Original Paper

# Evaluation of Gastric Carcinomas Histological Patterns in Relation to Tumors Aggressiveness Parameters

MARIA DOBRIȚOIU[1], ALEX EMILIAN STEPAN[2], CRISTIN-CONSTANTIN VERE[3], CRISTIANA EUGENIA SIMIONESCU[2]

[1]PhD, University of Medicine and Pharmacy of Craiova

[2]Department of Pathology, University of Medicine and Pharmacy of Craiova

[3]Department of Gastroenterology, University of Medicine and Pharmacy of Craiova

**ABSTRACT:** Gastric carcinomas are frequent tumors with variable growth patterns that may interfere with the evaluation of histopathological prognostic parameters of the lesions. In this study we analyzed the incidence and statistical relation of histological growth patterns depending on the prognostic parameters of gastric carcinomas for 95 cases. Pure forms were present in 82.2% of cases, from which more frequent subtypes were low grade tubular carcinomas and poorly cohesive with signet-ring cells carcinomas. Mixed forms were present in 17.8% of cases, with the highest incidence of tumors containing well differentiated tubular carcinoma and poorly differentiated papillary carcinoma areas. Analysis of the identified types and subtypes in relation to the histological prognostic parameters indicated significant differences regarding the tumor stage, the mixed subtypes being more frequent in advanced stages. Although mixed subtypes were more commonly associated with vascular and perineural invasion, the aspects were statistically insignificant. Together with tumor stage, the lymphovascular and/or perineural invasion should be taken into consideration as prognostic indicators in the postoperative management of gastric cancer.

***KEYWORDS:*** *Gastric carcinoma, histological pattern, prognostic parameters*

## Introduction

Gastric cancer is the fourth most common cancer and the second most common cause of mortality from this disease worldwide [1,2]. Although the incidence of gastric cancer has declined gradually over the last half century, the proximal gastric cancer incidence is growing [3].

Histopathologically, gastric carcinoma exhibits a marked architectural and cytological heterogeneity, often with the coexistence of multiple aspects. World Health Organization (WHO) classification recognizes four major histological patterns of gastric cancers: tubular, papillary, mucinous and poorly cohesive, along with some less uncommon histological variants [4]. The classification into these different subtypes is based on the dominant histological pattern, which often coexists with other histological patterns. The histopathological type is one of the major prognostic factors for carcinomas, which underlies the basic surgical management and consequently the extent of the surgical resection [5,6]. However, for gastric cancer, the prognostic value of the growth pattern has not been consistently recognized.

The mixed histological type accounts for about 25% of all gastric cancers, the coexistence of different histological patterns determining the behavior and prognosis as compared to pure forms of this neoplasia [7,8].

The present study followed the association of various histological patterns of gastric cancer with prognostic severity factors such as vascular and perineural invasion as well as tumor stage.

## Material and methods

The present study included a number of 95 cases of gastric carcinomas. The biological material was represented by surgical excision specimens obtained from the Surgical Clinics of the Emergency County Hospital of Craiova, which were fixed in 10% neutral buffered formalin, then processed by automated tissue processor (BioOptica) and hematoxylin-eosin stained. Interpretation and acquisition of images was performed using the Nikon E600 microscope. Tumors classification and staging was done according to the latest WHO classification [4].

The lymphovascular invasion was defined by the presence of cancer cells in the endothelium-lined area, and the peri/intraneural invasion was defined by the presence of peri/intraneural cancer cells.

The study was approved by the local ethical committee (no. 201/24$^{th}$ October 2017), and written informed consent was obtained from all the patients.



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## Results

The analyzed 95 cases of gastric carcinomas corresponded in 78 cases (82.2%) to pure forms and in 17 cases (17.8%) to mixed forms of the tumors (Table 1). The pure forms of tumors took the aspect of low-grade tubular carcinoma (35.7%) or poorly cohesive, with signet-ring cells carcinoma (18.9%) and poorly cohesive without signet-ring cells forms (12.6%). These were followed in the frequency order by high grade tubular carcinomas and papillary carcinomas of low or high grade. Mixed carcinoma forms have associated two tumor growth patterns in different proportions. Thus, we found more frequent tumors containing low grade tubular carcinoma areas and poorly differentiated papillary (9.5%) or high grade papillary and poorly cohesive areas (7.4%), and rarely the mucinous and poorly cohesive association pattern.

The classification of tumors analyzed in the pTNM staging system revealed for the pure forms carcinomas stage I eight cases (10.3%), 37 cases (47.4%) in stage II, 31 cases in stage III (39.7%) and two cases in stage IV (2.6%). Regarding the mixed forms, we found six cases in stage I (35.3%), nine cases in stage III (52.9%) and two cases in stage IV (11.8%). Tumor staging analysis based on the number of tumors with pure or mixed growth patterns indicated a higher incidence of the advanced stages (III and IV) for mixed forms (58.8%) compared to pure forms (42.3%).

The lymphovascular invasion was identified in 32 cases, representing 33.6% of the investigated cases. This aspect was observed in 12 cases of tubular low grade carcinomas (33.3%), in three cases for each of papillary high grade carcinomas (60%), poorly cohesive carcinomas with and without signet-ring cells (20%) and in two cases of mucinous carcinomas (50%). For subtypes of tubular high grade, mucinous and mixed with papillary high grade and signet ring cells, we found two cases of lymphovascular invasion for each form, as well as for the mixed form with mucinous carcinoma and signet ring cell carcinoma areas.

Related to the number of pure or mixed growth pattern carcinoma cases, the incidence of lymphovascular invasion was slightly higher in mixed forms (35.2%) compared to the pure ones (32%).

The peri-or intraneural invasion was present in 29 cases with an aspect of fascicle disposal of cancer cells in peri-or intraneural areas. In most cases the tumors corresponded to pure forms, respectively in 23 cases and in six cases to mixed forms. However, related to the number of cases, we noticed that 29.5% of pure carcinomas associated the peri/intraneural invasion compared with the mixed tumors which had this aspect in 35.2% of cases.

***Table 1. Histopathological parameters depending on carcinomas growth pattern***

| Growth pattern | | TNM stage | | | | Lympho-vascular invasion | Peri /intraneural invasion |
|---|---|---|---|---|---|---|---|
| | | I | II | III | IV | | |
| Pure (PGC) | tubular low grade (TGC-LG) | 6 | 20 | 8 | 0 | 12 | 9 |
| | tubular high grade (TGC-HG) | 0 | 2 | 2 | 1 | 3 | 2 |
| | papillary low grade (PGC-LG) | 2 | 0 | 0 | 0 | 0 | 0 |
| | papillary high grade (PGC-HG) | 0 | 0 | 3 | 0 | 3 | 3 |
| | mucinous (MGC) | 0 | 2 | 2 | 0 | 2 | 2 |
| | poorly cohesive without signet ring cells (PC-GC) | 0 | 5 | 7 | 0 | 3 | 3 |
| | poorly cohesive with signet ring cells (PC-GCS) | 0 | 8 | 9 | 1 | 3 | 4 |
| Mixed (MGC) | tubular low grade and papillary high grade (MGC-TP) | 0 | 4 | 5 | 0 | 3 | 3 |
| | papillary high grade and poorly cohesive signet ring cells (MGC-PS) | 0 | 2 | 4 | 1 | 2 | 3 |
| | mucinous and poorly cohesive signet ring cells (MGC-MS) | 0 | 0 | 0 | 1 | 1 | 0 |
| **Total** | | **8** | **43** | **40** | **4** | **32** | **29** |

In this study, the statistical analysis of histopathological parameters related to the mixed or pure type of lesions indicated insignificant differences ($p>0.05$, $\chi 2$ test), although the advanced stage, lymphovascular and peri-/intraneural invasion were more common in mixed carcinomas (Fig.1A-C).

The statistical analysis of mixed and pure carcinomas subtypes depending on the histopathological parameters indicated significant differences related to tumor stage ($p<0.001$, $\chi 2$ test), the mixed subtypes being more commonly diagnosed in stages II-IV compared to pure subtypes, frequently diagnosed in stages I-III (Fig.1D).

On the contrary, although mixed subtypes were more often associated with lymphovascular and peri-/intraneural invasion, the aspects were statistically insignificant (Fig.1E-F).

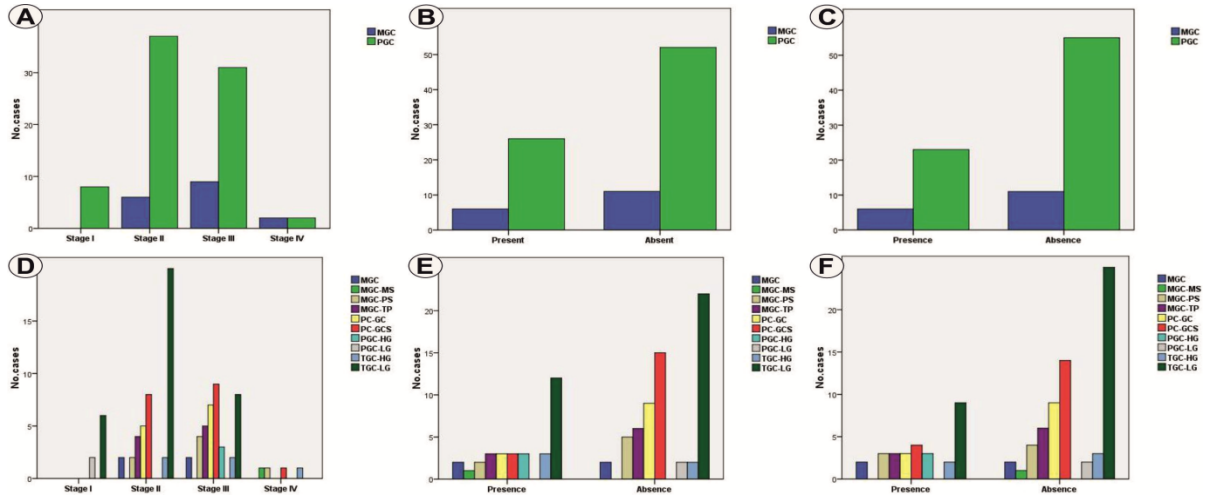


***Fig.1. Cases distribution related to tumor type and stage (A), lymphovascular invasion (B) and peri-/intraneural invasion invasion (C). Cases distribution related to tumoral subtype and stage (D), lymphovascular invasion (E) and peri-/intraneural invasion (F)***

## Discussions

The practical value of some of the histopathological variables is limited due to the histological complexity of the various growth patterns of gastric carcinomas, and especially of their coexistence, which often leads to an ambiguity in assessing the biological behavior [9,10].

It is generally accepted the fact that in the treatment guidelines the histological type is defined as one of the crucial factors in determining the need for practicing lymphadenectomy [11,12], as well as chemotherapy for advanced gastric cancer. Several studies have been concerned with identifying a more accurate stratification of prognosis for patients with gastric carcinoma based on morphological criteria [13-16].

A special place in the two most commonly used classifications of gastric cancer, WHO and Lauren classifications, is occupied by mixed carcinomas, which in various studies have been reported with variable incidence. Thus, in our study, mixed carcinomas represented 17.8% of all cases, compared to other studies that reported incidences of 21.9% [14], 13% [17], 14% [18], 14.1% [15], 27.2% [19] and 38.5% [20].

Concerning the results on mixed-type gastric cancer, several studies reported that it is associated with in lymph nodes metastasis [21-23] and large size tumors [24].

Analyzing the incidence of the histopathological negative prognostic factors, such as advanced stage, lymphovascular and peri-/intraneural invasion related to the mixed or pure tumor growth patterns, we observed for all the analyzed histopathological parameters a higher incidence in the mixed forms compared to the pure ones. Thus, the advanced stages (III/IV) of the tumors were present in 64.7% of the mixed forms cases and in 42.3% of the pure ones. For lymphovascular invasion, we found an incidence of 35.2% in mixed pattern cases, compared to 32% for pure ones, and for peri-/intraneural invasion an incidence of 29.5% in pure carcinomas versus 35.2% in mixed forms. Moreover, for 25 cases we found the presence of both lymphovascular and peri-/intraneural invasion, with an incidence of 29.4 in the mixed growth pattern tumors compared to 26.9% in the pure ones.

In gastric cancers, it was proven that the pTNM stage had a prognostic significance for both the 5 years survival rate and the local recurrence rate [25].

The lymphvascular invasion is an unfavorable prognostic indicator, its presence providing useful information for the prognosis and clinical management of patients with gastric carcinoma regardless of the disease stage [26].

Several studies have shown that the presence of lymphvascular invasion is correlated with tumor recurrence and a low survival rate independently of the lymph node status [27-32].

The incidence of lymphvascular invasion in gastric cancer ranges from 5.4% to 86%, the lowest incidence being reported in patients with lymph node negative tumors [33,34].

Several studies have shown that lymphovascular invasion is an unfavorable prognostic indicator independent of the


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clinical-pathological factors of gastric cancer without lymph node metastasis, concluding that this parameter invasion can provide useful information for prognosis and clinical management in the subgroup of patients with gastric cancer and lymph node metastasis [33,35].

Kooby DA et al. reported that vascular invasion in patients with negative lymph node was an independent predictor of unfavorable evolution and identified more aggressive lesions independent of tumor size and depth of invasion [36].

The combination of traditional TNM staging and the assessment of lymphovascular invasion could lead to a more accurate indication for the patient's prognosis [37].

On the other hand, perineural invasion is an independent prognostic factor that affects overall survival and disease-free survival of gastric cancer patients undergoing curative resection, independently of lymph node status, tumor size, and depth of invasion [38].

Several studies have reported that lymphovascular or perineural invasion is associated with poor survival and/or early recurrences in gastric cancer, but only a small number of studies compared the prognostic superiority of lymphovascular and perineural invasion association [39-42].

## Conclusions

In mixed type gastric carcinomas, the negative prognostic factors, represented by the advanced stage, lymph-vascular invasion and peri-/intraneural invasion have a higher incidence compared to pure forms.

As a result, alongside the tumor stage, lymphovascular and/or intra-/perineural invasion should be taken into consideration in the postoperative gastric cancer management, and the concomitant presence of the two parameters may be used as a prognostic factor.

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***Corresponding Author: Alex Emilian Stepan, Department of Pathology, University of Medicine and Pharmacy of Craiova, 66 1 May Avenue, 200628 Craiova, Romania, e-mail: astepan76@yahoo.com***