

The metastatic lymph node ratio is a better prognostic factor than the number of metastatic lymph node after curative resection for gastric cancer

Mario Giuffrida, Lorenzo Viani, Gioacchino Giovanni Iapichino, Federico Cozzani, Paolo Dell'Abate, Paolo Del Rio,

General Surgery Unit, Parma University Hospital, Italy

Abstract. *Aim:* Evaluate impact of lymph node ratio as prognostic factor in gastric cancer. *Methods:* We studied 463 patients with gastric cancer who underwent curative gastric surgery with D1 or D2 lymphadenectomy, Data were collected from May 1996 through December 2010 at Department of General Surgery of Parma University Hospital. We divided patients in two groups according to number of nodes removed. *Results:* The results of the present nonrandomized retrospective single center study confirm the promising role of the LNR as an independent prognostic factor. Overall survival between LNR categories are statistically significant different between LNR0 and LNR1. *Conclusion:* The ratio between the number of metastatic and analyzed lymph nodes in patients with gastric cancer can discriminate patients better than the AJCC/UICC staging system: it seems to be related to a more sensitive in the evaluation of overall survival. (www.actabiomedica.it)

Key words: gastric cancer, gastrectomy, survival, lymphadenectomy, lymph node ratio.

Background

Gastric cancer is one of the most important causes of cancer-related death in the world.

The long-term prognosis for patients with gastric cancer following radical resection remains poor.

Five-year survival varies from 15% to 55% when the disease is localized to the stomach, lymph nodal invasion reduces the survival to approximately 20 per cent. (1)

The most important prognostic factors of gastric cancer are the Tumor invasion (T) and nodal status (N). (2,3)

The lymph node ratio (LNR), defined as the ratio of metastatic lymph nodes to the total lymph nodes examined, has been demonstrated as a valuable prognostic factor for the overall survival (OS) of resectable gastric cancer. (4)

Many studies have been demonstrated that LNR is an independent prognostic

more reliable and accurate than N stage in predicting survival outcomes. (5-7)

Therefore, the aim of our study was to evaluate the role of the LNR as a prognostic

factor in gastric cancer patients treated with D1 or D2 gastrectomy.

Methods

We retrospectively report 463 patients who underwent curative gastric surgery with biopsy-proven adenocarcinoma between January 1996 and December 2010 at Department of General Surgery at University Hospital of Parma. Exclusion criteria included: distant metastasis (including macroscopically evident nodal metastasis to lymph nodes of the superior mesenteric vein and middle colic vein and para-aortic lymph nodes), previous gastric surgery, post-operative death

(within 30-days after surgery) and palliative surgery (R1 or R2). Of 463 patients, 349 were included in our study while 114 were excluded for the following reasons: 11 were lost during follow-up, 20 patients had incomplete pathology reports, 21 had gastric stump cancers, 19 dead within 30 days after surgery and 43 were underwent palliative surgery.

A D1 lymphadenectomy was performed in 117 patients and in the other cases a D2 dissection was performed. Nodal status was classified according to the AJCC 8th Edition 2017 TNM stage: N0 no regional lymph node metastasis, N1 metastasis in 1-2 regional lymph nodes, N2 metastasis in 3-6 regional lymph nodes, N3 metastasis in 7 or more lymph nodes (N3a: metastasis in 7 – 15 regional lymph nodes; N3b: metastasis in 16 or more regional lymph nodes). The LNR intervals were determined as described elsewhere. (8-11) We found: LNR0: 0%, LNR1: 1-10%, LNR2: 11-25% and LNR3: > 25%. We divided patients in two groups according to number of nodes removed (group 1 = less than 15 lymph nodes, and group 2 = more than 15 lymph nodes) and we calculated survival stratified by this parameter.

Five-years overall-survival, survival by N group (N status of the AJCC 8th Edition 2017 TNM stage) and LNR group were calculated using the Kaplan and Meier method and was used log rank test to determine statistically significance differences. For each

LNR and N category, 5-years overall-survival was calculated in group 1 and 2 and the differences were calculated using the log rank test.

We considered only death for events related to disease. Statistical analysis was performed with the Statistical Product and Service Solution, SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). Values of $p < 0,05$ were considered significant.

Variable examined for statistical analysis were: sex (male vs female); type of procedure performed (subtotal vs total gastrectomy); location of the primary tumor (upper, middle or lower third and whole cancer); Lauren histotype; type of lymphadenectomy; pT stage of the AJCC TNM 8th Edition; number of nodes retrieved; number of metastatic nodes (pN stage of the AJCC TNM 8th Edition) and LNR. Relationship between the number of metastatic nodes, total number of removed nodes and LNR were evaluated with the Pearson correlation test.

Results

The patients' characteristics and analysis of variance for the total population are shown in Table 1.

At univariate analysis, statistically significant prognostic factors were: T and N of TNM staging system and LNR. The number of retrieved nodes was

Table 1. Clinical and histopathological records of patients analyzed and Univariate Analysis

Variables	p value	n (%)
Sex	ns	
Males		205 (59%)
Females		144 (41%)
Età	ns	mean: 71 ± 10.6
<70		228 (65.3%)
>70		121 (34.7%)
Surgical procedure	ns	
Total gastrectomy		171 (49%)
Subtotal gastric resection		178 (51%)
Anatomic site of primary tumor	ns	
Upper third		45 (12.8%)
Middle third		107 (30.6%)
Lower third		187 (53.7%)
Whole		10 (2.9%)

Variables	p value	n (%)
Lauren histo-type	ns	
Diffuse		155 (44.4%)
Intestinal		194 (55.6%)
Number of lymph nodes retrieved	ns	7761; mean 22.2 ± 12.1
<15		117
>15		232
pT (7th UICC/AJCC TNM)	p < 0.05	
T1		64 (18.3%)
T2		34 (9.7%)
T3		47 (13.5%)
T4		204 (58.5%)
pN (7th UICC/AJCC TNM)	p < 0.05	
N0		115 (33%)
N1		45 (12.9%)
N2		54 (15.5%)
N3		135 (38.6%)
Number of metastatic nodes	p < 0.04	2779
LNR	p < 0.05	
LNR0		115 (33%)
LNR1		39 (11%)
LNR2		43 (12.4%)
LNR3		152 (43.6%)

ns: not significant

not significant. Univariate analysis was performed separately on group 1 and group 2 and the number of removed nodes was not identified as a prognostic factor in any of the two groups.

We also calculated five-years overall survival according to Lauren histotype. In the analysed groups we found a worse prognosis for patients with diffuse type in group 1 (p < 0,0006). No significant differences in survival were found in group 2 between intestinal and diffuse histotype and between group 1 and 2 for intestinal type.

The mean follow-up was 49,43 months (range: 0-225 months); overall five-years survival was 34% and significant differences in survival between group 1 and group 2 were not found (30 % vs 36 %,).

Overall survival for both groups inside each pN and LNR classes was calculated using the Kaplan-Meier curves as showed in figures 1 and 2 and the results are summarized in table 2.

Considering the stratification by N class, in the N2 group, patients with more than 15 removed lymph nodes had a better survival rate than group 1 (p < 0,0001); within N0, N1 and N3 classes there was no significant differences in survival between group 1 and 2. If we observe the results obtained when the patients were divided according to their LNR category, the p value was significant for LNR 0 and LNR 2, indicating that LNR may be more sensitive when compared to pN (Table 2). In table 2, patients with less than 15 lymph nodes removed have lower five-year overall survival than group 2 confirming that 15 lymph nodes, the minimum number of nodes to be retrieved according to AJCC guidelines, was significant in term of survival benefit. (12)

Patients were classified according to their N and LNR classes: N0=115 (33%), N1= 45 (12.9%), N2= 54 (15.5%), N3= 135 (38.6%); LNR0=115 (33%), LNR1= 39 (11%), LNR2= 43 (12.4%) and LNR3=152 (43.6%). In figure 3, patients were divided according

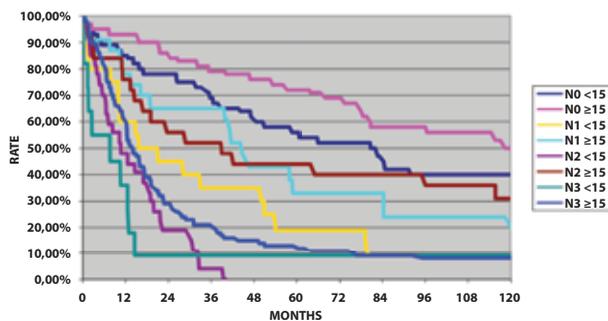


Figure 1. Overall survival according to pN.

to their LNR category for each N class. In the group N0 patients belonged to the same LNR class (LNR0). However, inside the N1, N2 and N3 categories, different LNR groups were found and five year-overall survival of these subgroups proven to be statistically different at log rank test ($p < 0.05$). N0 patients survived longer than N1 patients ($p < 0.0001$) but there weren't significant differences in survival between other classes (N1 vs N2 and N2 vs N3). Analysing five-year overall survival between LNR categories we found a statistically significant difference between LNR0 and LNR1 ($p < 0.003$), between LNR1 and LNR2 ($p < 0.002$) and between LNR2 and LNR3 ($p < 0.03$). These results may indicate that LNR is more sensitive than pN to discriminate subpopulations of patients with similar characteristics and prognosis. The Pearson correlation test showed that the number of metastatic lymph node was related to the number of lymph nodes removed ($p < 0.05$) but it wasn't related to LNR. The same test was applied within groups 1 and 2: in both groups the

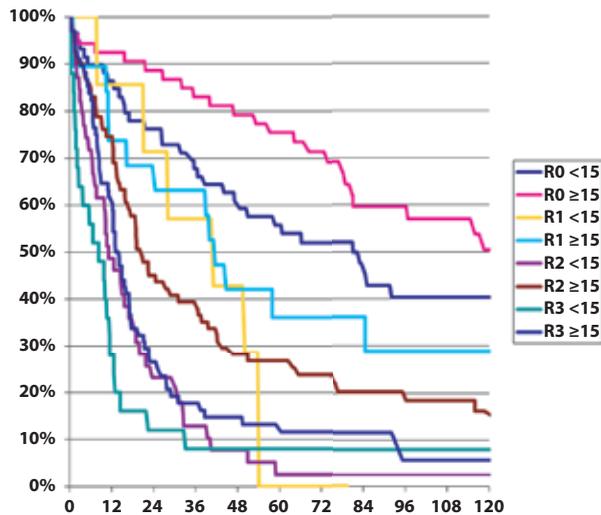


Figure 2. Overall survival according to LNR.

number of metastatic lymph nodes wasn't related to the number of retrieved lymph nodes. Moreover, Cox regression proved that LNR is an independent prognostic factor on multivariate analysis ($p < 0.05$).

Discussion

Adequate dissection of regional lymph nodes in patients with gastric cancer is important to enable appropriate determination of the lymph nodes status and the extent of lymph node dissection. To date, there is still much debate about the creation of uniform guidelines regarding the staging and the treatment of

Table 2. Five-years overall survival according to pN and LNR in group 1 (less than 15 lymph nodes removed) and 2 (more than 15 lymph nodes removed).

N	Number of patients	five-year survival	p value	LNR	Number of patients	five-year survival	p value
N0 <15	48	56%	ns	0 <15	48	56%	$p < 0.03$
	>15	67		72%	>15	67	
N1 <15	16	19%	ns	1 <15	11	0%	ns
	>15	29		33%	>15	28	
N2 <15	21	0%	$p < 0.0001$	2 <15	18	3%	$p < 0.001$
	>15	33		44%	>15	25	
N3 <15	16	9%	ns	3 <15	34	8%	ns
	>15	119		12%	>15	118	

ns: not significant

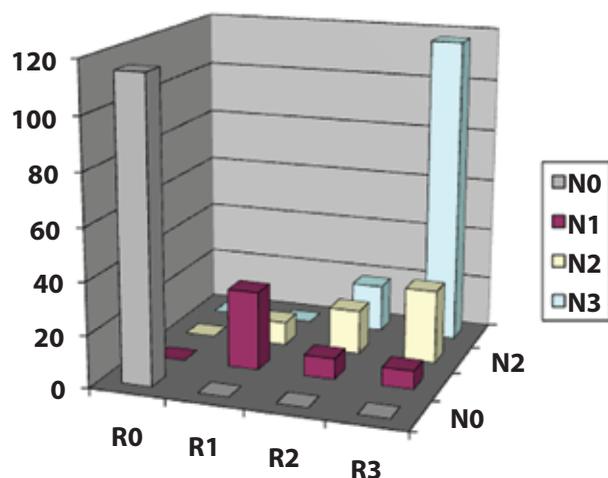


Figure 3. LNR in different pN classes.

patients with gastric cancer. Although the TNM staging system, the most widely used, is simple and reproducible, the appropriate classification of nodal status is still debated, and different staging systems have been proposed and investigated (13-17). The limitations of the TNM system are that it demands the examination of at least 15 lymph nodes, with inadequate staging (under-staging) as a result of limited nodes dissection (17); indeed, an analysis by Italian Research Group for Gastric Cancer (GIRCG) on quality assessment of lymph node dissection identified a median of 14 examined lymph nodes after D1 lymphadenectomy (29).

In limited lymph nodes dissections, a complete nodal staging is not possible because there are no informations regarding the extra-perigastric nodes and to overcome the problem of stage migration induced by extended lymphadenectomy (25), a new independent prognostic factor was investigated on a large scale and subsequently validated. During the last decades several studies evaluated the role of lymph node ratio as a strong independent indicator of prognosis in patients with gastric cancer, even in case of inadequate nodal staging (< 15 examined lymph nodes) (9,11,23-28).

This paper points out two major considerations.

Firstly, patients with limited lymph nodes dissections (< 15 lymph nodes removed) may experience stage migration (14,31,32); in fact, De Manzoni et al. (17) observed that the number of metastatic nodes increase with the extension of nodal dissection, which is an expression of the disease progression. LNR has

been proposed as a way to stage gastric cancer in order to minimize confounding factors. This study suggests that a better stratification of overall survival can be obtained using LNR: inside the N1, N2 and N3 categories, different LNR groups were found and the five years-overall survival of these subgroups were statistically different at log rank test ($p < 0.05$) (figure 3). N0 patients survived longer than N1 patients ($p < 0.0001$) but there were no significant differences in survival between other classes. Conversely, significant differences in survival were demonstrated between LNR0 and LNR1, LNR1 and LNR2, LNR2 and LNR3. The LNR was confirmed to be a more sensitive prognostic tool compared to AJCC staging system. Nitti et al. (8) suggested for the first time that the LNR has a greater prognostic value than the TNM and JGCA systems after D2 resection. LNR may reduce the influence of confounding factors such as the number of lymph nodes removed and individual differences in the number of gastric nodes. LNR present a clear advantage: it is minimally influenced by the extent of lymph node dissection, as confirm in our work and in a lot of papers in literature (6,16,28-32).

Secondly, a limited nodal dissection may not allow an appropriate staging of the gastric cancer (33,34): in case of D1 dissection the number of lymph nodes would be more susceptible to the pathologist's accuracy in isolating and identifying nodes and nodal metastasis (35-39). Furthermore, in this paper, despite the number of retrieved lymph nodes didn't result significantly related to the survival, patients in N2, LNR 0 and LNR 2 groups with more than 15 lymph nodes removed had a statistically longer survival than group 1 (Table 2). These data confirm the literature: nowadays gastrectomy with D2 lymphadenectomy is not only the standard of care for advanced curable gastric cancer according to the Japanese Guideline (40) but it is also recommended by European Union Network of Excellence for Gastric Cancer (II EUNE Gastric Cancer International Workshop, Madrid 2010).

The results of the present nonrandomized retrospective single centre study confirm the promising role of the LNR as an independent prognostic factor for patients with gastric cancer undergoing curative surgery at univariate and regression analysis. Our results suggest that LNR may be more sensitive than the number of metastatic lymph nodes in the stratification

of survival: LNR can identify classes of patients with similar behaviour and life expectancy (Figure 3).

However, LNR-system needs some improvements: in literature LNR intervals have not been universally established yet and many cut-off have been proposed (17,31,32- 41); the minimum number of nodes, if it exists, below which the LNR maintains its value and correlation with prognosis, has yet to be defined.

Multicentric randomized trials are still needed in the future to better define LNR's variables and to create a complete and accurate LNR staging system, helping to identify the best treatment option and the correct prognosis for patients affected by gastric cancer.

Conclusions

The ratio between the number of metastatic and analysed lymph nodes in patients with gastric cancer can discriminate patients better than the AJCC staging system: it seems to be more sensitive in evaluation of overall survival.

References

- Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors. 7th edition. Oxford: Wiley-Blackwell; 2010
- Dicken BJ, Bigam DL, Cass C, et al. Gastric adenocarcinoma: review and considerations for future directions. *Ann Surg* 2005; 241:27-39.
- Hogenberger O, Gretschel S. Gastric cancer. *Lancet* 2003;362: 305-15.
- Okusa T, Nakane Y, Boku T, et al. Quantitative analysis of nodal involvement with respect to survival rate after curative gastrectomy for carcinoma. *Surg Gynecol Obstet* 1990; 170: 488-94.
- Zhao LY, Li CC, Jia LY, Chen XL, Zhang WH, Chen XZ, Yang K, Liu K, Wang YG, Xue L, Zhang B, Chen ZX, Chen JP, Zhou ZG, Hu JK. Superiority of lymph node ratio-based staging system for prognostic prediction in 2575 patients with gastric cancer: Validation analysis in a large single center. *Oncotarget*. 2016 Aug;7(32):51069-51081. DOI: 10.18632/oncotarget.9714.
- Adachi Y, Kamakura T, Mori M, Baba H, Maehara Y, Sugimachi K. Prognostic significance of the number of positive lymph nodes in gastric carcinoma. *Br J Surg*. 1994 Mar;81(3):414-6.
- Fukuda N, Sugiyama Y, Midorikawa A, Mushiaki H. Prognostic significance of the metastatic Lymph node ratio in Gastric cancer patients. *World J Surg*. 2009 Nov;33(11):2378-82. doi: 10.1007/s00268-009-0205-1.
- 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(9): 1077-1085.
- Siewert JR, Bittcher K, Stein HJ et al. Relevant prognostic factors in gastric cancer: ten years results of the German gastric cancer study. *Ann Surg* 1998; 228: 449-461.
- Dicken BJ, Bigam DL, Cass C et al. Gastric cancer. *Lancet* 2003; 362: 305-315.
- Sianesi M, Bezer L, Del Rio P, Dell'Abate P, Iapichino G, Soliani P, Tacci S. The node ratio ad prognostic factor after curative resection for gastric cancer. *J Gastrointest Surg* (2010) 14: 614-619.
- Amin MB, Edge SB, Greene FL, Brierley JD. *AJCC cancer staging manual*. 8th ed. New York: Springer; 2017.
- Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* (2020). <https://doi.org/10.1007/s10120-020-01042-y>
- Persiani R, Rausei S, Antonacci V, Biondi A, Casella F, Ciccoritti L, D'Ugo D. Metastatic Lymph node ratio: a new staging system for gastric cancer. (2009) *World J Surg* 33: 2106-2111.
- Degiuli M, Sasako M, Ponti A, Calvo F. Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. *Br J Cancer*. 2004 May 4;90(9):1727-32.
- Bonenkamo JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, Meyer S, Plukker JT, Van Elk P, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H; Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. *N Engl J Med*. 1999 Mar 25;340(12):908-14.
- De Manzoni G, Verlato G, Roviello F, Morgagni P, Di Leo A, Saragoni L, Marrelli D, Kurihara H, Pasini F. The new classification of lymph node metastasis minimises stage migration problems in gastric cancer patients. *Br J Cancer*. 2002 Jul 15;87(2):171-4.
- Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistic for survival in cancer. *N Engl J Med* 1985; 312: 1604-1608.
- Imoue K, Nakane Y, Liyama H et al. The superiority of ratio-based lymph node staging in gastric carcinoma. *Ann Surg Oncol* 2002; 9 (1): 27-34.
- Yoshikawa T, Sasako M, Sano T et al. Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial. *Br J Surg* 2006; 93(12): 1526-1529.
- Liu C, Lu P, Lu Y et al. Clinical implications of metastatic lymph node ratio in gastric cancer. *BMC Cancer* 2007; 7:200.

22. Bonenkamp JJ, Hermans S, Sasako M et al. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999; 340: 908-914.
23. Marchet A, Mocellin S, Ambrosi A et al. The prognostic value of N-ratio in patients with gastric cancer: validation in a large multicenter series. *Eur J Surg Oncol* 2008; 34(2): 159-165.
24. Saito H, Fukumoto Y, Osaki T et al. Prognostic significance of the ratio between metastatic and dissected lymph nodes (n ratio) in patients with advanced gastric cancer. *J Surg Oncol* 2008; 97 (2): 132-135.
25. Marchet A, Mocellin S, Ambrosi A et al. 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. *Ann Surg* 2003; 245(4): 543-552.
26. Xu DZ, Geng QR, Long ZJ et al. Positive lymph node ratio is an independent prognostic factor in gastric cancer after d2 resection regardless of the examined number of lymph nodes. *Ann Surg Oncol* 2009; 16(2): 319-326.
27. Persiani R, Rausei S, Biondi A et al. Ratio of metastatic lymph nodes: impact on staging and survival of gastric cancer. *Eur J Surg Oncol* 2008; 34(5): 519-524.
28. Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study in surgery and pathology. Part 1. Clinical classificatio. *Jpn J Surg* 1981; 11: 127-139.
29. Verlato G, Roviello F, Marchet A et al (2009) Indexes of surgical quality in gastric cancer surgery: experience of an Italian network. *Ann Surg Oncol* 16: 594-602.
30. De Manzoni G, Verlato G, Guglielmi A et al (1999) Classification of lymph node metastases from carcinoma of the stomach: comparison of the old (1987) to new (1997) TNM system. *World J Surg* 23:664-669.
31. 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.
32. Volpe CM, Driscoll DL, Douglass HO jr. Outcome of patients with proximal gastric cancer depends on extent of resectionand number of rected lymoh nodes. *Ann Surg Oncol* 2000; 7(2): 139-144.
33. Ichikura T, Tomimatsu S, Ueguji K et al. Evaluation of the New American Joint Committee on Cancer/International Union against cancer classification of lymph node metastasis from gastric carcinoma in comparison with the Japanese classification. *Cancer* 1999;86(4):553-558.
34. Roder JD, Bottcher K, Busch R et al. Classification of regional lymph node metastasis from gastric carcinoma. *Cancer* 1998; 82(4):621-631.
35. Bunt AM, Hermans J, Smit VT et al. Surgical/pathologic-stage migration confronts comparisions of gastric cancer serviva rate between Japan and Western countries. *J Clin Oncol* 1995;13:19-25.
36. Xu D, Geng QR, Long ZJ, Zhan YQ, Li W, Zhou ZW, Chen YB, Sun XW, Chen G, Liu Q. Positive lymph node ratio is an independent prognostic factor in gastric cancer after D2 resection regardless of the examined number of lymph nodes. *Ann Surg Oncol*. 2009 Feb;16(2):319-26. doi: 10.1245/s10434-008-0240-4. Epub 2008 Dec 3.
37. Sun Z, Zhu GL, Lu C, Guo PT, Huang BJ, Li K, Xu Y, Li DM, Wang ZN, Xu HM. The impact of N-ratio in minimizing stage migration phenomenon in gastric cancer patients with insufficient number or level of lymph node retrieve: results from a Chinese mono-institutional study in 2159 patients. *Ann Oncol*. 2009 May;20(5):897-905. doi: 10.1093/annonc/mdn707. Epub 2009 Jan 29.
38. Wang XF, Sun YH, Liang DJ, Wang C et al. Clinical values of extended lymph node dissection for gastric cancer: a meta-analysis for D1 vs D2 gastrectomy. *Zhonghua Wei Chang Wai Ke Za Zhi*. 2007 Sep;10(5):425-30.
39. Kulig J, Popiela T, Kolodziejczyk P, Sierzega M, Szczepanik A, Polish Gastric Cancer Study Group. Standard D2 versus extended D2 (D2+) lymphadenectomy for gastric cancer: an interim safety analysis of a multicenter, randomized, clinical trial. *Am J Surg*. 2007 Jan;193(1):10-5.
40. Japanese Gastric Cancer Association (2004) Gastric cancer treatment guidelin, 2nd edn. Kanehara, Tokyo.
41. Maria Teresa Mita, Federico Marchesi, Stefano Cecchini, Francesco Tartamella, Matteo Riccò, Hariscine Keng Abongwa, Luigi Roncoroni. Prognostic assessment of gastric cancer: retrospective analysis of two decades. *Acta Biomed* 2016; Vol. 87, N. 2: 205-211

Correspondence:

Received: 1 May 2020

Accepted: 13 May 2020

Giuffrida Mario, General Surgery Unit,

Parma University Hospital, Italy

Borgo Sordo 12, 43125 Parma, Italy

E-mail: mario.giuffrida4@gmail.com