



## CLINICO-PATHOLOGICAL ANALYSIS OF GASTRIC CANCER – A SINGLE INSTITUTION EXPERIENCE

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### ABSTRACT

**Introduction:** Gastric cancer (GC) is one of the leading causes of cancer related morbidity and mortality. Morphologically, GC is a heterogeneous neoplasm consisting of several histological types. Majority of the patients are diagnosed in an advance stage of the disease. Conventional surgical and systemic treatment has demonstrated limited achievement. Evolution in personalized therapy is a main factor to improve the outcome, but for a successful application, a careful stratification of patients is required.

**Aim:** The purpose of the present paper was to analyze the mandatory clinical and pathological characteristics of patients with GC.

**Material and methods:** A total 74 patients who have undergone total or partial gastric resection, endoscopic and laparoscopic biopsy due to GC were included.

**Results:** The average age of the patients was 69,6 years, with a male predominance in all age groups. Most frequent histological type was intestinal type, according to Lauren and tubular type, according to WHO classifications. 82,3% ( $p < 0,05$ ) of GC located in cardia were diagnosed in males. 37/42 tubular, papillary and mucinous types by WHO classification were classified as intestinal type by Lauren. All signet ring cell and poorly cohesive adenocarcinomas by WHO classification were accordingly assigned as diffuse type by Lauren. 52,2% of the tubular/intestinal type of tumors were graded as G1 or G2, and 93,1% of signet ring and poorly cohesive/diffuse type GC were graded as G3. Significant correlations were observed between perineural invasion and histological type by Lauren ( $p < 0,043$ ), degree of differentiation ( $p < 0,04$ ) and lymphovascular invasion ( $p < 0,000$ ); between degree of inflammatory reaction and  $\bar{I}$  status ( $p < 0,022$ ).

**Conclusion:** Precise histological typification of GC is a key to better stratification of the patients. Certain histological types are associated with aggressive tumor behavior, as we found diffuse type to correlate with poor differentiation and presence of perineural invasion. Degree of inflammatory reaction may be an independent indicator of the presence of distant metastases.

**Keywords:** gastric cancer, pathological classification, morphological characteristics,

### INTRODUCTION:

According to GLOBOCAN data, gastric cancer (GC) occupies the fifth place in a term of morbidity among all newly diagnosed cancers. In 2020, just over 1 million cases were registered globally in 185 countries. Moreover, GC is the fourth cause of cancer related mortality worldwide, after lung, colon and liver cancers [1]. As to the latest published data from the National Cancer Registry in Bulgaria in 2017, among 31,905 newly diagnosed oncological diseases, 1394 (5%) cases were of GC. The mortality rate from GC in Bulgaria is 6,6%, which is 2238 patients who died from this disease in 2017 [2]. Overall survival of GS has improved, mostly due to advances in diagnostic and therapeutic strategies, especially with early detection by national screening programs with endoscopic and imaging methods [3].

Morphologically, GC is a heterogeneous neoplasm consisting of several histological types. Their frequency depends on genetic and environmental factors; therefore, the prevalence of each type can vary significantly in different populations. Two histological classifications are currently used to classify GC – Lauren and World Health Organization (WHO) classifications. The former, published by Finish pathologist Pekka Laurén in 1965, divides GC into three types: intestinal, diffused and mixed [4]. The latter, WHO classification, released in 2019, is the most detailed [5]. Importantly, that WHO classification includes not only adenocarcinoma of the stomach but also all other types of gastric tumors with a lower frequency. GC is divided into several subgroups, including papillary, tubular, mucinous, and mixed carcinomas. The group of poorly cohesive tumors includes those of the signet ring cell type. All other GCs covered by the WHO classification can be defined as rare due to their insignificant clinical value [5].

Conventional surgical and systemic treatment has demonstrated limited achievement. Evolution in personalized therapy is a main factor to improve the outcome, but for a successful application, a careful stratification of patients is required. An essential part of this process is a precise recognition of the main prognostic factors, such as dif-

ferent histological types of GC, degree of differentiation, presence or absence of lymphovascular and perineural invasion, and stage of disease.

The aim of the present study was to analyze the mandatory clinical and pathological characteristics of the patients with GS and to estimate the correlations between them in terms of establishment of the following treatment plan.

**MATERIALS AND METHODS:**

Medical documentation and paraffine-embedded and hematoxylin-eosin-stained samples of patients who have undergone total or partial gastric resection endoscopic and laparoscopic biopsy due to GC were collected from the archive in a period from January 2020 to December 2023. The materials were evaluated by a pathologist (SB) to confirm the histological type, grade of differentiation and inflammatory reaction, presence or absence of lymphovascular and perineural invasion, depth of invasion and nodular status. The clinical data as gender, age, tumor anatomical localization and presence or absence of distant metastases, were collected from the medical documentation by clinicians (LD and BT). Histological typification was performed according to Lauren and WHO (2019) classifications. Postoperative staging was performed according to TNM Classification of Malignant Tumours, 8th edition (UICC). SPSS 19.0 was used to analyzed the data, applying descriptive and correlative statistics. Statistically significant was accepted p value <0,05.

**RESULTS:**

Clinico-morphological characteristics of the patients  
 Totally 74 patients with GC were included in the study. The average age was 69,6 years, with a male predominance in all age groups. Most frequent histological type was intestinal type, according to Lauren and tubular type, according to WHO classifications. Majority of the patients were diagnosed in an advanced stage of the disease. Detailed clinic-pathological data are summarized in Table 1.

**Table 1.** Clinico-pathological characteristics of the patients (n=74).

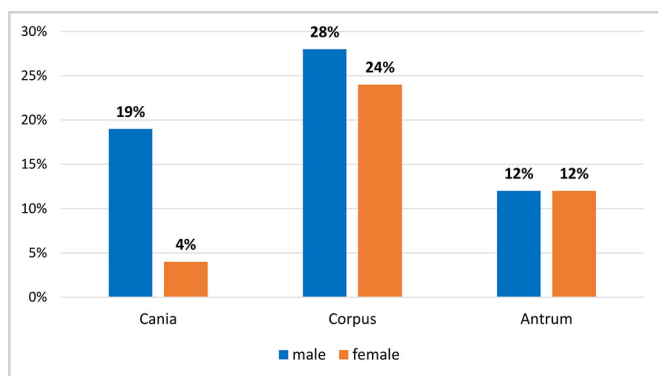
| Characteristics |                    |            |
|-----------------|--------------------|------------|
| Sex             | Male               | 44 (59.5%) |
|                 | Female             | 30 (40.5%) |
| Age             | Mean               | 69 years   |
|                 | Minimum            | 39 years   |
|                 | Maximum            | 87 years   |
|                 | Standard deviation | 9 years    |
| Tumor location  | Cardia             | 17 (23.0%) |
|                 | Corpus             | 38 (52.7%) |
|                 | Antrum             | 18 (24.3%) |

|                         |                  |            |
|-------------------------|------------------|------------|
| Lauren type             | Intestinal       | 42 (56.8%) |
|                         | Diffuse          | 29 (39.2%) |
|                         | Mixed            | 3 (4.1%)   |
| WHO type                | Tubular          | 30 (45.9%) |
|                         | Papillary        | 2 (2.7%)   |
|                         | Mucinous         | 1 (1.4%)   |
|                         | Signet ring cell | 7 (9.5%)   |
|                         | Poorly cohesive  | 22 (29.7%) |
|                         | Mixed            | 8 (10.8%)  |
| Differentiation         | G1               | 5 (6.8%)   |
|                         | G2               | 26 (35.1%) |
|                         | G3               | 43 (58.1%) |
| Inflammatory reaction   | Severe           | 26 (35.1%) |
|                         | Moderate         | 31 (41.9%) |
|                         | Mild             | 17 (23.0%) |
| Lymphovascular invasion | Present          | 34 (45.9%) |
|                         | Absent           | 40 (51.1%) |
| Perineural invasion     | Present          | 38 (51.4%) |
|                         | Absent           | 36 (48.6%) |
| T                       | T1               | 3 (4.1%)   |
|                         | T2               | 8 (10.8%)  |
|                         | T3               | 37 (50.0%) |
|                         | T4a              | 18 (24.3%) |
|                         | T4b              | 6 (8.1%)   |
|                         | Tx               | 2 (2.7%)   |
| N                       | N0               | 16 (21.6%) |
|                         | N1               | 15 (20.3%) |
|                         | N2               | 12 (16.2%) |
|                         | N3               | 25 (33.8%) |
|                         | Nx               | 6 (8.1%)   |
| M                       | M0               | 50 (67.6%) |
|                         | M1               | 24 (32.4%) |

Correlations between clinico-morphological characteristics

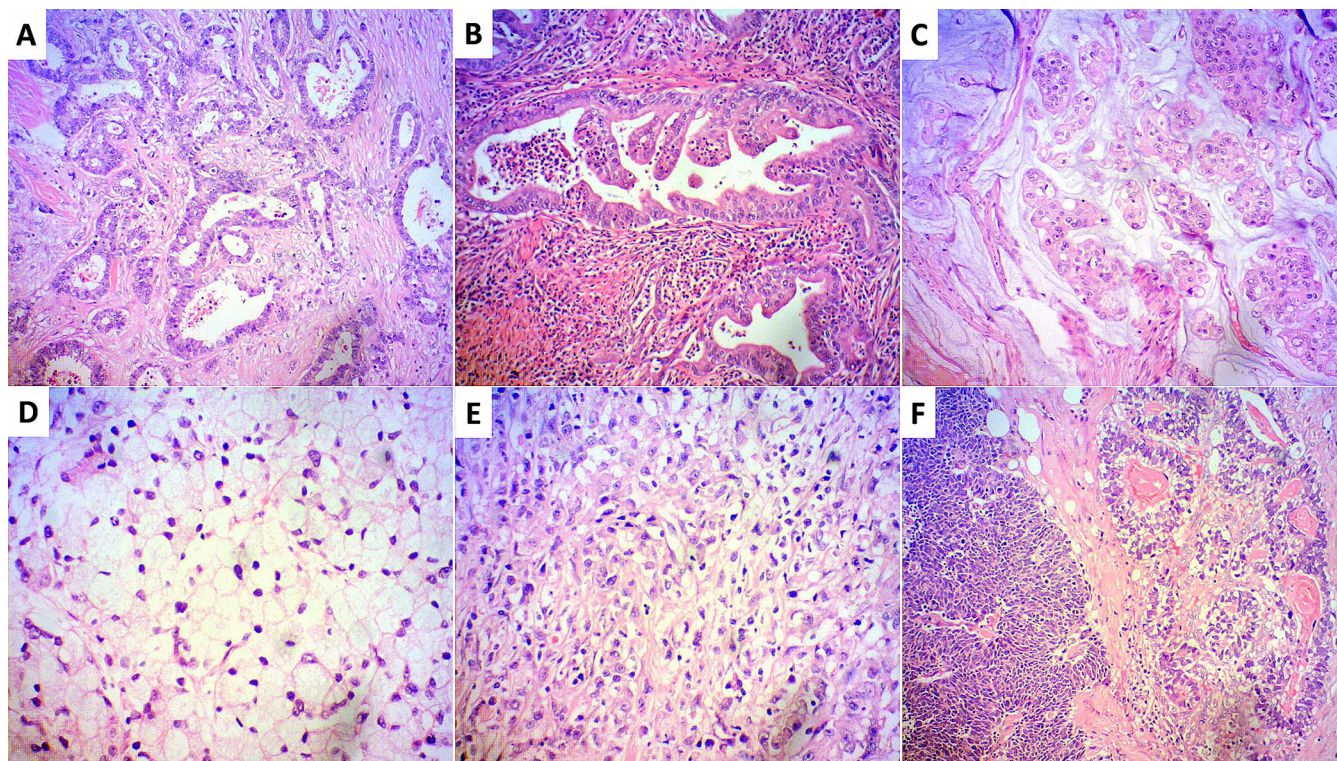
The authors did not find a statistically significant correlation in term of sex and age of the patients and all other parameters, except of location. There was a statistically significant correlation between tumor site and sex, as 82,3% (p<0,05) of GC located in cardia were diagnosed in males (Fig. 1).

**Fig. 1.** Correlation between sex of the patients and tumor site.



There was a highly statistically significant correlation between Lauren and WHO classifications ( $p < 0,000$ ) and between tumor type and tumor differentiation ( $p < 0,000$ ). Almost all (37/42) tubular, papillary and mucinous types by WHO classification were classified as intestinal type by Lauren. 5 cases of an intestinal type by Lauren were considered as mixed by WHO classification since they consisted of the two different histological intestinal types (tubular and papillary, or tubular and mucinous). All signet ring cell and poorly cohesive adenocarcinomas by WHO classification were accordingly assigned as diffuse type by Lauren. Three cases of the mixed type by both classifications were as follows: one case of tubular adenocarcinoma and small cell neuroendocrine carcinoma and 2 cases of tubular and poorly cohesive adenocarcinomas. Representative images of the histological types of GC are displayed on Figure 2.

**Fig. 2.** **A)** Tubular (intestinal) type GC. (HE, x100). **B)** Papillary (intestinal) type GC (HE, x100). **C)** Mucinous (intestinal) type GC (HE, x100). **D)** Signet ring cell (diffuse) GC (HE, x200). **E)** Poorly cohesive (diffuse) GC (HE, x200). **F)** Mixed type GC (small cell neuroendocrine carcinoma on the left side and tubular adenocarcinoma on the right side) (HE, x100).



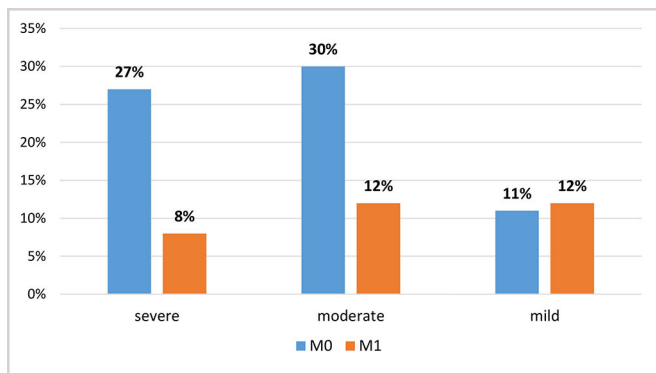
More than half (52,2%) of the tubular/intestinal type of tumors were graded as G1 or G2, almost all (93,1%) signet ring and poorly cohesive/diffuse type GC were graded as G3.

The following statistically significant correlations were observed in term of perineural invasion and histological type by Lauren ( $p < 0,043$ ), degree of differentiation ( $p < 0,04$ ) and lymphovascular invasion ( $p < 0,000$ ). The presence of perineural invasion was identified in 58,6% of diffuse type GC and in 42,8% of intestinal type GC; in 60,4%, 42,3% and 20% of G3, G2 and G1 tumors accord-

ingly. Expectedly, there was a statistically significant agreement between elements of the TNM staging system as advanced T was correlated with advanced N ( $p < 0,001$ ) and M ( $p < 0,000$ ), and advanced N was correlated with advanced M ( $p < 0,027$ ).

The most intriguing correspondence was found between a degree of inflammatory reaction and  $\bar{I}$  status ( $p < 0,022$ ). Only in the group of GC with a mild inflammatory reaction more than half of the patients have distant metastases (Fig.3).

**Fig. 3.** Correlation between a degree of inflammatory reaction and M status.



### DISCUSSION:

GC is a heterogenic disease in terms of epidemiology, morphology and biology. Sex is a significant factor that affects occurrence in GC. Worldwide, as well as in Bulgaria, the frequency of the GC among the male population is almost twice compared of females [1,2]. The results of our study demonstrated the same trend. Probable explanation of this phenomenon could be a poor daily routine, unhealthy diet and bad habits such as alcohol consumption and smoking [6]. A finding in our study regarding a higher frequency of development of GC in cardia in men may support this hypothesis.

There are several classification systems proposed for GC, of which practical value is still debated due to the complexity of the morphologic appearance of the GC. The WHO classification is distinguished by its exclusively morphological value and does not demonstrate a significant correlation with the histogenesis or biological behavior of GC, limiting its importance as a prognostic factor or as a surrogate for molecular classifications [7]. Recent studies have found that the Lauren classification is an independent prognostic factor in patients with

GC [8, 9], with observations showing that diffuse type is associated with a worse prognosis [8, 10]. This type demonstrated a higher T and N stage and a higher incidence of perineural invasion and distant metastasis [11, 12]. In the present research, diffuse type by the Lauren system was associated with poor differentiation (G3) and high frequency of perineural invasion. Modern studies describe perineural invasion as an indicator of advance GC with larger tumor size, advanced stage, undifferentiated type, and presence of invasion in lymphatic or venous vessels [13, 14, 15]. The present study revealed the same correlation between perineural and lymphovascular invasion.

The tumor microenvironment is an important element of the tumors progression and spread. This phenomenon incorporates three main components: tumor infiltrating lymphocytes (TILs), inflammatory cytokines and angiogenesis [16]. The ability to escape an immune reaction of the host is one of the mechanisms of GC progression. The other is a transformation of immune cells into tumor cell helpers [17]. Our results advocate this hypothesis – tumors with mild or almost absent inflammatory reaction demonstrated a higher level of progression. This specific topic needs to be further investigated in a term of prognostic significance.

### CONCLUSION:

The present study demonstrated correlations between some main clinico-pathological parameters in patients with GC in our institution. Precise histological typification of GC is a key to better stratification of the patients. Certain histological types are associated with aggressive tumor behavior, as we found diffuse type to correlate with poor differentiation and presence of perineural invasion. Degree of inflammatory reaction may be an independent indicator for the presence of distant metastases. Further investigation in larger cohorts is needed for better understanding of the correlations between tumor microenvironment and biological behavior.

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