



Prognostic value of metastatic lymph node ratio in patients undergoing D2 gastrectomy for gastric cancer

Mide kanseri nedeniyle D2 lenf nodu diseksiyonu yapılan hastalarda metastatik lenf nodu oranının prognostik değeri

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Abstract

Aim: Aim of this study was to investigate the prognostic value of metastatic lymph node ratio (MLNR) staging in gastric cancer patients who underwent curative D2 lymph node dissection.

Methods: Place and Duration of Study: Department of General Surgery, University of Health Sciences Prof. Dr. Cemil Taşcıoğlu City Hospital, Istanbul, Turkey, from January 2012 to April 2021. Medical records of 171 patients undergoing D2 curative gastrectomy for locally advanced gastric cancer between January 2012 and April 2021 were reviewed retrospectively. Metastatic lymph node ratio (MLNR) and TNM staging system node (Ns) staging was evaluated. Prognostic factors on overall and disease-free survival (DFS) were evaluated. MLNR was compared with number of lymph node metastasis.

Results: Mean age of patients included in present study was 60.7 (male: N = 118; female: N = 53). Based on TNM N staging, 62 patients N0, 25 patients N1, 35 patients N2, and 49 were N3 patients. According to classification based on metastatic lymph node ratio (MLNR), 62 patients MLNR 0, 35 patients MLNR 1, 35 patients MLNR 2 and 39 patients were in the MLNR 3 group. Stage migration were seen in 32 patients (% 18,7) in the classification of MLNR. Cox regression survival analysis showed MLNR is an independent prognostic factor.

(p =0.0001, 95% CI 81.31-101.04)

Conclusions: It has been found that using MLNR staging instead of number of positive lymph nodes in nodal evaluation can help to reduce the problem of stage migration. MLNR is an important prognostic factor for both OS and DFS.

Key words: Gastric cancer, lymph node metastasis, metastatic lymph node ratio, prognosis, stage migration.

Öz

Amaç: Bu çalışmanın amacı, küratif D2 lenf nodu diseksiyonu uygulanan mide kanseri hastalarında metastatik lenf nodu oranı (MLNR) evrelemesinin prognostik değerini araştırmaktır.

Yöntemler: Ocak 2012 ile Nisan 2021 arasında klinik olarak lokal ileri mide kanseri nedeniyle küratif gastrektomi ve D2 lenf nodu diseksiyonu uygulanan 171 hastanın kayıtları geriye dönük olarak incelendi. Metastatik lenf nodu oranı (MLNR) ve Tümör Lenf Nodu Metastazı (TNM) evreleme sistemine göre lenf nodu (N) evrelemesi değerlendirildi. Genel sağ kalım (OS), hastalısız sağkalım (DFS), klinikopatolojik özellikler ve prognostik faktörler değerlendirildi. MLNR, lenf nodu metastazı sayısı ile karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen hastaların ortalama yaşı 60.7 idi (erkek: N = 118; kadın: N = 53). TNM, N evrelemesine göre, 62 hasta N0, 25 hasta N1, 35 hasta N2 ve 49 hasta N3 idi. MLNR evrelemesine göre MLNR 0 62 hasta, MLNR 1 35 hasta, MLNR 2 35 hasta ve MLNR 3 grubunda 39 hasta vardı. MLNR evrelemesine göre 32 hastada (% 18,7) evre kayması görüldü. Cox regresyon sağkalım analizi, MLNR'nin bağımsız bir prognostik faktör olduğunu gösterdi. (p =0,0001, 95% CI 81.31-101.04)

Sonuç: Nodal değerlendirmede pozitif lenf nodu sayısı yerine MLNR evrelemesinin kullanılması, evre kayması sorununu azaltmaya yardımcı olabileceği bulunmuştur. MLNR, hem OS hem de DFS için önemli bir prognostik faktördür.

Anahtar kelimeler: Mide kanseri, lenf nodu metastazı, metastatik lenf nodu oranı, prognoz, evre kayması.

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Introduction

Gastric cancer is the fifth most common diagnosed malignancy and the third leading cancer related deaths in the world among the cancer patients [1]. Besides, gastric cancer is a loco-regional disease with high incidence of lymph node metastasis. Lymph node dissection is an important part of the surgical treatment. In Asian countries D2 lymphadenectomy is a standard surgical procedure for clinically node-positive (cN+) or local advanced (\geq cT2) gastric cancer [2]. In Western countries, D2 lymphadenectomy is carried out in specialised, high-volume centers with appropriate surgical expertise and postoperative care [3].

Adequate staging is essential in predicting prognosis. Lymph node metastasis is the most important prognostic factor in gastric cancer [4, 5]. But the classification of lymph node status (N categories) is still controversial. Currently, American Joint Committee on Cancer (AJCC) classification system is widely used, based on the number of metastatic lymph nodes [6]. This classification system is simple. However, it has been reported that there were some problems. It may lead to stage migration and inadequate prediction of prognosis in gastric cancer surgery with extended lymphadenectomy [7, 8]. Particularly, the small number of dissected lymph nodes may be insufficient to determine prognosis [9]. However, the optimal number of dissected lymph node is still uncertain in accurate staging [5].

Metastatic Lymph node ratio (MLNR) is defined as the ratio of the number of the metastatic lymph nodes to the total number of dissected lymph nodes. MLNR has been recommended as a new staging system for gastric cancer in recent studies [10–12]. This suggested classification system may reduce stage migration and have more accurate prediction of long-term survival results [4, 13, 14]. MLNR is also used as a staging system in different types of cancers [15–17].

The aim of the present study was to evaluate prognostic value of MLNR in gastric cancer patients who underwent curative D2 gastrectomy and to determine stage migration, prediction of overall and disease free survival.

Material and methods

Medical records of totally 200 patients underwent gastrectomy for gastric cancer were reviewed retrospectively. One hundred and seventy-seven patients were enrolled in the analysis based on the inclusion and exclusion criteria in Department of General Surgery, University of Health Sciences Prof Dr Cemil Tascioglu City Hospital, between January 2012 and April 2021. Clinicopathological characteristics such as age; sex; tumor location; preoperative chemotherapy; type of surgery; tumor size; depth of tumor invasion; tumor differentiation; vascular, lymphatic, and perineural invasion; total number of harvested lymph nodes; TNM stage; follow-up data and time of death were retrieved from medical records.

Preoperatively 96 patients had chemotherapy. Standart FLOT (5-fluorouracil, Leucovorin, Oxaliplatin, Docetaxel) chemotherapy was given to most of the patients for four cycles.

The inclusion criteria were the patients with preoperative histologically proven primary gastric adenocarcinoma, clinically locally advanced cancer and the patients who underwent curative D2 open gastric surgery. Presence of distant metastases, postoperative pathology confirmed as non-gastric adenocarcinoma, detection of synchronous tumors, detection of positive microscopic resection margin, patients' mortality within the first 30 days and patients' incomplete data were defined as exclusion criteria.

Disease-free survival (DFS) was defined as the duration from the operation date to the first date of recurrence or last follow-up date. Overall survival (OS) were calculated from the date of surgery to the time of death from any cause. 171 patients were included in this study. Stages were determined according to the 8th edition of the AJCC Cancer Staging Manual [6]. MLNR, which is defined as the ratio of the number of metastatic lymph nodes to the number of harvested lymph nodes. MLNR grouping was based on definition of the Italian Research Group for Gastric Cancer Study (GIRCG) [18]. MLNR categories were defined as MLNR 0, (0%); MLNR 1, (1-9%); MLNR 2, (10-25%); MLNR 3, (>25%).

This retrospective study was approved by Ethics Committee of University of Health Sciences Prof. Dr. Cemil Tascioglu City Hospital (2021/211).

Statistical analysis

Data obtained in the present study were analyzed using v.22.0 of SPSS software. In evaluating data, definitive statistical methods (mean, standard deviation, frequency) were used as well as Kaplan-Meier analysis in analyzing the survival and significance level (Log Rank). Mann Whitney-U, Kruskal Wallis were used for analysis of difference between groups. In the multivariate analysis, independent factors predicting survival were analyzed by using Cox regression analysis. The results were evaluated with 95 % confidence intervals (CIs) and level of significance was determined as $p < 0.05$.

Results

Of the patients, 118 were male and 53 were female. Mean age was 61 (29-89) years. Subtotal gastrectomy was performed in 62 patients (36.3 %). The correlations between lymph node metastasis and clinicopathological parameters of patients are summarized in Table 1.

With regard to tumor location, there were more patients who have tumors located on the proximal site. Number of patients with tumor diameter more than 6 cm were 35 of 171 (20.6%). The number of patients receiving neoadjuvant chemotherapy were 96 (56.1 %).

MLNR groups were shown according to N staging in Figure 1. When MLNR groups were examined, MLNR 0 was the same as N 0. MLNR 3 was relatively homogenous and mostly consisted of N3 patients. However, MLNR 1 and MLNR2 were heterogeneous groups. MLNR 2 included almost half of different N stages. MLNR 3 was consisted of 36 N3 patients (92,3%).

MLNR staging were migrated in total of 32 patients (18.7 %). Comparing N staging, 26 patients were understaged one level and 6 patients were overstaged one level. In understaged patients mean number of harvested lymph nodes were 51.3 (32-87). In all overstaged patients, the mean number of harvested lymph nodes were less than 15. In these patients with dissected lymph node below 15 all lymph node stations were dissected. The comparison of the clinicopathological characteristics of stage migrated patients are shown in Table 2.

Univariate regression analysis was performed to determine the predictors of OS and DFS. Univariate analysis factors affecting DFS were given in Table 3 and OS in Table 4. Cox regression analysis was performed to determine the independent predictors of OS and DFS. Cox regression test and the correlation between MLNR and clinicopathological parameters are analyzed. Lymphatic invasion, and MLNR were determined as independent prognostic factors in Cox regression analysis ($p=0.0001$ and $p=0.0001$ 95% CI 47.79-67.64; 95% CI 81.31-101.04) respectively.

Table 1. Clinicopathological characteristics of patients.

Patient characteristics	Lymph Node Metastasis Absent n=62	Lymph Node Metastasis Present n=109	P value
Age (mean ± SD, years)	62.97 (35-78)	59.45 (29-89)	-
Sex			
Male	41 (66.12)	77 (70.6)	0.330
Female	21 (33.87)	32 (29.4)	
Preoperative chemotherapy			
Not-received			
Received	34 (54.8)	41 (37.6)	0.020
Tumor differentiation			
Well or Moderate	46 (74.2)	44 (40.4)	0.0001
Poorly	16 (25.8)	65 (59.6)	
Tumor location			
Cardia-Corpus	40 (64.5)	63 (57.8)	0.240
Antrum	22 (35.5)	46 (42.2)	
Type of gastrectomy			
Total gastrectomy	43 (69.4)	66 (60.6)	0.160
Subtotal gastrectomy	19 (30.6)	43 (39.4)	
Lymphatic invasion			
Present	16 (25.8)	33 (30.3)	0.0001
Absent	46 (74.2)	26 (23.9)	
Vascular invasion			
Present	16 (25.8)	77 (70.6)	0.0001
Absent	46 (74.2)	32 (29.4)	
Perineural invasion			
Present	12 (19.4)	74 (67.9)	0.0001
Absent	50 (80.6)	35 (32.1)	
y/pTstage			
pT1-2	43 (69.4)	21 (19.3)	0.0001
pT3-4	19 (30.6)	88 (80.7)	
y/pTNMstage			
I-II	62 (100)	35 (32.1)	0.0001
III-IV	0 (0)	74 (67.9)	
Number of harvested lymph node			
≤ 15	0 (0)	4 (3.7)	0.160
> 15	62 (100)	105 (96.3)	
Tumor maximum diameter			
≤ 6	58 (93.5)	78 (71.6)	
> 6	4 (6.5)	31 (28.4)	0.0001

Data presented as mean ± Standard deviation (SD), median (1st-3rd quartiles) or number in parantheses represent percentage (%).

*: malignant cells in peritoneal washings.

Table 2. Clinicopathological characteristics of stage migrated patients.

	Overstaged n=6	Understaged n=26
Number of harvested lymph node		
≤ 15	4 (66.7)	0 (0)
> 15	2 (33.3)	26 (100)
Number of harvested lymph node (mean ± SD)	14.3 (10-17)	51.3 (32-87)

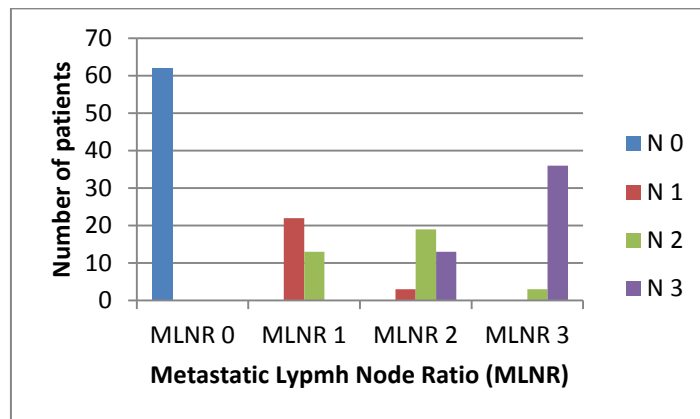


Figure 1. Metastatic lymph node ratio grouping.

Table 3. Disease-free survival analysis.

Patient characteristics	Median DFS (Month)	95 % confidence interval (CI)	P value	
Sex				
Male	118 (69.0)	30.18	91.45-109.92	1.28
Female	53 (31.0)	34.72	64.82-91.12	
Age (mean ± SD, years)				
≤ 60	75 (43.9)	35.37	83.38-107.49	0.86
> 60	96 (56.1)	28.63	83.09-104.86	
MLNR				
≤ 0.25	132 (77.2)	33.44	93.73-110.66	0.003
> 0.25	39 (22.8)	25.30	47.62-80.76	
Lymphatic invasion				
Present	99 (57.9)	26.74	61.58-81.61	
Absent	72 (42.1)	38.6	104.81-121.03	0.0001
Node metastasis				
≤ 2	25 (23.0)	38.38	85.80-123.26	0.049
> 2	84 (77.1)	27.0	62.23-88.54	
Tumor differentiation				
Well or Moderate	81 (47.4)	31.27	67.62-89.47	0.058
Poorly	90 (52.6)	31.87	93.85-113.46	
pTstage				
pT1 (early)	37 (21.6)	40.17	100.29-123.35	0.053
pT 2-4 (advanced)	134 (78.4)	29.22	79.71-98.68	

MLNR: Metastatic lymph node ratio, DFS: Disease-free survival.

Discussion

Lymph node metastasis is the most important prognostic factor in gastric cancer which is associated with a poor prognosis [5]. Classification of lymph nodes is controversial. Japanese Gastric Cancer Association (JGCA) first classified the lymph nodes based on anatomic location of the metastatic lymph nodes and then revised to the just number of the metastatic lymph nodes removed [2]. Union of International Cancer Control (UICC) and AJCC published a classification system based on number of the metastatic lymph nodes [6].

General approach for R0 resection and widespread lymph node dissection is to remove lymph nodes as many as possible in relation to tumor location. The more the depth of tumor, the more is the lymph node metastasis. Number of the removed lymph nodes may vary, even though the same technique is always used. Due to the factors such as surgical experience, surgical technique and biological factors. High body mass index (BMI) leads to decreased lymph node harvesting. Excessively adipose tissue, anatomical variations, insufficient surgical experience, and the pathologist's being less attentive to counting lymph nodes may lead to low number of lymph nodes examined following dissection [19]. The studies have shown that low

number of lymph nodes might lead to wrong decision in staging gastric cancer. For example, the tumor that should be stage 2 in fact, may be misdiagnosed as stage 3 (it may be overstaged). Stage migration will be more common especially in the patients with less lymph nodes removed [20].

Table 4. Overall survival analysis.

Patient characteristics	Median OS	95 % confidence interval (CI)	P value	
Sex				
Male	118 (69)	31.17	68.18-90.66	0.378
Female	53 (31)	37.83	66.01-92.03	
Age (mean ± SD, years)				
≤ 60	75 (43.9)	37.2	75.98-101.43	0.275
> 60	96 (56.1)	30.13	62.82-88.68	
MLNR				
≤ 0.25	132 (77.2)	34.76	81.31-101.04	0.0001
> 0.25	39 (22.8)	28.05	34.33-63.51	
Lymphatic invasion				
Present	99 (57.9)	28.86	47.79-67.64	0.0001
Absent	72 (42.1)	39.51	96.75-116.75	
Node metastasis				
≤ 2	25 (23)	39.81	70.60-112.8	0.054
> 2	84 (77.1)	29.54	47.79-73.08	
Tumor differentiation				
Well or Moderate	81 (47.4)	33.26	57.07-79.60	0.084
Poorly	90 (52.6)	33.2	76.07-100.87	
pTstage				
pT1(early)	37 (21.6)	41.00	82.46-115.98	0.045
pT2-4(advanced)	134 (78.4)	31.09	66.06-86.78	

MLNR: Metastatic lymph node ratio, OS: Overall survival.

In the present study, we performed total gastrectomy for proximally located tumors and subtotal gastrectomy for distal site. A standard D2 lymph node dissection was performed in all patients.

There is no consensus on the cut-off value of MLNR. Several cut-off categories of MLNR were used in other studies [21–23]. In this study we used GIRCG cut-off value for determined MLNR [18]. In multivariate analysis, MLNR (>0.25) was poor prognostic factor for OS. In terms of DFS, MLNR (>0.25) was found to be as an independent prognostic factor. In this study, MLNR was as an important prognostic factor for both OS and DFS.

MLNR might be reduced and thus the prognosis would be improved by increasing the number of lymph nodes harvested. It was also noted that staging wouldn't change in patients with involvement of metastatic lymph nodes following adequate number of the lymph node dissection but prognosis would be improved by increasing the number of removed lymph nodes. Cancer prognosis would be improved with more adequate surgery. It was specified that the lymph nodes containing micrometastatic cells which are undetectable pathologically could be removed by D2 dissection as mean wide surgical excision [24].

In this study, we have limitations like the small number of patients. The study should be repeated in high-volume setting. The number of harvested lymph nodes in four patients was less than fifteen. This is a strength of the study. The stage migration was more in patients with low number of lymph nodes dissected. The results we obtained in patients staged according to MLNR was similar to the literature, showing a more homogeneous distribution in accordance with patients' survival. Compatibility with the present literature is one of the strength of

the study. The reasonably even distribution of patients through tumor stage is another strength of the study.

Stage migration may be seen due to inadequate lymph node dissection. Mean survival extends in the group of patients with higher N stage as a consequence of stage-migration. MLNR can prevent stage migration. Thus, it may be recommended in nodal staging of gastric cancer.

As the results of the present study, it was seen that MLNR staging may be used especially in the patients with low number of removed lymph nodes. Thus, predicting the prognosis may be clarified. It is possible to prevent heterogeneous survival and stage-migration.

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