Saudi Journal of Medicine (SJM)
Scholars Middle East Publishers
Dubai, United Arab Emirates
Website: www.saudijournals.com

ISSN 2518-3389 (Print)
ISSN 2518-3397 (Online)

Evaluation of the Effect on Prognosis of Metastatic Lymphnode Ratio and Number of Metastatic Lymph Node for Patients with Gastric Cancer

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Article History
Received: 10.04.2018
Accepted: 20.04.2018
Published: 30.04.2018

DOI:
10.36348/sjm.2018.v03i04.010

Abstract: There is some controversy about assessment of nodal stage in staging systems used for gastric cancers. The goal of the this study is to assess the influence of metastatic lymph node ratio (MLNR) and number of resected lymph nodes on survival in patients with gastric cancer who were perfomed R0 resection due to gastric adenocarcinoma. Data from 125 patients with gastric carcinoma who underwent R0 resection due to from 2009 to 2015 investigated retrospectively. Cut-off values used for MLNR were 0.1-25%, 26-50% and >50%. Sex, age, size and location of tumor , differentiation, tumor invasion, lymphovascular invasion, number of metastatic lymph nodes and MLNR were analyzed as prognostic factors. Five-year survival rate was 45.6%. Five-year survival rates among patients with pN0, pN1, pN2, pN3aand pN3b disease were 79%, 41%, 34%, 25% and 17%, respectively (p=0.0001). Five-year survival rates among patients in MLNR0, MLNR1, MLNR2 and MLNR3 categories were 79%, 42%, 28% and 5%, respectively (p=0.0001). Due to our results, tumor size, differentiation degree, depth of invasion, presence of lymphovascular invasion, number of metastatic lymph nodes, MLNR and disease stage were found to be associated with survival (p=0.0001). According to results of multivariate analysis, differentiation degree, presence of lymphovascular invasion and MLNR were found as independent risk factors, while number of metastatic lymph nodes was not an independent risk factor regarding survival. MLNR is an independent risk factor in gastric adenocarcinoma patients undergoing R0 resection regarding survival.

Keywords: Gastric cancer, R0 resection, metastatic lymph node ratio, prognosis.

INTRODUCTION

Gastric cancer is a very frequent type among all cancers, and the second frequent cause among all cancer-related deaths [1]. Despite the advances in modern medicine, nearly one in every four patients looses their life due to this disease [2]. Although serious success rates have been reported with chemotherapy and other methods of treatment, surgery still remains the primary therapeutic option for gastric cancers. The state of metastatic lymph nodes has utmost significance for accurate prediction of prognosis and staging, and for accurate planning of adjuvant treatment. However, there is some controversy about the number of minimum lymph nodes that must be respected for accurate staging and survival prediction.

Increasing number of studies report that MLNR is an independent prognostic factor for predicting survival in gastric cancer [3-17]. However, in almost all of these studies, no consensus has been established regarding the optimal cut-off value. In this study, our goal was to evaluate the prognostic significance of the metastatic lymph node ratio and the number of resected lymph nodes on survival of patients with gastric cancer who underwent resection

PATIENTS AND METHODS

Patients

We retrospectively reviewed data from 125 patients who were diagnosed with gastric cancer upon histopathological examination from January 2009 to December 2014. The study was approved by the relevant ethics committee of the University's School of Medicine. Patients' data were retrieved from the hospital records. Totally 125 patients with these criterias were included in the study. All patients signed a detailed informed consent for using their data for research. Study inclusion criteria were:

- Curative gastric resection (R0: no residual tumor microscopically).
- No history of previous gastric resection
- No history of another malignancy
- Survival during hospital stay, or no mortality within one month after the operation

- In addition to the primary tumor resection, resection of at least 15 lymph nodes based on the AJCC classification
- Histopathologically confirmed diagnosis of adenocarcinoma
- No administration of neoadjuvant treatment.

Statistical Analysis

Descriptive statistics (frequency, percentdistribution) were used in statistical analysis. For survival analysis, univariate Kaplan–Meier and multivariate Cox Regression analysis were used. Means were expressed with standard deviation, and medians were expressed with min-max values. P<0.05 was accepted as statistically significant.

RESULTS

Patients demographics

We analyzed the data from 125 patients with gastric cancer who underwent R0 resection and D2 or D3 lymph node dissection. The median age of the patients was 62 (25-89) years. Of these patients, 88 were male and 37 were female. The median follow-up period was 19 (2-67) months. Median number of resected lymph nodes was 36 (15-97) and median number of metastatic lymph nodes was 4 (0-42). Patients were categorized depending on the total number of dissected lymph nodes as 15-25 lymph nodesand>25 lymph nodes; accordingly, 32 patients were in 15-25 lymph node group and 93 patients were in >25 group. Based on the American Joint Committee on Cancer(AJCC) (7th edition) TNM staging system, number of patients in N0, N1, N2, N3a and N3b groups were 37 (29.6%), 21 (16.8%), 23 (18.4%), 20 (16%) and 24 (19.2%), respectively. In our study, cut-off values for metastatic lymph node ratio were determined based on the study by Zhang *et al*., [15]. The number of patients in MLNR0, MLNR1, MLNR2 and MLNR3 groups were 37 (29.6%), 51 (40.8%), 18 (14.4%) and 19 (15.2%), respectively (Table-1). There was significant association between survival and the number of metastatic lymph nodes, male sex, large tumor size, poor differentiation, presence of lymphovascular invasion, increased number of metastatic lymph nodes, advanced stage and increased invasion depth (P<0.001) (Figure-1). However, when patients were grouped based on the number of resected lymph nodes as 15-25 and>25, median survival in the >25 lymph node group was longer, although the difference was not statistically significant (36 monthsvs. 39.3 months, P=0.401) (Figure-2). Similarly, when patients with lymph node metastasis and without lymph node metastasis were grouped based on the number of resected lymph nodes, the effect of the number of resected lymph nodes on survival was not statistically significant in either the lymph node metastasis group or the no-lymph node metastasis group(pN0) (p>0.05) (Table-2).

Univariate Analysis

Univariateanalysis results indicated that advanced age, large tumor size, poorly differentiated tumor, presence of lymphovascular invasion, increased number of metastatic lymph nodes, increased tumoral invasion depth, advanced stage and metastatic lymph node ratio were prognostic factors for gastric cancers (Table-2). There was no significant association of survival with sex or tumor location (P=0.340 and P=0.74, respectively).

Multivariate Analysis

Results of multivariate analysis (Table-3) that included the factors associated with prognosis based on the univariate analysis, including age, tumor size, differentiation degree, lymphovasccular invasion, depth of tumor invasion, stage, number of metastatic lymph nodes and metastatic lymph node ratio. For overall survival, age more than 65 years, poor differentiation and metastatic lymph node ratio of >0.5 were associated with poor survival rates (Table-3). Metastatic lymph node ratio was significantly associated with worse overall survival, with a hazard ratio of 1.025 with 1.015-1.035 confidence interval (P<0.0001). Although there was a trend towards poor survival rates with increasing number of metastatic lymph nodes, this associationwas not statistically significant.

Table-1: Clinicopathologic characteristics of patients

Variables	Number (%)	Median (Min-Max)
Sex		
Male	88 (70.4)	
Female	37 (29.6)	
Age (year)		
<65	75 (60)	
≥65	50 (40)	
Tumor size (cm)		
<4	34 (27.2)	
≥4	91 (72.8)	
Tumor location		
Upper third	25 (20)	
Middle third	55 (44)	
Lower third	40 (32)	
Diffuse	5 (4)	
Differansiation		
Well	18 (14.4)	
Moderate	38 (30.4)	
Poor	69 (55.2)	
Depth of tumor invasion		
T1	19 (15.2)	
T2	10 (8)	
T3	29 (23.2)	
T4	67 (53.6)	
Lymph node metastasis		
pN0	37 (29.6)	
pN1	21 (16.8)	
pN2	23 (18.4)	
pN3a	20 (16)	
pN3b	24 (19.2)	
Stage		
I	23 (18.4)	
II	20 (16)	
III	82 (65.6)	
Lmphovascular invasion		
Negative	60 (48)	
Positive	65 (52)	
Metastatic lymph node ratio		
MLNR0	37 (29.6)	
MLNR1 (0.01-0.25)	51 (40.8)	
MLNR2 (0.26-0.50)	17 (14.4)	
MLNR3 (>0.50)	20 (15.2)	
Number of Metastatic lymph node		4 (0-42)
Extracted Lymph Nodes		36 (15-97)
Overall Survival (months)		19 (1-67)

Table-2: Univariate analysis of various clinicopathological factors in patients

Variables	n	MedianSurvival (month)	Five-yearsurvival rate (%)	P values
Sex				0.340
Male	88	39.7	62.0	
Female	37	35.9	41.8	
Age (year)				**0.028**
<65	75	43.7	51.6	
≥65	50	30.3	36.6	
TumorLocation				0.742
Upperthird	25	36.0	55.1	
Middlethird	55	41.1	52.0	
Lowerthird	40	36.4	39.4	
Diffuse	5	30.6	0	
Tumor size (cm)				**0.030**
<4	34	48.1	64.8	
≥4	91	35.9	54.7	
Differansiation				**0.002**
Well	18	58.1	85.0	
Moderate	38	33.5	0	
Poor	69	31.3	29.2	
Lymphovascularinvasion				**0.003**
Negative	60	47.7	61.2	
Positive	65	27.9	32.0	
Depth of tumor invasion				**<0.0001**
T1-T2	29	57.7	76.8	
T3- T4	96	33.9	37.4	
TNM Stage				**0.002**
I	23	59.0	87.7	
II	20	34.5	0	
III	82	33.2	47.9	
eLN				0.401
15-25 LN	32	36.0	47.3	
>25 LN	93	39.3	62.8	
Lymph Node metastasis				**<0.0001**
pN0	37	56.3	79.3	
pN1	21	32.5	41.0	
pN2	23	36.5	33.9	
pN3a	20	19.3	24.4	
pN3b	24	20.6	17.3	
MLNR				**<0.0001**
MLNR0	37	56.3	79.3	
MLNR1 (0.01-0.25)	51	35.3	42.5	
MLNR2 (0.26-0.50)	17	26.4	28.2	
MLNR3 (>0.50)	20	12.6	5.3	
eLN				0.401
15-25 LN	32	36.0	47.3	
>25 LN	93	39.3	43.9	
MLN+				0.168
15-25 LN	21	23.1	27.6	
>25 LN	67	29.5	29.4	
MLN –				0.908
15-25 LN	11	54.0	81.8	
>25 LN	26	56.3	76.9	

eLN: extractedlymphnode, MLN: Metastatic Lymph Nodes, MLNR: Metastatic Lymph Node Ratio

Table-3: Multivariateanalysis of variousclinicopathlogicfactors in patients

Variables	Hazardratio	95%Confidenceinterval	P values
Age (years)	1.037	1.015-1.060	0.001
Differentiation	6.212	1.457-26.480	0.014
MLNR	1.025	1.015-1.035	0.0001

MLNR: Metastatic lymphnode ratio

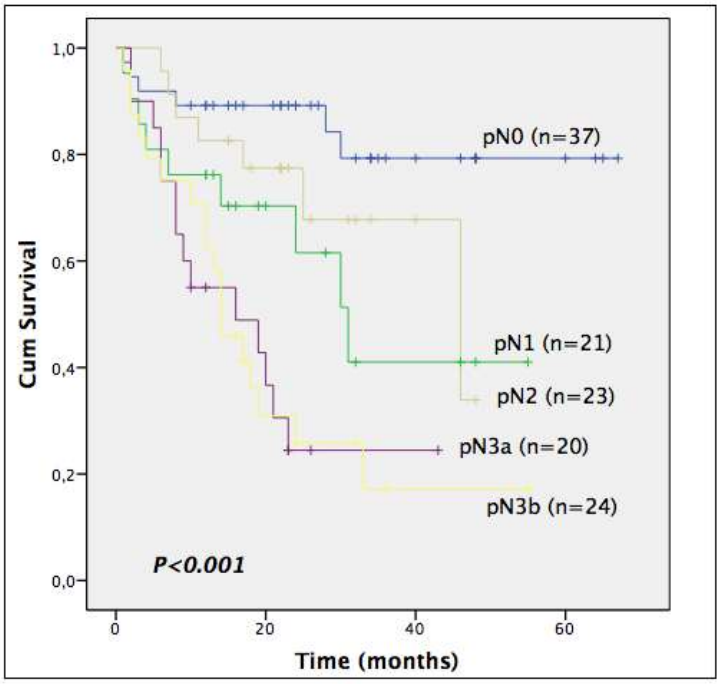

Fig-1: Five-year survival curves of patients with gastric cancer according to the number of metastatic lymph nodes. Five-year survival was correlated with the number of metastatic lymph nodes, and the difference between the groups was statistically significant (P<0.0001)

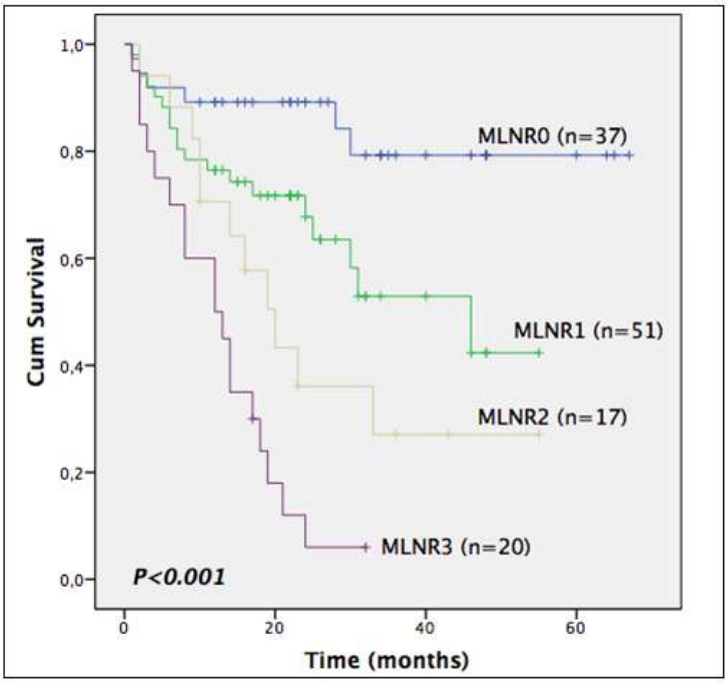

Fig-2: Five-year survival curves of patients with gastric cancer according to the metastatic lymph node ratio. Five-year survival was correlated with metastatic lymph node ratio, and the difference between the groups was statistically significant (P<0.0001).

DISCUSSION

Gastric adenocarcinomas are among the most common cancers. As with all types of cancers, accurate and invariable staging is essential for gastric cancers. Because, only then it is possible to evaluate the prognosis, treatment plan and treatment outcomes. Despite current medical advances, 5 year survival rates after R0 resection in gastric cancer is still low. Although there are many prognostic factors, the most important one among these is presence of lymph node metastasis and the number of the metastatic lymph nodes [18, 19]. However, whileUnion for International CancerControl /American Joint Committee on Cancer(UICC/AJCC) (7th edition) staging system uses the number of metastatic lymph nodes for nodal stage, eastern surgeons rather prefer the Japan staging system which classifies the disease based on the stations where the lymph nodes are present [20, 21]. According to the Japan staging system, at least D2 lymph node dissection is necessary in order assess the nodal status, whereas in AJCC system, D1 dissection, that is, resection of at least 15 lymph nodes, is considered sufficient. The difference between these two staging systems leads to difficulties and contradictions for comparison of data regarding gastric cancer. Several studies have investigated MLNR, the ratio of the number of metastatic lymph nodes to total number of resected lymph nodes, as an independent prognostic factor for the purpose of minimizing the differences between the two staging systems and determining the impact of lymph node status on prognosis [17, 22, 25]. In our retrospective study, we aimed to analyze the influence of MLNR and the number of resected lymph nodes on prognosis in patients with gastric cancer who underwent R0 resection.

Survival in patients who undergo gastrectomy due to gastric adenocarcinoma profoundly varies depending on both the number of metastatic lymph nodes and whether the resected lymph nodes are positive or negative [18, 19]. In our study, we also found significantly reduced 5-year survival rates with advanced nodal stage and in the presence of lymph node metastasis, and this result is in agreement with many studies from various centers. However, in addition to presence of lymph node metastasis, the number of resected lymph nodes has also been proposed as a prognostic factor [26, 27]. This view is strongly held particularly by eastern surgeons [28]. In their study including 1101 patients with gastric cancer, Chen *et al*., [17] showed that if the number of resected lymph nodes is lower than 15,nodal stage could be found lower, thus causing a change in the tumor stage [15]. Additionally, the same researchers reported that there was not significant difference between patients who had 15-29 lymph nodes resected and who had more than 30 lymph nodes resected in terms of their prognosis. Similarly, there are quite a few studies reporting that there is no difference between resection of <15 or ≥15 lymph nodes in terms of the effect on survival [18, 29, 30]. Our results are consistent with these studies, as we did not observe significant difference in survival rates between patients who had 15 to 25 lymph nodes resected and patients who had more than 25 lymph nodes resected, independent of the lymph node status.

As in other types of cancers including esophageal, colon and pancreatic cancers related study including 1075 patients, MLNR was shown as a better prognostic factor in comparison to the number of metastatic lymph nodes, independent of the number of resected lymph nodes [11]. In our study, we also found that high MLNR was significantly related with reduced survival. Multivariate analysis Cox regression model that included clinicopathologicalfactors which were found to have significant influence on survival according to the univariate analysis results suggested that when the number of metastatic lymph nodes and MLNR were included separately in the model, both parameters were found as independent prognostic factors for survival. On the other hand, when both parameters were included together in the model, presence of lymphovascular invasion, poor tumor differentiation and increased MLNR, particularly >50%, were found to be independent prognostic factors; however, the number of metastatic lymph nodes was not an independent prognostic factor in this model. Number of patients is the major limitation of this study, there is need for further studies with larger patient populations.

In our study, we observed that large lymph node dissection in patients whose TNM stage is N3 resulted in lower MLNR, thereby causing statistically significant increase in the survival. For this reason, we can say that MLNR is a more accurate prognostic indicator for survival in patients who undergo R0 resection and at least D2 lymph node dissection.

CONCLUSION

In our opinion, it is a more reliable indicator when there is contradiction about the lymph node status between the AJCC system used by particularly western surgeons and the JCGC system used by eastern surgeons. Nevertheless, large-scale randomized studies are necessary to confirm that MLNR is a better prognostic factor and to establish an optimal MLNR cut-off value.

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