CLINICAL STUDY

Impact of the anatomical location and the number of metastatic lymph nodes on gastric cancer patient´s survival

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ABSTRACT

BACKGROUND: The most serious problem in surgical treatment of gastric cancer includes the area of resection and the extent of lymphadenectomy. The extent of gastric resection is determined by the extent of tumor affection. The aim of radical surgical intervention is to achieve microscopically clear resection line, since R0 resection is the main criterion for the patient´s prognosis. Curative surgical resection for gastric cancer includes the lymph nodes dissection. In the treatment of gastric cancer, there are two views on the importance of lymphadenectomy. The Far East considers that operation improves the survival and the Europe considers that surgery is not curative, but it determines the staging and prognosis. There is also a difference in staging systems. The one from East is importance based on the anatomical location of affected lymph nodes, the second from Europe is based on the number of positive lymph nodes.

MATERIALS AND METHODS: This work is a retrospective observational study. In the study cohort, comparing the survival of patients according to different classification systems, depending on the N-stage of disease, 119 patients with gastric adenocarcinoma in clinical stage I to III, i.e. without metastasis, who underwent a radical surgical resection with D2 lymphadenectomy, were enrolled. For the evaluation of the survival versus the time after operation, we used Kaplan–Meier method. To evaluate the correlation between the survival rate and the explanatory variables, Cox regression and Kendall correlation coefficient were used.

RESULTS: The median survival, according to different classification systems, depending on the N-stage of the disease, was significantly correlated with the survival for the 6th and 7th editions of TNM classification system for the Japanese classification system, for N-ratio classification system).

The new finding was differentiation of patients in groups N1 vs N2 under the 6th TNM classification (HR=0.910249), also a little differentiation in groups N1 vs N2 according to the classification of N-ratio (HR=0.8750926) and equally a poor differentiation in the survival in groups N2 vs N3 according to the 7th TNM classification (HR=0.881797).

The strongest correlation reached the Japanese classification system, but not significantly different from the 6th TNM classification system. In the 7th edition of TNM classification system, we then found the weakest correlation with the survival time, but not significantly different from the previous two.

CONCLUSION: Our retrospective study confirmed the strongest correlation between the patient´s prognosis and the anatomic localization of the affected lymph nodes. This correlation was not statistically significant compared to the correlation between patient´s prognosis and the number of positive lymph nodes. It leads us to the conclusion that both classification systems are comparable and the difference is statistically insignificant *(Tab. 4, Fig. 8, Ref. 16)*. Text in PDF *www.elis.sk*.

KEY WORDS: gastric cancer, gastrectomy, lymphadenectomy, staging, prognosis.

Introduction

The most serious problem in surgical treatment of gastric cancer includes the extent of organ resection and the extent of lymphadenectomy.

The extent of gastric resection is determined by the extent of tumor affection. The aim of radical surgical intervention is to achieve microscopically clear resection line, since the R0 resection is the main criterium for the patient´s prognosis.

Affection of lymph nodes in gastric cancer is the second most important prognostic factor, after the R classification. Metastatic lymph node involvement depends on the T category and, according to the number of lymph nodes affected, the 5-year survival rate is as well as the favorable prognosis of the patient are decreasing (3). By enlarging the extent of lymphadenectomy there is a higher number of lymph nodes removed. This is affecting the staging because macroscopically negative lymph nodes that are proven positive by histologic examination move the patient to a higher stage of the disease, thus improving the prognosis of patients in the lower stage.

The results of surgical treatment of gastric cancer are improving by an earlier detection of early stages, lower perioperative

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morbidity and mortality, a higher amount of radical resections with a better survival (15). However, the problem of radicality, tactics and techniques of lymph node dissection remains unresolved.

Lymph node dissection is a complete removal of regional lymph drainage. Sufficiently performed lymphadenectomy and thorough processing of the specimen by a pathologist aims to investigate and find the greatest number of lymph nodes. It is essential to determine the staging, prognosis estimation, and decision on further treatment. For the correct staging of the disease, at least 15 lymph nodes must be examined. Currently, the importance of lymphadenectomy for the staging of the disease is not the matter of question. The therapeutic effect of lymphadenectomy is constantly debated.

Curative surgical resection for gastric cancer includes the lymph nodes dissection. In the treatment of gastric cancer, there are two views on the importance of lymphadenectomy. The Far East considers that the operation improves survival and the Europe considers that surgery is not curative, but it determines the staging and prognosis. There is also a difference in the staging systems. The one from East is important based on the anatomical location of affected lymph nodes, the second from Europe is based on the number of positive lymph nodes.

The survival of the patients is evaluated according to different classification systems that are based on different parameters:

TNM staging system (TNM)

The TNM staging for gastric cancer has been included in the first edition of UICC TNM since 1966. The 6th edition of UICC TNM staging system adopted a number-based system for N-staging that provides an easy and accurate prognostic stratification. The UICC TNM staging system is the global standard to evaluate gastric cancer in different institutions (1, 6).

Japanese staging systems for gastric cancer (JSGC) – Its anatomical-based N-staging was established based on analysis of lymphadenectomy effectiveness, and naturally provides a direct surgical guidance (12).

N-ratio staging system – the staging system based on the metastatic lymph node ratio between metastatic and examined lymph nodes (N-ratio) in gastric cancer patients (2, 5, 7, 8, 10, 11).

The 7th edition of TNM staging system (TNM 2010) – during this study, there was an update in TNM classification to the 7th edition of 2010, so we also classified according to this. The main change was in classification of carcinoma of oesophagogastric junction, which now belongs to the carcinoma of oesophagus (4, 13, 16).

Materials and methods

Input of clinical and demographic information comes from medical records of patients from the Department of surgical oncology Slovak Medical University (SMU) and National Cancer Institute. There was a total number of 156 patients, who underwent surgery due to gastric cancer in the period from January 2007 to December 2009, including.

Out of this number, we retrospectively analyzed a database of 135 patients, who had undergone a radical elective surgery with D2 lymphadenectomy for stages I–III of gastric adenocarcinoma, which was performed by three trained high-volume surgeons. Stages were diagnosed on the basis of pathological findings. Perioperative/neoadjuvant chemotherapy was not applied.

The primary aim of the study was to investigate the impact on the patient survival rate between the anatomical location of affected lymph nodes and the number of positive lymph nodes. We conducted a subanalysis of survival according to the current staging systems. Depending on the N-stage of disease, 119 patients were enrolled and classified according to 6th TNM and N-ratio classification, 83 according to JCGS and 85 according to 7th TNM 2010. All of them undergone a radical surgery with D2 lymphadenectomy. The present systematic comparison was performed according to the number of examined lymph nodes, histologically positive lymph nodes, their ratio and anatomical location of affected lymph nodes (depending on the location of the primary finding of the stomach). Within each staging systems, patients were divided into the groups N0–N3.

Survival was evaluated by statistical tools "Survival analysis". The starting point was the date of surgery. For the evaluation of the survival versus the time after operation, we used Kaplan Meier method. To evaluate the correlation between the survival rate and the explanatory variables, Cox regression and Kendall correlation coefficient were used. Credibility of the model and the conformity prediction and the actual outcome were tested by Chi^2 test.

Results

Comparison of survival according to different staging systems, depending on the N-stages of the disease

TNM classification system (6th edition)

According to the 6th TNM classification, we classified 119 patients. The numbers of patients in individual N-stage and corresponding Median survival time analysis are indicated in the Table 1.

The relationship between the survival time (counted from the time of surgery) and the number of positive lymph nodes was analyzed using the Kaplan-Meier method and is shown in the Figure 1.

Tab. 1. Number of patients, median survival time and confidence interval for each N-stage of 6th TNM staging system.

N-stage of disease	N0	N1	N2	N3
Number of patients	32	35	36	16
Median survival time (days)	2050	600	734	309
Brookmeyer-Crowley 95% CI	1300–2153	441–1093	516–1111	196–429

Tab. 2. Number of patients, median survival time and confidence interval for each N-category of JCGC.

N-stage of disease	N0	N1	N2	N3
Number of patients	21	25	17	13
Median of survival (days)	1792	909	545	255
Brookmeyer–Crowley 95% CI	1268–2153	590–1341	398–1217	206–482
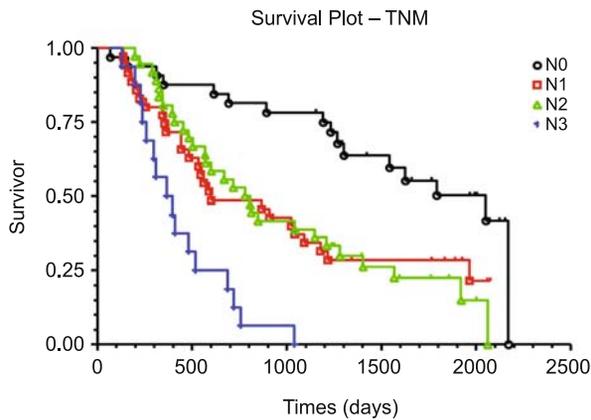
Fig. 1. Survival depending on the N-stage of the disease according to the 6th TNM.
Chi-square test of equivalence mortality = 40.192352 p < 0.0001
Comparison of risk categories according to N (approximate 95% confidence interval)
N0 vs N1 = 0.430191 (0.255011 to 0.725711)
N1 vs N2 = 0.910249 (0.517242 to 1.601866)
N2 vs N3 = 0.355525 (0.133008 to 0.950306)
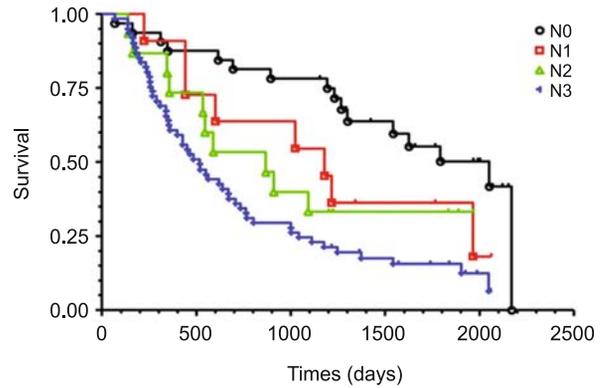
Fig. 3. Survival depending on the N-stage of the disease according to the N-ratio staging system.
Chi-square for equivalence of death rates = 22.5222618 p = 0.0000508
Comparison of risk categories according to N (approximate 95% confidence interval)
N0 vs N1 = 0.5423127 (0.2623302 to 1.1211178)
N1 vs N2 = 0.8750926 (0.358933 to 2.1335099)
N2 vs N3 = 0.6235607 (0.3087509 to 1.2593584)
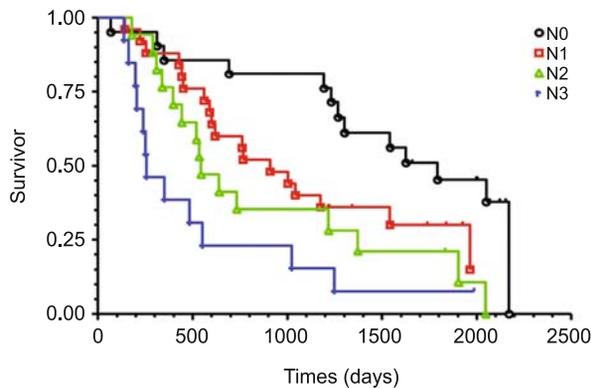
Fig. 2. Survival depending on the N-stage of the disease according to the JSGC.
Chi-square for equivalence of death rates = 19.0073607 p = 0.0002724
Comparison of risk categories according to N (approximate 95% confidence interval)
N0 vs N1 = 0.5319622 (0.2896063 to 0.9771328)
N1 vs N2 = 0.7045064 (0.3299183 to 1.5044006)
N2 vs N3 = 0.5744514 (0.1964117 to 1.6801161)
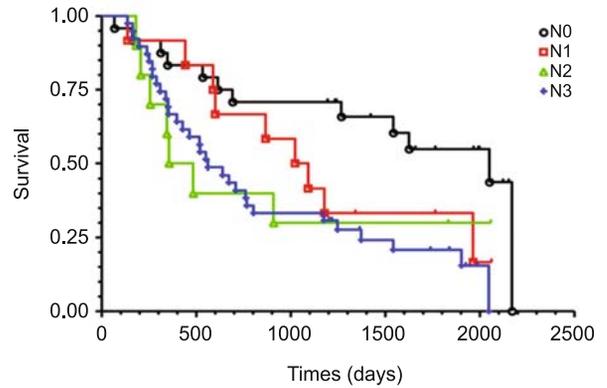
Fig. 4. Survival depending on the N-stage of the disease according to the 7th TNM.
Chi-square for equivalence of death rates = 10.785182 P = 0.0129
Comparison of risk categories according to N (approximate 95% confidence interval)
N0 vs N1 = 0.539013 (0.251817 to 1.153755)
N1 vs N2 = 0.758567 (0.264318 to 2.177014)
N2 vs N3 = 0.881797 (0.346505 to 2.244025)

Japanese staging system of gastric cancer

According to the Japanese system, we classified 76 patients, the numbers of patients in each N-stage and the corresponding Median survival time is shown in Table 2.

The evaluation of survival according to the anatomical location of affected lymph nodes according to the time of surgery using the Kaplan–Meier method is shown in the Figure 2.

N-ratio staging system

According to N-ratio staging system, we classified 119 patients, the numbers of patients in each N-stage and the corresponding Median survival time is shown in the Table 3.

The evaluation of survival according to the ratio of metastatic and total lymph nodes examined in concordance with the time of surgery using the Kaplan–Meier method is shown in the Figure 3.

The TNM staging system 2010 (7th edition)

According to the 7th TNM we classified 85 patients, numbers of patients in each N-category and the corresponding Median survival time is shown in Table 4.

Evaluation of survival according to the ratio of metastatic and total lymph nodes examined in concordance with the time of surgery using the Kaplan–Meier method is shown in Figure 4.

Tab. 3. The number of patients, median survival time and confidence interval for each N-stage of N-ratio classification system.

N-stage of disease	N0	N1	N2	N3
Number of patients	32	11	15	61
Median survival time (days)	2050	1179	868	516
Brookmeyer–Crowley 95% CI	1300–2153	441–1765	532–1966	360–670

Tab. 4. Number of patients, nedian survival time and confidence interval for each N-category of the 7th TNM.

N-stage of disease	N0	N1	N2	N3
Number of patients	24	12	10	39
Median survival time (days)	2050	1021	482	560
Brookmeyer–Crowley 95% CI	1268–2153	600–1765	255–2058	398–768

Fig. 5. Non-parametric correlation for 6th TNM.
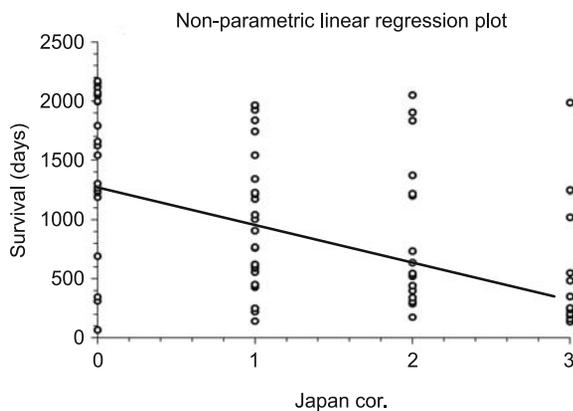
Fig. 6. Non-parametric correlation for JSGC.

A comparison of nonparametric correlation N-stage disease with the survival for the individual staging systems

Correlation 6th TNM staging system vs survival-days (Fig. 5)

Non-parametric linear regression
   Correlation survival-days vs 6th TNM
   Observation of the sample = 119
   Median slope (95% CI) = –279 (–400.666667 to –150.333333)
   Y-intercept = 1082

Kendall´s tau b correlation coefficient = –0.333416

Kendall sequential correlations
   Survival-days vs 6th TNM classification system, observation of a sample of 119 patients
   Kendall´s tau b correlation coefficient = –0.333416
   Approximate 95% CI = –0.440676 to –0.226155

Correlation JSGC vs survival-days

Non-parametric linear regression (Fig. 6)
   Correlation survival-days vs JCGC
   Observation of the sample = 76
   Median slope (95% CI) = –316.666667 (–461.5 to –156)
   Y-intercept = 1272.666667
   Kendall´s tau b correlation coefficient = –0.385601

Kendall sequential correlations

   JSGC vs survival-days
   Observation of a sample = 76
   Kendall´s tau b correlation coefficient = –0.385601
   Approximate 95% CI = –0.532939 to –0.238264

Correlation of N-ratio staging system vs survival-days (Fig. 7)

Non-parametric linear regression
   Correlation of survival-days vs N-ratio classification system
   Observation of the sample = 119
   Median slope (95% CI) = –247 (–342 to –130.3333333)
   Y-intercept = 1544
   Kendall´s tau b correlation coefficient = –0.3343553
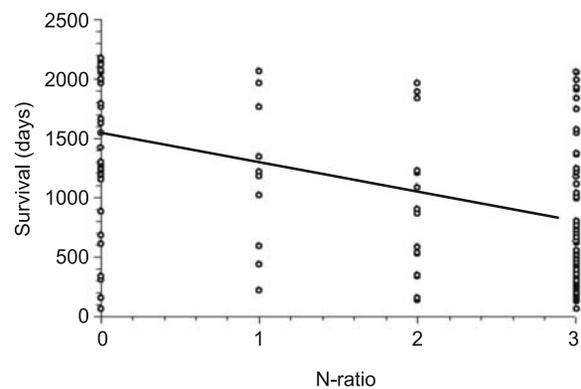
Fig. 7. Non-parametric correlation for N-ratio staging system.

Non-parametric linear regression plot
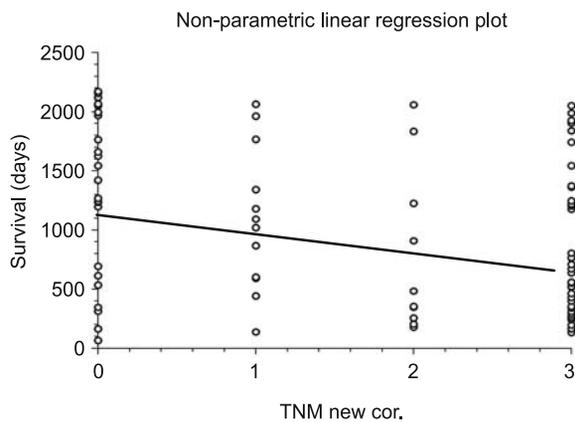
Fig. 8. Non-parametric correlation for 7th TNM.

Kendall sequential correlations

Survival-days vs N-ratio classification system
Observation of a sample = 119
Kendall´s tau b correlation coefficient = –0.3343553
Approximate 95% CI = –0.4394892 to –0.2292214

Correlation of the 7th TNM staging system vs survival-days (Fig. 8)

Non-parametric linear regression
Survival-days vs 7th TNM
Observation of the sample = 85
Median slope (95% CI) = –162.75 (–309 to –42)
Y-intercept = 1128.5
Kendall´s tau b correlation coefficient = –0.245884

Kendall sequential correlations
Survival-days vs 7th TNM classification system
Observation of a sample = 85
Kendall´s tau b correlation coefficient = –0.245884
Approximate 95% CI = –0.380356 to –0.111411

Conclusion and discussion

The existence of several staging systems has resulted in the emergence of various comparative studies and retrospective analyzes to evaluate the most appropriate staging system.

The survival of patients is evaluated according to different staging systems that are based on different parameters mentioned before.

Several studies confirmed the superiority of the 7th UICC N-staging system to the 6th UICC N-staging classification in prognosis of overall survival (6).

In study from Italy, the staging systems based on the rate between the node counts was proved to be more reliable and accurate than the 7th TNM in the prognostic stratification of gastric cancer patients (1).

In our work, we assumed that the comparison of survival of the same patient classified according to various systems answers

the question of the importance of number vs anatomic location of affected lymph nodes (comparison of TNM vs JSGC).

In the first phase, we measured the survival in different groups of patients classified according to various staging systems (these are the same patients, only evaluated with the different classification systems except the patients excluded because of the specific criteria).

Due to the fact that while research has been in process, there was an update in 6th TNM classification to the 7th edition of TNM classification, patients were classified according to 7th TNM as well. For the evaluation of the survival versus the time after operation, we used Kaplan Meier method (Figs 1 – 4).

The median survival, according to different staging systems, depending on the N-stage of the disease, we found a significantly correlated with survival (p < 0.0001 for 6th TNM, p = 0.0002724 for the JSGC, p = 0.0000508 for N-ratio staging system, p = 0.0129 for the 7th TNM).

The new finding was a differentiation of patients in the groups N1 vs N2 under the 6th TNM staging system (HR = 0.910249), also a little differentiation in the groups N1 vs N2 according to the staging of N-ratio (HR = 0.8750926) and equally a poor differentiation survival in the groups N2 vs N3 according to the 7th TNM (HR = 0.881797).

In order to assess, which staging system most reliably distinguishes patients according to their survival, based on the assumption that the best system is the one, according to which the classification depending on N-stage of the disease, has the most fundamental effect on survival. The question is whether we can tell where the statistical differences between N0, N1, N2 and N3 by individual classification systems significantly distinct. We conducted correlation using a parametric linear regression between the staging and the survival time that best differentiates patients. It should be taken into account that the individual analyzes are not identical in the number of patients. The most appropriate for this type of analysis in terms of design would be to do the analysis with the same patients in all staging systems.

The strongest correlation reached the Japanese classification system (tau b = –0.385601), but not significantly different from the 6th TNM (tau b = – 0.333416). In the 7th TNM, we then found the weakest correlation with the survival time (tau b = –0.245884), but not significantly different from the previous two.

According to the results above, we can conclude that the patient survival significantly affected both the number of metastatic lymph nodes and their anatomical localization. The anatomical localization of the metastatic lymph nodes correlated with a better survival, but this difference was not confirmed as statistically significant.

We confirmed the strongest correlation between the patient´s prognosis and the anatomic localization of metastatic lymph nodes in our study. However, this correlation was not statistically significant compared to the correlation between the patient´s prognosis and the number of metastatic lymph nodes. We can therefore conclude that both classification systems are comparable and the difference is statistically insignificant. In future, probably a combination of the number and anatomic location of positive lymph nodes would be the solution to improve the stratification of patients

with gastric cancer, allowing a better staging and then to indicate postoperative adjuvant therapy.

Well-designed randomized controlled trials are necessary to evaluate the most appropriate staging system.

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