The Role of Metastatic Lymph Node Ratio in Gastric Cancer

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Authors' contributions

This work was carried out in collaboration between all authors. Author IE designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors MT and CEG, EG managed the analyses of the study. Author MOK managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Introduction: Lymph node metastases at the gastric cancer is the one of the important prognostic risk factors. In this study, we evaluate the prognostic importance of the Metastatic Lymph Node Ratio in the gastric cancer cases.
Methods and Technique: In this study, we included 56 gastric adenocarcinoma patient who had curative surgery and evaluated retrospectively. Forty one of them were male (%73.2) and fifteen (%26.7) were female. Statistical analysis of the results of this study was done by using SPSS 17 for Windows. Survey analysis was calculated with Kaplan-Meier test and the multivariant analysis was calculated with Cox proportional hazard model.
Results: In our study the factors that effect the survey were the ratio of number of the metastatic lymph node and the dissected total lymph node (MLR-Metastatic Lymph Node Ratio), stage, number of the not involved lymph nodes, the diameter of tumor and differentiation of the tumor.

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The multivariant analysis showed that stage and the MLR were the independent prognostic factors.
Conclusion: MLO based staging is a simple, effective, and reproducible method for the evaluating the prognosis of the gastric cancer patients who had curative surgery and had involved lymph nodes.

1. INTRODUCTION AND PURPOSE

Gastric cancer (GC) is among the most common and lethal malignancies worldwide [1]. Lymph node (LN) status is widely accepted as one of the most important prognostic factors in this cancer [2]. Today, LN staging mainly depends on the number of metastatic LNs as defined by Union Internationale Contre le Cancer (UICC) and American Joint Committee on Cancer (AJCC) or anatomical localizations of LNs according to the guideline by Japanese Gastric Cancer Association (JGCA) [3,4]. However, optimal staging of LN metastasis in patients with GC remains an important controversial issue. The JGCA system is not widely accepted in western countries while the main disadvantage of the UICC/AJCC system is the stage shift that might emerge since the number of metastatic LNs is dependent on the number of resected LNs. In addition, a minimum of 16 total harvested LNs is essential for accurate nodal staging and prediction of survival in classic AJCC TNM classification [4]. In recent years, several studies have aimed to prove that the resulting metastatic lymph node ratio (MLR) obtained by the division of the number of metastatic lymph nodes lowering stage shift by a total number of resected nodes is a highly reliable system [5-10]. However, a global consensus on the effectiveness of MLN-based optimal nodal staging system has not been reached yet due to some inconsistent results from those studies Kwon et al. grouped the ratio of the number of dissected lymph nodes to metastatic lymph nodes (MLO) as 0.1-25%, 26-50% and over 50%, and reported 5-year survival as 83%, 66%, 30% and 23%, respectively [9]. Bando et al. investigated the effects of MLO on lifetimes in 650 D2 dissected patients; if there was no lymph node involvement, they evaluated MLO as 0,0-1; if there was lymph node involvement, they evaluated MLO as 1,1-25; if there was lymph node involvement, they evaluated lymph node involvement with more than 2,25 MLO as 3, and they reported 5-year survival as 86%, 68%, 35% and 16%, respectively [10].

In this study, we aimed to investigate the prognostic value of MLR-based nodal staging system in a group of Turkish patients who underwent curative resection for gastric cancer.

2. MATERIALS AND METHODS

2.1 Patients and Method

A total of 56 patients who underwent curative resection and extended lymphadenectomy for gastric adenocarcinoma in Ankara Numune Training and Research Hospital were included in this study. All Clinicopathologic data were retrospectively collected from medical records and pathologic reports. The patients with a history of cancer at other sites, patients who received neoadjuvant systemic therapy, and patients who died due to complications within the postoperative 30 days were excluded from the study. R0 resection and D2 lymphadenectomy, or extensive lymphadenectomy if necessary were the standard surgical method in all patients. The specimens obtained during the operations were investigated by the pathology department for tumor depth, nodal involvement, tumor diameter, lymphatic invasion, vascular invasion, neural invasion, Bormann classification, tumor stage and Lauren classification. All tumors were staged in accordance with the TNM classification of AJCC [4]. In the postoperative period, the patients were consulted by the oncology department for adjuvant chemotherapy and/or radiotherapy. All patients were checked every three months for the first year and every six months after the first year of the operation.

2.2 Statistical Analysis

All the statistical analyses were performed using the SPSS 20.0 statistical package (SPSS Inc., Chicago, IL). Survival analysis was made by Kaplan-Meier method. All the parameters that were statistically significant in the univariate analysis were included in the multivariate Cox proportional hazard model. The accuracy of the prognostic evaluation of different staging systems was compared using receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC) were used to compare the accuracy of the prognostic evaluation of classic

TNM classification and MLR-based nodal staging. P<0.05 was accepted as a level of statistical significance.

3. RESULTS

3.1 Clinicopathological Characteristics

A total of 56 patients were enrolled, including 41 (73.2%) men and 15(26.7%) women, with a mean age of approximately 59 years. The majority of the tumors were located in the upper and middle parts of the stomach, hence total gastrectomy plus D2 lymphadenectomy was the most common type of surgery (71.4%). In order to provide a curative resection, splenectomy and distal pancreatectomy were also applied in 15 (26%) and 5 (8%) patients, respectively. The mean number of total retrieved LNs was 22.8 per case (range, 15-48). The mean number of involved LNs was 4.61 (range, 0-33). The histopathological diagnosis was adenocarcinoma in all patients. The majority of the tumors (83.9%) were in stage 3 according to the final pathological reports. In the postoperative period, 35 of the patients (67.3%) were given chemotherapy whereas the number of the patient's given radiotherapy was 28 (53.8%). All clinical and pathological findings of the patients were given in Table 1.

3.2 Survival Analysis and Comparison of Prognostic Ability of pN and MLR

The mean overall survival of the patients was 10.3±9.5 (1-38) months.

A total number of lymph node per patient was 22.8±10.4. In post-operative period, 35 of the patients (67.3%) were given chemotherapy whereas the number of the patient's given radiotherapy was 28 (53.8%). The mean overall survival of the patients was 10.3±9.5 months. Of all patients, 1 was in stage 1 (1.9%), 8 were in stage 2 (15.1%), 47 were in stage 3 (83.9%). Total gastrectomy + D2 lymph node dissection was applied to 40 patients (71.4%) and sub-total gastrectomy+D2 lymph node dissection was applied to 16 (28.5%) patients. Apart from total and sub-total gastrectomy, splenectomy to 15 patients (26%) and distal pancreatectomy to 5 patients (8%) was applied. After the investigation of pathologic reports of the patients, 31 cases were intestinal type, 12 were the diffuse type and 13 were non-classifiable type according to LAUREN classification. According to BORRMAN

classification, 5 (8.9%) cases were the polypoid type, 6 (10.7%) were the superficial elevated type, 26 (46.4%) were the ulcerative type, 19 (33.9%) were the diffuse type. According to differentiation types, 15 (26.7%) were well-differentiated, 14 (25%) were mid-differentiated and 27 (48.2%) were low-differentiated type. When tumor dimensions of the cases were compared, it was observed that 10 (17.8%) were smaller than 5cm and 46 (82.1%) were greater than 5cm. When the cases were compared to a total number of dissected lymph nodes, it was observed that maximum 15 and minimum 48 lymph nodes were dissected. In 42 of the patients (76.7%), 15 to 30 lymph nodes were dissected whereas 30 lymph nodes were dissected in 13 (23.2%) patients.

Table 1. Clinicopathologic characteristics of the patients

Variables	n(%)
Age(Year)	
<70	11 (%19)
≥70	45(%80)
Gender	
Men	41(73.2)
Women	15(26.7)
STAGE	
I	1(%1.9)
II	8(%15.1)
III	47(%83.9)
Gastrectomy type	
Total	40(%71.4)
Sub-total	16(%28.5)
LAUREN	
Diffuse	12(%21.4)
Intestinal	31(%55.3)
Non-classifiable	13(%23.2)
BORRMAN	
Polypoid	5(%8.9)
Superficial elevated	6(%10.7)
Ulcerative	26(%46.4)
Diffuse	19(%33.9)
Tumor dımensıon	
< 5cm	10(%17.8)
≥5cm	46(%82.1)
Dıfferentıatıon	
Well	15(%26.7)
Mid	14(%25)
Low	27(48.2)
Total number of dıssected lymph node	
15-30	43(%76.7)
>30	13(23.2)

n: number of patients

Total survival of patients was 10.3±9.5 months. Cox Regression Analysis showed that age had no affect on survival. There was a statistical correlation between MLR and survival (p=0.014). After the evaluations of stages of the patients, it was observed that stage had a significant impact on survival (p=0.0000). A total number of lymph nodes and the number of positive lymph nodes did not have significant effects on survival (p=0.342, p=0.143). However, the number of negative lymph nodes and the differentiation type were significantly effective on survival (p=0.001, p=0.0159). The dimension of the tumor was observed to have a significant impact on survival (p=0.007), but vascular invasion had no significant effects on survival (p=0.202). It was also found that Lauren and Borrman classifications were not significantly effective on survival (p=0.069, p=0.164). In our study, the factors affecting survival were MLR, stage, the number of negative lymph nodes, tumor diameter, and differentiation.

The total number of dissected lymph nodes was not observed as a prognostic factor (p=0.342). However, in the multi-variants analysis; stage and ratio were independent prognostic factors.

In ROC analysis, the ratio of metastatic lymph nodes (MLR) was a good prognostic test. AUC (area under the curve) = 0.718.

That MLR was higher than 0.34 (sensitivity 90%, specificity 72%) was accepted to be a cut-off value.

4. DISCUSSION

A staging system should be decisive and repeatable for the classification of lymph nodes around malign tumors. Therefore, it will be possible to compare prognosis estimation, treatment plan and the results of the studies carried out in different institutions. Currently, JGCA [11] and UICC/AJCC [12] systems are used for lymph node metastases in gastric cancer. JGCA [13] classification system mainly depends on the localizations of lymph node metastasis according to the primary tumor. However, UICC/AJCC classification system focuses on the number of metastatic lymph nodes. JGCA system might be useful for systematic lymphadenectomy in gastric cancer, however, pathologists and surgeons in western countries consider that it's a very complicated classification system for clinical use. On the other hand, some studies have revealed that

UICC/AJCC system developed in 1977 is more repeatable and has better properties for prognostic differences than JDCA system [13,14]. The only significant constraint in UICC/AJCC system is that the number of metastatic lymph nodes is affected by the total number of dissected lymph nodes. Mostly used by Japanese researchers, extended lymph node dissection, is not a routine procedure for gastric cancer surgeries in several western countries. In a compilation study published in the USA regarding gastric cancer treatments, it was reported that D2 lymph node dissection was applied to 4% to 7% of the patients [15]. In several gastric cancer cases, the number of metastatic lymph nodes is higher than the number of dissected lymph nodes. Thus, after a limited lymph node dissection, gastric cancer classified as N1 might be classified as N2 or N3 after extended lymphadenectomy. For the moment, the classification made in accordance with N staging system of UICC/AJCC might be particularly affected by D1 lymph node dissection commonly used in western countries as well as lymph node dissection made by the surgeon [16,17]. In both classification systems of JGCA and UICC/AJCC, a stage shift more than 15% might be observed [17].

Table 2. Factors affecting survival in one-way analysis

Factors affecting survival	p-value
MLR	0.0140
Stage	0.0000
The number of negative lymph nodes	0.0010
Tumor diameter	0.0070
Differentation	0.0159

MLR calculated by the division of the number of metastatic lymph nodes by a total number of lymph nodes is suggested as a new prognostic factor that lowers stage shift and is independent of the number of dissected lymph nodes. In 1990, Okusa et al. [18] identified the effects of "metastasis frequency" for the first time in their study. Then, several studies reported two significance of MLR in gastric cancer and this was determined as a strong prognostic factor after radical resection made for gastric cancer. Siewert et al. [19] conducted a prospective multicenter study including the 10-year examinations of 1653 patients with gastric cancer and they identified that MLR (≤0.2 vs. >0.2), the state of MLR and residual tumor were independent prognostic factors. Yu et al. [20] examined 886 cases including R0 gastrectomy

ROC Curve
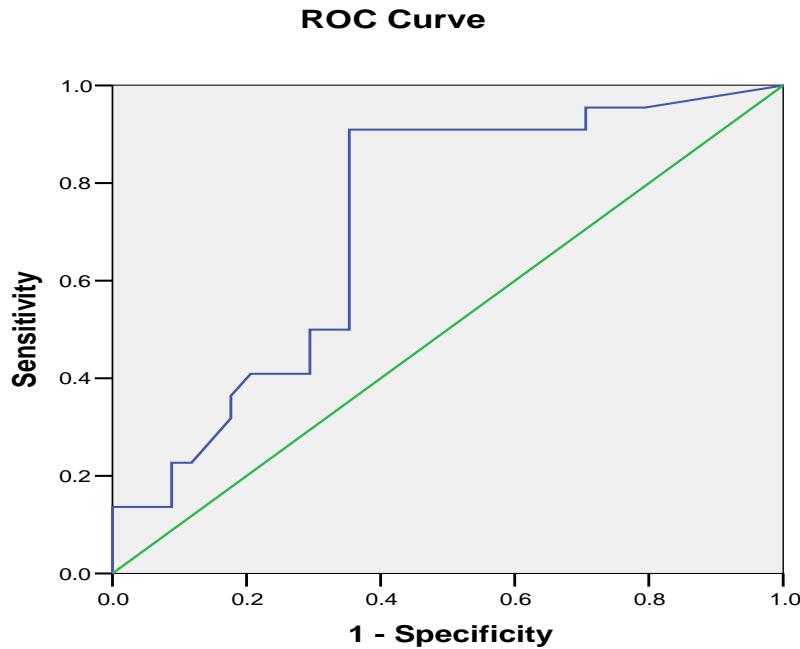
Diagonal segments are produced by ties.

Fig. 1. ROC analysis

and D2 lymphadenectomy and showed that there existed significant prognostic differences in all sub-groups based on MLR (N0:0; N1:0.01-0.25,N2:>0.25). The authors of the study also concluded that MLR-based classification is a simple, convenient and repeatable method and it can be used in estimations of results of surgical operations. In some studies using multi-variants analysis, MLR-based system is superior to UICC/AJCC and JGCA systems in staging of lymph node metastasis in gastric cancer [16,17, 21]. In this study, when lymph node involvements compared by multi-variants analysis, that MLR system is a much more significant prognostic factor for patients with gastric cancer was revealed. The reason is that the number of gastric lymph nodes varies from a patient to another [17,22]. The total number of lymph nodes obtained changes for each patient depending on whether D2 lymphadenectomy was applied. However, the number of metastatic lymph nodes affected by the total number of dissected lymph nodes changes depending on experience of surgeons and pathologists that examine. When the prognostic value of MLR was observed in terms of the number of total lymph nodes in the patient and the number of lymph node obtained, it is resulted from the elimination of factors causing individual-induced illusion [16]. Actually, it was found that when patients with

gastric cancer with the lymph node involvement including the same amount of MLR were staged by using MLR, regardless of the total number of lymph nodes obtained, they had the same similar clinical results [17]. Therefore, it can be predicted that by comparison with UICC/AJCC and JGCA, MLR classification system provides a better prognostic evaluation after D2 lymphadenectomy in patients with gastric cancer [22].

There isn't a consensus on the suitable cut-off values of MLR in gastric carcinoma and various cut-off values were used in previous studies [11-17,21,23,22]. In a study carried out by Fukuda et al., lymph node involvement was classified according to cut-off values. MLR 0 =0 MLR1 =0.01-0.19 MLR2≥0.2 MLR1 and MLR2 sub-groups were divided by 0.19 cut-off value.

Table 3. Multi-variants analysis

Variants	P
MLR	0.024
Stage	0.007

5. CONCLUSION

In our study, the factors affecting survival were revealed as MLR, which is the proportion of the number of metastatic lymph nodes to the total

number of lymph nodes, stage, number of negative lymph nodes, tumor diameter and differentiation. And again, in our study, in multi-variants analysis stage and MLR were found as prognostic factors. That MLR was higher than 0.34 (sensitivity 90%, specificity 72%) was accepted to be a cut-off value. Besides, mean MLR value might change when examined by another institution and it might be affected by the number of cases. In patients with lymph node involvement, the usage of MLR-based staging is observed to be a simple, effective and repeatable method to evaluate the prognoses of patients with gastric cancer to whom curative gastrectomy was applied.

CONSENT

As per international standard or university standard written patient consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical permission has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics. CA Cancer J Clin. 2012;2015:65:87-108

2. Prognostic value of three different lymph node staging systems in the survival of patients with gastric cancer following D2 lymphadenectomy Chen Jian-hui 1,2 & Cai Shi-rong1,2 & Wu Hui 1,2 & Chen Si-le1,2 & Xu Jian-bo1,2 & Zhai Er-tao1,2 & Chen Chuang-qi1,2 & He Yu-long1,

3. Kutlu OC, Wachtell M, Dissanaike S. Metastatic lymph node ratio successfully predicts prognosis in western gastric cancer patients. Surg Oncol. 2015;24:84–8.

4. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines (ver. 3). Gastric Cancer. 2010;2011:113–23.

5. Wang W, Xu DZ, Li YF, et al. Tumor-ratio-metastasis staging system as an alternative to the 7th edition UICC TNM system in gastric cancer after D2 resection--results of a single-institution study of 1343 Chinese patients. Ann Oncol. 2011;22:2049-56

6. Bueno S, Marcilla G, Flores P et al. Prognostic factors in a series of 297 patients with gastric adenocarcinoma undergoing surrgical resection. Br J Surg 1998;85:255-60.

7. Allgayer H, Heiss M, Schildberg W. Prognostic factors in gastric cancer. Br J Surg 1997;84:1651-64.

8. Shen KH, Wu CW, Lo SS ett al. Factors correlated with number of metastatic lymph nodes in gastric cancer. Am J Gastroenterol. 1999;94:104-8.

9. Kwon SJ, Kim GS. Prognostic significance of lymph node metastasis in advanced carcinoma of the stomach. Br J Surg. 1996;83:1600-3.

10. Bando E,Yonemura Y, Taniguchi K et al. Outcome of ratio of lymph node metastasis in gastric carsinoma. Ann Surg Oncol. 2002;9:775-84.

11. Japanase gastric cancer association japanese classification of gastric carcinoma,2nd Englısh edition. Gastric Cancer. 1998;1:10-24.

12. Sobin LH, Fleming ID. TNM classification of malignant tumors. Fifth edition Union Internationale Contre le Cancer and American Joint Committee on Cancer.Cancer. 1997;80:1803.

13. Ichikura T, Tomimatsu S, Uefuji K et al. Evaluation of the New American Joint Committee on Cancer /Internationel Union against cancer classification of lymph node Metastasis from gastric carcinoma in comparison with the Japanese classification Cancer. 1999;86:553-558.

14. Hameneek P. The superiorty of the new International Union Against Cancer and American Joınt Committee on Cancer TNM staging of gastric carcinoma. 2000;88:1763-1765.

15. Hundahl SA, Philips Jl, Menck HR. National Cancer Data Base report on poor survival of U.S. gastric carcinoma patients treated with gastrctomy: Fifth edition. Cancer. 2000;88:921-932.

16. Nitti D, Marchet A, Olivieri M et al. Ratio between metastaic and examined lymph nodes is an Independent prognostic factor after D2 resection for gastric cancer:analysis of a large Europan monoinstitutional experience. Ann Surg Oncol. 10:1077-1085.

17. Bando E Yoneyama Y, Taniguchi K et al. Outcome of ratio lymp node metastasis in gastric carcinoma. Ann Surg Oncol. 2002;9:27-34.

18. Okusa T, Nakame Y, Boku T et al. Quantitative analysis of nodal involvement with respect to survival rate after curative gastrectomy for carcinoma. Surg Gynecol Obstet. 1990;448-494.

19. Siewert JR, Bottcher FK, Stein HJ. Relavant prognostic factors in gastric canser: Ten years results of the German gastic cancer study. Ann Surgy. 1998;228:449-461.

20. Yu W,Chi Gs, Whang J et al. Comparison of five systems for staging lympf node metastasis in gastric cancer. Br J Surg 1997;84:1305-1309.

21. Persiani R, Rausei S, Biondi A et al. Ratio pf metastic lymph nodes: impact on staging and survival of gastric cancer. Euro J Surg Oncol. 2008;34:519-524.

22. Naoto F,Yasuyuki S,Akira M et al. Prognostic significance of the metastaic lymph node ratio in gastric cancer patients. World J Surgy. 2009;33:2378-2382.

23. Wagner PK, Ramaswamy A, Schmitz-Moormann P et al. Lymph node counts in the upper abdomen : Anatomical basis for lymphadenectomy in gastric cancer. Br J Surg . 1991;78:825-827.

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