

## ORIGINAL PAPER

# Gastric cancer: correlation between clinicopathological factors and survival of patients (III)

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### Abstract

**Purpose:** The purpose of this study was to identify the clinicopathological factors that influence the prognosis of patients having undergone surgery for gastric cancer. The analysis of the potential prognosis factors has included in this study parameters concerning the patient (sex, age), as well as parameters related with the tumor (histological type according to the *WHO* classification; degree of tumor differentiation; tumor location; stage of disease; pT and pM parameters according to the TNM classification of *AJCC/UICC*). **Material and Methods:** From the total number of 265 patients (186 men and 79 women) diagnosed with gastric cancer in the period 1998–2002, 61 operated patients were selected. On this group, we performed a prospective study regarding the evolution and aggressiveness of gastric cancer, on a duration of 5 years. Survival time was calculated from the month of the surgical intervention until the month of death or confirmation of survival, and survival rate was represented by the percentage of survivals at the end of the observed interval (in years and months). **Results:** The studied group consisted of 61 patients (43 men and 18 women), with ages between 30 and 80 (average age = 59.34 years). According to the maximum level of tumor invasion we identified: pTis – one case (1.6%); pT1 – four cases (6.6%); pT2 – nine cases (14.7%); pT3 – 17 cases (27.9%); most gastric cancers were included in the pT4 category (49.2%). We identified 43 gastric carcinomas with metastases in regional lymph nodes (70.5% of the cases). According to the number of lymph nodes involved: pN0 – 18 cases (29.5%); pN1 – 16 cases (26.2%); pN2 – 23 cases (37.7%); pN3 – four cases (6.6%). Distance synchronous metastases were present in 14 gastric carcinomas (pM1 – 23% of the cases), nine cases with hepatic metastases and five cases with distance peritoneal disseminations. Classification of gastric carcinomas: we identified one single case listed in the 0 stage, three cases in the IA stage, five cases in the IB stage, seven cases in the II stage, 11 cases in the IIIA stage, eight cases in the IIIB stage, and 26 cases in the IV stage. From the total of carcinomas, stage IV consisted of the greatest number of tumors, representing 42.6%. We generally remarked the increase of the number of cases in advanced stages. **Conclusions:** In the studied group, we noted a great number of gastric carcinomas diagnosed in stages T3 and T4 (77.1% of cases). Cardial tumor locations and gastric stump locations, as well as "signet-ring" cell and undifferentiated carcinomas prove to be aggressive, being diagnosed in advanced stages. 70.5% of gastric neoplasms presented lymph node metastases, most cases representing pN2 tumors (37.7%). 23% of neoplasms studied presented distance metastases at the time of diagnosis. We noted a significant correlation between the degree of tumor differentiation and the level of invasion, as well as the presence of distance and lymph node metastases. Survival at 5 years of patients included in the study was correlated significantly with the level of tumor invasion, the presence of lymph node and distance metastases, and the TNM stage.

**Keywords:** gastric cancer, clinicopathological factors, survival.

### ☐ Introduction

Gastric cancer represents one of the most frequent neoplasias. Although its incidence decreased over the last few decades in industrialized countries, it still represents nowadays a major cause of death through cancer throughout the world.

Prognosis of gastric cancer is generally reserved. The low survival rate is due to the delay in diagnosis, most cases being diagnosed in an advanced stage, as well as to the frequent local recurrences.

The purpose of this study was to identify clinicopathological parameters that influence the prognosis of patients operated for gastric cancer. Literature studies offer controversial data related to factors that influence prognosis in gastric cancer.

The analysis of potential prognosis factors has included in this study parameters related to the patient (sex, age) as well as parameters related to the tumor (histological type according to the *WHO* classification, degree of tumor differentiation, tumor location, stage of disease, pT, pN, and PM parameters according to the TNM classification of *AJCC/UICC*).

### ☐ Material and Methods

From the total number of 265 patients (186 men and 79 women) diagnosed clinically and histopathologically with gastric cancer in the period between 1998 and 2002, 67 patients were selected, who underwent surgery for this pathological condition in the Departments of Surgery of the Emergency County

Hospital in Timisoara. On this group, we performed a prospective study regarding the evolution and aggressiveness of gastric cancer, over a period of 5 years. Surgical interventions performed, with curative or palliative intentions, were not preceded by chemotherapy or radiotherapy. The patients or their families were contacted periodically, on the phone, or through medical letters, at intervals of 6 months, the survival being monitored over a variable period between 1 and 68 months. Patients who died in the period after the surgery, through various complications, or due to other conditions, were excluded from the study. Clinical and morphological (macroscopic and microscopic) data were gathered for each case. Gastric carcinomas were classified and interpreted according to the evaluation protocol recommended by the *American Joint Committee on Cancer (AJCC)* and *International Union Against Cancer (IUC)*.

Survival time was calculated from the month of surgery until the time of death or confirmation of survival, and survival rate was represented by the percentage of survivals at the end of the observed interval (in years and months). From the total of cases included in the prospective study, six patients died at intervals variable between 7 and 26 months, due to other medical causes, being excluded from the study.

Statistical analysis was performed using the EpiInfo 6.04, Epi 3.2.2 and OpenEpi and consisted in computing the frequency counts and percentages for the qualitative variables, the means and standard deviations for the quantitative variables. The comparison of the percentages and the means was performed using the  $\chi^2$ -square test and the unpaired *t*-test.

For statistical analysis, *p*-values of less than 0.05 were considered significant, and *p*-values of less than 0.01 were considered very significant.

### Morphological evaluation of tumor extension (pT)

In order to evaluate the maximum level of invasion, we examined transversal histological sections through the gastric wall with tumor, and perigastric tissues, dyed with Hematoxylin-Eosin, van Gieson and trichrome Gömöri stains.

In our study, gastric tumors were classified according to the TNM system recommended by the *American Joint Committee on Cancer (AJCC)* and *International Union Against Cancer (UICC)*, in which the primary tumor is assessed in the following manner:

- pT<sub>x</sub> – primitive tumor cannot be evaluated;
- pT<sub>0</sub> – primary tumor is absent;
- pT<sub>is</sub> – carcinoma *in situ*: intraepithelial tumor, with no invasion of lamina propria;
- pT<sub>1</sub> – tumor invades lamina propria or submucosa;
- pT<sub>1a</sub> – tumor invades lamina propria;
- pT<sub>1b</sub> – tumor invades submucosa;
- pT<sub>2</sub> – tumor invades muscular layer or subserosa;
- pT<sub>3</sub> – tumor penetrates serosa (visceral peritoneum), with no invasion of adjacent structures;
- pT<sub>4</sub> – tumor invades directly adjacent structures.

Cancers that infiltrate the own muscle layer and extend into the gastro-colic or the gastro-hepatic

ligaments, without perforating the visceral peritoneum which covers these structures, are classified as pT2 tumors. Tumors, which perforate the visceral peritoneum covering the gastric ligaments or the epiploon are listed in the T3 category. Structures adjacent to the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal glands, kidneys, small intestine, and retroperitoneum.

### Morphological evaluation of lymphonodular metastases (pN)

Microscopic examination of resection pieces allowed identifying the lymph nodes in the perigastric adipose tissue. In some cases, lymph nodes were sent separately to the Laboratory of Pathology, by the surgeon.

For each case, we noted the number of regional lymph nodes identified and the number of lymph nodes with carcinomatous metastases. All lymph nodes were prepared histologically, regardless of their size. We examined serried sections (on average five sections/lymph node) in order to identify the possible micro-metastases.

The pN stage was quantified according to the TNM system, recommended by the *AJCC/UICC*, in which:

- pN<sub>x</sub> – lymph nodes cannot be evaluated;
- pN<sub>0</sub> – no lymph nodes metastases;
- pN<sub>1</sub> – metastases in 1–6 perigastric lymph nodes;
- pN<sub>2</sub> – metastases in 7–15 perigastric lymph nodes;
- pN<sub>3</sub> – metastases in over 15 lymph nodes.

### Evaluation of distance metastases (M)

According to the TNM staging, distance metastases are noted as follows:

- M<sub>x</sub> – distance metastases cannot be evaluated;
- M<sub>0</sub> – no distance metastases;
- M<sub>1</sub> – distance metastases present.

Involvement of intra-abdominal, hepatoduodenal, retropancreatic, mesenterial, and para-aortic lymph nodes are classified as distance metastases.

### Staging the gastric carcinomas investigated

In order to classify the gastric carcinomas studied we used the TNM staging, recommended by the *AJCC/UICC* (Table 1).

Table 1 – TNM staging of gastric cancer

TNM			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage II	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIIA	T2	N2	M0
	T3	N1	M0
Stage IIIB	T4	N0	M0
	T3	N2	M0
Stage IV	T4	N1–3	M0
	T1–3	N3	M0
	Any T	Any N	M1

## Results

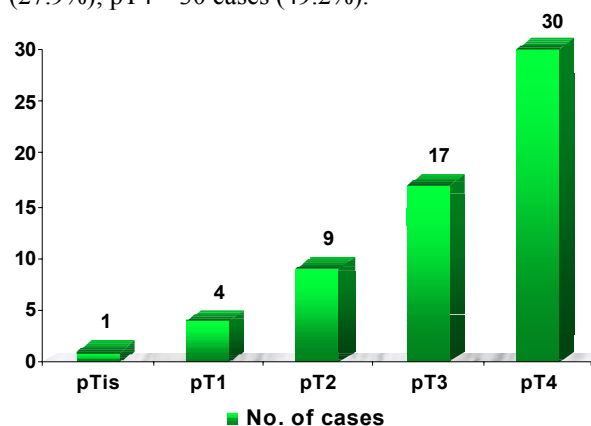
The final group consisted of 61 patients (43 men and 18 women) with ages between 30 and 80 (average age = 59.34 years).

The main clinicopathological features of cases of gastric cancer investigated are presented in Table 2.

**Table 2 – Clinicopathological features of gastric cancers studied**

Clinicopathological factors	No. of cases
Men	43
Women	18
Average age (min.–max.) [years]	59.34 (30–80)
Location	
Antrum	31
Body	15
Pangastric	10
Eso-cardia	2
Gastric stump	3
Early carcinoma	5
Advanced carcinoma	56
Borrmann	
I	5
II	20
III	22
IV	9
pTis/T1/T2/T3/T4	4/6/7/21/23
pN0/N1/N2/N3	18/16/23/4
pM0/M1	47/14

According to the maximum level of tumor invasion, we identified the following types of gastric cancers (Figure 1): pTis – one case (1.6%); pT1 – four cases (6.6%); pT2 – nine cases (14.7%); pT3 – 17 cases (27.9%); pT4 – 30 cases (49.2%).

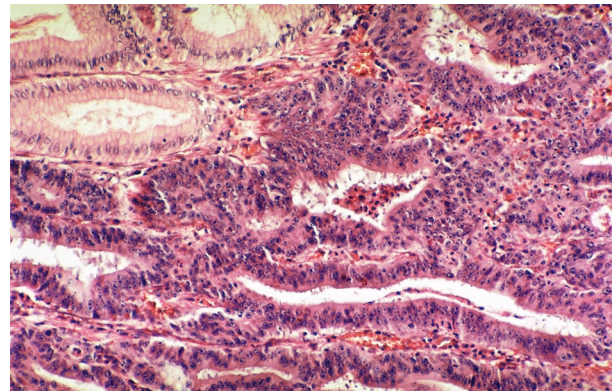


**Figure 1 – Classification of gastric cancers according to level of invasion.**

From the study group (61 cases) we identified one single case of a young woman patient, aged 37, who presented in the antral mucosa areas of epithelial dysplasia of high-degree/intraepithelial carcinoma, without invading the chorion of the mucosa (Figure 2).

In only four cases, the malignant tumor proliferation invaded the chorion of the mucosa with/without invasion of the submucosa. These tumors were listed in the pT1 category. Infiltration of the muscular layer and of the subserosa was identified in nine cases (14.7%), malignant cells dissecting muscular fibers or the conjunctive-vascular tissue of the subserosa. Rarely, tumors infiltrate as a wide front the gastric wall, accomplishing

a “pushing” pattern of infiltration. A large group of tumors (27.9%), classified as pT3, are constituted from malignant proliferation that infiltrate the gastric wall totally, perforating the visceral peritoneum, but do not penetrate into the adjacent organs. In most cases, perforation of the visceral peritoneum is accompanied by important acute inflammatory reactions at this level, with hyperemic vessels, leukocyte marginations, lymphoplasmocytic and granulocytic inflammatory infiltrate, and fibrin deposits.



**Figure 2 – Intraepithelial carcinoma (pTis). HE stain, ob. ×10.**

Most gastric cancers were included in the pT4 category (30 cases – 49.2%), due to the direct invasion of neighboring organs. We noted the direct tumor involvement of the pancreas, spleen, liver, transverse colon, gastro-colic ligament, diaphragm, main biliary ducts and the retroperitoneal space. The relationship between the pT stage and various clinicopathological factors is listed in Table 3.

**Table 3 – pT stage and clinicopathological factors in gastric cancers studied**

Clinicopathological factors	Tis (one case)	T1 (four cases)	T2 (nine cases)	T3 (17 cases)	T4 (30 cases)
Men	–	3	7	11	22
Women	1	1	2	6	8
Average age [years]	37	61.75±19.19	62.22±9.2	58.12±12.65	59.6±10.05
Antrum	1	4	6	8	12
Body	–	–	1	8	6
Pangastric	–	–	1	1	8
Eso-cardial	–	–	–	–	2
Gastric stump	–	–	1	–	2
TA (tubular adenocarcinoma)	–	4	5	7	11
PA (papillary adenocarcinoma)	–	–	2	1	2
MA (mucinous adenocarcinoma)	–	–	2	1	5
SRCC (“signet-ring” cell carcinoma)	–	–	–	8	9
AC (anaplastic carcinoma)	–	–	–	–	3
G1	1	1	–	–	–
G2	–	2	5	5	8
G3	–	1	4	12	22
Average survival [months]	60	56.5	38	13.9	6.6
Survival at 5 years	1 (100%)	3 (75%)	4 (44.4%)	1 (5.9%)	1 (3.3%)

We noted the large number of gastric carcinomas in the T3 and T4 stages, in men as well as women. Though the average ages of patients in various pT stages are nearly similar, we remarked a slight decrease in the average age in infiltrative carcinomas. All pT1 tumors developed at the antrum. For T3 and T4 carcinomas, we noted an increase in the incidence of body and pangastric carcinomas. Eso-cardial and stump locations of the tumor prove to be aggressive, infiltrating all the layers of the wall and neighboring structures.

Tubular, papillary and mucinous adenocarcinoma presents a diffuse distribution for all pT categories. Carcinomas with “signet-ring” cells and undifferentiated carcinomas are aggressive forms, associated with invasions of the visceral peritoneum and neighboring organs.

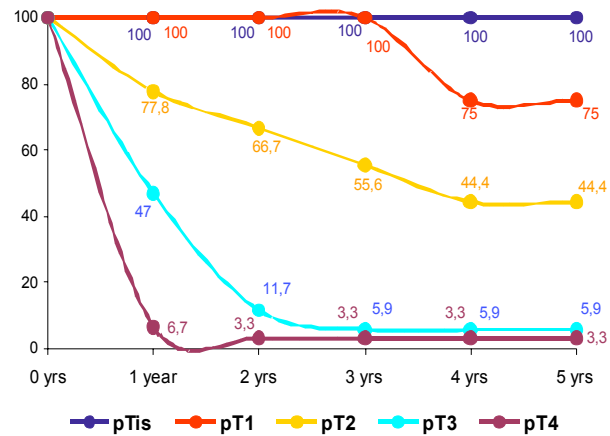
We remarked a significant correlation between the degree of tumor differentiation and the level of invasion. Well-differentiated carcinomas G1 proved to be tumors with low degree of invasion, infiltrating the chorion of the mucosa and submucosa. Most poorly differentiated tumors are deeply infiltrative tumors. 70.6% of T3 carcinomas and 73.3% of T4 carcinomas were listed histologically in the group of poorly differentiated or undifferentiated malignant proliferations.

Survival at 5 years according to the pT stage demonstrated the significant increase in the number of deaths with the stage of the tumor. We noted a survival rate of 100% in the Tis stage, 75% in the T1 stage, 44.4% in the T2 stage, 5.9% in the pT3 stage, and only 3.3% in the T4 stage.

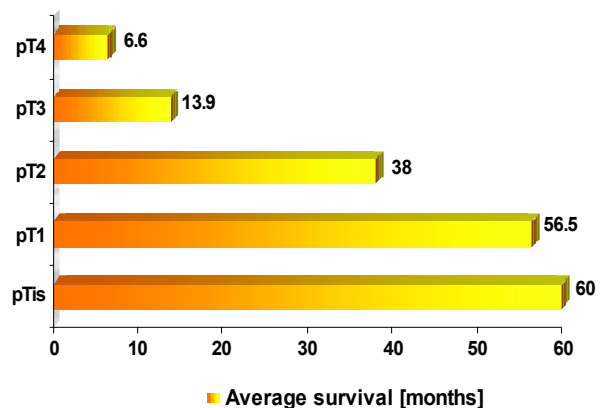
The diagram of survival according to pT stage demonstrates the linear evolution in Tis stage, with 100% survival at 5 years. pT1 carcinomas presented a slight decrease in survival over 4 years from surgery. In T3 and T4 stages, survival curves are rapidly descending, with survival rates of 47% and 6.7% at one year, 11.7% and 3.3% at two years, 5.9% and 3.3% at three years, the values being constant thereafter (Figure 3).

We noted the significant correlation between the pT stage and the average survival of patients, calculated in months ( $p < 0.001$ ). Thus, the woman patient with gastric tumor in the pTis survives at the end of the 5 years. For the pT1 carcinomas, we calculated an average survival rate of 56.5 months, close to the 60 months survival of the patient in the pTis stage. Carcinomas in advanced stages have associated the following average rates: 38 months for pT2 carcinomas, 13.9 months for pT3 carcinomas, and only 6.6 months for pT4 carcinomas (Figure 4).

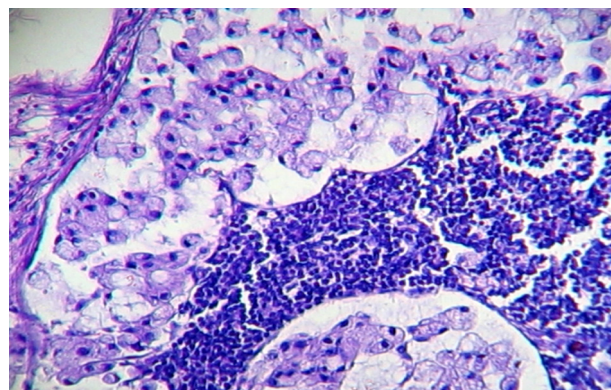
In our study, we identified 43 gastric carcinomas with metastases in regional lymph nodes, representing 70.5% of the cases. Histopathological examination showed in 36 cases massive metastases (Figure 5), with replacement of the lymph node structure by malignant cells. In seven cases, we observed the presence of small groups of malignant cells or adenocarcinomatous pseudo-glands, arranged predominantly in the cortical layer of the lymph nodes, or the presence of malignant cells in subcapsular lymphatic vessels, representing micro-metastases in regional lymph nodes.



**Figure 3 – Survival at 5 years according to the pT stage.**



**Figure 4 – Survival of patients and the pT stages.**



**Figure 5 – Massive lymph node metastasis of a carcinoma with “signet-ring” cells. HE stain, ob.  $\times 20$ .**

According to the number of lymph nodes involved, gastric carcinomas in the study group were classified in the following categories: pN0 – 18 cases (29.5%); pN1 – 16 cases (26.2%); pN2 – 23 cases (37.7%); pN3 – four cases (6.6%) (Figure 6).

Out of the total of carcinomas investigated, 29.5% did not present lymph nodes metastases. We identified 16 cases with metastases in 1–6 lymph nodes, listed in the pT1 category (26.2%). Most cases presented



carcinomatous involvements in 7–15 lymph nodes, representing pN2 tumors (37.7%). Only in four cases (6.6%), histopathological exam showed the presence of malignant structures in over 15 lymph nodes. Correlation between pN stage, clinicopathological factors, and survival of patients is presented in Table 4.

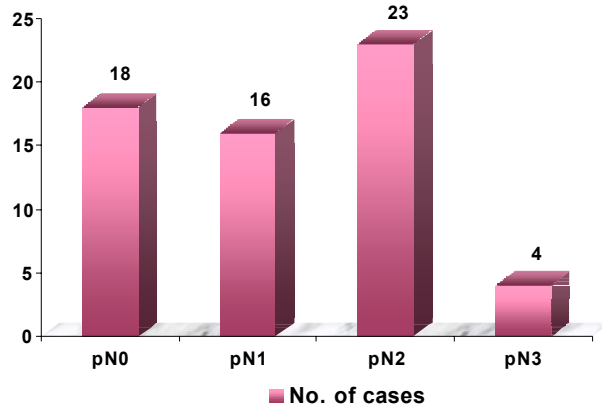


Figure 6 – Classification of gastric carcinomas according to the pN stage.

Table 4 – Relationship between pN stage and clinicopathological factors

Clinicopathological factors	pN0	pN1	pN2	pN3
Men	15	9	16	3
Women	3	7	7	1
Average age [years]	56.44±13.54	65.38±9.46	57.61±9.99	58.25±12.04
Antrum	11	10	9	1
Body	3	3	8	1
Pangastric	2	3	3	2
Eso-cardial	–	–	2	–
Gastric stump	2	–	1	–
TA (tubular adenocarcinoma)	11	9	7	1
PA (papillary adenocarcinoma)	–	–	5	–
MA (mucinous adenocarcinoma)	3	3	2	–
SRCC ("signet-ring" cell carcinoma)	4	2	8	3
AC (anaplastic carcinoma)	–	2	1	–
G1	2	–	–	–
G2	7	6	7	–
G3	9	10	16	4
Average survival [months]	30.9	19.3	8.2	2
Survival at 5 years	5 (27.8%)	4 (25%)	1 (4.3%)	0 (0%)

We observed the presence of lymph node metastases more frequently in women (83.3%) than in men (65.1%), however without reaching the threshold of statistical significance ( $p=0.470907$ ). Though the average ages of patients are relatively close, one can remark a slight increase in the average age in advanced pN stages. Also, there is an important difference between the average age of patients in the pN0 stage (56.4 years) and the average age of patients in the pN1 stage (65.4 years).

In the pN0 stage, tumors located at the antrum predominate. Cancers identified at the body or pangastric

associate more frequently lymph nodes metastases. Also, eso-cardial locations and cancers developed on gastric stump seem to be particularly aggressive in most cases, with metastases in 7–15 lymph nodes (pT2).

Amongst histological forms, we noticed the large frequency of lymph node metastases in papillary adenocarcinomas, "signet-ring" cell carcinomas and undifferentiated carcinomas.

The degree of tumor differentiation is correlated significantly with the pN stage. G1 carcinomas do not associate with lymph node metastases. In pN2 and pN3 stages, G3 carcinomas predominate neatly.

Survival at 5 years presented various values according to the pN stage, decreasing proportionally with the increase of the pN stage. We noted survivals of 27.8% in the pN0 stage, 25% in the pN1 stage, only 4.3% in the pN2 stage, and 0% in the pN3 stage. It appears that the presence of lymph node metastases in 1–6 of the perigastric lymph nodes does not alter significantly survival at 5 years, although the number of deaths is much larger at one year from surgical intervention for the pN1 tumors. Metastases in over seven lymph nodes are associated with drastic decrease of the average survival. Patients with pN3 tumors died during the first year after surgery (Figure 7).

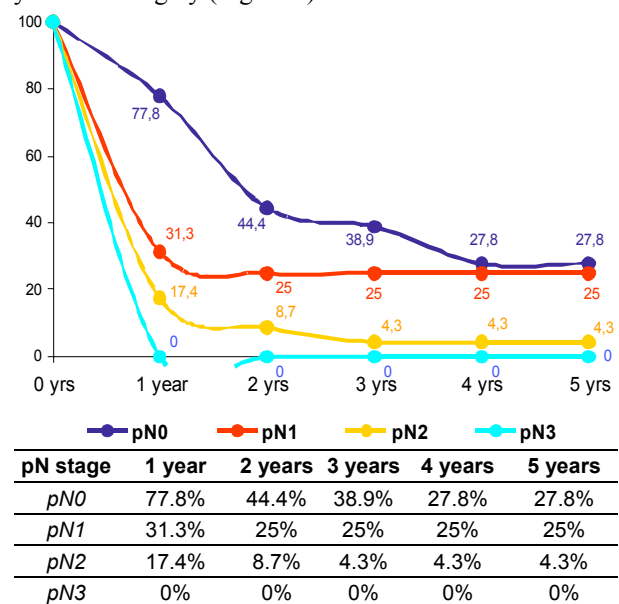


Figure 7 – Survival at 5 years and the pN stage.

Calculation of the average survival rate in months showed the following values: 30.9 months for pN0 tumors, 19.3 months for pN1 tumors, 8.2 months for pN2 tumors, and 2 months for pN3 tumors. Presence of lymph node metastases determines a significant decrease in survival rate ( $p=0.001609$ ) (Figure 8).

Clinico-paraclinical and imagistic evaluations allowed identification of distance synchronous metastases in 14 gastric carcinomas studied (23% of the cases studied). In all cases, carcinomatous metastases were confirmed histopathologically.

From gastric carcinomas studied, we identified nine cases with hepatic metastases (Figure 9) and five cases with distance peritoneal disseminations.

According to the presence of distance metastases, tumors examined classify as follows: pM0 – 47 cases

(77%); pM1 – 14 cases (23%). The relationship between the M stage, the clinicopathological factors, and survival is presented in Table 5.

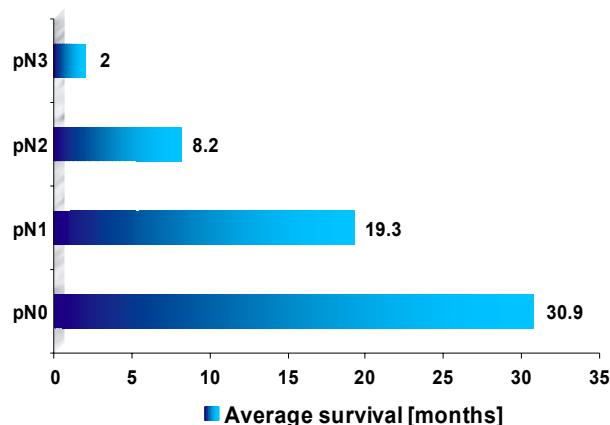


Figure 8 – Survival of patients and the pN stage.

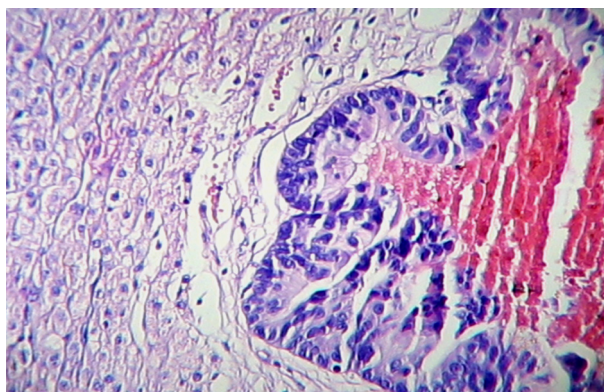


Figure 9 – Hepatic metastasis of a gastric adenocarcinoma. HE stain, ob.  $\times 20$ .

Table 5 – pM stage and clinicopathological factors

Clinicopathological factors	pM0 (47 cases)	pM1 (14 cases)
Men	34	9
Women	13	5
Average age [years]	58.14 $\pm$ 11.96	63.36 $\pm$ 8.85
Antrum	25	6
Body	11	4
Pangastric	8	2
Eso-cardial	1	1
Gastric stump	2	1
TA (tubular adenocarcinoma)	24	4
PA (papillary adenocarcinoma)	3	2
MA (mucinous adenocarcinoma)	8	–
SRCC ("signet-ring" cell carcinoma)	11	6
AC (anaplastic carcinoma)	1	2
G1	2	–
G2	17	3
G3	28	11
Average survival [months]	21.40 $\pm$ 22.59	4.07 $\pm$ 4.34
Survival at 5 years	10 (21.3%)	0 (0%)

We noted no correlation between the pM stage and patients' sex, but the average age of patients with metastases (63.36 $\pm$ 8.85 years) is greater than that of

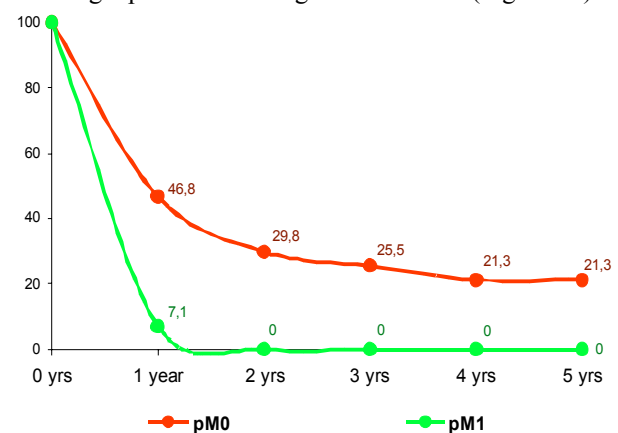
patients with no metastases (58.14 $\pm$ 11.96 years), but with no statistical significance ( $p=0.136129$ ).

pM0 cancers were located at the antrum in 53.2%, at the gastric body in 23.4%, pangastric in 17%, esocardial in 2.1%, and gastric stump in 4.3% of cases. pM1 stage is associated with antral tumors in 42.8%, gastric body tumors in 28.7%, pangastric in 14.3%, esocardial in 7.1%, and tumors of gastric stump in 7.1% of cases.

From histological forms most frequently encountered in pM0 cancers, we should note: tubular adenocarcinoma (85.7%), mucinous adenocarcinoma (100%), and "signet-ring" cell carcinoma (64.7%). 33% of anaplastic carcinomas are without distance metastases at the time of diagnosis. Aggressive histological forms are frequently accompanied by distance metastases: "signet-ring" cell carcinoma (35.3%) and anaplastic carcinoma (66.7%).

The two cases of well-differentiated carcinomas (G1) are not accompanied by synchronous metastases. The degree of tumor differentiation is correlated with the pM stage, 78.6% of pM1 carcinomas being poorly differentiated.

Survival at 5 years demonstrated the unfavorable evolution of patients with distance metastases, all of them deceasing during the followed interval. In pM0 gastric carcinomas, survival is of 21.3% at 5 years. From 14 patients with synchronous distance metastases, 13 patients died in less than one year after surgery, one single patient surviving for 15 months (Figure 10).



pM stage	1 year	2 years	3 years	4 years	5 years
pM0	46.8%	29.8%	25.5%	21.3%	21.3%
pM1	7.10%	0%	0%	0%	0%

Figure 10 – Survival at 5 years according to the pM stage.

Calculating the average survival in months showed the significant difference between the average survival of 21.4 months of patients with pM0 tumors and the average survival of 4.1 months from the pM1 tumors ( $p=0.030036$ ) (Figure 11).

Classification of gastric carcinomas in the study group is presented in Table 6.

We identified one single case listed in the 0 stage, three cases in the IA stage, five cases in the IB stage, seven cases in the II stage, 11 cases in the IIIA stage, eight cases in the IIIB stage, and 26 cases in the IV stage. From the total of carcinomas, stage IV consisted

of the greatest number of tumors, representing 42.6%. We generally remarked the increase of the number of cases in advanced stages.

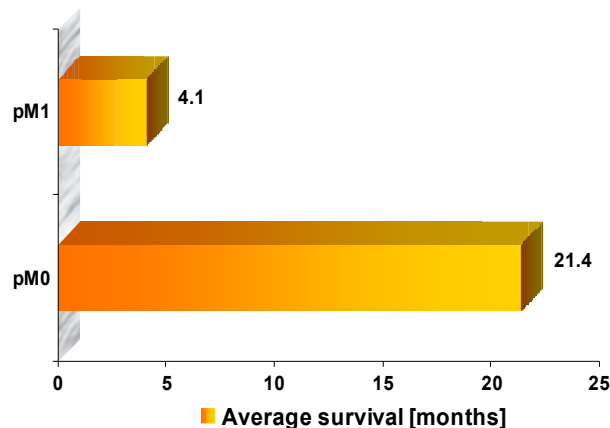


Figure 11 – Survival of patients and the pM stage.

Table 6 – Staging of gastric carcinomas in the study group

TNM stage	No. of cases	%
0	1	1.6
IA	3	4.9
IB	5	8.2
II	7	11.5
IIIA	11	18.1
IIIB	8	13.1
IV	26	42.6

Correlations between the TNM stage and various clinicopathological factors are listed in Table 7.

We noted an important increase in the number of cases in women of advanced ages (57.1% in stage IIIA, 50% in stage IIIB and 27% in stage IV). Our results showed no correlation between the average age of patients and the TNM stage.

Table 7 – Correlation between TNM stage and clinicopathological factors

Clinicopathological factors	0 n=1	IA n=3	IB n=5	II n=7	IIIA n=11	IIIB n=8	IV n=26
Men	–	2	5	6	7	4	19
Women	1	1	–	1	4	4	7
Average age [years]	37±0	61±23.43	59.4±3.51	52.57±16.10	65.09±6.79	58.88±11.18	59.54±10.32
Antrum	1	3	4	5	3	5	10
Body	–	–	–	2	4	2	7
Pangastric	–	–	1	–	2	1	6
Eso-cardial	–	–	–	–	–	–	2
Gastric stump	–	–	–	–	2	–	1
TA (tubular adenocarcinoma)	1	3	4	3	6	2	9
PA (papillary adenocarcinoma)	–	–	–	–	1	1	3
MA (mucinous adenocarcinoma)	–	–	1	1	3	1	2
SRCC ("signet-ring" cell carcinoma)	–	–	–	3	1	3	10
AC (anaplastic carcinoma)	–	–	–	–	–	1	2
G1	1	1	–	–	–	–	–
G2	–	1	4	–	7	3	5
G3	–	1	1	7	4	5	21
Average survival [months]	60±0	55.33±8.08	51.2±12.38	30.71±20.16	12.91±15.86	9.63±8.53	5.65±11.65
Survival at 5 years	100%	66.6%	60%	28.6%	9.1%	0%	3.8%

Antral location of tumors is frequently encountered in all TNM stages, but it seems to be predominant in incipient stages (0, IA, IB, and II). Tumors developed in the proximal region of the stomach, on the gastric stump and pangastric, are detected in advanced stages.

The tubular type of adenocarcinoma is predominant in stages 0 (100%), IA (100%), and IB (80%). Papillary adenocarcinoma appears in our study as an aggressive histological form, encountered in the IIIA, IIIB, and especially IV type tumors. "Signet-ring" cell carcinoma and anaplastic carcinoma predominate in stages IIIB and IV.

Well-differentiated tumors (G1) are observed in stages 0 and IA. Medium differentiated tumors presented a diffuse distribution in all TNM stages. The exception is represented by stage II, constructed only of G3 carcinomas. In stages IIIB and IV, we identified poorly differentiated tumors (G3) in proportions of 62.5% and 80.8%.

Evaluating the survival rate at 5 years showed the decrease in the survival rate with the increase of tumor

stage (Figure 12). In stage 0, the patient, aged 37, survives at the end of the interval monitored. In stage IA, three patients were included, from which one died after 3 years from surgery, survival rate being of 66.6%. Stage IB showed a slightly more decreased survival rate, of 60%. Stage II marked the drastic decrease of survival rates (28.6%). A possible explanation would be that this case comprised only poorly differentiated carcinomas (G3). Out of 11 patients included in the IIIA stage, only one survived at 5 years, the average value being of 9.1%. Stage IIIB meant the death of all patients included (eight patients). In stage IV we noted the death of 25 patients (23 patients in the first year and one patient in the second year of monitoring), and the survival of just one patient at 5 years (survival rate of 3.8%).

According to the TNM stage we obtained the following values of survival, calculated in months: stage 0 – 60 months; stage IA – 55.3 months; stage IB – 51.2 months; stage II – 30.7 months; stage IIIA – 12.9 months; stage IIIB – 9.6 months; stage IV –

5.6 months. In the first three stages, the average survival rates are relatively similar. However, we noted two significant decreases in the survival of patients with gastric cancers: from stage IB in stage II, and from stage II in stage IIIA. One can observe a significant decrease in the survival rate of patients, calculated in months, proportionally with the advancement of the TNM stage ( $p < 0.001$ ) (Figure 13).

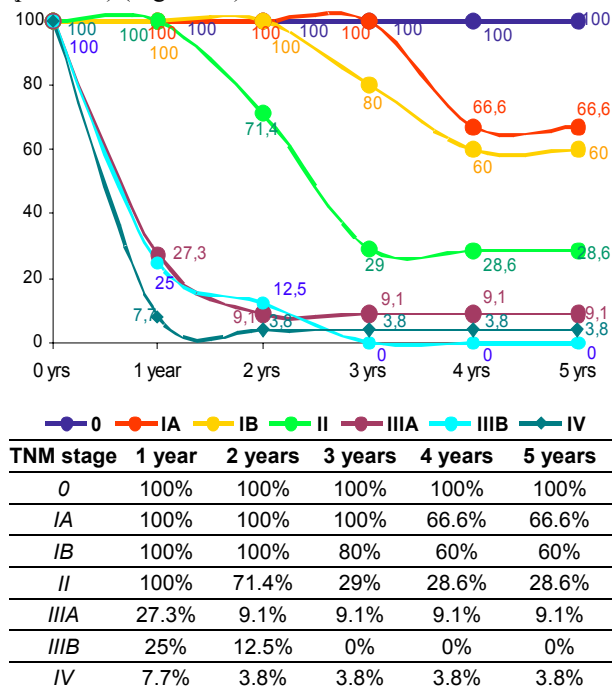


Figure 12 – Survival at 5 years and the TNM stage.

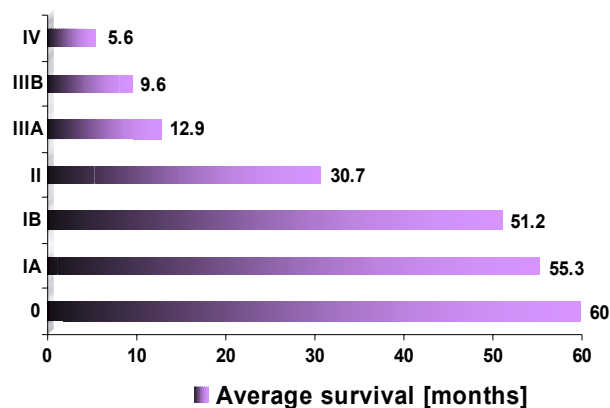


Figure 13 – Average survival according to the TNM stage.

## Discussion

The Japanese classification of gastric cancer (JC) [1, 2] takes into consideration the lymph nodes stations involved, enclosed in the distinct anatomical areas of the regional lymph nodes. This classification is based upon studying the lymph flow and surgical results. Unlike this classification, *American Joint Committee on Cancer* (AJCC) – “Manual of staging in cancers”, and the *International Union Against Cancer* (UICC) – “TNM staging of malignant tumors” [3] adopted a classification system based on the number of metastatic lymph nodes, proven to be an independent prognostic factor in gastric cancer [4–6].

Kunisaki C *et al.* [7] evaluated comparatively the two systems of classification, applying these systems simultaneously on a group of 1244 patients in which curative gastrectomy was practiced, associated with lymph node dissection. Heterogeneity of N1 and especially N2 lymph node categories of JC was observed in this study. Concerning the surgical results, significant differences were noted concerning TNM staging of patients in each category of JC. On the other hand, there were no significant differences of surgical results concerning JC listing of each TNM category. These results demonstrate that the subgroup defined through JC is composed of a heterogeneous batch of patients, while the TNM categories are constituted of a homogenous group of patients. These aspects prove the superiority of the TNM classification system [8–10]. The advantage of TNM staging consists of classifying according to the number of lymph nodes metastasized, not taking into consideration their location. Moreover, this classification has the disadvantage of listing the para-aortic lymph nodes as distance metastases (M1), not as regional lymph nodes. Surgical results in M1 patients were heterogeneous, and the postoperative prognosis for patients presenting 1–6 metastatic lymph nodes was relatively good, suggesting that listing by TNM of para-aortic lymph nodes as distance metastases is not justified. For these reasons, the authors suggest the elaboration a new classification resulted through joining JC and TNM, based on the total number of metastatic lymph nodes and including the para-aortic lymph nodes in the group of regional lymph nodes [7].

In our study, gastric tumors were classified according to the TNM system recommended by the *American Joint Committee on Cancer* (AJCC) and the *International Union Against Cancer* (UICC).

From the study group (61 cases) we identified one single case (1.6%) pertaining to a young woman patient, 37-year-old, who presented areas of epithelial dysplasia of a high level/intraepithelial carcinoma at the level of the antral mucosa. In only four cases (6.6%), malignant tumor proliferation invaded the chorion of the mucosa with/without invasion of the submucosa, the tumors being listed in the pT1 category. Infiltration of the muscular layer and of the subserosa (pT2 stage) was identified in nine cases (14.7%). A large group of tumors (27.9%), classified as pT3, consisted of malignant proliferations which infiltrate the gastric wall totally, with perforation of the visceral peritoneum, without penetrating into the adjacent organs. Most gastric cancers were included in the pT4 category – encountered in approximately half of patients – due to the direct invasion of neighboring organs, with direct involvement of the pancreas, spleen, liver, transverse colon, gastrocolic ligament, diaphragm, main biliary ducts, and of the retroperitoneal space.

Numerous Western studies show that approximately 2/3 of patients with GC are diagnosed in a local advanced stage (T3 and T4) [11–13]. In the studied group, we noted the large number of gastric carcinomas in T3 and T4 stages, in men as well as in women, summing 77.1% of cases. Even though the average ages of patients in various pT stages are relatively close, we noted a slight



decrease in the average age in deeply infiltrative carcinomas, which could correspond to the poorly differentiated histological types, extremely aggressive, which are predominant in younger ages. In the studied group, all pT1 tumors developed at the level of the antrum, while for T3 and T4 carcinomas we noted an increase of carcinomas with location at the level of the gastric body, and pangastric ones. Tumor cardiac locations and gastric stump locations prove to be aggressive, infiltrating all layers of the wall and neighboring structures. "Signet-ring" cell carcinomas and undifferentiated carcinomas are aggressive forms, associated with invasions of the visceral peritoneum and neighboring organs.

We noted a significant correlation between the degree of tumor differentiation and the level of invasion. Well-differentiated G1 carcinomas have proved to be tumors with a low degree of invasion (mucosa and submucosa), while most poorly differentiated tumors were associated with a deep invasion of the gastric wall. 70.6% of T3 carcinomas and 73.3% of T4 carcinomas were listed histologically in the group of poorly differentiated or undifferentiated malignant proliferations.

Studies showed that the depth of invasion of the wall represents one of the main prognosis factors in gastric cancer [14–18]. A study performed by Dicken BJ *et al.* [14], analyzing clinicopathological aspects and survival on 577 operated patients with gastric cancer, did not show statistically significant differences regarding survival at 5 years between tumors in T1 stage, respectively T2 stage ( $64 \pm 18\%$  vs.  $53 \pm 7\%$ ). T3 tumors were associated with a 5-year survival significantly lower compared with tumors in T1 and T2 stages ( $11 \pm 5\%$ ). A study performed in Korea proved that invasion of the serosa represents an independent prognosis factor [19].

In our study also, 5-year survival according to the pT stage proved the significant increase in the number of deaths, in parallel with increasing of the depth of tumor invasion. We noted a survival rate of 100% in the Tis stage, 75% in the T1 stage, 44.4% in the T2 stage, 5.9% in the pT stage, and only 3.3% in the T4 stage.

The depth of tumor invasion at the level of the gastric wall can be considered as a significant factor, being the determinant of other prognosis indicators. Lesions in the T1 and T2 stages are associated in a more reduced percentage with the appearance of lymph node metastases, while tumors in T3 and T4 stages generally present lymph node invasion. Lymph node metastases (identified in numerous studies as an independent prognosis factor) represent a reflection of the depth of invasion and of the advanced stage [20–22]. Gorbunov EA *et al.* proved a survival rate at 5 years of 41.2% in patients without lymph node metastases, while patients with lymph node metastases presented a much more reduced 5-year survival rate, of only 13.4% [20].

From the total of carcinomas investigated in our study, 29.5% did not present lymph node metastases. We identified 16 cases with metastases in 1–6 lymph nodes, listed in the pN1 category (26.2%). Most cases presented carcinomatous involvements in 7–15 lymph nodes, representing pN2 tumors (37.7%), and only in

four cases (6.6%) histopathological exam showed the presence of metastases in over 15 lymph nodes pN3.

We observed the presence of lymph node metastases more frequently in women and a slight increase in the average age in advanced pN stages. Cancers identified at the level of the body, or pangastric, associate more frequently lymph node metastases. Also, cardiac locations and cancers developed on the gastric stump seem to be particularly aggressive, being frequently associated with metastases in 7–15 lymph nodes (pN2). From the histological forms, we observed the great frequency of lymph node metastases in papillary adenocarcinomas, carcinomas with "signet-ring" cells, and undifferentiated carcinomas.

The degree of tumor differentiation is correlated significantly with the pN stage. G1 carcinomas are not accompanied by lymph node metastases. In pN2 and pN3 stages, G3 carcinomas are neatly predominant.

Survival at 5 years presented different values according to the pN stage, decreasing as the pN stage was increasing. We noted survivals of 27.8% in the pN0 stage, 25% in the pN1 stage, only 4.3% in the pN2 stage, and 0% in the pN3 stage. All patients with pN3 tumors died during the first year after surgery.

Rigueiro Veloso MT *et al.* [23] analyzed on a group of 2334 patients the forms of presentation and the prognosis of patients with advanced gastric cancer at the time of diagnosis. Distance metastases were present in 585 (25.1%) patients at the time of diagnosis. The liver (346 cases, 14.8%) and peritoneum (161 cases, 6.9%) represented most frequent locations. Concerning the numbers of the organs involved simultaneously in a patient, we concluded that the metastases were present most frequently in a single organ. Exclusive hepatic involvement was moved to 213 (9.1%) cases, peritoneal involvement in 70 (3.3%), and that of other organs was detected in 181 (7.8%) patients, the liver–peritoneum association being the most frequent (40 patients, 1.7%). The average duration of survival was significantly more reduced in patients presenting distance metastases at the time of diagnosis, in comparison with those in which no secondary determination was detected (3.4 vs. 14.6 months).

Fourteen patients from our group (23% of neoplasms studied) presented distance metastases, from which nine cases with hepatic metastases and five cases distance peritoneal disseminations. Comparing the clinicopathological characteristics of patients with distance metastases vs. patients without metastases, we noted that the average age of patients with metastases (63.4 years) is significantly greater in comparison with the average age of patients without metastases (58.1 years). Concerning location, pM1 stage is associated with antral tumors in 42.8%, gastric body tumors in 28.7%, pangastric tumors in 14.3%, eso-cardial in 7.1%, and tumors at the level of the gastric stump in 7.1% of cases. Histologically aggressive forms are frequently associated with distance metastases: carcinoma with "signet-ring" cells (35.3%) and anaplastic carcinomas (66.7%). The degree of tumor differentiation is correlated with the pM stage, 78.6% of pM1 carcinomas being poorly differentiated.

Survival at 5 years demonstrated the unfavorable evolution of patients with distance metastases, in accordance with literature data [24–29]. In pM0 gastric carcinomas, survival is of 21.3% at 5 years, while most patients with metastases died under one year from surgical intervention, survival not exceeding two years from surgery. Calculation of the average survival in years showed the significant difference between survival of patients with pM0 tumors and those with pM1 tumors (21.4 months vs. 4.1 months).

The study performed by Zhang XF *et al.* [30] on 1498 patients with surgically resected gastric neoplasm showed rates of survival at 5 years according to the TNM stage, as follows: 91.1% for stage IA; 86.7% for stage IB; 51.1% for stage II; 34.5% for stage IIIA; 29.1% for stage IIIB; and only 5.9% for stage IV. As can be seen, survival at 5 years of patients reduced as the TNM stage advanced.

We identified in our study one single case listed in the 0 stage (1.6%), three cases in the IA stage (4.9%), five cases in the IB stage (8.2%), seven cases in the II stage (11.5%), 11 cases in the IIIA stage (18.1%), eight cases in the IIIB stage (13.1%) and 26 cases in the IV stage (42.6%). It is to be remarked that from the total of carcinomas, stage IV was constituted of the greatest number of tumors, representing 42.6%.

We noted an important increase in the number of cases in women in advanced stages. Our results did not show a relationship between the average age of patients and the TNM stage. As mentioned before, tumors developed in the proximal region of the stomach, on the gastric stump and pangastric, are detected in advanced stages. The tubular type of adenocarcinoma is predominant in stages 0 (100%), IA (100%), and IB (80%). Carcinoma with “signet-ring” cells and anaplastic carcinoma are predominant in IIIB and IV stages. In stages IIIB and IV, we identified poorly differentiated tumors (G3) in proportions of 62.5% and 80.8%.

Evaluation of survival rate at 5 years showed the decrease of survival with the increase in stage, as follows: stage 0 – 100%; stage IA – 66.6%; stage IB – 60%; stage II – which marked a drastic decrease in survival – 28.6%; stage IIIA – 9.1%; stage IIIB – 0%; stage IV – 3.8%. According to the TNM stage, we obtained the following values of survival, calculated in months: stage 0 – 60 months; stage IA – 55.3 months; stage IB – 51.2 months; stage II – 30.7 months; stage IIIA – 12.9 months; stage IIIB – 9.6 months; stage IV – 5.6 months. In the first three stages, survival rates are relatively similar. We remarked however two significant decreases in the survival of patients with gastric cancers: from stage IB in stage II, and from stage II in stage IIIA.

## ☒ Conclusions

In the studied group, we noted a great number of gastric carcinomas diagnosed in stages T3 and T4, in men as well as women, summing up to 77.1% of cases. Cardial tumor locations and gastric stump locations prove to be aggressive, infiltrating all layers of gastric wall and adjacent structures, frequently with

lymph node metastases (pN2) and distance metastases, being diagnosed in advanced stages. The aggressive phenotype characterizes carcinomas with “signet-ring” cells and those undifferentiated.

70.5% of gastric neoplasms presented lymph node metastases. Most cases presented carcinomatous involvements in 7–15 lymph nodes, representing pN2 tumors (37.7%).

Twenty-three percent of neoplasms studied presented distance metastases at the time of diagnosis. The average age of patients with metastases (63.4 years) was significantly higher in comparison with the average age of patients without metastases (58.1 years).

It is to be noted that from the total of carcinomas, stage IV was constituted of the largest number of tumors, representing 42.6% of cases. “Signet-ring” cell carcinoma and anaplastic carcinoma are predominant in stages IIIB and IV. In these stages, we identified poorly differentiated tumors (G3) in proportions of 62.5% and 80.8%, respectively.

We noted a significant correlation between the degree of tumor differentiation and the level of invasion, as well as the presence of distance and lymph node metastases.

Survival at 5 years of patients included in the study was correlated significantly with the level of tumor invasion, the presence of lymph node and distance metastases, and the TNM stage.

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