ORIGINAL PAPER

Gastric cancer – histopathological correlations between tumor and non-tumor gastric mucosa changes

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Abstract

Gastric cancer is a widely geographically distributed malignancy with high prevalence, therefore being a serious health problem that needs standardized methods for early diagnosis and treatment. The aim of the study was to evaluate the correlation of some epidemiological and clinical data with the histological features. The study group was made up of 66 patients that underwent surgical removal of the gastric neoplasm, and the pathological exam showed the morphological features of the tumor, as well as the ones of the unaffected mucosal tissue. Topographically, the highest incidence of the tumor was registered in the gastric antrum, but in recent years, an increased incidence of the superior gastric pole localization was recorded. The macroscopic aspects reveal that the ulcerated type 2 Borrmann is the most frequent, and alongside type 3 Borrmann, the ulcer-infiltrative type represents most of the gastric antrum cancers. The analysis of the tumor invasion showed that most carcinomas underwent surgery when the tumor invaded the serosa (pT3) or even the perigastric tissues (pT4). In our research, we chose Goseki's microscopic classification because of its best coverage of the histological heterogeneity of the gastric carcinomas, providing information about the percentage of the cellular and secretory differentiation with direct impact on the invasion of the tumor. In more than 70% of the cases, the patients showed lesions of severe chronic atrophic gastritis of the non-tumor mucosa. Lately, the incidence of *Helicobacter pylori* has been 5.5%, lower than indicated by mainstream literature. We observed that the incidence of type 3 incomplete intestinal metaplasia, as the most commonly involved factor in the etiopathogenesis of gastric neoplasms, was encountered in 36.3% of the cases, this percentage rising proportionally with age and being frequently associated with antrum tumors. In conclusion, the permanent analysis of the relation between epidemiological data and some histological features might be relevant for the characterization of the tumoral process or the non-tumor gastric mucosa, leading to an evaluation of the prognosis.

Keywords: gastric cancer, pathological correlation tumor, gastric mucosa, Goseki classification, prognosis.

⧉ Introduction

Gastric cancer is one of the most severe widely spread malignancies, with a multifactorial etiology and a clinical and morphological multiform profile that coupled with a late diagnosis results in low life expectancy. Although, worldwidely, the gastric neoplasm displays a decreasing tendency, it still remains the fourth most frequent cancer and the second cause of death [1–3]. The reduction of the mortality rate in gastric cancer is the result of the application of medical strategies for the early detection of incipient tumor lesions or of premalignant gastric lesions [4–6].

Many studies showed that the greatest risk factor for non-cardiac gastric cancer is represented by the *Helicobacter pylori* infection [7–10]. The prevalence of the *H. pylori* infection is highly variable across countries, and even across regions in a country, raising to 70–90% in developing countries [11, 12].

H. pylori infection occurs most commonly in childhood, has an intra-family transmission and, in most cases, it persists if not eliminated by treatment. As such, most researchers believe that according to the *Kyoto Global Consensus Report*, it is recommended that all infected patients should be treated, regardless of age, to prevent the development of gastric cancer [13, 14].

The clinical and morphological multiform profile is influenced by the geographic distribution, lifestyle, genetic profile, localization of the gastric tumor – there is a more aggressive phenotype for the superior pole tumors with morphological heterogeneity of the same tumor or for different tumors, and also for diverse clinically non-specific tumors [15, 16].

Currently, there are numerous classifications of the gastric neoplasm, each trying to establish o correlation between the clinical manifestations, histological features, evolution and etiopathogenesis of the tumor.

Aim

The present paper aims to analyze the possible relation between the epidemiological factors and some histopathological (HP) aspects that we consider relevant for either the characterization of the tumor or the unaffected gastric mucosa, all of them being likely to impact on the prognosis of the gastric cancer.

⊡ Patients, Materials and Methods

The research was conducted on a group of 66 gastric cancer patients hospitalized and operated within the Surgery Unit of the Railways Clinical Hospital, Craiova, Romania, between 2010–2015.

All the patients underwent excision surgery, regardless of the progression stage, preserving only cases of malignant epithelial tumors of the stomach.

In the target group, we excluded the carcinomas developed at the level of the esogastric junction and those of the gastric abutment. The gastrectomy specimens referred to the pathological anatomy laboratory were opened along the great curve.

After placed on a wooden plate, the pieces were fixed in a 10% neutral buffered formalin solution for about 24 hours.

After fixation, the specimens were oriented, obtaining multiple blocks.

Fragments of mucosa were collected from 1–2 cm and 4–5 cm away from the tumor to highlight the peritumoral lesions. Between 4–8 fragments were also collected from the passage area between the non-tumor mucosa and the tumor, as well as a variable number of fragments from the tumor, which would indicate the histological type, the depth of the invasion and other associated lesions.

After impregnation with paraffin, the blocks were sectioned into 5 μm-thick sections.

The sections were stained by various methods to highlight HP changes and detect *H. pylori*.

In most cases, the standard Hematoxylin–Eosin (HE) staining allows for the specification of the diagnosis, being capable of highlighting the histological traits of the lesions, the changes of the tissue architecture and the nucleo-cytoplasmic details.

On the HE staining, *H. pylori* with lower sensitivity can be highlighted in situations where the bacteria are very numerous in the mucus on the surface of the fovea.

Giemsa staining showed to be extremely useful for:
▪ highlighting the presence of *H. pylori* in the foveolar mucus, especially when bacterial colonization is reduced;
▪ featuring the morphological characteristics of the nuclei, especially the contour of the nuclear membrane, the chromatin densities and the appreciation of the characters of the nucleoli;
▪ the morphological assessment of cellular elements belonging to the intra- and peritumoral inflammatory reaction.

The Gömöri trichrome staining shows the arrangement and density of reticulin networks, being particularly useful for assessing aspects of tumor microinvasion and early changes in the basement membrane, knowing that there is a similarity between the arrangement of the basement membrane and fibronectin deposits.

Some sections were histochemically stained for mucin, such as Alcian Blue (AB) pH 2.5/Periodic Acid–Schiff (PAS) and AB pH 1/PAS, to detect neutral mucins (stained red), acidic mucins (sialomucins and sulfomucins) stained blue or purple.

The immunohistochemical staining was useful to highlight the severity of gastric mucosal dysplasia lesions by assessing the proliferation cell nuclear antigen (PCNA) expression index, mouse monoclonal antibody, clone PC10, Ig2a kappa isotype.

⊡ Results

Of the 66 patients included in the study, 51 (77.2%) were men aged between 30–77 years old and 15 (22.8%) women aged between 46–73 years old (Figures 1 and 2).
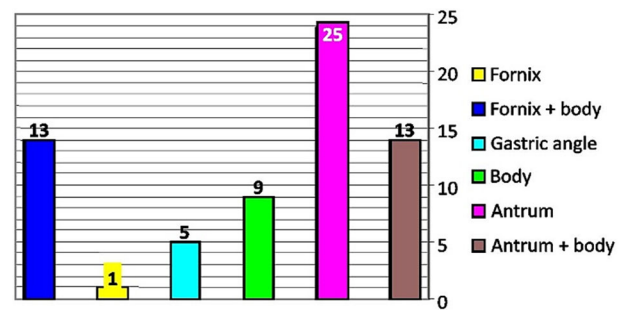

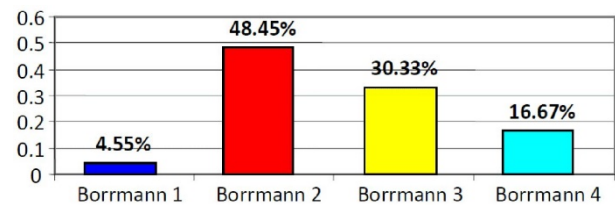*Figure 1 – Distribution of gastric carcinoma cases by topography.*

Figure 2 – Distribution of gastric carcinoma cases by Borrmann types.

The distribution of cases of gastric carcinoma by age group is presented in Table 1. Most patients (almost half of our group) were in the age group 60–69 years old, but gastric cancer can occur in patients aged 30 to 80 years old.

Table 1 – *Distribution of cases of gastric carcinoma by age group*

Age [years]	Male (M) patients	Female (F) patients	M:F ratio
30	1	0	Exclusively male patients
31–39	3	0	Exclusively male patients
40–49	2	1	2:1
50–59	11	3	3.6:1
60–69	25	8	3.1:1
70–77	9	3	3:1
Total	51	15	3.4:1

The global distribution of cases of gastric carcinoma by localization is shown in Figure 1. It is observed that

antral localizations with extension to the body of the stomach are the most common types [38 (57.5%) cases], while the upper polar localizations totalized 14 (21.28%) cases.

In both men and women, the most common localization is the antrum corresponding to the age range of 60–69 years old. All four cases of tumors occurring before the age of 40 were recorded in men.

The global distribution of gastric carcinoma cases by macroscopic criteria using Borrmann classification is presented in Figure 2. The most common morphological expression is represented by Borrmann type 2, which more often correlates with the age range 60–69 years old in patients with gastric carcinoma (24.25% of cases) – see Table 2.

Table 2 – *Correlations between Borrmann microscopic type and patients' age*

| Age [years]	Borrmann 1	Borrmann 2	Borrmann 3	Borrmann 4
30	0	0	1 (1.52%)	0
31–39	0	1 (1.52%)	1 (1.52%)	1 (1.52%)
40–49	0	2 (3.03%)	1(1.52%)	0
50–59	0	7 (10.61%)	5 (7.58%)	2 (3.03%)
60–69	4 (6.06%)	16 (24.25%)	8 (12.13%)	5 (7.58%)
70–77	0	5 (7.58%)	3 (4.55%)	4 (6.06%)

Below, we present some images of the surgical specimens belonging to the cases studied and which illustrate various macroscopic aspects (Figure 3).


Figure 3 – *Gastric neoplasm of the vegetative body (type 1 Borrmann).*

These tumors are initially vegetative (type 1 Borrmann), resembling either a multi nodular sessile polypoid or a group of several polypoid formations, of various sizes, most frequently sessile ones. Over time, these lesions undergo ulceration, turning into type 2 Borrmann, a vegetative ulcer.

Figures 4 and 5 present two cases of gastric cancer of Borrmann type, antrally developed. In the first case (Figure 4), the ulcerated lesion shows characteristics similar to those of a gastric ulcer, developed in a 50-year-old patient who was hospitalized for clinical phenomena such as perforated ulcer. There is a crater with relatively straight edges and convergence of the mucosal folds. In the second case (Figure 5), in a 53-year-old man, the ulcerated lesion developed at the level of the gastric angle, showing macroscopic signs of malignancy: the edges of the ulceration are budded, irregular; the surrounding mucosa has an atrophic appearance, and the folds stop at a distance from the edges of the ulceration.
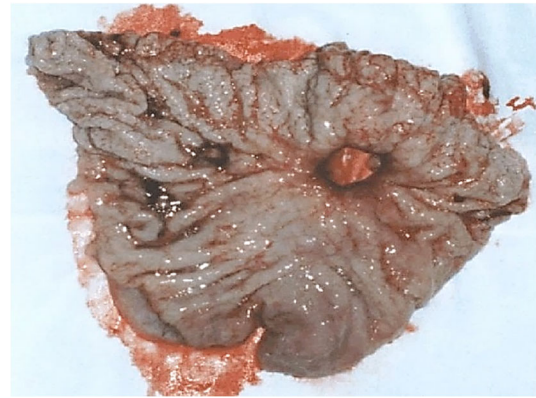
Figure 4 – *Ulcerated antrum neoplasm (type 3 Borrmann).*
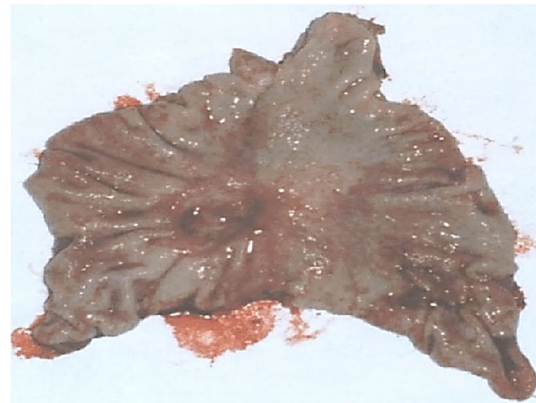
Figure 5 – *Ulcerated gastric angle neoplasm (type 3 Borrmann).*

The staging classification of the studied group of patients reveals the predominance of cases of advanced stages (stages 3 and 4), which justifies the palliative nature of most of the surgeries performed (Table 3).

Table 3 – *Staging classification of the cases in the studied group*

Stage 1 – 0 (0%) cases
Stage 2 – 7 (11%) cases
Stage 3 – 42 (64%) cases
Stage 4 – 17 (25%) cases

The distribution of cases according to the level of tumor invasion (pT) is shown in Figure 6, where it can be seen that the majority of cases belong to categories pT3 and pT4.
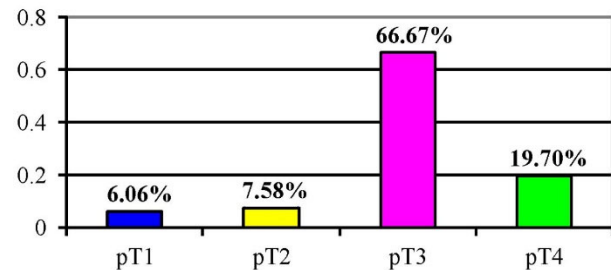
Figure 6 – *Distribution of gastric carcinoma cases according to the level of tumor invasion (pT).*

The distribution of cases of gastric carcinoma according to the level of tumor invasion (pT) by age group is shown in Table 4.

Table 4 – *Distribution of gastric carcinoma cases according to the level of tumor invasion (pT) by age group*

Age [years]	pT1	pT2	pT3	pT4
30	0	0	1 (1.52%)	0
31–39	0	0	2 (3.03%)	1 (1.52%)
40–49	0	0	2 (3.03%)	1 (1.52%)
50–59	2 (3.03%)	1 (1.52%)	9 (13.68%)	2 (3.03%)
60–69	2 (3.03%)	4 (6.06%)	19 (28.88%)	8 (12.16%)
70–77	0	0	11 (16.72)	1 (1.52%)

In the age group 60–69 years old, where most cases are concentrated, we encounter the highest frequency in the pT3 category (28.88%).

The level of invasion according to topography is presented in Table 5.

Table 5 – *Level of invasion according to topography*

	Fornix	Fornix and body	Body	Gastric angle	Antrum	Antrum and body
T1	0	0	1 (1.52%)	0	3 (4.56%)	0
T2	0	0	1 (1.52%)	0	3 (4.56%)	0
T3	8 (12.8%)	0	5 (7.6%)	5 (7.58%)	15 (22.8%)	10 (15.2%)
T4	5 (7.58%)	1 (1.52%)	2 (3.04%)	0	4 (5.08%)	3 (4.56%)

We note that no case of gastric carcinoma with high localization was detected in the early stage of the carcinoma. Most carcinomas were located antrally, in the pT3 stage (22.8%).
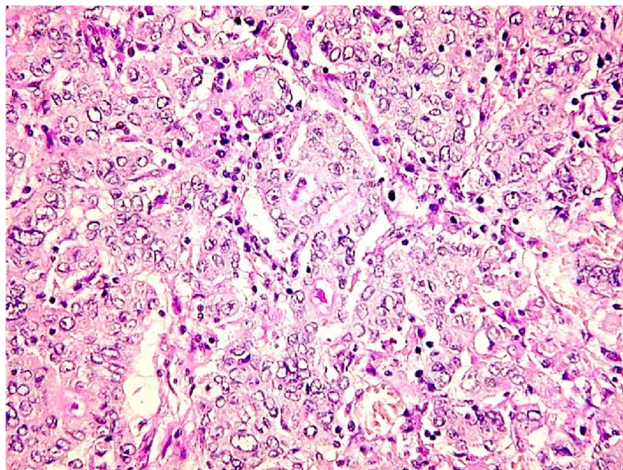
The examination of microscopic aspects, including both cellular differentiation and secretory differentiation, are performed using the Goseki system applied to our stage.

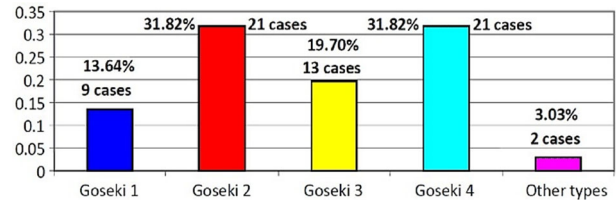The distribution of cases in this system is shown in Figure 7.

Thus, Goseki classes 2 and 4 appear in equal proportions, being the best represented (31.82%).

The distribution of Goseki types of gastric carcinoma, according to age and gender, is shown in Tables 6 and 7.

It can be observed that most cases in men (21.57%) belong to the age range of 60–69 years and Goseki class 4.

Figure 7 – *Distribution of gastric carcinoma cases according to microscopic criteria – Goseki classification.*

Table 6 – *Distribution of Goseki microscopic types in women by age range*

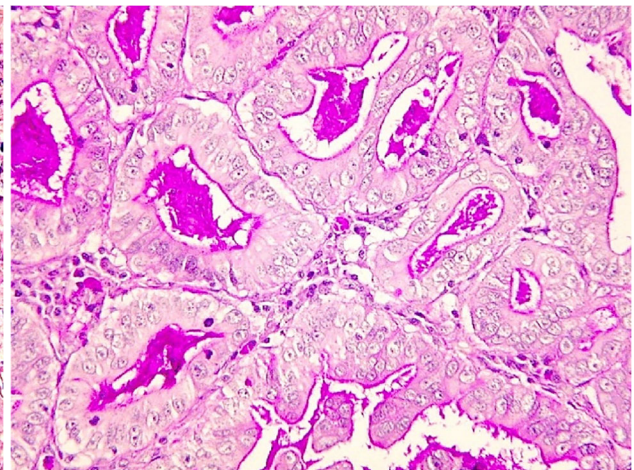| Age [years]	Women	Goseki 1	Goseki 2	Goseki 3	Goseki 4
30	0	0	0	0	0
31–39	0	0	0	0	0
40–49	1	0	0	1 (6.67%)	0
50–59	3	0	0	1 (6.67%)	2 (13.34%)
60–69	8	1 (6.67%)	3 (20.01%)	2 (13.34%)	2 (13.34%)
70–77	3	1 (6.67%)	0	1 (6.67%)	1 (6.67%)

Table 7 – *Distribution of Goseki microscopic types in men by age range*

| Age [years]	Men	Goseki 1	Goseki 2	Goseki 3	Goseki 4
30	1	0	0	0	1 (1.96%)
31–39	3	0	1 (1.96%)	2 (3.92%)	0
40–49	2	0	1 (1.96%)	1 (1.96%)	0
50–59	11	3 (5.88%)	4 (7.84%)	1 (1.96%)	1 (1.96%)
60–69	25	3 (5.88%)	8 (15.68%)	3 (5.88%)	11 (21.57%)
70–77	9	2 (3.92%)	2 (3.92%)	2 (3.92%)	3 (5.88%)

In women, the most numerous cases belong to the age group 60–69 years old, but the most common classes are Goseki class 2, followed by Goseki classes 3 and 4 in equal proportions.

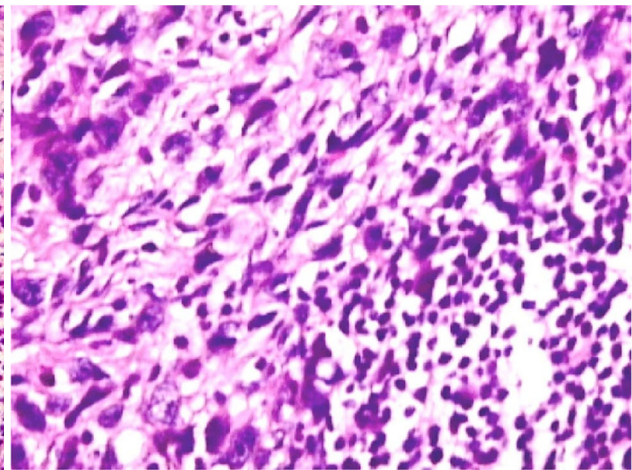We present some HP aspects specific to the Goseki classes (Figures 8–11).

The correlation between the macroscopic aspects according to the Borrmann classification and the microscopic aspects according to the Goseki classification is presented in Table 8.

Figure 8 – *Gastric carcinoma Goseki 1: good tubular differentiation and reduced secretory differentiation. PAS-H, staining, ×100.*

Figure 9 – *Gastric adenocarcinoma Goseki 2: good tubular and secretory differentiation. PAS-H staining, ×200.*
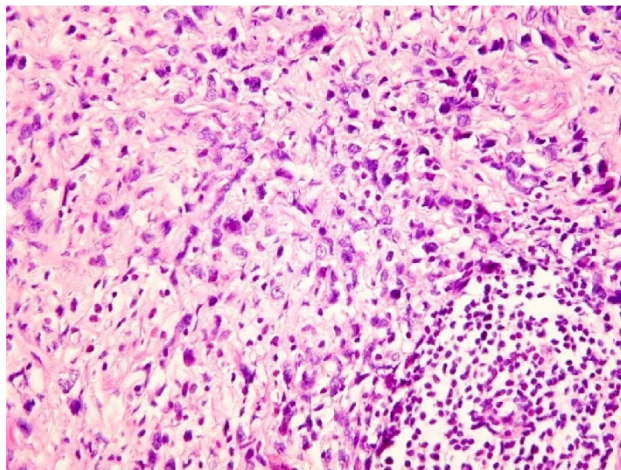
Figure 10 – *Gastric carcinoma, Goseki 3 areas: poorly tubular and secretory differentiation. HE staining, ×100.*

Figure 11 – *Carcinoma with cu signet ring cells, Goseki 4: poorly tubular differentiation (possible lack of tubular differentiation) and good secretory differentiation. HE staining, ×200.*

Table 8 – *Correlation between the macroscopic aspects according to the Borrmann classification and the microscopic aspects according to the Goseki classification*

	Goseki 1	Goseki 2	Goseki 3	Goseki 4
Borrmann 1	2 (3.02%)	2 (3.02%)	0	0
Borrmann 2	4 (6.04%)	16 (24.16%)	6 (9.16%)	5 (7.81%)
Borrmann 3	3 (4.58%)	4 (6.04%)	4 (6.04%)	8 (12.08%)
Borrmann 4	0	0	4 (6.04%)	8 (12.08%)

It may be observed that the most common macroscopic type encountered Borrmann type 2 is very frequently associated with Goseki class 2, whereas Borrmann types 3 and 4 of gastric carcinoma belong to Goseki class 4.

In all the cases studied, we found that a process of chronic gastritis with varying degrees of atrophy occurs in the non-tumor gastric mucosa. Thus, Figure 12 shows the distribution of gastritis lesions depending on the intensity of the atrophy process.
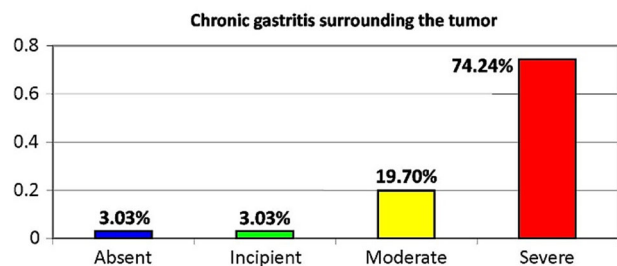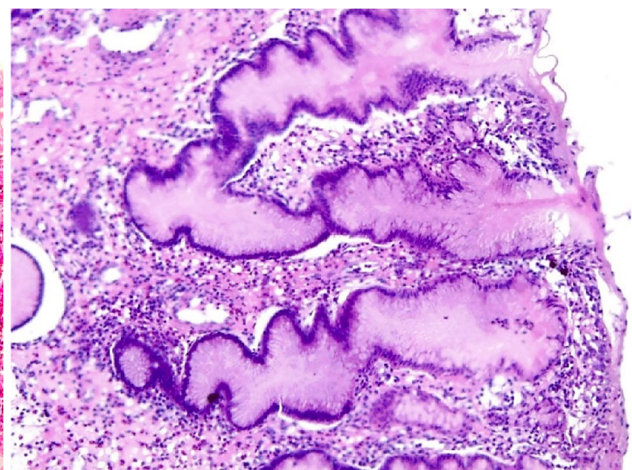

Figure 12 – *Presence of chronic atrophic gastritis lesions in the non-tumoral gastric mucosa.*

It is worth mentioning that most cases of gastric cancer (74.24%) developed against the background of lesions of severe chronic atrophic gastritis (Figures 13 and 14).
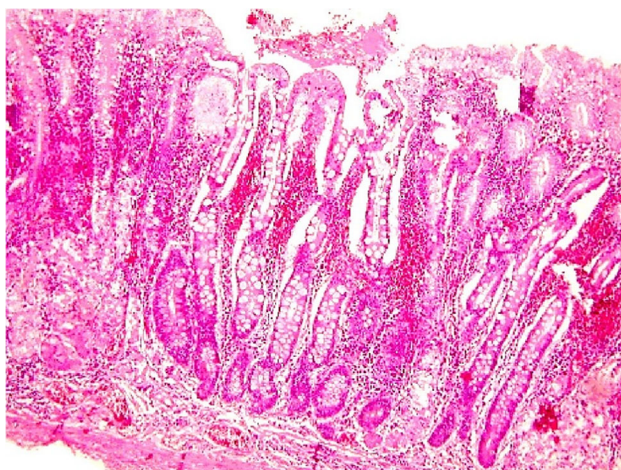
Figure 13 – *Aspects of severe atrophic chronic gastritis associated with high-grade dysplasia lesions against a background of intestinal metaplasia. Exulcerations and extensive hemorrhagic suffusions in the chorion. HE staining, ×100.*

Figure 14 – *Severe atrophic chronic gastritis. HE staining, ×100.*

The distribution of chronic atrophic gastritis lesions by Goseki classes is presented in Figure 15, and it is observed that most cases with severe atrophic gastritis (49%) are associated with Goseki class 4.

Table 9 shows the association of various types of chronic atrophic gastritis with *H. pylori* infection, the absence of chronic atrophic gastritis lesions marking it by the indication gastritis 0, while the indications gastritis 1,

2 and 3 correspond to the incipient, moderate and severe forms.
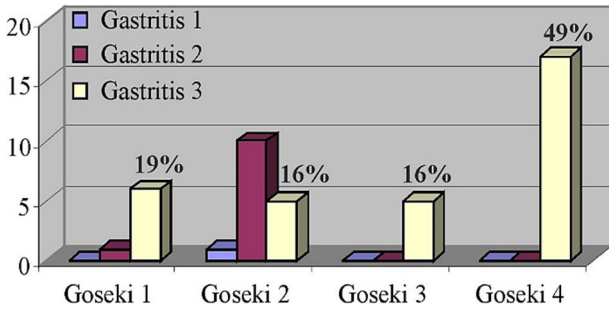
Figure 15 – *Correlation between cases of chronic atrophic gastritis and Goseki classes.*

There is an increase recorded in the incidence of *H. pylori* germ infection as the degree of atrophy increases. We also note the high percentage of negative *H. pylori*

cases in cases of severe atrophic chronic gastritis. We consider that this percentage should be correlated with the topography of neoplastic lesions (upper polar cancers), age (patients less than 40 years old) and cases with extensive mucosal ulcerations.

Table 9 – *Association of various types of chronic atrophic gastritis with H. pylori infection*

Type of gastritis	*H. pylori* positive	*H. pylori* negative
Gastritis 0	0	2 (3.04%)
Gastritis 1	1 (1.52%)	1 (1.52%)
Gastritis 2	10 (15.15%)	2 (3.04%)
Gastritis 3	35 (53%)	15 (22.73%)

Below, we present two images of a case in which the non-tumoral mucosa displays lesions of severe chronic atrophic gastritis, with a high degree of *H. pylori* activity (Figure 16, A and B).
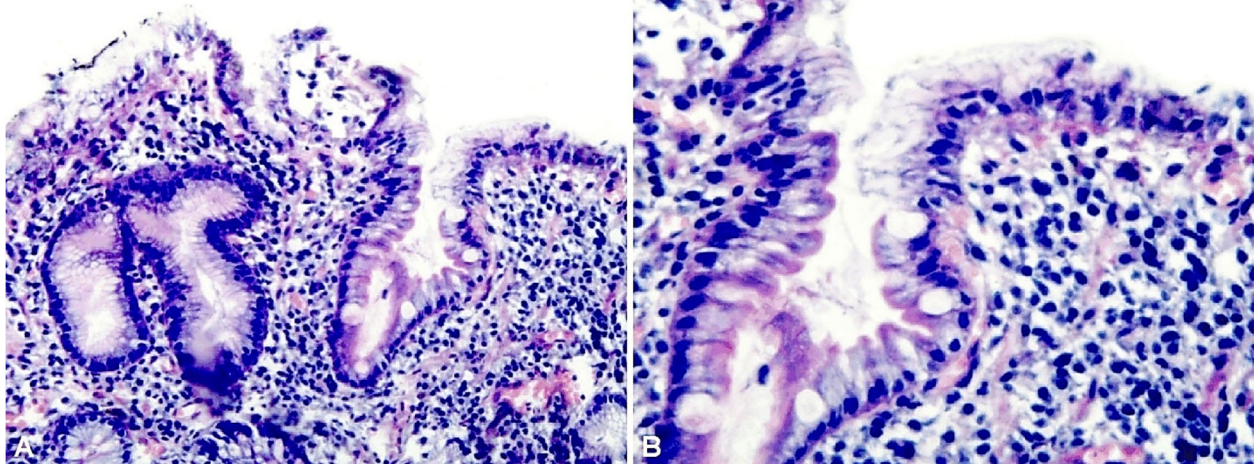
Figure 16 – *Severe chronic atrophic gastritis with a high degree of H. pylori activity: (A) H. pylori positive; (B) Details of the same case – the presence of numerous H. pylori-type germs in the foveolar mucus is observed. HE staining: (A) ×200; (B) ×400.*

Table 10 shows the percentage distribution of *H. pylori* infection in Goseki classes of gastric carcinoma. The analysis of the Table 10 shows that the highest incidence of *H. pylori* infection occurs in Goseki class 4, characterized by poorly secretory differentiation, while the lowest incidence of infection belongs to Goseki class 3 defined by a poorly differentiation, both tubular and secretory.

Table 10 – *Correlation between Goseki classes of gastric carcinoma and the presence or absence of H. pylori infection*

Goseki class	*H. pylori* positive	*H. pylori* negative
1	77.79%	22.23%
2	76.20%	23.81%
3	38.47%	61.55%
4	80.96%	19.05%

The presence of intestinal metaplasia in the evolution of chronic gastritis was reported by different authors in various percentages.

Our research indicated that 42.42% of gastric carcinoma cases were not associated with lesions of intestinal metaplasia, in the remaining cases, the most common type of metaplasia being type III (colonic), a lesion considered to be a precursor of intestinal gastric cancers (Figure 17).
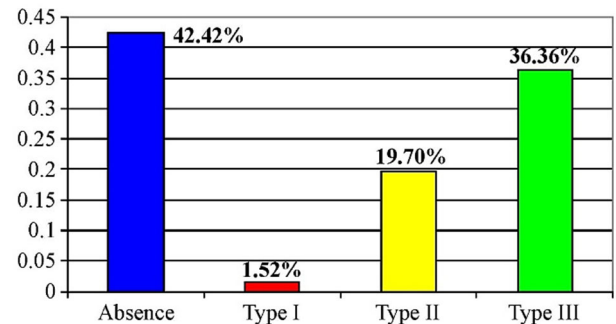
Figure 17 – *Distribution of the types of intestinal metaplasia in the studied cases.*

Figure 18 (A–C) shows some HP aspects of various types of intestinal metaplasia.

The distribution of the types of intestinal metaplasia by age group is shown in Table 11 [type I – complete intestinal metaplasia; type II – incomplete intestinal metaplasia (small intestine type); type III – incomplete intestinal metaplasia (colonic type)].

It may be observed that the absence of intestinal metaplasia is associated with significant percentages at a young age and that it significantly increases the form of intestinal metaplasia of the colonic type after the age

of 60 years old. The absence of intestinal metaplasia in young patients is due to the relatively slow evolution of these types of lesions, which manifest after the age of 45 years old.
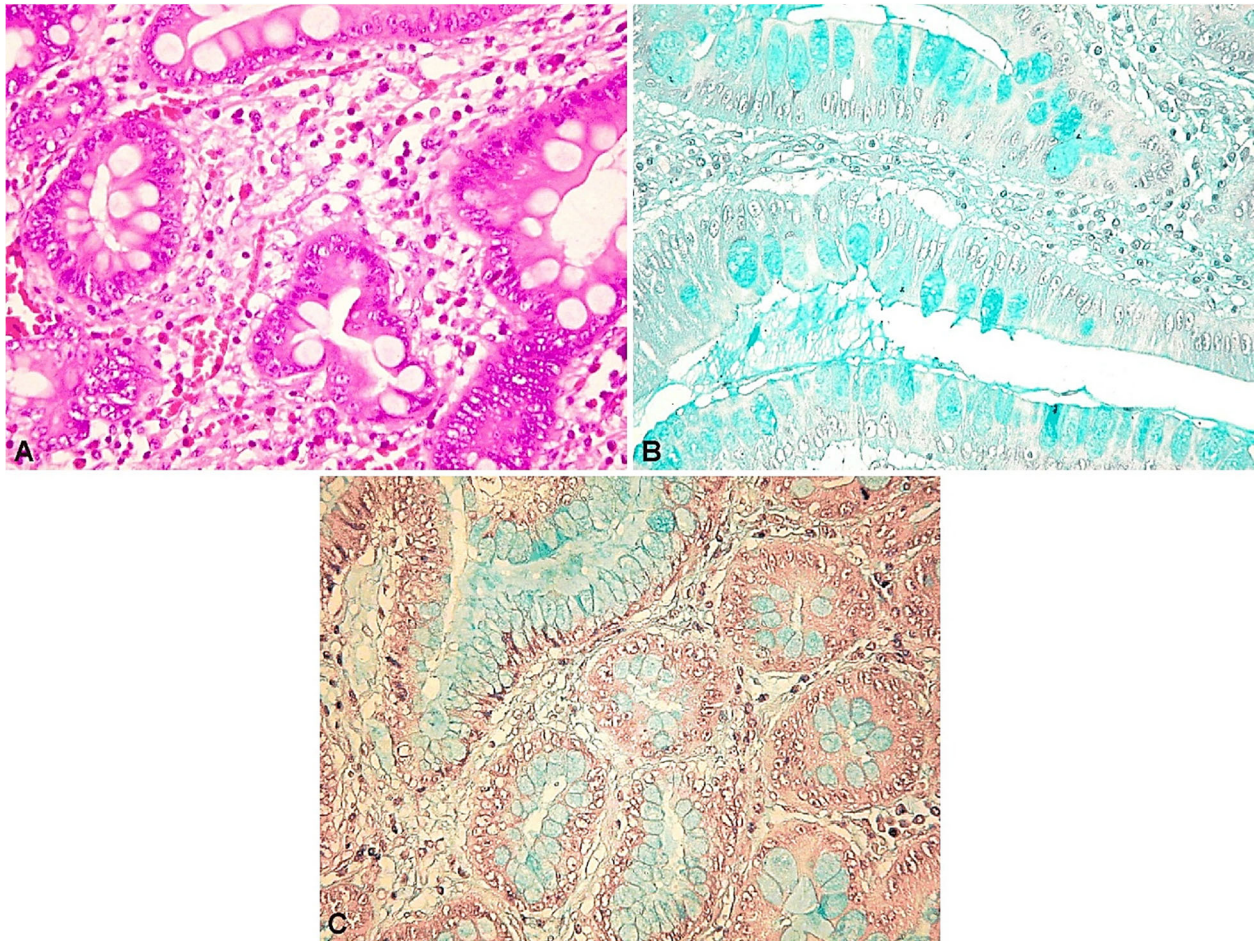
Figure 18 – *(A) Gastric mucosa at a distance from the tumor with lesions of intestinal metaplasia, developed against a background of severe atrophic chronic gastritis (HE staining, ×200); (B) The same case as in the previous image, indicating a sialomucin-rich content of mucus (Alcian Blue pH 2.5 staining, ×100); (C) The same case, in which the weak reaction of the foveolar mucus to the Alcian Blue pH 1 staining is observed (×200).*

Table 11 – *Distribution of types of intestinal metaplasia by age group*

Age [years]	Absence of metaplasia	Metaplasia type 1	Metaplasia type 2	Metaplasia type 3
30	100%	0	0	0
31–39	66%	0	0	33%
40–49	66%	0	33%	0
50–59	57%	0	15%	28%
60–69	36%	4%	15%	45%
70–77	0	0	0	100%

The correlation between the types of intestinal metaplasia and the topography of the neoplastic process is presented in Table 12. There is an increased incidence of intestinal metaplasia type III lesions in the distal topographies of neoplastic lesions.

The correlation between the presence of *H. pylori* infection and the development of intestinal metaplasia lesions is still a controversial issue. In our study, this correlation is shown in Table 13. The data in this table indicate that there cannot be established a correlation between the type of metaplasia and the presence of *H. pylori* infection, which can be explained by the disposition to focal infection as well as of the lesions of intestinal metaplasia.

Table 12 – *Correlation between the types of intestinal metaplasia and the topography of the neoplastic process*

	Fornix	Fornix and body	Body	Gastric angle	Antrum	Antrum and body
Absence of metaplasia	9 (13.68%)	0	5 (7.6%)	1 (1.52%)	6 (9.12%)	6 (9.12%)
Metaplasia type I	0	0	0	4 (6.08%)	1 (1.52%)	0
Metaplasia type II	3 (4.56%)	0	1 (1.52%)	0	6 (9.12%)	2 (3.04%)
Metaplasia type III	1 (1.52%)	1 (1.52%)	3 (4.56%)	0	12 (18.24%)	5 (7.6%)

Table 13 – *Correlation between the presence of H. pylori infection and the development of intestinal metaplasia lesions*

Metaplasia type	*H. pylori* positive	*H. pylori* negative
0	56%	44%
1	52%	48%
2	76.92%	23.08%
3	95.83%	4.17%

At present, the correlation between intestinal metaplasia (colonic type) type III and the risk for developing a gastric carcinoma is well established. In this context, we aimed

to analyze the correlation between the degree of atrophy of the gastric mucosa and the types of intestinal metaplasia (Table 14).

	Metaplasia 0	Metaplasia 1	Metaplasia 2	Metaplasia 3
Gastritis 0	2 cases	0	0	0
Gastritis 1	1 case	0	1 case	0
Gastritis 2	3 cases	3 cases	4 cases	2 cases
Gastritis 3	21 cases	2 cases	7 cases	20 cases

We determined the existence of an approximately equal distribution of the number of cases characterized by the absence of metaplasia lesions (metaplasia 0) and cases of metaplasia type III associated with forms of severe chronic atrophic gastritis. The above-mentioned data confirm the role of severe chronic atrophic gastritis as a pre-cancer lesion in most cases of gastric carcinoma, regardless of the association with lesions of intestinal metaplasia.

Next, we present a HP aspect of a case of severe atrophic chronic gastritis with extensive lesions of intestinal metaplasia type III (Figure 19, A–C).

Figure 19 – *(A) Aspects of severe atrophic chronic gastritis with large areas of intestinal metaplasia type III; (B and C) Details of the previous case. Alcian Blue pH 1 staining: (A) ×40; (B) ×100; (C) ×200.*

In a sequence of successive details, the absence of deep chorionic glandular structures is to be noted, alongside the transformation of the foveolar epithelium into a colonic type, consisting of columnar absorbing cells, with a marked Alcian Blue staining reaction at pH 1, indicating the presence of sulfated acid mucopolysaccharides, characteristic of colonic mucus.

The correlation between Goseki classes and the incidence of metaplasia types is analyzed in Table 15.

Table 15 – *The correlation between Goseki classes*

Goseki class	Absence of metaplasia	Metaplasia type 1	Metaplasia type 2	Metaplasia type 3
1	1.56%	0.00%	1.56%	10.94%
2	9.38%	1.56%	9.38%	12.50%
3	17.19%	0.00%	1.56%	1.56%
4	12.50%	0.00%	7.81%	12.50%

There is an extremely low incidence of intestinal metaplasia lesions in Goseki class, namely in three patients, characterized by poorly tubular differentiation and poor mucus secretion.

The presence of dysplasia in the non-tumor mucosa is shown in Figure 20.
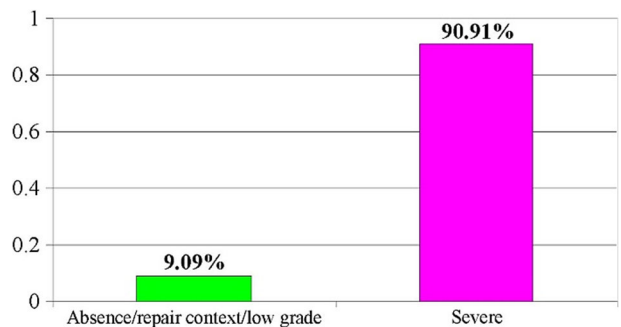
Figure 20 – *Distribution of cases of dysplasia of non-tumor mucosa.*

We separated all cases of severe dysplasia from cases

of mild, moderate or repair dysplasia (indefinite lesions for dysplasia), considering that the presence of a severe form of dysplasia is rather concomitant with a carcinoma, having a well-defined diagnosis and therapeutic consequences. These statements are confirmed by the percentage of over 90% of severe dysplastic lesions found in the cases studied.

Figure 21 (A and B) presents lesions of severe dysplasia of the peritumoral mucosa developed on extensive lesions of intestinal metaplasia of colonic type.
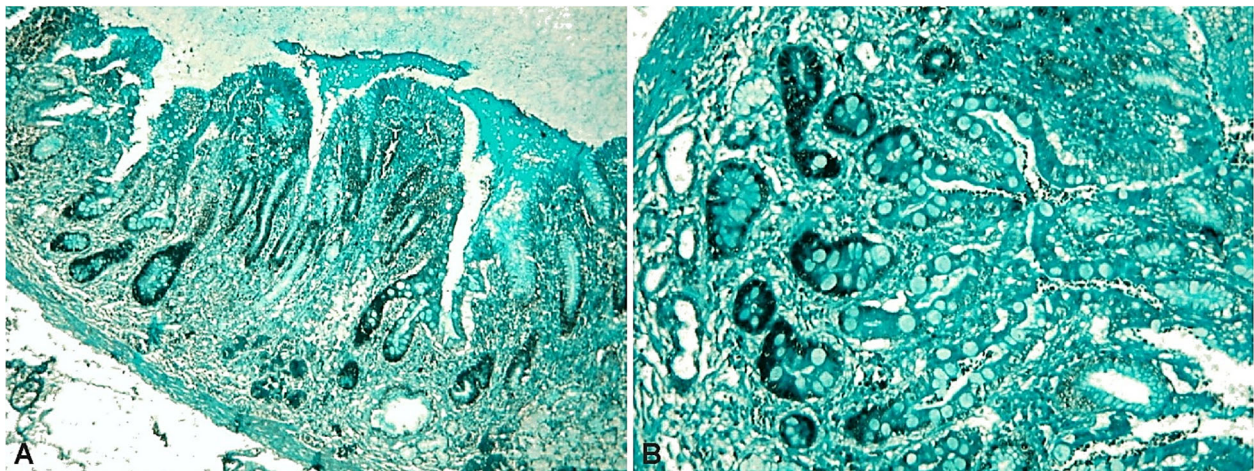

Figure 21 – *(A) High expression of PCNA in dysplastic glandular structures; (B) Details of the previous image. Anti-PCNA antibody immunomarking: (A) ×40; (B) ×200. PCNA: Proliferating cell nuclear antigen.*

The severe degree of dysplasia results from both cytoarchitectonic changes in the epithelium structures and the high expression PCNA index, mouse monoclonal antigen, PC10 clone, IgG2a kappa isotype, which mark cells in phase S of the cell cycle.

The correlation between dysplasia and intestinal metaplasia is shown in Table 16.

Table 16 – *Correlation between dysplasia and intestinal metaplasia lesions*

	Metaplasia 0	Metaplasia 1	Metaplasia 2	Metaplasia 3
Dysplasia 0	5 (7.6%)	0	1 (1.52%)	0
Dysplasia 1	23 (34.96%)	1 (1.52%)	12 (18.24%)	24 (36.43%)

It is observed that, in the studied group, there is a relatively equal distribution of metaplastic and non-metaplastic dysplasia lesions. We also found a relatively large proportion of cases that associate severe dysplasia lesions with a process of incomplete intestinal metaplasia type II.

The distribution of cases according to the degree of cell differentiation is presented in Figure 22, indicating the predominance of poorly differentiated carcinomas G3 as well as a significant percentage of cases with a medium degree of cell differentiation G2.
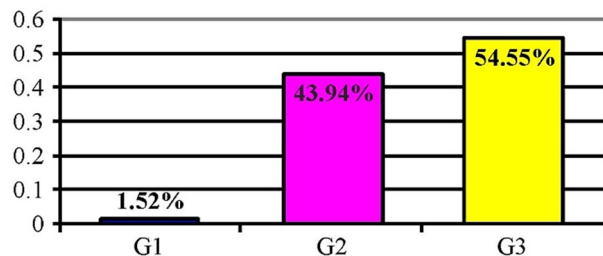

Figure 22 – *Distribution of cases according to the degree of cell differentiation (G).*

The correlation of the tumor invasion level (pT) with the degree of cell differentiation is presented in Table 17: there is a correlation between the degree of cell differentiation and the level of tumor invasion.

Table 17 – *Correlation of the tumor invasion level (pT) with the degree of cell differentiation*

	G1	G2	G3
pT1	1 (1.52%)	3 (4.56%)	0
pT2	0	2 (3.08%)	3 (4.56%)
pT3	0	16 (24.64%)	28 (42.56%)
pT4	0	8 (12.32%)	5 (7.6%)

Finally, the comparative analysis of the G system proposed by the *World Health Organization* (WHO) and of the Goseki classification highlights a strong correlation between the two systems of assessing cell differentiation (Table 18).

Table 18 – *Correlation between the degree of cell differentiation (G) and microscopic tumor aspects according to Goseki classification*

	G1	G2	G3
Goseki 1	1 (1.52%)	8 (12.16%)	0
Goseki 2	0	21 (31.92%)	0
Goseki 3	0	2 (3.04%	13 (19.76%)
Goseki 4	0	0	21 (31.92%)

⛶ Discussions

Gastric cancer remains a neoplasm which has a large geographic coverage, and with a high incidence. According to the GLOBOCAN 2002 data, this neoplasm had an incidence of 22/100 000 in men and 10.4/100 000 in women, with a 16.3/100 000 mortality rate in male patients, and 7.9/100 000 in female patients, respectively [1].

The 5-year survival rate for treated patients with gastric cancer, according to several studies conducted across Europe and USA, ranges between 10 to 20% [2, 3]. In

Romania, according to the *Romanian Society of Digestive Endoscopy*, the incidence of gastric cancer in the adult population (over 18 years old) was of 2.9/100 000 inhabitants in 2003, of which 66.4% were men and the rest were represented by women [15].

The above data show that the morbidity and mortality rate of gastric neoplasm in our country and worldwidely is a public healthcare problem, a standardized algorithm for the screening and early detection of this disease becoming mandatory. Our study was conceived as a constant analysis of a possible relation between the epidemiological factors and some histological aspects considered relevant for either the characterization of the tumor or the unaffected gastric mucosa.

The epidemiological data [15] revealed a male/female ratio of 2.5/1, but in our study group it was even higher raising to 3.5/1, with an incidence peak between the age range of 60–69 years old, similar to the one mentioned in the literature [2, 3]. Topographically, the highest incidence was registered at the antrum (57.5%), but, for the past years, based on other studies [1–3], we noticed an increasing trend of the superior gastric pole localization (22.7%). Our study indicated that all the cases that emerged over 40 years old of age were in men, with a tendency for the tumor localization in the superior gastric pole.

The most frequent macroscopic tumor pattern was type 2 Borrmann, *i.e.*, ulcero-vegetative, occurring mainly over 60 years old of age, with the peak incidence of this sort of cancer in this age group. Although not numerous, the gastric neoplasms before 50 years old showed an equal frequency of Borrmann types 2, 3 and 4.

At the gastric antrum, type 2 (ulcero-vegetating) and type 3 (ulcerated) Borrmann were predominant, whereas at the superior pole types 1 and 2 Borrmann prevail. We mention that the tumor that initially vegetated subsequently underwent necrosis and ulceration processes due to apoptosis, peptic destruction and ischemic processes resulting in ulcero-vegetating and ulcerated forms.

Regarding the invasion, most of the carcinomas were surgically removed when the tumor reached the serosa (pT3) or even the perigastric tissues (pT4). This fact is due to the lack of the early detection methods of neoplastic lesions on a par with poor level of medical knowledge among the population that leads to a late referral of the patients. It might be explained also due to the unspecific clinical manifestations of the tumors in the early stages that can mimic other diseases; besides, most often the symptoms have a remissive character at these stages.

Even though when the endoscopy reveals peptic ulcer like lesions, the errors regarding the biopsy associated with a pathogenic treatment might mask a variable evolution with remission of the gastric carcinoma with pseudo ulcerated macroscopic aspect (type 3 Borrmann) [16]. Unlike peri-orifice tumors (cardia and pillory orifices), the ones localized at the fornix and body are clinically silent for a long period of time, being sometimes difficult to be approached endoscopically (fornix), therefore being diagnosed in the late stages – pT3, pT4 [16, 17].

In our study, we discarded the use of the microscopic classifications recommended by *WHO* or some other authors,

such as Lauren & Ming, because they do not associate the tumor architecture with the functional differentiation of the tumor cell.

Therefore, we consider that the above classifications do not properly reflect the pathogenic and morpho-functional aspects and they are not practically relevant. For this reason, we chose Goseki's classification, which covers better the histological heterogeneity of the gastric carcinomas, providing information over the percentage of the cell and secretory differentiation with direct impact on the invasion of the tumor [18].

The most frequent Goseki classes were 2 and 4, encountered in an almost equal percentage. In men, the most frequent histological type was the vegetating Goseki class 4, whereas in women Goseki class 2 shows the highest frequency. Macroscopically, types 1 and 2 Borrmann are most commonly associated to Goseki class 2, characterized by good tubular and secretory differentiation, being a moderately differentiated tumor (G2) with a well-defined tumor architecture and with exophytic macroscopic expression. In opposition, types 3 and 4 Borrmann are associated with Goseki classes 3 and 4 carcinomas with poorly tubular differentiation, irrespective of the secretory differentiation, resulting in infiltrative or ulcerated growth.

The anamnestic reconstruction of the clinical evolution along with the histological type showed that Goseki classes 3 and 4 progress more rapidly and have a poor prognosis [15, 16]. These cases count most of the tumors localized at the superior gastric pole.

More than 70% of the patients in our study group presented lesions of severe chronic atrophic gastritis of the non-tumor mucosa. These are the results of a prolonged process of 10 to 15 years with a plurifactorial etiology [19], where we only searched for *H. pylori* infection. The correlation between the types of gastritis and Goseki classes of gastric carcinomas shows a clear association of the severe atypical forms with Goseki class 4, characterized by poorly tubular differentiation but a good secretory differentiation. This is due to the association of chronic atrophic gastritis with intestinal metaplasia [20–22].

The chronic infection with *H. pylori* interferes with many pathogenic pathways, disrupting the protective mechanism of the mucosa, thus leading to lesions of the foveolar epithelium such as vacuolization followed by exulcerations that need repairing. The persistence of the infection determines the accumulation of numerous lymphocytes that in time will destroy the epithelial structures of the deep chorion, thus developing an atrophy [23–26].

The repetitive repairing of the foveolar epithelium leads, in some cases, to its phenotypic variation, resulting in an intestinal like epithelium with diverse patterns of intestinal metaplasia [12, 27, 28].

The incidence of *H. pylori* infection in severe chronic atrophic gastritis was about 50%, lower than the one mentioned in other studies [24, 29–32]. In a study conducted by Solcia *et al.* (1996) it is mentioned a percentage of 85% of *H. pylori* infection on gastrectomy samples in early cancer, out of which 76% were in intestinal cancer (associated with well differentiated secretory

Goseki's classes), and 100% in the diffuse ones associated with poorly differentiated tubular Goseki's classes [33].

The presence of *H. pylori* was highlighted in the corporal intestinal cancer rather than in antral carcinoma, whereas in the diffuse forms of neoplasm there were no statistically significant differences [33]. The epidemiological studies revealed that the risk of cancer increases with *H. pylori* infected persons compared to *H. pylori* negative people, and the infection with these bacteria is correlated to distal gastric adenocarcinomas (corporal, antral) and never to superior pole cancers [24, 29]. In our study, we observed an increased incidence of the latter infection type that led to aggravated atrophy, which contradicts the data mentioned above [33].

The correlation of the *H. pylori* infection with intestinal gastric cancer (Lauren's classification) occurs more frequently in our study due to the strong association between the infection and well-differentiated secretory types belonging to Goseki's classes [34, 35]. We also observed an increased percentage of positive *H. pylori* in Goseki class 1, which presented a good tubular differentiation. In Goseki class 3 with poorly secretory and tubular differentiation, the incidence of *H. pylori* infection decreased because of the lack of favorable growing conditions for these bacteria [34, 35].

The epidemiological data suggests that chronic atrophic gastritis is associated with two types of tumors: intestinal gastric cancer and gastric carcinoid type 1, but the physio-pathogenic mechanism of this association is different [19].

Currently, the relation between the *H. pylori* infection and chronic inflammation of the gastric mucosa that progresses to chronic atrophic gastritis followed by intestinal metaplasia, dysplasia and finally resulting in the development of gastric neoplasm it is widely accepted [19, 36]. Likewise, the type 1 gastric carcinoma is a tumor associated with a high level of chronic atrophic gastritis, the gastrin excess stimulating the growth of enterochromaffin-like cells (ECL), while their hyperplasia leads to the development of the carcinoid tumor [37, 38].

In our study group, almost half (42.4%) of the cases did not show lesions of intestinal metaplasia. On the other hand, the incidence of intestinal metaplasia rises with age, being more common in antral gastric carcinomas. We also noted that there is no relation between that metaplasia type and the presence of *H. pylori* infection. That might be explained either by the focal localization of the infection and of the intestinal metaplasia lesions or by the fact that an accurate diagnosis of the infection requires some other investigations (feces serology).

The correlation between Goseki's classes and metaplasia grades shows that in Goseki's classes intestinal metaplasia is almost absent due to the lack of tubular differentiation in these types of cancers.

The incidence of gastric neoplasm associated with intestinal metaplasia varies between 0–10% according to research, an incomplete type of metaplasia [22, 39] being present in the vast majority. Furthermore, the scientific data show that the risk of cancer is four to 11 times higher in patients with incomplete metaplasia compared with the ones that do not have this type of lesions [22, 27, 40].

Without a shadow of doubt, all carcinomas are the result of progressive dysplastic lesions with or without a metaplastic epithelial base. The analysis of our data revealed an approximately equal number of cases with no metaplasia and of the ones showing metaplasia type 3. Many authors describe gastric dysplasia as a dynamic process with a negative potential or a potential to progress to gastric carcinoma [3, 17, 41]. In this context, several studies report that the time needed ranging from the identification of severe dysplasia to the diagnosis of gastric cancer varies from one month to 39 months, with an average of 23 months. According to those studies, it can be concluded that gastric dysplasia lesions represent an important marker for the evaluation of the risk of gastric neoplasm and that the higher the dysplasia grade, the higher the risk of developing invasive gastric cancer [15–17, 41, 42].

⊡ Conclusions

Gastric cancer continues to remain a neoplastic lesion with a widespread geographic distribution and increased incidence in men and persons over 60 years old. Lesions such as chronic atrophic gastritis, incomplete intestinal metaplasia and high-grade dysplasia are precursors of the gastric cancer and, in many cases, they accompany the malignant gastric tumor. The chronic infection with *H. pylori* interferes with many pathogenic pathways, disrupting the protective mechanism of the mucosa, leading to lesions of the foveolar epithelium that in time will result in the destruction of the epithelial structures and atrophic processes. The repetitive repairing of the foveolar epithelium determines, in some cases, a phenotypic alteration, resulting in intestinal epithelium with various patterns of intestinal metaplasia. Currently, it is considered that all gastric carcinomas develop based on progressive dysplastic lesions on the metaplastic or non-metaplastic epithelium. From all the microscopic classifications of the gastric cancer mentioned in the literature, we chose Goseki's microscopic classes on account of their best coverage of the histological heterogeneity of gastric carcinomas, providing information on the percentage of cellular and secretory differentiation with direct impact on the invasion of the tumor.

Conflict of interests
The authors declare no conflict of interests.

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