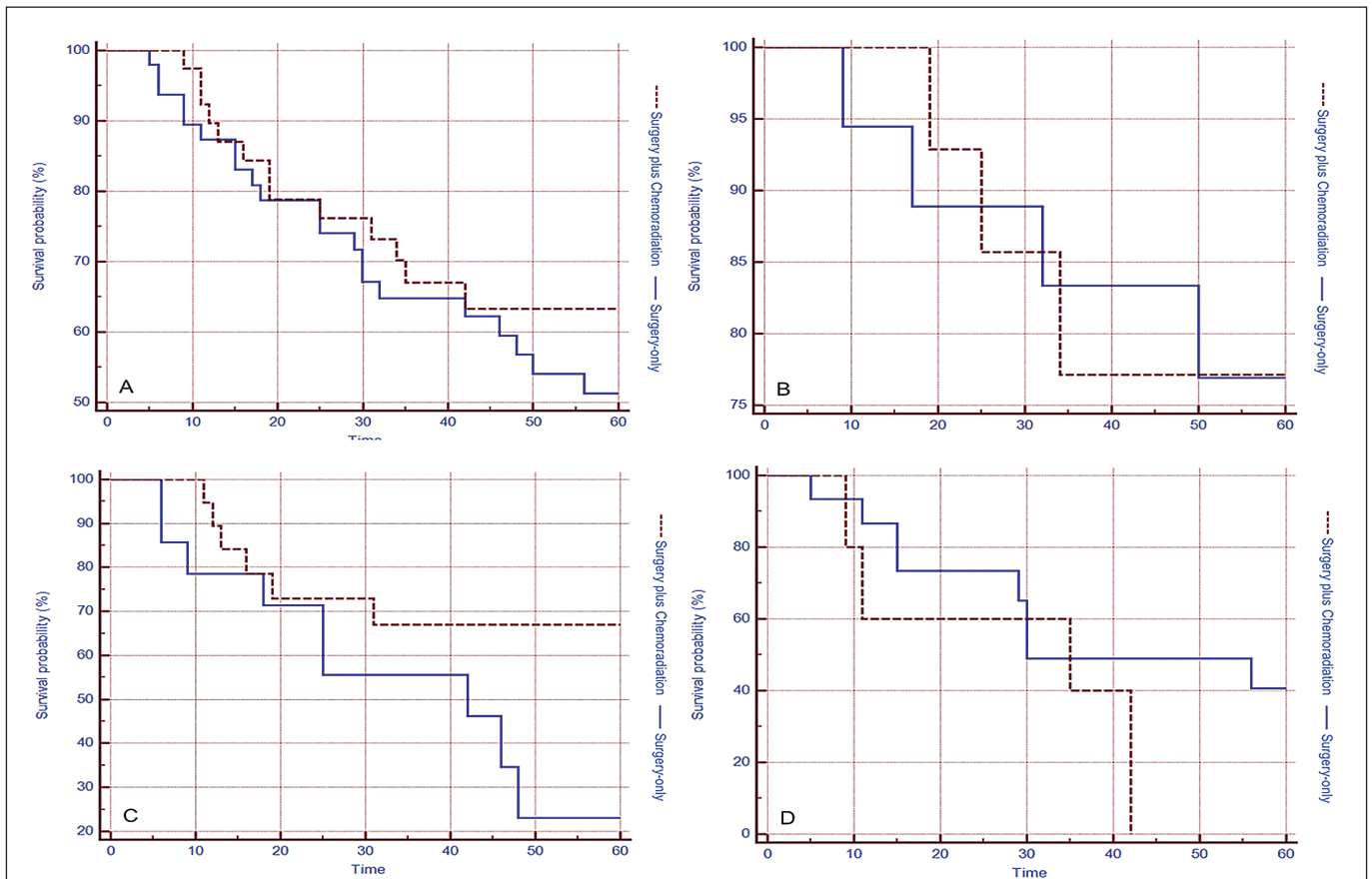


FIGURE 3. Survival analyses in regards to treatment groups stratified according to the N-Ratio categorization described by Marchet et al.⁽¹⁶⁾ and N(+) subset of patients. A. Kaplan-Meier analysis for the subset of patients with any lymph node metastasis; B. Subset of NR1 patients; C. Subset of NR2 patients; D. Subset of NR3 patients.

5-year survival rates were 76.9% vs 77.1% for the surgery-only vs surgery plus adjuvant chemoradiotherapy groups, respectively (HR = 1.012, 95% CI 0.226–4.529; $P = 0.987$) (Figure 3B). For the NR2 category, corresponding survivals were 23.1% vs 66.9% (HR = 0.426, 95% CI 0.150–1.202; $P = 0.092$) (Figure 3C), while NR3 category presented respective survivals of 40.7% vs 0% (HR = 1.803, 95% CI 0.457–7.117; $P = 0.308$) (Figure 3D). Additionally, we explored survival among all patients with any lymph node metastasis and observed 5-year survival rates of 51.2% vs 63.3% for the surgery-only vs surgery plus adjuvant chemoradiotherapy groups, respectively (HR = 0.760, 95% CI 0.386–1.494; $P = 0.431$) (Figure 3A).

DISCUSSION

Recently, gastric cancer lymph node metastasis staging was updated in the UICC/AJCC 7th edition. This system classifies patients with one to two positive lymph nodes as N1, patients with three to six positive lymph nodes as N2, and patients with seven or more positive lymph nodes are classified as N3. However, while there is increased complexity on stage grouping, there is no clear improvement in predictive accuracy with this new version of the TNM system⁽⁷⁾. In order to improve prognosis prediction by minimization of the stage migration phenomenon, modified staging systems utilizing N-Ratio has been proposed as an alternative to this current system, which demands the examination of at least 15 lymph nodes for an optimal assessment of N-category^(6, 9, 12, 16, 18, 20, 22). Accordingly, the proposed system has predicted survival more accurately in comparison with the 7th edition UICC/AJCC system for gastric cancer^(21, 22).

Previously, we had stressed the interaction between N-category and N-Ratio as a new tool to improve lymph node metastasis staging in gastric cancer⁽⁴⁾ and its role in patient's selection for adjuvant chemoradiotherapy⁽⁵⁾. In this current study, we have explored the clinical utility of N-Ratio in selecting patients for adjuvant chemoradiotherapy in a subset of patients who underwent D2-dissection, using multiple statistical methods, such as c-statistic, adjusted Cox's regression and stratified survival analysis. Accordingly, we first explored the N-Ratio as a continuous variable in order to minimize some loss in the statistical power of our analysis and the occurrence of residual confounding factors related to the methods of categorizing continuous variables^(1, 17). Herein, we confirm the prognostic accuracy of N-Ratio in predicting cancer-specific survival and also observed an AUC value slightly higher than the number of metastatic nodes itself. Instead of calculating our own cutoffs for categorized analysis, we preferred to use clinically relevant cutoff intervals previously tested in large samples including more than one thousand patients^(9, 16, 18, 20, 22). In this step, only the N-Ratio categories as provide by Marchet et al.⁽¹⁶⁾ displayed an AUC>0.7, a value that usually indicates clinically usefulness and discriminating power. Finally, we also confirm the clinical relevance of that categorized N-Ratio using adjusted

multivariate analyses in order to control the effect of other clinical/pathologic prognostic factors.

After selecting the best N-Ratio tool, we explore the role of adjuvant chemoradiotherapy after D2-gastrectomy applying stratified survival analysis. Herein, we noticed a trend of better cancer-specific survival by the adding of adjuvant chemoradiotherapy to the D2-gastrectomy only in patients with milder degrees of metastatic lymph node spread (i.e., NR2; 10%–25%). As a likely explanation to our findings, we hypothesized that our high quality surgery played a role for patients with a reduced lymphatic spread (i.e., patients classified as NR1; 1%–9%), while patients with more advanced lymphatic spread (i.e., NR3; >25%) means a highly systemic disease^(11, 14) that needs improvement in systemic treatment using chemotherapy regimens more effective than those delivered in the INT-0116 protocol.

Whether adjuvant chemoradiotherapy is equally beneficial for patients with extended lymphadenectomy (D2 or greater dissection) remains unclear⁽²⁾. The ARTIST trial⁽¹³⁾ investigated the efficacy of postoperative chemoradiotherapy using a capecitabine plus cisplatin regimen, but failed to provide a disease-free survival benefit in comparison to the adjuvant chemotherapy alone. Although there was no significant difference in survival between the two treatment arms, the chemoradiotherapy regimen significantly prolongs survival of patients with positive pathological lymph node and more advanced stages. The main limitation of this trial was that the planned events were not reached at the end of the study, possibly due to the fact that approximately 60% of the patients in each arm had stages IB and II disease. In contrast, Zhu et al.⁽²³⁾ very recently presented their phase III trial comparing postoperative intensity-modulated radiotherapy plus chemotherapy (IMRT-C) with chemotherapy-only after a curative D2-dissection. Using a 5-FU/leucovorin chemotherapy regimen, the authors found no significant difference in overall survival between groups, but the chemoradiotherapy arm experienced increased disease-free survival. This trial was the first to show the disease-free survival benefit of the postoperative chemoradiotherapy therapy in D2-resected gastric cancer patients, while this inconsistency with the results of the ARTIST trial appears mainly linked to its higher rates of positive lymph node and more advanced stages^(13, 23).

Despite the limitations of this study related to our retrospective and non-randomized approach, the main scientific merit of this report was to explore the clinical utility of N-Ratio in selecting gastric cancer patients for adjuvant chemoradiotherapy applying multiple statistical methods in a subset of patients who underwent D2-dissection. To our best knowledge, this is the first study in these settings. Accordingly, our data suggests the N-Ratio is likely a useful tool to select patients for adjuvant chemoradiotherapy after a D2-gastrectomy. However, further prospective and larger studies are still warranted to confirm our findings.

In conclusion, this study confirms the N-Ratio as a method to improve lymph node metastasis staging in gastric cancer and suggests the cutoffs provided by Marchet et al.⁽¹⁶⁾

as the best way for its categorization after a D2-gastrectomy. In these settings, the N-Ratio appears a useful tool to select patients for adjuvant chemoradiotherapy, and the benefit of

adding this type of adjuvancy to D2-gastrectomy is suggested to be limited to patients with milder degrees of lymphatic spread (i.e., NR2, 10%-25%).

Costa Junior WL, Coimbra FJF, Batista TP, Ribeiro HSC, Diniz AL. Avaliação do N-Ratio para a seleção de pacientes candidatos à quimiorradioterapia adjuvante após gastrectomia D2. *Arq Gastroenterol.* 2013;50(4):257-63.

RESUMO - Contexto - A utilização de quimiorradioterapia adjuvante permanece controversa após a realização de gastrectomia D2. **Objetivo** - Explorar a utilidade clínica do N-Ratio para a seleção de pacientes com câncer gástrico candidatos à quimiorradioterapia adjuvante após gastrectomia D2. **Métodos** - Realizou-se estudo de coorte retrospectivo incluindo pacientes com câncer gástrico submetidos a gastrectomia D2, isoladamente ou associada à quimiorradioterapia adjuvante (protocolo INT-0116), no Hospital A.C. Camargo, de setembro de 1998 a dezembro de 2008. As análises estatísticas foram realizadas utilizando-se diversos métodos, tais como análise de área sob curvas ROC, regressão de Cox's ajustada e análise estratificada da sobrevivência. **Resultados** - A análise envolveu 128 pacientes. Por análise das áreas sob curvas ROC, o N-Ratio apresentou AUC de 0,713 como variável contínua, enquanto o número total de linfonodos metastáticos apresentou AUC de 0,705. Na análise categorizada, os pontos-de-corte propostos por Marchet et al. apresentaram o maior poder de discriminação, com valor de AUC de 0,702. A categorização N-Ratio segundo estes autores foi confirmada como um preditor independente de sobrevivência, utilizando-se análises multivariadas. Observou-se tendência de melhor sobrevivência acrescentando-se quimiorradioterapia adjuvante apenas para pacientes com moderado grau de disseminação linfática (NR2, 10%-25%), entre os quais a sobrevivência em 5 anos foi de 23,1% vs 66,9%, respectivamente (HR = 0,426, IC 95% 0,150-1,202, P = 0,092). **Conclusões** - Este estudo confirma o N-Ratio como uma medida para melhorar o estadiamento linfonodal no câncer gástrico e sugere que os pontos-de-corte descritos por Marchet et al. sejam a melhor opção para sua categorização após gastrectomia D2. Nesse contexto, o N-Ratio parece uma opção útil para selecionar pacientes para quimiorradioterapia adjuvante, ao passo que os benefícios de se adicionar este tipo de adjuvância após gastrectomia D2 parece ser limitada a pacientes com moderada disseminação linfática (NR2, 10%-25%).

DESCRITORES - Neoplasias gástricas. Escisão de linfonodo. Quimioterapia adjuvante. Radioterapia adjuvante.

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