

COMPARISON OF LYMPHATIC SYSTEM STAGING CLASSIFICATIONS IN PATIENTS WITH GASTRIC CANCER

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Despite an observed decrease in the incidence of gastric cancer, it still remains an important clinical problem. It is the fourth most common cancer in the world and the second cause of death in cancer patients. The quality of lymphadenectomy procedure and the number of analysed lymph nodes are both important factors influencing the treatment of the patient.

The aim of the study was to compare the lymph node ratio staging system with the 6th and 7th edition of the TNM classification.

Material and methods. A group consisting of 493 patients who underwent surgery in 1998–2010 due to gastric cancer was used to compare the staging systems. Following statistical analysis, the following cut-off points were adopted for the lymph node ratio for the purpose of comparison: 0, from 0.05 to 0.3, from 0.3 to 0.5 and over 0.5. Subsequently the homogeneity (using chi-square test for linear trend) and the predictive value of the different classifications (using Akaike information criterion) were assessed in order to compare the lymph node ratio staging system with the 6th and 7th edition of the TNM classification.

Results. The lymph node ratio classification has a higher discriminatory value than the TNM classifications (higher linear trend result). What is more, the lymph node ratio classification (LNR) had a lower Akaike information criterion value, which means that it has a higher prognostic value than the other classifications. ROC curves and the area under the curve (AUC) were utilised for the analysis of predictive value of the different classifications in patients with gastric cancer.

Conclusion. One may conclude, therefore, that the lymph node ratio staging system is the best classification of the lymphatic system in the presented group of patients.

Key words: gastric cancer, lymph node ratio staging system

Despite an observed decrease in the incidence of gastric cancer, it still remains an important clinical problem. It is the fourth most common cancer in the world and the second cause of death in cancer patients. In Poland, the incidence of gastric cancer has decreased three-fold over the last four decades. Unfortunately, treatment outcomes for gastric cancer in Poland are unsatisfactory: in 2010, mortality due to this cancer was 25% higher for men and 10% higher for women than the European Union average (1). The most important prognostic factors in gastric cancer patients are the depth of tumour infiltration (the T parameter in the TNM classification) and metastases in the regional lymphatic system.

The condition of the regional lymphatic system does not only influence the total patient survival, but is also an independent relapse factor following radical resection (2). At present, on the basis of research, D2 lymphadenectomy is considered to be the most appropriate course of action in the vast majority of patients. D2 lymphadenectomy was associated with better control of local relapse and a lower number of deaths caused by gastric cancer during a 15-year-long follow-up period in comparison with limited (D1 or less) lymphadenectomy (3, 4). Extended D2+ lymphadenectomy allows for safe harvesting of a larger number of lymph nodes; however, its influence on treatment outcomes remains a matter of dispute (5).

The quality of lymphadenectomy procedure and the number of analysed lymph nodes are both important factors influencing the treatment of the patient. The removal and assessment of fewer than 15 lymph nodes affects the patients' prognosis negatively, accounts for underestimation of the stage of the tumour and causes inappropriate selection of supplementary treatment (6-9). According to pooled data from the United States, 10 lymph nodes are assessed on average in gastric cancer patients, while in 9% of patients the lymphatic system is not evaluated at all. 15 or more lymph nodes are removed and assessed only in 29% of patients (10, 11). The US Intergroup 0116 trial showed that only 10% of patients had a D2 lymphadenectomy, 36% had a D1 lymphadenectomy, while the majority (54%) had an incorrect and inadequate D0 lymphadenectomy (12). Similar results were found in a study which evaluated the quality of gastric cancer surgery on the basis of the number of removed lymph nodes. Only 42.3% of patients in the studied group had at least 15 lymph nodes removed and examined (13).

The selection of supplementary treatment and assessment of prognosis for patients with gastric cancer in Europe is based on the TNM classification. Does the 7th edition of the classification, introduced in 2010, solve the problem of underestimated staging of gastric cancer in the lymphatic system domain?

The aim of the paper was to compare the lymph node ratio staging system with the 6th and 7th edition of the TNM classification.

MATERIAL AND METHODS

A group consisting of patients who underwent surgery in 1998-2010 due to gastric cancer was used to compare the staging systems. 493 patients who underwent total or partial gastrectomy were included in the analysis. Patients with distant metastases, a family history of gastric cancer or with a history of other malignant tumours were excluded from the study. The mean age of the patients was 62.5 years (median: 64). The women-men ratio was 0.59. Histopathological examination in the above group revealed metastases in the lymph nodes in 340 out of 493 (68.96%) patients. An average of 16.97 lymph nodes were examined in one patient and in 267

out of 493 (54.15%) patients over 15 lymph nodes were identified. All patients were assessed for the N parameter according to the 6th and 7th edition of the TNM classification and had their lymph node ratio calculated. The group profile is presented in tab. 1.

Statistical analysis

The Cox proportional hazard model was used to assess the influence of prognostic factors on patients' survival. Univariate analysis was performed on the data and subsequently the factors which turned out to be statistically significant were included in multivariate analysis.

During lymph node ratio assessment, those patients who were found to have metastases in lymph nodes were divided into different groups formed every 0.05 of the lymph node ratio value in the range of 0.05–0.95. On the basis of a Martingale analysis, two important cut-off points for the lymph node ratio were identified: 0.30 and 0.50. Subsequently, all analysed patients were assigned to one of 4 subgroups: WW0 – patients without metastases in the lymph nodes, WW1 – patients with the lymph node ratio of 0.5% to 30%, WW2 – patients with the lymph node ratio of 31% to 50%, WW3 – patients with the lymph node ratio of 51% to 100%. The homogeneity (using

Table 1. Profile of the group used to compare different staging systems

Whole group	493 patients (%)
Stomach resection:	
Total resection	370 (75,05)
Partial resection	123 (24,94)
Stage of advancement:	
T1	54 (10,95)
T2	240 (48,68)
T3	180 (36,51)
T4	19 (3,85)
Lauren classification	
Intestinal	211 (42,79)
Diffuse	138 (27,99)
Mixed	144 (29,20)
Location of the tumour	
Upper 1/3 of the stomach	165 (33,46)
Middle 1/3 of the stomach	138 (27,99)
Lower 1/3 of the stomach	190 (38,53)

chi-square test for linear trend) and the predictive value of the different classifications (using Akaike information criterion) were assessed in order to compare the 6th and 7th edition of the TNM classification with the lymph node ratio staging system.

RESULTS

Factors which influence patient survival were assessed first. The factors which were statistically significant in the univariate analysis included the level of infiltration of the tumour according to the TNM classification – the T parameter ($p < 0.0001$), the level of lymph node invasion according to the TNM classification – the N parameter ($p < 0.0001$), the level of malignancy of the tumour – G (grading, $p < 0.00354$), the radicality of the resection ($p < 0.00001$), infiltration into other organs found during the surgery ($p < 0.00305$), type of gastric cancer according to the Lauren’s classification ($p < 0.01013$). Following multivariate analysis, the stage of advancement of the tumour T, condition of the lymphatic system N and the radicality of the surgery were regarded as significant factors ($p < 0.05$). If $p < 0.01$ is assumed as the significance level, only the stage of advancement of the tumour T and the condition of the lymphatic system are considered significant. The condition of the regional lymphatic system upon diagnosis reached the highest value of the hazard ratio: 1.719, i.e. it had the highest prognostic significance in the analysed group (tab. 2).

Statistical analysis revealed that the lymph node ratio staging system has a higher discriminatory value than the TNM classifications (higher linear trend). What is more, the lymph node ratio classification (LNR) had a lower Akaike information criterion value, which means that it has a higher prognostic

value than the other classifications (tab. 3). ROC curves and area under the curve (AUC) were utilised for the assessment of the predictive value of the different classifications in patients with gastric cancer (fig. 1). The area under the curve value for the Union for International Cancer Control TNM 6 classification (UICC 6) was 0.796, for UICC 7 it was 0.796 and for LNR it was 0.830. This corroborates the superiority of the lymph node ratio predictive value. Probability of five-year survival (pOS) was analysed for patients with gastric cancer depending on the disease staging system. According to the TNM 6 classification, five-year survival was 70% for the N0 group, 35.3% for the N1 group, 12.6% for the N2 group and 0.3% for the N3 group ($p < 0.001$) (fig. 2). According to the TNM 7 classification, the probability of five-year survival was 69.7% for the N0 group, 42.5% for the N1 group, 24.6%

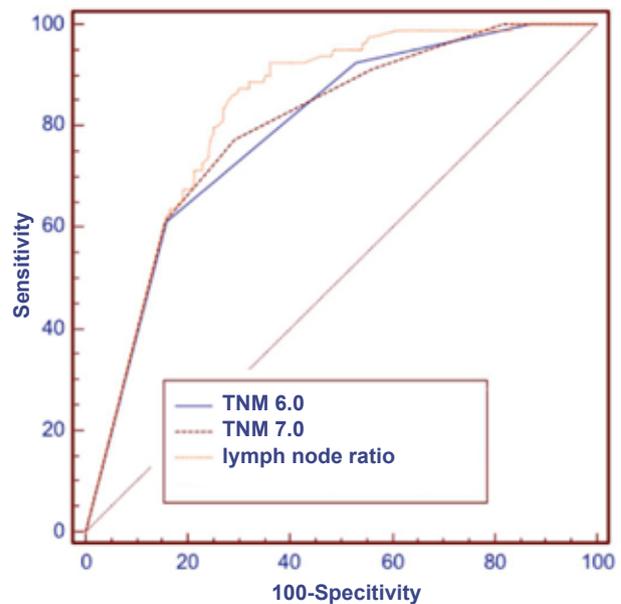


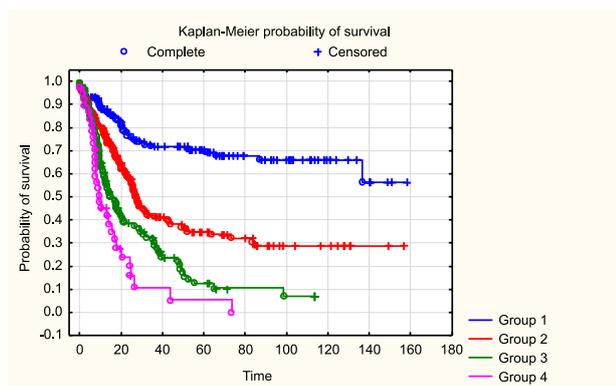
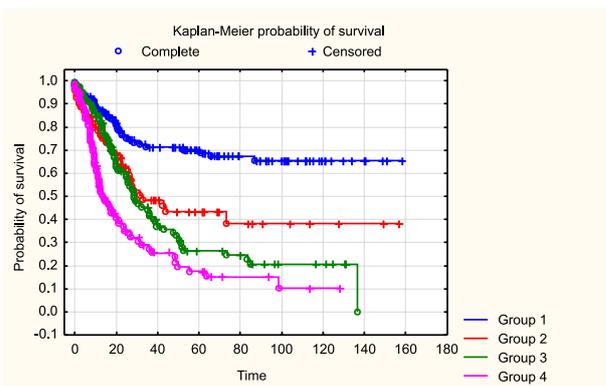
Fig. 1. Area under the curve (AUC) analysis for the assessment of predictive value of the TNM classification

Table 2. Results of analysis of factors affecting survival according to the Cox proportional model

	Beta	Statistical error	t value	p value	Hazard ratio
T parameter	0,309045	0,088708	3,483857	0,000495	1,362124
N parameter	0,541743	0,071676	7,558180	0,000000	1,719000
Stage of malignancy	0,137487	0,117167	1,173425	0,240634	1,147386
Radicality of surgery	0,301659	0,151194	1,995183	0,046031	1,352100
Presence of infiltration into other organs	0,303420	0,1739303	1,744764	0,081036	1,354484
Type of gastric cancer according to Lauren classification	0,053677	0,087160	0,615845	0,538001	1,055143

Table 3. Values of linear trend and Akaike information criterion (AIC) for different lymphatic system staging classifications

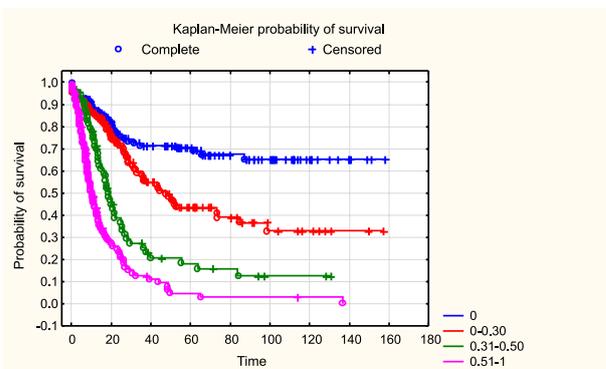
Classification	Subgroups	Chi-square linear trend	Akaike information criterion (AIC)
UICC 6	N 0,1,2,3	41.347	2656.017
UICC 7	N 0,1,2,3	45.316	2639.705
Lymph node ratio	WW 0,1,2,3	48.481	2576.140

Fig. 2. Probability of 5-year survival of patients with gastric cancer classified according to the 6th edition of the TNM classification ($p < 0.001$)Fig. 3. Probability of 5-year survival of patients with gastric cancer classified according to the 7th edition of the TNM classification ($p < 0.001$)

for the N2 group and 17.8% for the N3 group ($p < 0.001$) (fig. 3). The lymph node ratio staging system revealed the following probability of five-year survival: 69.8% for the LNR0 group, 43.3% for the LNR1 group, 18.4% for the LNR2 group and 0.51% for the LNR3 group ($p < 0.001$) (fig. 4).

DISCUSSION

Currently there are two gastric cancer staging systems commonly used in the world: JCGC (Japanese Classification of Gastric Cancer) and UICC TNM. The former is based on a division and numbering of different groups of lymph nodes and the location of metastases. The latter classifies patients according to the stage of their disease on the basis of the quantity of metastatic lymph nodes found. The classification system by Ueno et al. should in principle be assessed for three basic criteria: intra-group homogeneity (small differences in the times of survival between patients assigned to the same prognostic group), inter-group discriminatory ability (large differences

Fig. 4. Probability of 5-year survival of patients with gastric cancer classified according to the lymph node ratio ($p < 0.001$)

in the times of survival between patients assigned to different groups) and gradient monotonicity as a result of the correlation between the stage of the disease and the probability of survival (within one stratification system, patients with a lower clinical stage have a longer time of survival than patients at a more advanced stage of the disease) (14).

The 7th edition of the TNM classification, introduced in 2010, differs from the previous

5th and 6th editions by the number of metastatic lymph nodes which are the basis for the assignment of patients to one of the different stages: N1, N2 or N3. Research has shown that the reduction of the number of metastatic lymph nodes necessary for rating the patient as N1 and N2 resulted in increasing the intergroup discriminatory ability (15 – 19). In a study on a group of 456 patients clinically controlled logistic regression was used for comparison of the 5th and 6th editions of the TNM classification with its 7th edition. This study found that the 7th edition of the TNM classification had a higher ability to predict the total patient survival rate than the previous versions ($p < 0.001$). In addition, this study identified the most appropriate selection of cut-off points for the number of metastatic lymph nodes, which provides for the highest intragroup discrimination power and gradient monotonicity. These were the following ranges: 0, 1–2, 3–6, 7–8 and ≥ 9 , which are similar to the 7th edition of the TNM classification (15). Marelli et al. analysed patients treated for distal gastric cancer and observed a significant difference in the survival rate of patients assigned to the N1 (1–2 metastatic nodes) and N2 parameter (3–6 metastatic nodes) ($p < 0.001$) according the 7th edition of the TNM classification. The authors highlight the fact that they also observed a difference for the N3a parameter (7–15 metastatic nodes) and N3b (≥ 15 metastatic nodes) ($p < 0.001$) (18). Do the 7th edition of the TNM classification and the cut-off values between the different parameters N1, N2 and N3 therefore ensure better stratification of patients in the lymphatic system domain?

The lymph node ratio expresses the relationship between the number of metastatic and removed lymph nodes. The classification of patients and stratification of risk on the basis of the lymph node ratio value has a substantial advantage in that it does not depend on the number of resected and examined lymph nodes. Some papers prove the superiority of the lymph node ratio in relation to the TNM classification (20, 21, 22). The present authors used statistical tests similar to those used by Xiao et al. to compare the value of the lymph node ratio staging system with the 7th and 6th edition of the TNM classification (23). Following statistical analysis, it was concluded that the most adequate classification for patient

survival was the lymph node ratio. The ranges identified during Martingale analysis were: 0, from 0.05 to 0.3, from 0.3 to 0.5 and over 0.5. Identical cut-off levels were presented by Xiao et al. (23). In a study on 18,043 patients Wang et al. identified cut-off points for the lymph node ratio of 0.06, 0.3 and 0.7 (24). Other authors used the following cut-off points: 0, 0.01, 0.05, 0.06, 0.1, 0.2 and 0.3 on the basis of analysis of their own material (25, 26). During similar analysis performed on a group of 738 patients, Kulig et al. used the following cut-off points: 0, 0.01–0.4 and over 0.4 (27). When the lymph node ratio is used for the staging classification of the lymphatic system, it is necessary to identify specific cut-off points on the basis of which the patients may be assigned to different groups. The identification of universal cut-off points which might be used for every population is disputable and definitely requires statistical analyses on very large groups of patients. If lymph node ratio classification was to be used for such a purpose, it would be necessary to standardise the cut-off points to allow for its widespread use.

After the lymph node ratio has been calculated for every patient and the patients have been assigned to the different groups, it should be checked whether the system meets all the conditions provided above. The homogeneity (using chi-square test for linear trend) and the predictive value of the different classifications (using Akaike information criterion) were assessed in order to evaluate and compare the classifications. ROC curves and the assessment of the size of the area under the curve were used to determine the accuracy of a given classification as well as its sensitivity and specificity. A similar manner of comparison was presented by other authors (23, 26). Other authors used the log-rank test to conduct a similar comparison of the TNM classifications: their homogeneity, intergroup discriminatory ability and gradient monotonicity. The results obtained from the presented material stand as evidence of the best predictive value of the lymph node ratio. Similar results were obtained by the majority of authors (20–26). In a linear chi-square test, the lymph node ratio classification scored 48.481, while the 7th edition of the TNM classification scored 45.316, and the Akaike criterion result was 2576.10 and 2639.705, respectively. Xiao obtained a

linear chi-square test result for the lymph node ratio classification of 203.476 and 138.342 for TNM 7. The Akaike criterion result was 7240.017 and 7325.731, respectively (23).

On the basis of the above results and the areas under the ROC curves, we may conclude that the lymph node ratio classification obtained the best results in every aspect under assessment. Similar observations were presented by Lorenzo et al.: the value of the area under the ROC curve was 0.69 for the lymph node ratio staging system, taking into account the total patient survival rate. In our material, this value was 0.830 (26). Xiao gave an AUC value of 0.754, while Lee provided an AUC value of 0.822. One should bear in mind that the closer the AUC result is to the value of 1, the better adjustment of the staging system is. The majority of publications which assessed AUC for the lymph node ratio strati-

fication system obtained a value of > 0.6, which was higher than the one for the TNM classification. On the basis of the presented calculations, one may conclude that the lymph node ratio stratification system is more accurate and sensitive than the 6th and 7th edition of the TNM classification.

CONCLUSIONS

On the basis of the analysis of the group of patients who underwent surgery, one may conclude that the best cut-off points for the lymph node ratio staging system were 0, from 0.05 to 0.3, from 0.3 to 0.5 and over 0.5. The classification based on the above cut-off points of the lymph node ratio was more precise and had a better predictive value than the 6th and 7th edition of the TNM classification.

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