Study of Survival in Gastric Cancer with Emphasis on Lymph Node Status as an Independent Prognostic Factor

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ABSTRACT

Background: Lymph node status in gastric cancer is known as an independent prognostic factor that guides the surgical and oncological treatment and independently influences long-term survival. Several studies suggest that the lymph node ratio has a greater importance in survival than the number of metastatic lymph nodes. **Aim:** The aim of this study was to evaluate the clinical and morphological factors that can influence the survival of gastric cancer patients, with an emphasis on nodal status and the lymph node ratio. **Material and methods:** We conducted a retrospective study in which 303 patients with gastric cancer admitted to the Department of Surgery of the Mureș County Hospital between 2008 and 2018 were screened for study enrolment. Data were obtained from the records of the department and from the histopathological reports. The examined variables included: age, gender, tumor localization, T stage, histological type, grade of differentiation, surgical procedure, lympho-vascular invasion, excised lymph nodes, metastatic lymph nodes, lymph node ratio. After screening, the study included a total number of 100 patients, for which follow-up data was available. **Results:** The mean age of the study population was 66.43 ± 10 years, and 71% were males. The average survival period was 21.42 months. Statistical analysis showed that the localization of the tumor ($p = 0.021$), vascular invasion ($p < 0.001$), T ($p = 0.004$) and N ($p < 0.001$) stages, type of surgery (partial gastrectomy 59% vs. total gastrectomy 41%, $p = 0.005$), as well as the lymph node ratio ($p < 0.001$) were prognostic factors for survival in patients with gastric cancer undergoing surgical therapy. **Conclusions:** The survival of gastric cancer patients is significantly influenced by tumor localization, T stage, vascular invasion, type of surgery, N stage and the lymph node ratio based on univariate analysis. Also, the lymph node ratio proved to be an independent prognostic factor for survival.

Keywords: gastric cancer, survival, prognosis, lymph node ratio

BACKGROUND

Gastric cancer is known as the fourth most common type of cancer worldwide and the second most common cause of death related to cancer.¹ The incidence shows a large geographical variation, but more than 50% of new cases occur in developing countries.²

In general, gastric cancer has a poor survival rate. In Europe, the 5-year survival varies from 10 to 30%. The highest survival rates were observed in Japan,

almost 90%, probably due to the implementation of intense screening programs, making possible the diagnosis in “early gastric cancer” stage, and the possibility of endoscopic resection in early stages.³

There are several tumor- and patient-related factors of prognostic importance in gastric cancer. Previous studies have shown that some of the significant factors that influence survival are age, invasion of the underlying layers, and lymph node involvement. Furthermore, factors such as cardiovascular disease, diabetes, immune disorders, and malnutrition lead to increased intraoperative mortality and reduced long-term survival in elderly patients.⁴

Lymph node involvement in gastric cancer is known as an independent prognostic factor; it guides surgical and oncological treatment and influences long-term survival independently.⁵ In cancer research, the lymph node ratio (LNR) is defined as the number of excised lymph nodes reported to the number of metastatic lymph nodes.⁶ There are several studies suggesting that the lymph node ratio has a greater importance in survival than the amount of positive lymph nodes. Studies have also shown that the LNR is an independent factor for survival regardless of the number of lymph nodes excised during the operation.^{7,8}

The TNM staging system groups gastric cancer patients in different categories based on tumor dimensions, and the number of lymph node metastases and distant metastases.⁹ Based on this classification, “stage migration” is frequently encountered.¹⁰

Regarding the evaluation of nodal status in gastric cancer, it is recommended to analyze at least 15 lymph nodes in order to obtain a reliable nodal stage.⁹ Surgical experience, the precision of the histopathological examination, and other biases can lead to a lower node number, which has been considered insufficient.¹⁰

The stage migration phenomenon occurs during the examination of excised lymph nodes and may lead to inaccurate classification, affects the postoperative multimodal decision-taking process.¹¹ To diminish stage migration, studies recommend using the LNR as an independent factor for survival. This is a simple and consistent prognostic tool, which can be used in any type of lymphadenectomy.¹²

The LNR may also be a helpful tool in selecting eligible patients for adjuvant oncological therapy, because patients with a higher level of lymphatic involvement (i.e., LNR >0.25) can benefit more from chemo-radiation.¹³

AIM

In this study, we aimed to assess the clinical and morphological variables that can influence the overall survival of

patients with gastric cancer, focusing on nodal status and the LNR.

MATERIAL AND METHODS

We conducted a retrospective study, including all patients who underwent surgery for gastric cancer in the Department of Surgery of the Mureș County Hospital, Târgu Mureș, Romania, between 2008 and 2018. Patient data were obtained from the electronic database of the Department of Surgery and from the histopathological reports.

Tumor staging was carried out according to the 7th edition of the TNM staging system. We grouped the cases into four categories based on the number of metastatic lymph nodes (N0, N1, N2, N3), corresponding to the recommendations of the American Joint Committee of Cancer.

We determined the value of metastatic LNR by dividing the number of metastatic lymph nodes by the total number of excised nodes. The patients were assigned into different categories based on the results: LNR0 if the ratio was 0%, LNR1 if it was 1–20%, LNR2 if it was 21–50%, and LNR3 if it was >50%.

Variables such as age, gender, tumor localization (upper, middle, lower third, diffuse), T stage, histological type (adenocarcinoma, signet ring cell carcinoma, other types), grade of differentiation, type of operation (partial/total gastrectomy), lymphovascular invasion (present or absent), the number of retrieved and metastatic lymph nodes, and the LNR were grouped and analyzed in both univariate and multivariate analyses as prognostic factors for survival.

Statistical analysis was performed using GraphPad Prism 8 (GraphPad Software, San Diego, California, USA), and we considered a test statistically significant at a value of α below 0.05. All tests were two-tailed.

Survival in different groups was graphically represented using Kaplan-Meier curves, and the statistical difference between survival groups was determined using the log-rank test.

The study was approved by the local ethics committee of Mureș County Hospital.

RESULTS

A total number of 303 patients were treated surgically for gastric cancer in the Department of Surgery of the Mureș County Hospital between 2008 and 2018. We excluded patients with incomplete clinical or morphological data and those for which survival data was not available. One hundred patients were enrolled in the study. The mean survival

TABLE 1. Patient characteristics and variables used in the study

Variables		n	Median survival (months)	p value
Age	<66 years	48	16	0.864
	>66 years	52	27	
Gender	Male	71	19	0.077
	Female	29	21	
Tumor localization	Upper 1/3	19	16	0.021
	Middle 1/3	15	21	
	Lower 1/3	55	41	
	Diffuse	10	11	
Histological type	Adenocarcinoma	80	27	0.359
	Signet ring cell	10	9	
	Other	10	13	
Differentiation	Well	30	46	0.111
	Moderate	27	17	
	Poor	43	17	
T stage	T1	3	67.5	0.004
	T2	8	105	
	T3	41	33	
	T4	48	16	
Lymphatic invasion	Yes	43	14	0.509
	No	57	23	
Vascular invasion	Yes	58	14	<0.0001
	No	42	67	
Surgery	Partial gastrectomy	59	27	0.005
	Total gastrectomy	41	13	
Excised lymph nodes	≤15	80	27	0.037
	>15	20	27	
N stage	N0	25	105	<0.0001
	N1 (1–2)	27	23	
	N2 (3–6)	23	17	
	N3 (>7)	25	11	
LNR	0%	25	105	<0.0001
	1–20%	15	23	
	21–50%	25	46	
	>50%	35	11	

time for the included subjects was 21.42 months. The studied parameters are shown in Table 1. The mean age of the patients was 66.43 ± 10 years, and 71% of them were male.

We found tumors localized in the upper third of the stomach in 19 cases, in the middle third in 15 cases, in the lower third in 55 cases, and the tumor was diffuse in 10 cases. The histopathological examination revealed gastric adenocarcinoma in 80% of cases, signet ring cell carcinomas in 10% of cases, and other histological types in 10% of cases.

Regarding the grade of differentiation, there were 30 cases of well differentiated, 27 cases of moderately differentiated, and 43 cases of poorly differentiated tumors.

We observed a high rate of advanced-stage tumors, 48% of cases being staged T4, 41% T3, 8% T2, and only 3% T1

at the moment of admission to our department. We found lymphatic invasion in 43 cases and vascular invasion in 58 cases during the histopathological examination of the operatory specimen. Fifty-nine per cent of the patients underwent partial gastrectomy, while total gastrectomy was performed in 41% of the patients.

A mean of 11.23 ± 5.23 lymph nodes were excised during surgery, and a median of 3 lymph nodes were positive (range: 1–21); in 80% of cases, ≤15 lymph nodes were excised.

Twenty-five cases were staged as N0, 21 as N1, 23 as N2, and 25 as N3 at the histological examination.

Statistical analysis showed that the localization of the tumor ($p = 0.021$), vascular invasion ($p < 0.001$), T ($p = 0.004$)

FIGURE 1. Kaplan-Meier curves for overall survival in relation to different prognostic factors

and N (<0.001) stage, the type of gastrectomy ($p = 0.005$) as well as the LNR ($p < 0.001$) were prognostic factors for survival in univariate analysis (Figure 1, panels A–F).

Other variables such as age ($p = 0.864$), gender ($p = 0.077$), histological type ($p = 0.359$) and differentiation ($p = 0.111$), and lymphatic invasion ($p = 0.509$) did not influence survival significantly.

DISCUSSION

There are numerous known prognostic factors, and there is an ongoing debate in the literature whether or not they have an independent effect on long-term survival in gastric cancer patients.

In 2009, Japanese researchers published an article on the effect of age on the outcomes of gastric cancer patients. Studying 1,473 patients, they observed a lower 10-year survival rate and a higher postoperative mortality rate in elderly patients. The study concluded that age represents a simple prognostic factor for survival in patients with gastric cancer and would be helpful to take in consideration besides other clinicopathological variables.¹⁴ In our study, the majority of the patients were older than 60 years, and we did not observe any differences between the studied age groups regarding overall survival.

An article published in 2011 by Yang *et al.* searched for predictive and prognostic markers in metastatic gastric cancer. Their results suggest that the localization of the tumor and the patients' gender and age are independent factors for overall survival in advanced-stage gastric cancer.¹⁵

In our study, the patients' survival was influenced by age and tumor localization.

The prognostic value of histological types in gastric cancer is not well defined. In an article published in 2014, Zu *et al.* found in a study conducted on 741 gastric cancer patients that cell differentiation was an independent prognostic factor in advanced gastric cancer cases but not in mucinous carcinoma and signet ring cell carcinoma. Advanced-stage signet ring cell carcinoma had more aggressive features and poorer prognosis than the other subtypes.¹⁶ The conclusion of the study was that the degree of cell differentiation is an important predictor of survival in gastric cancer.¹⁶ Contrary to these results, in our study, the histological type of the tumor and cell differentiation had no influence on survival.

In gastric cancer patients, nodal status is one of the most important factors that have a high impact on survival. However, the classification of lymph node involvement is not standardized; in the Japanese classification it relies on the localization of the tumor and the number of metastatic nodes, while the UJCC/AJCC TNM staging system is based only on the number of metastatic nodes, which depends on the extent of nodal clearance in each case.^{17–20}

The LNR was recommended as a novel staging tool because of its ability to reduce the stage migration phenomenon. In a study conducted by Nitti *et al.*, the LNR was the strongest predictor for survival after radical surgical treatment.²¹

The value of the LNR is not based on the extent of lymphadenectomy or on the accuracy of the histopatho-

logical examination.^{22,23} Therefore, the LNR has become a reliable and independent marker for survival, and some authors recommended the inclusion of this parameter in cancer staging systems for its potential to minimize stage migration.²⁴ In our study, the N stage and the LNR were strong prognostic factors for the overall survival of gastric cancer patients.

CONCLUSIONS

In our study, the survival of gastric cancer patients was significantly influenced by the patients' age, tumor localization, T stage, vascular invasion, type of surgery, N stage, and LNR based on univariate analysis. Also, the LNR proved to be an independent prognostic factor for survival. We consider that it would be useful to implement a probability calculator tool in order to obtain a more accurate prediction of survival, which can be very useful in the daily medical practice.

CONFLICT OF INTEREST

Nothing to declare.

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