Proposal of a Dukes-MAC-like staging system for gastric cancer

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ABSTRACT

The aim of this study was to present an epidemiological update regarding the classical prognostic parameters of gastric cancer (GC) in 3 countries from Eastern Europe and to suggest a modification of the pTNM staging system. In 333 consecutive cases which were diagnosed between 2003 and 2012 in 3 departments of pathology from Romania, Hungary, and Poland, the following parameters were analyzed: age and gender of patients, tumor localization, macroscopic and microscopic aspects including the degree of discohesivity, depth of tumor infiltration, and pTNM stage. From all of the studied parameters, the following proved to have independent prognostic value, indicating a lower survival rate: presence of distant metastases (p=0.001), lymph node positivity (p=0.0009), depth of tumor infiltration (p=0.04), age over 50 (p=0.02), proximally located tumors (p=0.03), and ulceroinfiltrative or diffusely infiltrative macroscopic aspect (p=0.0002). The pT2N1-3 staged cases showed a worse prognosis compared with the pT3N0 ones (p=0.02). Regardless of depth of invasion, the lymph node status remains the strongest indicator of the survival rate in GC. The pTN staging system should be adapted and a Dukes-MAC-like staging system should include the following groups: stage A1—T1N0, stage A2—T1N1-3, stage B1—T2N0, stage B2—T2N1-3, stage C1—T3N0, stage C2—T3N1-3, and stage D—T4N0-3. The grade of discohesivity/budding is not a prognostic factor in GC.

Significance of this study

What is already known about this subject?

- Gastric cancer is staged based on the depth of tumor infiltration (pT stage) and presence or absence of metastases (pN and pM stages).
- According to the present guidelines, the patients with pT1 stage gastric cancer do not receive postoperative chemotherapy.
- Although an intention for classification of gastric cancer based on the molecular profile is proposed, the classic parameters such as the lymph node status remains the most important prognostic factor.
- Lack of cancer registries in countries from Eastern Europe do not allow comprehensive epidemiological studies.

What are the new findings?

- The pT2 staged cases (invasion of the muscularis propria) have a better overall survival than pT3 (invasion of the serosal layer).
- The pN stage is a stronger prognostic parameter than pT.
- This comprehensive analysis shows that in Eastern Europe more than 50% of the patients die in the first year after surgery.
- A pTN combined staging system, similar to the Dukes-MAC system, is proposed for a proper selection of cases that could benefit by postoperative chemotherapy.

How might these results change the focus of research or clinical practice?

- Similar to the colorectal cancers, a combined Dukes-MAC-like pTN stage system could improve the postoperative therapeutic protocols used for gastric cancer and can be used for a proper selection of patients in early stages that could benefit by postoperative chemotherapy.

INTRODUCTION

Gastric cancer (GC) is a malignant tumor which heterogeneity makes difficult its therapeutic management. Despite the screening programmes and slightly decreasing incidence in the past decades, it remains the fifth most common malignancy and the third leading cause of cancer death worldwide, with a median 5-year survival rate of 15–29%.[1–5]

Even though the pTNM staging system, which was updated by the WHO in 2010, is relatively easy to use in the daily diagnosis, no specific criteria are indicated in the international guidelines to select which of the patients with tumors limited to the mucosa/submucosa (pT1) or muscularis propria (pT2) are indeed 'aggressive' and might benefit by postoperative chemoradiotherapy.

In this paper, we aimed to present an update regarding the epidemiological aspects of GCs

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which were diagnosed in three hospitals from Romania, Hungary, and Poland. We also proposed a lymph node-based classification of GC, with prognostic impact, and a review of literature regarding the epidemiological trends of GC in Eastern Europe and the newest proposals of modification of the pTNM staging system of GC.

MATERIAL AND METHODS

Selection of patients

Data of 333 patients with GC who underwent standard gastrectomy in three departments of pathology in Eastern Europe were collected between 2003 and 2012. This retrospective observational study was approved by the Ethical Committee of University of Medicine and Pharmacy of Tirgu Mures, Romania. It was also approved by the local committees of the two departments of pathology from Poland and Hungary.

The admittance criteria were patients with potentially curable histologically proved primary GCs, curative resection (R0, microscopically negative margins), with no previous gastrectomy, without any synchronous or metachronous malignant tumors.[4] Those patients who died in the first month after surgery or underwent preoperative radiotherapy or chemotherapy and cases with incomplete information have been excluded from this study. All of the patients underwent gastrectomy with D1 or D2 lymphadenectomy. The clinicopathological features were compared between Romanian, Hungarian, and Polish patients.

Tumor characteristics

The macroscopic classification was performed according to the Bornmann's criteria: I-polypoid; II-ulcerated; III-ulceroinfiltrative; IV-linitis plastica; and V-unclassifiable tumor. Microscopically, the tumors were divided into intestinal-type carcinomas (well differentiated and undifferentiated types) and diffuse-type (poorly cohesive) carcinomas, according to Lauren's classification and WHO criteria.[6 7]

The GCs were staged based on the WHO 2010 and American Joint Committee on Cancer (AJCC) 7th edition systems in pT1 to pT4 and pN0 to pN3, respectively.[7] They were additionally classified into seven groups, based on a Dukes-MAC-like staging system: stage A1—T1N0, stage A2—T1N1-3, stage B1—T2N0, stage B2—T2N1-3, stage C1—T3N0, stage C2—T3N1-3, and stage D—T4N0-3 (figure 1 and table 1).

In the invasion front, quantification of the tumor cell dissociation grade was performed, similar to the tumor buds' quantification criteria used for colorectal cancer. Based on the number of isolated cells forming the invasion front, the cases were histologically classified into G1 (single cells or clusters with fewer than 5 cells), G2 (clusters of 5–9 cells), and G3 (at least 10 isolated cells in the invasion front in a high-power field).[8 9] The poorly cohesive carcinomas were considered as a distinct group and classified as G4 cases.

Statistical data

Statistical analysis was performed using the Graph Pad InStat 3 program and the two-tailed Fisher's exact test and Wilcoxon test. A value of $p<0.05$ with 95% CI was considered statistically significant. To evaluate the overall survival (OS), a Kaplan-Meier analysis was performed.

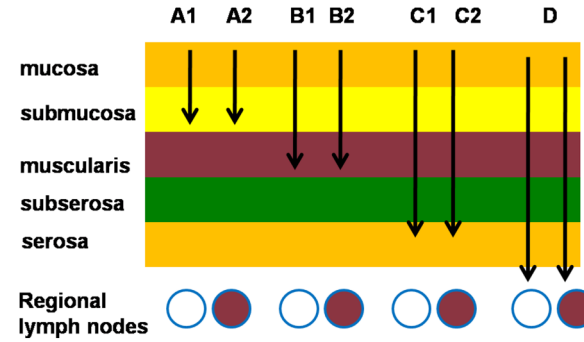

Figure 1 Diagram of the Dukes-MAC-like classification of gastric cancer (the arrows represent the depth of invasion, empty circles represent absence of metastases and brown circles show presence of lymph node metastases).

Follow-up was possible in 166 cases from the 333 patients (98 Romanian patients and 68 Polish patients). The median follow-up time was 68.77±41.12 months (range 12–168 months). For these patients, the Kaplan-Meier survival curves were performed to estimate the OS. OS was considered the time from the date of surgery until death or last follow-up.

RESULTS

Demographic data

The mean age of the patients was 62.19±13.96 (range 21–98 years). The ages ranged from 22 to 98 years in males and 21 to 90 years in females. The Polish patients were significantly younger than the Hungarian patients ($p=0.02$). Taking into account all of the 333 patients, the females were diagnosed at an age younger than males ($p<0.001$).

Table 1 Comparison of criteria currently used in clinical practice[7] and the newest proposed pTN staging system of gastric cancer

WHO's staging system		Dukes-MAC-like proposed system	
IA	T1N0	A1	T1N0
IB	T2N0	B1	T2N0
IB	T1N1	A2	T1N1-3
IIA	T3N0	C1	T3N0
IIA	T2N1	B2	T2N1-3
IIA	T1N2	A2	T1N1-3
IIB	T4aN0	D	T4N0-3
IIB	T3N1	C2	T3N1-3
IIB	T2N2	B2	T2N1-3
IIB	T1N3	A2	T1N1-3
IIIA	T4aN1	D	T4N0-3
IIIA	T3N2	C2	T3N1-3
IIIA	T2N3	B2	T2N1-3
IIIB	T4bN0-1	D	T4N0-3
IIIB	T4aN2	D	T4N0-3
IIIB	T3N3	C2	T3N1-3
IIIC	T4bN2-3	D	T4N0-3
IIIC	T4aN3	D	T4N0-3

This difference was kept for Romanian patients ($p<0.001$), but the age of diagnosis was older in females from Hungary ($p<0.001$) and Poland ($p<0.001$), compared with males from the same country. Regardless of the geographic origin, the males were two times more affected than females (table 2).

Tumor location

In the 234 patients from Romania, the tumors were mainly located in the lower third of the stomach (n=95; 40.60%), followed by the upper third (n=73; 31.19%), middle third (n=46; 19.66%) and whole stomach (n=20; 8.55%). In the 73 Polish patients, only tumors of the upper third (n=50; 68.49%) and lower third of the stomach (n=23; 31.51%) were encountered. In the Hungarian patients, the upper third location predominated (n=11; 42.31%), followed by the middle third (n=8; 30.77%) and lower third stomach (n=7; 26.92%) in similar proportions. For statistical purposes, the upper third-located tumors were included in the proximally located tumors, whereas those that involved the middle/distal third or the whole stomach were included in the category of distally located GCs. It was seen that the proximally located GCs were predominant both in Polish and Hungarian patients, whereas an equal distribution was observed between proximal and distal stomach cancer localization in patients from Romania ($p=0.02$) (table 2).

Bormann's type

Macroscopic features were almost similar in cases from Hungary and Poland, and ulcerated-type tumors (Bormann types II and III) predominated in both groups ($p=0.20$). However, linitis plastica (Bormann type IV) was slightly more frequent in Hungarian than Polish patients ($p=0.02$). In the Romanian group, the ulceroinfiltrative tumors (Bormann type III) constituted more than 68% of the

Table 2 Geographic-related clinicopathological features of patients

Parameter	Total (n=333)		A. Romania (n=234)		B. Poland (n=73)		C. Hungary (n=26)		p Value
	No	%	No	%	No	%	No	%	
Sex									A vs B vs C −0.81
M	225	67.57%	158	67.52%	50	68.49%	17	65.38%	A vs B −1.00
F	108	32.43%	76	32.48%	23	31.51%	9	34.62%	A vs C −0.70
									B vs C −0.70
M:F ratio	2.08:1		2.08:1		2.17:1		1.88:1		NA
Age (mean±SD)									A vs B vs C −0.12
Total	62.19±13.96		62.46±14.53		59.84±12.07		66.42±13.12		A vs B −0.11
									A vs C −0.10
									B vs C −0.02
M	62.41±13.37		63.25±13.91		59.14±11.42		64.11±12.76		**A vs B vs C <0.0001**
									A vs B <0.0001
									A vs C <0.0001
									B vs C <0.0001
F	61.76±15.23		60.95±15.77		60.78±13.48		70.77±13.42		**A vs B vs C <0.0001**
									A vs B <0.0001
									A vs C <0.0001
									B vs C <0.0001
Location									**A vs B vs C −0.02**
Proximal	188	56.46%	119	50.85%	50	68.49%	19	73.08%	**A vs B −0.01**
Distal	145	43.54%	115	49.15%	23	31.51%	7	26.92%	**A vs C −0.02**
									B vs C −0.64
Bormann type									
I	32	9.61%	19	8.12%	10	13.70%	3	11.54%	**A vs B vs C <0.0001**
II	63	18.92%	19	8.12%	34	46.58%	10	38.46%	**A vs B <0.0001**
III	188	56.46%	160	68.38%	22	30.13%	6	23.08%	**A vs C <0.0001**
IV	50	15.01%	36	15.38%	7	9.59%	7	26.92%	**B vs C −0.02**
Microscopic type									
Diffuse	134	40.24%	94	40.17%	29	39.73%	11	42.31%	A vs B vs C −0.41
Intestinal well-differentiated	118	35.44%	80	34.19%	27	36.99%	11	42.31%	A vs B −0.85
Intestinal undifferentiated	81	24.32%	60	25.64%	17	23.28%	4	15.38%	A vs C −0.14
									B vs C −0.35
Grade of discohesivity									
G1	56	16.82%	48	20.51%	6	8.22%	2	7.69%	**A vs B vs C −0.01**
G2	63	18.92%	34	14.53%	23	31.51%	6	23.08%	**A vs B −0.006**
G3	80	24.02%	58	24.79%	15	20.54%	7	26.92%	**A vs C −0.05**
G4	134	40.24%	94	40.17%	29	39.73%	11	42.31%	B vs C −0.5

F, female; M, male; NA, not applicable.
Bold typeface indicates statistically significant values.

Table 3 Geographic-related staging of gastric cancer

Parameter	Total (n=333)		A. Romania (n=234)		B. Poland (n=73)		C. Hungary (n=26)		p Value
Tumor depth									**A vs B vs C <0.0001**
pT1	32	9.61%	13	5.56%	13	17.81%	6	23.08%	**A vs B <0.0001**
pT2	24	7.21%	18	7.69%	4	5.48%	2	7.69%	**A vs C <0.0001**
pT3	91	27.33%	73	31.20%	7	9.59%	11	42.31%	**B vs C <0.0001**
pT4	186	55.85%	130	55.55%	49	67.12%	7	26.92%	
Lymph node status									
N0	76	22.82%	45	19.23%	21	28.77%	10	38.46%	**A vs B vs C −0.01**
N1	51	15.32%	37	15.81%	10	13.70%	4	15.38%	A vs B −0.4
N2	64	19.22%	46	19.66%	12	16.44%	6	23.08%	**A vs C −0.002**
N3	142	42.64%	106	45.30%	30	41.10%	6	23.08%	**B vs C −0.04**
pTN stage									
A1: T1N0	26	7.81%	11	4.70%	11	15.07%	4	15.38%	**A vs B vs C <0.0001**
A2: T1N1-3	6	1.80%	2	0.86%	2	2.74%	2	7.69%	**A vs B −0.002**
B1: T2N0	12	3.60%	8	3.42%	3	4.11%	1	3.85%	**A vs C −0.0002**
B2: T2N1-3	12	3.60%	10	4.27%	1	1.37%	1	3.85%	**B vs C <0.0001**
C1: T3N0	20	6.01%	16	6.84%	1	1.37%	3	11.54%	
C2: T3N1-3	71	21.32%	57	24.36%	6	8.22%	8	30.77%	
D1: T4N0	18	5.41%	10	4.27%	6	8.22%	2	7.69%	
D2: T4N1-3	168	50.45%	120	51.28%	43	58.90%	5	19.23%	

cases, followed by linitis plastica (Bormann type IV), and a few cases (16%) were classified as polypoid or ulcerated GCs (Bormann types I and II). These proportions were significantly different in comparison with the Hungarian and Polish groups (p<0.001) (table 2).

Microscopic features

Regardless of the geographic origin of the patients, the intestinal type adenocarcinomas were slightly predominant in comparison with the diffuse types (59.76% vs 40.24%). In the intestinal-type adenocarcinomas, apart from their histological grade of differentiation, the discohesivity grades G1, G2, and G3 in the invasion front were almost equal. However, the discohesivity was of higher grade in the Polish and Hungarian groups in comparison with the Romanian cases (p=0.01) (table 2).

Staging

More than 50% of the cases were diagnosed as significantly advanced lesions, up to the pT4N1-3 stage, except in the Hungarian group that showed only 26.92% of patients diagnosed in the pT4 stage. The number of patients who presented with pT1 staged tumors was significantly higher in Poland and Hungary than in Romania (23.08%, 17.81% vs 5.56%, respectively). Taking into account the whole pTN staging system, the D2/C1 cases predominated in the Romanian group, D2/A1 in the Polish group, and C2/D2/A1 in the Hungarian group (table 3).

Table 4 Geographic-related overall survival (OS) data

OS	Total (Romania +Poland) (%)	A. Romania (n=98) (%)	B. Poland (n=68) (%)	p Value
6 months	81.33	75.51	89.71	A vs B −0.37
12 months	51.81	48.98	55.88	
36 months (3 years OS)	36.14	38.78	32.25	
60 months (5 years OS)	15.66	12.24	20.59	

Overall survival

From the 166 patients who were followed up, 60 were alive at 36 months after surgery. The 5-year OS rate was 15.66% without any geographic-related dependence (table 4) as was the patients' gender.

A better OS was noted for patients below 50 years of age with distally located well-differentiated adenocarcinomas (figure 2). Patients with polypoid or ulcerated tumors (Bormann's type I+II) had a better OS than those with Bormann's type II+III tumors (p=0.0002). The grade of discohesivity/budding did not influence the OS (p=0.19).

Regarding the tumor stage, the best survival was seen for cases diagnosed subsequently as pT1, pT3, pT2, and pT4. A significant survival benefit was shown by cases without lymph node metastases, in comparison with the metastatic ones (figure 3).

The pTN Dukes-MAC-like staging of the tumors showed the best survival benefits for patients with tumors diagnosed in the pT1 stage, apart from the lymph node status (stage A1/A2), followed by the pT3N0 (C1) and pT2N0 (B1) stages. The pT2N1-3 (B2) and pT3N1-3 (C2) stages showed similar survival rates as intermediary groups. The worst survival rate was observed for cases diagnosed in the pT4N1-3 (D) stage (figure 4). Presence of distant metastases was also an independent prognostic factor (p=0.001).

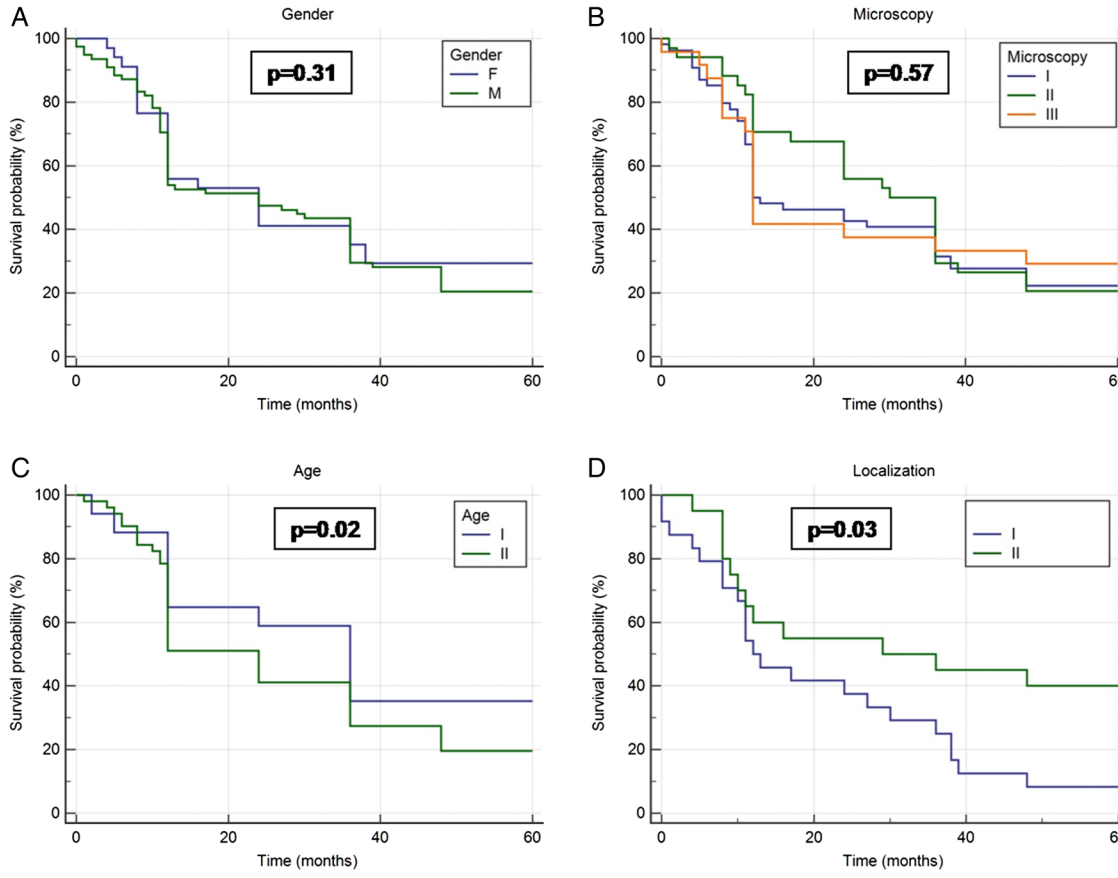

Figure 2 Gastric cancer overall survival does not depend on the patient's gender (A—F: female, M: male) or microscopic type of carcinoma (B—I: diffuse-type; II: undifferentiated intestinal-type; III: differentiated intestinal-type). The longer survival is noted for patients below 50 years (C—I: below 50; II: over 50) and with tumors localized in the distal stomach (D—I: proximal; II: distal).

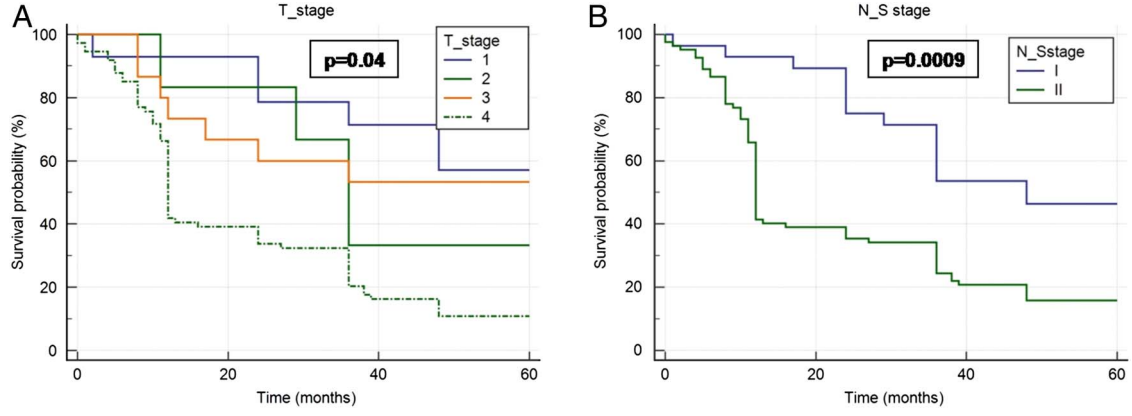

Figure 3 Overall survival in patients with gastric cancer. (A) The longer survival is noted for patients diagnosed in the stage pT1 (1), followed by pT3 (2), pT2 (3), and pT4 (4). (B) The longer survival is noted for patients without lymph node metastases (I) than those diagnosed with lymph node positive tumors (II).

DISCUSSION

In European countries, including Eastern Europe, the most recent studies showed a tendency of increasing number of GCs diagnosed in the proximal stomach with cardiac involvement.[1 10 11] This tendency seems to be related to the economic aspects; the distally located tumors are more frequent in developing countries, in contrast to proximal ones found more frequently in Northern Europe.[1 11] The proximally located GCs are more frequent in white patients.[1 6 11]

In line with our data, articles referring to the gender-related differences showed a double risk for males, in comparison with females, having a GC especially proximally located and of intestinal type. This tendency did not change over the years.[1–3 6 8 10 11]

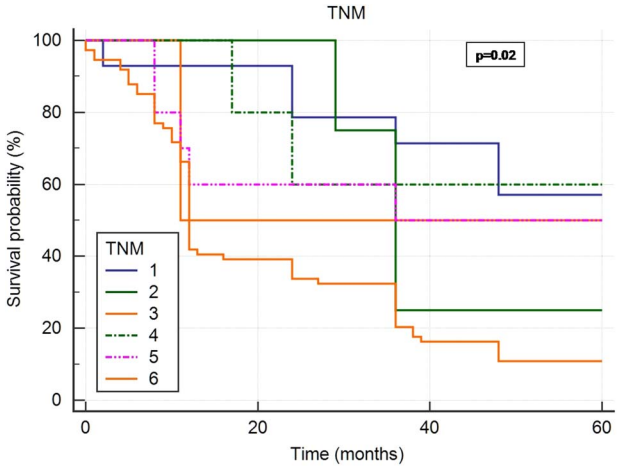

Figure 4 Overall survival in patients with gastric cancer, according to the newly proposed tumor/node-based Dukes-MAC-like staging system (1: stage A1/A2 or pT1N0-3; 2: stage B2 or pT2N1-3; 3: stage C2 or pT3N1-3; 4: stage B1 or pT2N0; 5: stage C1 or pT3N0; 6: stage D1/D2 or pT4N0-3).

Regarding the histological types, the incidence of poorly cohesive carcinomas rises in comparison with the intestinal-type GCs, regardless of the geographic areas.[1 11] However, the intestinal-type GCs seem to be predominant in the gastric body and also the most frequent histological type in Eastern Europe.[1 11 12] They are also more frequent in black patients than in white patients.[1 6 11]

The reported 5-year survival rate in Eastern European countries is about 15–16% in Hungarian and Polish patients and below this rate in Romania.[1 13 14] In Chinese patients, survival benefit was proved for Bormann type I/II intestinal-type carcinomas without lymph node metastases.[4] Although some differences were observed in our material regarding the clinicopathological features of the patients, the prognostic parameters proved to be similar in all of the patients, independently by their geographic origin. Similar to our data, irrespective of the geographic origin or race of the patients and irrespective of the molecular profile of the GC cells, it was observed that the only gold standard that proved to predict the patient's prognosis remains the lymph node status.[15] At the moment, the WHO system recommends lymph nodes positivity classification from N0 to N3, based on the number of nodes with metastases; examination of at least 15–16 lymph nodes is considered as standard of care in GC.

In the past years, another three lymph node-based changes of the pTNM staging system have been proposed. They are synthesized in table 5 and presented in this paragraph. The first one (TNrM system) takes into account the metastatic lymph node ratio (LNR), which was defined as the ratio between metastatic lymph nodes and total lymph nodes found in the resected specimen. Several authors agreed with this system's prognostic value.[16 17] The second one refers to the log odds of positive lymph nodes (LODDS), which is known as the log of the ratio between the number of positive and negative lymph nodes.[17] The third one was proposed by Choi *et al*[18] in 2016, in East Asia, and is a topographic-based classification. The authors suggested that location of the lymph node metastases (smaller curvature, greater curvature, or perigastric extension) can influence the prognosis. All of these three systems proved to have similar prognostic performance in comparison with the current pN staging system.[14 16–18] Compared with the current WHO-pN stage sytem, the Choi's system and LNR seems to be more adequate for evaluation of the lymph node status,[17 18] whereas LODS could be used as a prognostic parameter.[16 17] The LNR system is especially useful as a prognostic parameter for patients with pT2 staged tumors and few dissected lymph nodes.[16 17]

Our results showed that N0 status significantly influences the higher survival rate. An aberrant better survival was seen in the patients with pT3 compared with those

Table 5 New proposal for modification of the pTN staging system of gastric cancer

Author and year	Suggested criteria	Suggested groups	Characteristics
Lee *et al* (2010)[16] Jian-Hui *et al* (2016)[17]	Lymph node ratio system (TNrM system)	A numeric value: MLR0=0 MLR1≥0.1-0.3 MLR2>0.3–0.6 MLR3>0.6	The ratio between the number of positive LNs and total dissected LNs.
Jian-Hui *et al* (2016)[17]	LODDS	A numeric value	The log of the ratio between the number of positive and negative LNs.
Choi *et al* (2016)[18]	Topographic and numeric	New N0 New N1 New N2 New N3	No metastatic LN in any group 1 positive LN among 3 groups (LC alone, GC alone, or EP alone), regardless of number 2 positive out of 3 groups (LC+GC, LC+EP, or GC+EP), regardless of number Positive results for all 3 groups (LC+GC+EP)
Gurzu *et al*[8] (2016-present proposal)	Depth of infiltration combined with LN status	Stage A1 Stage A2 Stage B1 Stage B2 Stage C1 Stage C2 Stage D	T1N0 T1N1-3 T2N0 T2N1-3 T3N0 T3N1-3 T4N0-3

EP, extraperigastric regional lymph nodes; GC, greater curvature; LC, lesser curvature; LN, lymph node; LODDS, log odds of positive lymph nodes; MLR, metastatic lymph node ratio.

diagnosed in pT2 stage. Moreover, the patients diagnosed with pT3N0 GC have a better survival rate than those with pT2N1-3.

On the basis of these facts, we propose a new Dukes-MAC-like pTN combined staging system, with possible prognostic and predictive value. The cases were divided into the following seven groups: stage A1—T1N0, stage A2—T1N1-3, stage B1—T2N0, stage B2—T2N1-3, stage C1—T3N0, stage C2—T3N1-3, and stage D—T4N0-3. This pTN combined system proved to have superior prognostic value than the current WHO staging system (table 1). Moreover, the patients diagnosed in groups A2, B2, and C2 could benefit with postoperative chemotherapy. We realize that this system should be validated in much more numerous groups and in western patients too.

The limitations of the study are the small number of cases and absence of correlation with the distant metastases rate. However, since the number of cases with lymph node skip metastases was reported to increase, a lymph node-based staging system is mandatory to be used in the daily diagnosis. This is a proposal that should be tested in daily practice.

Contributors SG designed the research and drafted the article. HS performed the interpretation of data form western point of vision. JO provided data of Polish patients. JS managed the statistical data. ZS provided data of Hungarian patients. TB participated at the surgical interventions and managed the clinical data. TB. participated at the surgical interventions and managed the data from literature. AF performed the histological daily diagnosis and checked the English quality. IJ reviewed the data and approved the final variant.

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