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Metastatic Lymph Node Ratio as a Prognostic Factor in Gastric Adenocarcinoma

Mide Adenokarsinomunda Prognostik Faktör: Metastatik Lenf Oranı

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ABSTRACT

Objective: Gastric cancer remains an important health problem. Although the classical staging system is the tumor, node, metastasis (TNM) system, stage migration phenomenon may occur depending on the number of lymph nodes removed. Therefore, although there are opinions that lymph node metastasis rate can be used as an alternative to TNM, a clear cut-off value has not been determined. In our study, we aimed to evaluate the survival in TNM staging according to the metastatic lymph node rate.

Methods: Patients operated for gastric adenocarcinoma between 2015 and 2022 were evaluated retrospectively. Patients were divided into quartiles according to the metastatic lymph node rate. Mean survival times were compared between the two groups according to TNM stages and metastatic lymph node rate.

Results: One hundred ninety-nine patients were included in the study. When survival was evaluated, it was observed that survival decreased with increasing disease stage and metastatic lymph node ratio. All patients with stage 1 and 2 were in the 1st quartile (25%) according to metastatic lymph node ratio. In the evaluation of stage 3 patients, it was seen that survival decreased as the metastatic lymph node ratio increased.

Conclusion: Our study revealed that metastatic lymph node ratio of 25% and above is an important parameter in predicting prognosis. Especially in stage 3 patients, metastatic lymph node ratio was shown to be a valuable parameter in predicting survival.

Keywords: Gastric adenocarcinoma, metastatic lymh node ratio, prognosis

ÖZ

Amaç: Mide kanseri önemli bir sağlık sorunu olmaya devam etmektedir. Klasik evreleme sistemi tumor, node, metastasis (TNM) sistemi olmasına rağmen, çıkarılan lenf nodu sayısına bağlı olarak evre kayması fenomeni ortaya çıkabilmektedir. Bu nedenle lenf nodu metastaz oranının TNM'ye alternatif olarak kullanılabileceği yönünde görüşler olmasına rağmen net bir kesme değeri belirlenmemiştir. Çalışmamızda metastatik lenf nodu oranına göre, evreler içerisinde sağkalımı değerlendirmeyi amaçladık.

Yöntem: 2015-2022 yılları arasında mide adenokarsinomu nedeniyle opere edilen hastalar retrospektif olarak değerlendirildi. Hastalar metastatik lenf nodu oranına göre çeyreklere ayrıldı. İki grup arasında ortalama sağ kalım süreleri TNM evrelerine ve metastatik lenf nodu oranına göre karşılaştırıldı.

Bulgular: Çalışmaya 199 hasta dahil edildi. Sağkalım değerlendirildiğinde hastalık evresi ve metastatik lenf nodu oranı arttıkça sağkalımın azaldığı görüldü. Evre 1 ve 2 olan tüm hastalar metastatik lenf nodu oranına göre 1. çeyrekte (%25) yer aldı. Evre 3 hastaların değerlendirilmesinde metastatik lenf nodu oranı arttıkça sağ kalımın azaldığı görüldü.

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Sonuç: Çalışmamız %25 ve üzeri metastatik lenf nodu oranının prognozu tahmin etmede önemli bir parametre olduğunu ortaya koydu. Özellikle evre 3 hastalarda metastatik lenf nodu oranının sağ kalımı tahmin etmede değerli bir parametre olduğu gösterildi.

Anahtar Kelimeler: Mide kanseri, metastatik lenf nodu oranı, prognoz

INTRODUCTION

Gastric cancer continues to be a major health problem worldwide. According to GLOBOCAN data, gastric cancer is the fifth most common malignancy and the third most common cause of cancer-related death.[1] Curative surgical resection is the mainstay of gastric cancer management. Many factors affect survival after surgery, including tumor type, invasion of the gastric wall, and lymph node metastases.[2]

Evaluation of prognostic factors is critical for disease management. Classical staging is based on tumor, node, metastasis (TNM) staging. TNM staging evaluates the infiltration of the tumor in the stomach wall, the number of pathological lymph nodes, and the presence of distant metastasis. Although the 8th edition of the American Joint Committee on Cancer (AJCC) is superior to the 7th edition, it has some limitations.[3] At least 16 lymph nodes are required for effective staging. Lymph node metastasis is associated with poor prognosis.[4]

More extensive lymph node dissection in Japan compared to more limited lymph node dissection in Western countries may lead to differences in the staging of patients. In this situation, known as "stage migration phenomenon", the survival times of patients may vary depending on the stage. The stage migration phenomenon occurs in 10-25% of cases, and is one of the major limitations of TNM staging.[3-5]

To overcome this limitation of TNM staging, the use of metastatic lymph node ratio, or logarithmic metastatic lymph node ratio, has been proposed. The presence of metastatic lymph nodes is one of the most important prognostic parameters for predicting recurrence and survival. Although there are studies suggesting that metastatic lymph node ratio is superior to classical TNM staging, a common cut-off value has not been determined.[6-9] There is still a need for studies showing the prognostic value of metastatic lymph node ratio in the literature. The aim of our study was to evaluate the survival times within stages according to the metastatic lymph node ratio.

METHODS

Patient Selection Criteria

Between 2015 and 2022, patients operated with a prediagnosis of gastric cancer were retrospectively evaluated. Patients with non-adenocarcinoma pathology, neoadjuvant systemic therapy, perioperative peritoneal or liver metastasis, preoperative distant metastasis, and fewer than 16 lymph nodes in the pathology examination were excluded. Patients over 18 years old with pathological results of gastric adenocarcinoma and 16 or more lymph nodes were included in the study. Preoperative distant metastasis assessment was performed by whole-body computed tomography or fluorodeoxyglucose positron emission tomography scan.

Metastatic Lymph Node Ratio

Metastatic lymph node ratio was defined as the ratio of metastatic lymph nodes to the total number of resected lymph nodes.

Metastatic lymph node ratio: (number of metastatic lymph nodes/total number of resected lymph nodes).

According to the metastatic lymph node ratio, patients were divided into four groups: 0-24% (first quartile), 25-49% (second quartile), 50-74% (third quartile), and 75-100% (fourth quartile).

Tumor, Node, Metastasis Staging

TNM staging of the patients was performed according to the AJCC 8th edition. Patients were grouped as stage 1, stage 2, and stage 3.

Statistical Analysis

Retrospectively obtained data were analyzed using the Statistical Package for Social Sciences (SPSS, Version 26.0. Armonk, NY: IBM Corp.). Demographic data were analyzed by descriptive statistical methods. Patients were grouped according to their stage and metastatic lymph node ratio. Survival of both groups was compared. Survival analysis was evaluated using the Kaplan-Meier test. Cox regression analysis was used to evaluate the factors affecting survival. Survival analysis was conducted using stage 3 patients who were defined as locally advanced according to the metastatic lymph node ratio using the same statistical methods.

Ethical Statement and Informed Consent

This study was approved by the Ege University Medical Research Ethics Committee (decision number: 23-10T/33, date: 05.10.2023) and written informed consent was obtained from all participants.

RESULTS

A total of 199 patients [77 females (38.7%) and 122 males (61.3%)] were included in the study. The mean age of the patients was 65.81 (±10.72) years. One hundred thirty-four patients (67.3%) underwent total gastrectomy, 34 (17.1%) distal gastrectomy, and 31 (15.6%) proximal gastrectomy. The mean number of total resected lymph nodes was 27.04 (±10.57), and the mean number of metastatic lymph nodes was 7.72 (±9.47). Pathologic features are shown in Table 1.

During the follow-up period, 19 patients (9.5%) developed local recurrence, while 51 patients (25.6%) developed distant organ metastasis. One hundred patients (50.3%) died during follow-up. The mean disease-free survival was 31.93±24.19 months, while overall survival was 55.29±24.30 months. The evaluation of the patients according to the (AJCC) 8th edition and metastatic lymph node ratio is shown in Tables 2 and 3.

When evaluated, it was observed that the survival time shortened with the advancement of the disease stage and the metastatic lymph node rate. According to AJCC, all patients in stages 1 and 2, were in the first quartile for metastatic lymph node ratio. When stage 3 patients were evaluated individually, it was seen that survival decreased as the metastatic lymph node ratio increased (p: 0.001). (p: 0.001). Survival times according to stages and metastatic lymph node ratios are shown in Tables 4 and 5, with stage 3 patients' survival times according to metastatic lymph node ratio in Table 6. When the factors affecting survival were evaluated, it was observed that distant organ metastasis was associated with survival (p<0.001).

Table 1. Pathological features

Invasion	Number of patients (n)	%
Lymphovascular invasion	108	54.3
Perineural invasion	125	62.8
Venous invasion	58	29.1
Subtype		
Poorly cohesive	47	23.6
Tubuler	49	24.6
Mixed	38	19.1
Poorly differentiated	53	26.6
Mucinous	7	3.5
Signet cell	5	2.5

Table 2. Staging according to AJCC 8th edition

AJCC staging	Number of patients	%
1A	20	9.9
1B	18	9.1
2A	22	11.1
2B	22	11.1
3A	27	13.5
3B	27	13.5
3C	63	31.8

AJCC: American Joint Committee on Cancer

DISCUSSION

Lymph node dissection in gastric cancer surgery reduces the risk of local recurrence and provides more accurate staging. Determining the patient's stage is an important step in individualized treatment planning. The metastatic lymph node ratio can be used to predict survival and recurrence, and to determine the treatment protocol.[7]

There are studies advocating the superiority of metastatic lymph node ratio over the classical TNM classification. Hou et al.[6] showed that the metastatic lymph node ratio can be used as a prognostic marker even if fewer than 15 lymph nodes are removed. Deng et al.[10] also compared the metastatic lymph node ratio with TNM staging and showed that the metastatic lymph node ratio was an effective factor in survival and significantly associated with recurrence. Similarly, in a study conducted in Italy involving 463 patients, metastatic lymph node ratio was shown to be

Table 3. Quartiles according to metastatic lymph node ratio

Metastatic lymph node ratio quarters	Number of patients	%
1st quartile (0-24%)	110	55.3
2nd quartile (25-49%)	41	20.6
3rd quartile (50-74%)	29	14.6
4th quartile (75-100%)	19	9.5

Table 4. Mean survival time according to AJCC staging (p<0.001)

Staging	Mean survival (month)	Std. Error	95% CI	
			Min.	Max.
1A	84.3	3.60	77.23	91.36
1B	74.34	7.20	60.22	88.45
2A	70.64	7.24	56.45	84.83
2B	58.06	8.38	41.63	74.48
3A	58.59	6.86	45.13	72.04
3B	39.50	7.56	24.68	54.33
3C	33.14	3.79	25.71	40.58
Mean	55.29	3.79	49.46	61.13

AJCC: American Joint Committee on Cancer, CI: Confidence interval, Min.: Minimum, Max.: Maximum

a better prognostic marker than standard staging.[11] Ergenç et al.[9] also found that metastatic lymph node ratio was more sensitive in predicting survival, especially in stage 3 disease. Our study supports these studies. Metastatic lymph node ratio was found to be an effective parameter in predicting survival. When stage 3 patients were evaluated by stage, it was observed that survival decreased as the metastatic lymph node ratio increased. Metastatic lymph node ratio can be used as a valuable parameter, especially in the subgroup analysis of stage 3 patients. Gulmez et al.[12] obtained similar results to our study; they showed that metastatic lymph node ratio was superior to TNM staging for overall survival in stage 3 disease, and discussed that it should be included in the treatment algorithm.

It may not always be possible to remove at least 16 lymph nodes required for TNM staging. In this case, the proportion of metastatic lymph nodes can be used as a predictor.[6,8] In the study of the Spanish group, a metastatic lymph node was found to be a prognostic factor, and compared to other studies, a metastatic lymph node rate of more than 25% was shown to be an important parameter, especially in cases where less than 16 lymph nodes were removed.[8]

The metastatic lymph node rate is not accurate in all cases. For example, if two lymph nodes are metastatic in patients with four lymph nodes dissected, the patients may fall into a lymph node metastasis rate group of 50%, which may cause patients to receive more treatment than necessary. In patients with inadequate lymph node dissection, the metastatic lymph node rate can also yield inaccurate results. Although the Italian study group proposed a logarithmic lymph node ratio to solve this problem, the same limitation applies to this method.[3] In contrast to these studies, we believe that at least 16 lymph nodes should be examined in the evaluation of metastatic lymph node ratio, as in TNM staging, and for this reason, patients with less than 16 lymph nodes were excluded in our study. In patients with less than 16 lymph nodes, the minimum number of lymph nodes should be clarified in future studies so that the metastatic lymph node ratio can be accepted as a prognostic factor. Extensive lymph node dissection during surgery is necessary for accurate staging and to reduce local recurrence.[7]

In patients who have undergone adequate surgical resection, the metastatic lymph node ratio will be useful in the choice of treatment; however, there is no consensus in the literature regarding its threshold values. Various studies have used different thresholds. In our study, the threshold value that increased mortality was 25%. Marchet et al.[13] used N0 (0%), N1 (1%-9%), N2 (10%-25%), N3 (>25%). Persiani et al.[14] and Zhao et al.[15], N0 (0%), N1 (1%-15%), N2 (16%-

Table 5. Mean survival time according to metastatic lymph node ratio (p<0.001)

Metastatic lymph node ratio	Mean survival (month)	Std. Error	95% CI	
			Min.	Max.
1st quartile (0-24%)	72.26	3.95	64.50	80.01
2nd quartile (25-49%)	44.82	5.62	33.79	55.85
3rd quartile (50-74%)	33.74	5.70	22.56	44.93
4th quartile (75-100%)	22.66	4.78	13.28	32.03
Mean	55.29	2.97	49.46	61.13

CI: Confidence interval, Min.: Minimum, Max.: Maximum

Table 6. Stage 3 patients' mean survival time according to metastatic lymph node ratio

Stage		Mean survival (month)	Std. Error	95% CI		p value
				Min.	Max.	
3	1st quartile (0-24%)	57.96	7.54	43.19	72.75	0.001
	2nd quartile (25-49%)	44.82	5.63	33.79	55.86	
	3rd quartile (50-74%)	33.75	5.71	22.56	44.93	
	4th quartile (75-100%)	22.66	4.78	13.28	32.03	
Total		41.52	3.33	34.98	48.06	

CI: Confidence interval, Min.: Minimum, Max.: Maximum

40%), N3 (>40%). Zhang et al.[16] used N0 (0%), N1 (1%-25%), N2 (26%-50%), N3 (>50%), similar to our study. Pedrazzani et al.[17] used 25% percentiles similarly. In all of the studies, the prognosis worsens as the metastatic lymph node ratio increases. Indeed, no clear threshold value has been found in the literature, and further studies on this subject are still needed. In our study, a metastatic lymph node rate of 25% was associated with an aggressive prognosis. We advocate that 25% should be accepted as the threshold value when evaluating metastatic lymph node rate.

Study Limitations

Adjuvant treatment protocols were not evaluated in our study. This is one of the limitations of the study, however, since we evaluated survival in the same patient group, adjuvant treatments of the patients do not affect the results of the study. Hwang et al.[18] argued that the metastatic lymph node ratio can be used to determine the chemotherapy protocol. In their study, they suggested that the prognosis of patients with a metastatic lymph node ratio of 10% or more was worse, especially in the stage 3 patient group, and that platinum-based chemotherapy protocols should be given to those patients who also had lymphovascular invasion. In stage 3 disease, the metastatic lymph node ratio may guide the selection of the chemotherapy protocol by evaluating it together with other risk factors; however, further studies on this subject are needed.

In our study, patients with neoadjuvant systemic treatment were also excluded. Indeed, metastatic lymph node ratio continues to be an important prognostic parameter after neoadjuvant systemic therapy. In the study by Jiang et al.[19], the 3-year survival of patients with a metastatic lymph node ratio of 30% or less after neoadjuvant chemotherapy was 81.9%, while the 3-year survival of patients with a metastatic lymph node ratio of more than 30% decreased to 18.5%. The metastatic lymph node ratio was also found to be effective in predicting disease-free survival.

The retrospective design is one of the main limitations; however, this limitation is offset by the fact that it was conducted on a large group of patients. An important factor that increases the reliability of our study is that the data were obtained from hospital records in a complete and objective manner.

CONCLUSION

In patients with adequate lymph node dissection, a metastatic lymph node rate above 25% is an important prognostic factor. When additional evaluation is performed in stage 3 patients, especially, themetastatic lymph node ratio can be used to determine the treatment protocol.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Medical Research Ethics Committee (decision number: 23-10T/33, date: 05.10.2023).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.D., T.Ö.S., Ö.F., S.E., Concept: C.U., T.G., B.D., S.E., Design: C.U., T.G., S.E., Data Collection or Processing: C.U., R.T., Analysis or Interpretation: C.U., V.S., R.T., Literature Search: C.U., V.S., Writing: C.U., R.T., S.E.

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