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ORIGINAL ARTICLE

Lymph node staging in gastric cancer: new criteria, old problems

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ABSTRACT

Purpose: Our study aims to test the prognostic accuracy of the N parameter of the 7th TNM in a Western series of D1-gastrectomies for gastric cancer (GC).
Methods: Retrospectively considering a series of 224 non-metastatic GC patients who underwent surgery with curative intent and limited lymphadenectomy, we analyzed 5-year overall survival (OS) related to pN status according to both TNM editions (pN_6 and pN_7) and to lymph node ratio (LNR; LNR0, 0%, LNR1, 1–19%; LNR2, >20%). We stratified pN_6- and pN_7-related OS by LNR.
Results: Both pN_6 and pN_7 were shown to significantly stratify different subsets of GC patients, but there was no significant difference between $pN_7$1 and $pN_7$2, nor between $pN_6$2 and $pN_6$3. A multivariate model specific for pN_7 eliminated the N2 group, while the pN_6 model maintained all 3 N groups with highly discriminating hazard ratios. LNR was able to further stratify one category of pN_6 (N2) and two categories of pN_7 (N1 and N2).
Conclusions: The 7th TNM edition for GC does not seem to be superior to the 6th edition in evaluating the prognostic relevance of lymph-nodal status: in particular, it does not allow an accurate stratification of OS in patients with less than 6 positive lymph nodes.

1. Introduction

Lymph node metastases are considered to be one of the most relevant prognostic factors in gastric cancer patients. [1,2] In the seventh edition of the TNM staging system for gastric cancer, the classification of the number of regional involved lymph nodes (N) has been revised into the conventional four categories N0, N1, N2 and N3, according to new cutoffs, in order to improve its reproducibility and prognostic validity. [3] Actually, although supported by literature, [2,4,5] the reduced cutoffs seem to be in contrast with the suggested principles of extended lymphadenectomy. [6] Although the UICC recommends a minimum number of 16 lymph nodes to be removed, the latest edition of the TNM gives the possibility of discriminating between different prognostic categories even when a very limited lymphadenectomy is performed (e.g., to distinguish between the N1 and N2 groups by only 3 analyzed nodes). Hence, the reduction of the number of lymph nodes to be removed appears consistent with the poor diffusion of extended lymphadenectomy in Western countries, but its prognostic capability remains doubtful.

The aim of this study is to verify the staging efficacy of the new N parameter in a consecutive series of gastric cancer patients undergoing surgery with curative intent and limited lymphadenectomy.

2. Patients and methods

2.1. Patients

Clinical data have been collected from case sheets and from the histological exams of the specimens. Between January 1995 and December 2011, 224 patients with non-metastatic gastric adenocarcinoma underwent surgery with curative intent. Subtotal gastrectomy was performed in most cases (53.6%). Multivisceral resection was required in 11 (4.9%) patients for suspected T4 tumors. Two hundred and thirteen patients (95.1%) underwent a limited lymphadenectomy (D1); a more extended lymphadenectomy (D2) was performed in 11 cases (4.9%) with evident lymph node metastases in second level lymph node stations. For the analysis we considered the following factors: patient's age and gender; tumor location (1/3 proximal versus 2/3 distal); type of surgery (total versus subtotal gastrectomy), number of nodes removed, and intraoperative blood transfusions; residual tumor (R), tumor diameter, Lauren's classification, Borrmann's classification, grading of differentiation (G), pT classified according to the seventh TNM edition, [3] pN classified according to both the sixth (pN_6) [7] and the seventh (pN_7) [3] TNM, and lymph node ratio (LNR0, 0; LNR1, <20%; LNR2, ⩾20%). Retrospectively, we considered cancer-related death as the end-point to evaluate rates of overall survival (OS).

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Table 1
Clinical and pathological features. Overall survival rates and univariate analysis of the sample.

Variable	Number	%	5-year OS (%)	p-value
Age (years)				0.518
⩽67	108	48.2	75.9	
>67	116	51.8	73.3	
Gender				0.544
M	147	65.6	74.3	
F	77	34.4	34.4	
Tumor location				0.961
1/3 proximal	47	21.1	74.6	
2/3 distal	176	78.9	74.8	
Type of gastrectomy				0.614
Total	104	46.4	74.5	
Subtotal	120	53.6	75.2	
Number of lymph nodes removed				0.122
<16	92	41.1	72.0	
⩾16	132	58.9	77.0	
Peri-operative blood transfusions				0.026
Yes	46	20.6	64.7	
No	178	79.4	77.0	
R				<0.001
0	205	91.8	79.0	
1–2	19	8.2	38.7	
Tumor diameter (mm)				0.01
⩽40	138	58.9	83.4	
>40	86	41.1	63.1	
Lauren's classification				0.081
Diffuse	122	54.5	69.3	
Intestinal	102	45.5	81.8	
Borrmann's classification				0.016
1	8	5.1	100	
2	58	36.9	79.6	
3	79	50.3	62.7	
4	12	7.6	42.4	
Grading				0.026
1	10	4.5	100	
2	95	43.0	82.1	
3	119	52.5	69.3	
pT				<0.001
1a	33	14.8	97.0	
1b	33	14.8	95.8	
2	26	11.6	87.1	
3	80	35.7	66.6	
4a-b	52	23.1	53.9	
pN_6 (2002)				<0.001
0	99	44.2	94.8	
1	85	37.9	70.9	
2	27	12.1	35.0	
3	13	5.8	22.0	
pN_7 (2010)				<0.001
0	99	44.2	94.8	
1	43	19.2	74.4	
2	42	18.7	76.7	
3a	27	12.1	36.7	
3b	13	5.8	20.1	
Lymph node ratio (LNR)				<0.001
0	99	44.2	94.8	
<20%	57	25.5	79.7	
⩾20%	68	30.3	38.8	

2.2. Statistical analysis

All variables were expressed as mean ± standard deviation (SD) or median and range. Continuous variables were categorized around their median value or a well-known cutoff. Survival was calculated from the day of surgery until June 2011 (actuarial OS). Patients who died of non-cancer-related causes were censored at the time of death. Survival rates were calculated by the Kaplan–Meier method and log-rank test was used for univariate analysis. The Cox proportional hazard model was used for multivariate analysis, including only variables with $p < 0.1$ at log-rank test, with a backward elimination model for all covariates. Hazard ratio (HR) and 95% confidence interval (CI) were calculated in the model for each variable included. The regression model was controlled with goodness of fit tests. In order to avoid co-linearity problems we used two different models for the multivariate analysis: one for pN_6 and another for pN_7. $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 13.0 for Windows©.

3. Results

The mean number of lymph nodes harvested was 19.3±12.1, and the mean number of metastatic lymph nodes was 3.4±5.5: 99 patients out of 224 (44.2%) had no metastatic lymph nodes.

After a median follow up of 48.0 months, 50 (22.3%) patients had died from gastric cancer. Overall survival at 12, 24, 36, 48 and 60 months was, respectively, 96.2%, 87.2%, 80.0%, 74.9% and 74.1%. Clinical and pathological characteristics of the sample with survival rates and univariate analysis are reported in Table 1. In particular, pN_6 and pN_7, as well as LNR, significantly stratified patients with different OS (all $p < 0.001$). Applying the log-rank test to each stratum of both pN_6 and pN_7, we observed that pN_6 showed a loss of statistical significance between $pN_6 2$ and $pN_6 3$ patients ($p = 0.127$) (Fig. 1) and, similarly, pN_7 showed a loss of statistical significance between $pN_7 1$ and $pN_7 2$ patients ($p = 0.844$) (Fig. 2). Moreover, stratifying each pN category according to LNR only one pN_6 group ($pN_6 1$, with $p = 0.012$) (Fig. 3) and two pN_7 categories ($pN_7 1$ and $pN_7 2$, with $p = 0.07$ and $p = 0.04$, respectively) were further stratified (Fig. 4). Cox regression selected lymph node status as the only

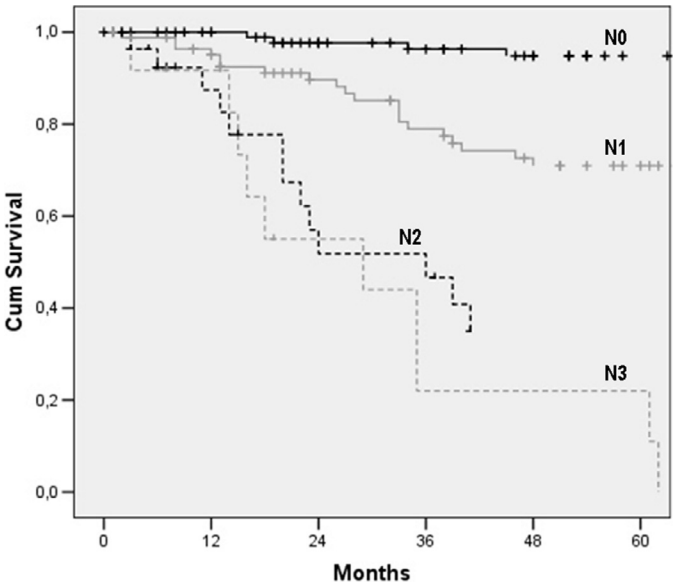

Fig. 1. Overall survival according to pN_6 staging.

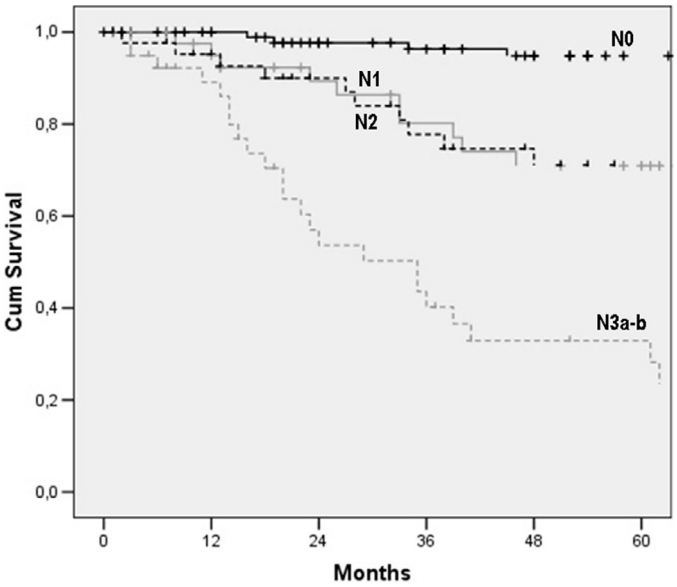

Fig. 2. Overall survival according to pN_7 staging.

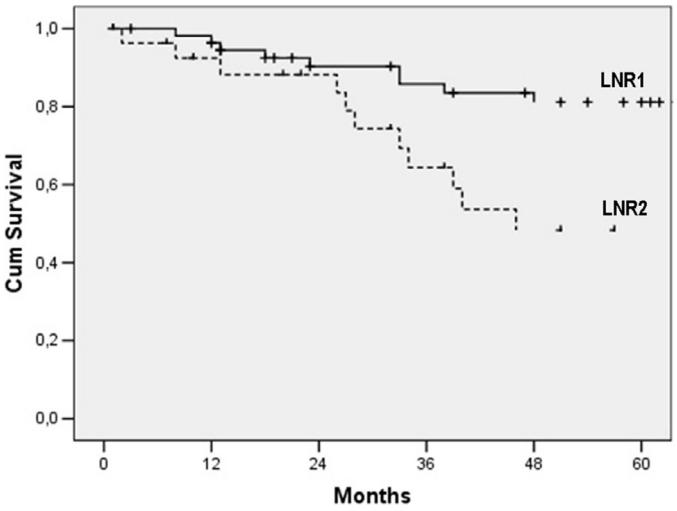

Fig. 3. Overall survival of $pN_6 1$ patients stratified by lymph node ratio (LNR).

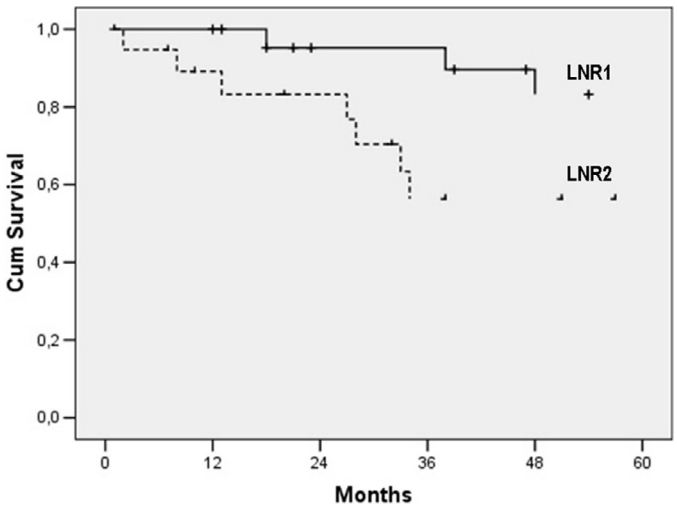

Fig. 4. Overall survival of $pN_7 2$ patients stratified by lymph node ratio (LNR).

Table 2
Multivariate analysis by Cox regression

pN	Hazard ratio	p-value
(A) Model including pN_6 (goodness of the model: −2 Log likelihood, 172.555; χ^2, 67.290; P < 0.00001)		
pN_6 (2002)		
0	1	–
1	10.79	0.002
2	120.14	<0.001
3	376.91	<0.001
(B) Model including pN_7 (goodness of the model: −2 Log likelihood, 171.862; χ^2, 60.387; P < 0.00001).		
pN_7 (2010)		
0	1	–
1	10.20	0.004
2	4.553	0.73
3	49.36	<0.001

independent significant prognostic factor, in both the pN_6 and the pN_7 model (Table 2). However, while pN_6 kept all of its categories with high HRs until the last step of the multivariate analysis, pN_7 lost its pN2 category at the last step, and its model resulted in less relevant HRs (Table 2).

4. Discussion

Many efforts have been made to reach a higher accuracy in the staging of the N parameter, since regional lymph node metastases are one of the variables influencing treatment strategy. At present, the clinical evaluation of lymph node status by imaging is still unreliable,[8] and many controversies remain about its pathological staging too. A shift occurred in 1997 from an anatomic to a numeric criterion for pN, on the basis of a presumed better prognostic stratification, and this necessarily required the introduction of arbitrary cutoffs,[9] validated on the simple basis of statistical observations. For the first time since then, the seventh TNM edition modified these cut-offs: $pN_6$1 (1–6 positive regional lymph nodes) was divided into new groups $pN_7$1 (1–2 positive regional lymph nodes) and $pN_7$2 (3–6 positive regional lymph nodes), while $pN_6$2 (7–15 positive regional lymph nodes) and $pN_6$3 (>15 positive regional lymph nodes) were united into the new $pN_7$3 group (>6 positive regional lymph nodes).[3] Even though the recommended minimum number of lymph nodes to be removed has increased to 16,[3] the possibility of discriminating different tumor stages even by few harvested nodes seems to satisfy the principles of reproducibility and standardization needed to obtain comparable survival curves worldwide. In fact, an ideal staging system should be independent of the type of treatment and be able to correctly stratify different prognostic groups too.

The literature presents only few contributions, with controversial results, about comparison between the sixth and the seventh TNM. Ahn et al., analyzing survival of 9998 patients having undergone R0 gastrectomy, and considering only patients with 15 or more retrieved lymph nodes, maintain that the new TNM edition shows a more detailed classification of different prognostic groups, especially for $pN_7$1 and $pN_7$2 patients (p = 0.0018), and an increased homogeneity in each TNM stage.[4] Similarly, Wang et al., analyzing 1503 patients who underwent limited or extended lymphadenectomy, with less than 15 harvested nodes on average, confirm a better prognostic stratification of the latest TNM edition; however, they state that subdividing the pN3 category into pN3a and pN3b may be unnecessary.[5] Similar conclusions derive from the study by Fang et al., as they obtained significant differences in 5-year OS rates for the pN1 and pN2 groups among 1380 patients who underwent D1α/D2 gastrectomy, and classified according to the seventh edition (71.4% vs 44.1%, p < 0.001).[10] Consistently, Chae et al. report for the seventh TNM more reliable prognostic results than for the sixth, analyzing 295 patients who underwent D2 gastrectomy and excluding patients with less than 15 retrieved nodes.[2] Finally, McGhan et al., in a retrospective review of gastric cancer patients from Surveillance, Epidemiology and End Results Registry data, considering 3-year survival in 13,547 cases without any specifications about lymphadenectomy, affirm that the latest TNM has a better survival discrimination and risk stratification.[11] On the contrary, analyzing 1000 patients (49% with less than 15 harvested nodes), Qiu et al. did not observe a superior prognostic power of the seventh TNM edition in comparison to the sixth edition.[12] Jung et al. propose a hybrid TNM classification, using the seventh edition for T classification, and the sixth for N, as they observed a low power of discrimination between $pN_7$1 and $pN_7$2, which may result in unwarranted stage migration.[13] Kikuchi et al., analyzing 609 patients with advanced gastric cancer, state that the seventh TNM is not always superior to the previous edition, even after an extended lymphadenectomy.[14]

In our study we aimed to verify the efficacy of the latest TNM in a series of limited lymphadenectomies, typical of the Western world. Actually, our study confirmed the relevant and independent prognostic role of lymph node status despite the classification (Table 2 and Figs. 1, 2). Therefore, potentially, our series of limited lymphadenectomies could be an ideal sample for testing the staging efficacy of the new cutoffs; our results justified the merging of $pN_6$2 and $pN_6$3, but surprisingly they did not show any statistically significant OS differences between $pN_7$1 and $pN_7$2 patients (74.4% vs 76.7%) (Fig. 2). Additionally, in our series, the multivariate analysis (which has not always been considered in other similar studies published so far) selected all of the three N categories only for pN_6, by highly discriminating HRs, differently from the model specific for pN_7 (Table 2).

Furthermore, we aimed to verify the prognostic power of both staging systems using LNR, a potential measure of lymphadenectomy and a well-known predictor of survival.[1,15–17] Even in a series of limited lymphadenectomies, LNR significantly stratifies the seventh TNM, demonstrating its prognostic superiority on it. Amazingly, we observed that stratification by metastatic LNR almost reached or reached statistical significance in discriminating OS right in the newly introduced groups $pN_7$1 and $pN_7$2 (Fig. 4). Consistently with these data, Wang et al., comparing the latest TNM to a staging system including LNR, observed that LNR staging shows superiority to the 7th edition of pN staging in a series of 1343 D2 gastrectomies.[18] Indeed, the influence of metastatic LNR on the new N staging system may suggest that the latest TNM edition also might be affected by the extension of lymphadenectomy with the potential exposure risk to stage migration phenomenon.

4.1. Limitations of the study

Five-year survival rates reported in this study could appear much better than in other Western series, but patients included in the analysis were not selected. Moreover, because of the retrospective nature of our study, not all data for each variable are available in every analysis: the reported rates refer to samples where all data are available. Although UICC/AJCC recommend a minimum number of 16 lymph nodes to be retrieved,[3] we decided to include also patients who underwent a lymphadenectomy with less than 16 harvested

nodes for deriving data from a real-world analysis, adherent to Western attitudes and to some previous contributions.[5,12] Consistently, in order to evaluate the real impact of the new staging system, we chose to adjust the analysis for residual tumor factor too and therefore R+ patients have not been excluded.

5. Conclusion

Our analysis has not found any prognostic superiority of the seventh TNM edition with respect to the N parameter in comparison to the sixth edition. The best possible prognostic stratification and the stage migration phenomenon are still a matter of debate, with the TNM staging system apparently dependent on the type of treatment. Hence, the new cutoffs can be considered a compromise between extent of surgery and conventional numeric criterion.[6] At the moment, its "few theoretical defects"[19] seem to compromise a reliable prognostic prediction, at least in some small Western series of gastric cancer patients who underwent limited lymphadenectomy.

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

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