Comparative study of clinical-morphological profiles of different types of gastric carcinoma

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Abstract

Aim: Gastric carcinoma shows considerable variation in the histological pattern and degree of differentiation. The aim of the study was to assess especially the morphological differences between gastric carcinomas revealing one morphological feature and those including two morphological features. Materials and Methods: Two groups of patients were selected: Group 1, including 43 patients with tumors revealing only one architectural pattern, and Group 2, including 16 patients with two architectural patterns within the tumor. In addition to gender and age, the main morphological parameters were: lesion location and macroscopic appearance on the surgical excision sample and microscopic appearance of the surgical excision sample, assessed for architectural pattern, secretory properties and prognosis based on histological features, degree of tumor extension and the degree of tumor aggressiveness, using a wide range of histological and immunohistochimical stainings. All data were compared between the two groups using statistical tests. Results and Discussion: Significant differences were observed between the values and distributions of morphological parameters in the two groups and were discussed comparatively. Conclusions: Tumors with two dominant histological aspects present simultaneously are a reality that cannot be argued but whose morphological and biological profile needs to be completed and validated.

Keywords: gastric carcinoma, morphology, classification.

5 Introduction

Gastric cancer is one of the most redoubtable malignancies worldwide with a multifactorial determinism, a distribution and development influenced by a wide spectrum of predisposing, favoring and driving factors, and a polymorphic clinical-morphological profile, which are all ultimately leading to a very low life expectancy from detection. One of the reasons pleading for this is the very reserved prognosis of advanced forms, with survival rates less than 23% and rarely more than 15% [1, 2].

The last data in the literature show that, in 2013, gastric cancer was the 5th type of cancer as incidence and the second cause of death by cancer, with some differences between developed countries where it ranked 5th for incidence and 3rd for mortality and developing countries where it was in the 3rd position for both incidence and mortality. However, in terms of crude cancer Years of Life Lost (YLLs), gastric cancer descended from the second position in 1990 to the 3rd position in 2013 [3]. There are also differences between genders. Thus, while among men stomach is the 5th common site of cancer diagnosed in 2012 with 9% of all male cancers, among women, stomach is the 4th common site of cancer diagnosed in 2012 with 5% of all female cancers [4, 5].

The considerable dynamic variation of its clinical morphological profile includes: differences regarding genetic susceptibility, geographical location, life style, location in the stomach, with a more aggressive phenotype in proximal tumors, morphological heterogeneity both between different tumors but even within the same tumor, a wide range of clinical manifestations and prognosis factors [6–10].

This complex picture of gastric cancer led to a large number of attempts to set up a classification system, which would include those aspects of tumor morphology with a proved prognostic significance. However, the unsatisfactory results of the treatments applied following these classifications prove that we still lack of a consistent number of indicators for the clinical behavior, which could result in establishing the diagnosis and effective therapeutic strategies [8, 11]. One reason of failing in finding the most effective parameters for diagnosis and prognosis could be, as Song et al. were saying, the use only of major diagnostic principles and the ignoring of the highly heterogeneous histological features of gastric cancer, of tumor biological behavior and of prognostic value of minor histological type [12].

In this study, we attempted to evaluate the possible differences mainly from morphological point of view between gastric carcinomas revealing only one architectural pattern and those made up of two distinct architectural patterns.
Materials and Methods

The basis for this study was originally composed of a group of 59 patients admitted and operated in the Surgical Clinics of the Emergency County Hospital and Railroad University Hospital, Craiova, Romania, in which the post-operative histopathological examination established the diagnosis of gastric carcinoma. The inclusion criteria for patients in groups and subgroups were: existence of surgical intervention, histopathological diagnosis of gastric carcinoma. From the initial batch, two study groups were individualized: (a) Group 1, consisting of 43 patients in whom histopathological examination revealed within the tumor mass the existence of a single morphological aspect according to the World Health Organization (WHO) classification [13] and (b) Group 2, consisting of 16 patients in whom histopathology revealed, within the tumor mass, two areas with different morphological classification according to the WHO.

The study material was represented by two types of data sources: (a) The first category included the medical records of the selected patients: clinical records, surgery protocols, histopathological diagnosis registers). (b) The second category included: surgical excision samples from cases operated during the study, paraffin blocks from cases operated before the beginning of the study, and histological preparations obtained from all cases included in study.

The study was both retrospective and prospective, and was also comparative between the two groups of tumors. “Database”-type files were created in the computer in which all parameters considered were included. They were divided into: (a) clinical parameters – gender, age, and (b) morphological parameters – lesion location on the surgical excision sample, macroscopic appearance of the lesion on the surgical excision sample, microscopic appearance of the surgical excision sample, assessed for architectural pattern following WHO classification [13], for architectural pattern and secretory properties following Goseki et al. classification [14], and for prognosis based on histological features following Zhu et al. classification [15], degree of tumor extension (invasion of gastric wall assessed on the surgical excision sample, lymph node invasion, distant dissemination, TNM stage) and degree of tumor aggressiveness (assessment of the proliferation marker Ki67, and p53).

Histopathological examination

Tumor tissue fragments were subjected to conventional histological processing techniques (fixation and paraffin embedding). Serial sections were cut from each block. The first five sections were stained using classical staining methods [Hematoxylin–Eosin (HE), Masson’s trichrome, Gömöri, Mucicarmine, Alcian Blue]. The following six sections were used for immunohistochemical (IHC) labeling with the following antibodies: CD34, alpha-smooth muscle actin (α-SMA), Ki67, p53, MUC1 and MUC2.

Acquisition of microscopic images

Histopathological aspects were selected using the ×4 eyepiece. For image acquisition, optical planapo corrected objectives with magnification of ×4, ×10, ×20 and ×40 were used. The most significant images were obtained with a digital video camera, transferred directly into the computer, and processed using a specialized image analysis software.

The tumor aggressiveness was assessed by calculating the Ki67 proliferation index and the p53 index. To obtain these indices, at least 1000 nuclei of malignant cells in several microscopic fields photographed with ×40 objective were counted.

Processing and interpretation of results

In order to analyze the correlations between parameters, the filtering of the primary data with their division into groups was required. For numeric parameters, the following statistical indicators were calculated: VMIN, VMAX, MMEAN, STDEV. For parameters divided into classes using stratification scales, the $\chi^2$ correlation test was used. The graphic expression of the results and their interpretation were carried out using specialized statistical software.

Results

Gender distribution

Overall, gastric carcinomas were encountered more frequently in men. However, it is interesting to point out that tumors with two architectural patterns had a significant frequency in women, 1.6 times higher than that in tumors with only one architectural pattern (Figure 1).

Age distribution

Patients of Group 1 had a mean age of slightly over 65 years, with a wide dispersion interval of values, from 4th until 8th decade of life. However, most of the cases concentrated around the mean age, between 6th and 8th decades of life (Figures 2 and 3). The age trend was an ascending one, with more than 40% of the cases belonging to 70 to 79 decade of live (Figure 3). Patients of Group 2, in turn, had a different profile of age distribution. Thus, mean age was less than 60 years of life, with a dispersion interval of values as wide as previously but moved to younger ages, the youngest age being of 30 years and the oldest age being of 70 years. Likewise, most of cases concentrated in an interval defined by STDEV with the lower limit around 45 years, as seen in Figure 2 and 3. The age trend was also somehow different, with a reduced increase until 6th decade of live, with a peak and a concentration of more than half of the cases between 60 and 70 years of age and only one case over the latter limit (Figure 3).
Tumor site

Tumors belonging to Group 1 were placed in almost one half of the cases in the distal region of the stomach (antro-pyloric region – AP-R) the rest being distributed somehow evenly in the other regions (cardia region – CAR, corpus region, including fornix – CO and lesser and greater curvatures – LC and GC, respectively). Tumors belonging to Group 2 were almost exclusively situated in the antro-pyloric region (Figure 4).

Gross aspect

The assessment of tumor gross aspect based on the acknowledged system proposed by Borrmann in the 30s (type I: polypoid – P; type II: fungating – F; type III: ulcerated – U; and type IV: infiltrated – INF) [16].

We further grouped Borrmann subtypes in two main patterns of gross expression: the predominantly protruding pattern developed in the luminal space and including polypoid and fungating aspects and the predominantly flat pattern developed in the thickness of the gastric wall and including ulcerated and infiltrated aspects.

In Group 1 tumors, the ratio between the protruding and infiltrated patterns was slightly in favor of the latter. All subtypes were observed but most frequently the pure infiltrated and the fungating ones (Figures 5 and 6).
In Group 2, the predominantly flat pattern was present in almost two-thirds of the cases and clearly dominated by the infiltrated type. The protruding pattern was represented, with one exception, by the fungating type (Figures 5 and 6).

**Ulceration**

The analysis of ulceration presence, sole or multiple, directly noticeable on the tumor surface showed that while in Group 1 almost two-thirds of the tumors had ulceration(s) on their external surface (10 of the 17 infiltrated tumors revealed ulcerations), in the Group 2, because only three of the nine infiltrated tumors had also ulcerations on the surface, the distribution was more balanced but still slightly in favor of ulceration presence (Figures 7 and 8).

**Tumor morphology**

**WHO classification**

WHO classification system is still one of the main assessment tools of gastric carcinomas morphology. One of its inconveniences is the presence of two areas comparable as extension but with different architectural patterns in the same tumor in a significant number of cases because the system has not a “mixed” category to include these cases. Therefore, in the Group 2 we took into consideration the areas with distinct architectural pattern from each tumor, thus, assessing 32 tumor areas instead of the 16 cases as a whole.

In Group 1, the most frequently observed architectural pattern was the undifferentiated one (Figure 10e), representing almost one-half of the cases, followed by the tubular pattern (Figure 10a), with almost one-third of the cases (Figure 9).

In Group 2, the distribution is totally different. Thus, the tubular pattern is the most frequently observed, with more than 40% of tumor areas, followed by the mucinous pattern (Figure 10c), observed in almost one-third of the tumor areas. The undifferentiated pattern is decreasing until less than 15%. Papillary and “signet ring cell” patterns (Figure 10, b and d) are present in both groups but not so frequently (around or less than 10% of tumor areas (Figure 9).

Regarding the profile of architectural patterns associations in Group 2, tubular pattern was present in 13 of the 16 cases. It was associated with all the other architectural types but most frequently with mucinous pattern, in more than half of the cases (7/13), in which it was observed (Table 1).

In the three remaining cases without tubular pattern, the undifferentiated pattern was associated with mucinous pattern in one case and with papillary pattern in a second case, the third case harboring an association between the two secretory patterns: mucinous and “signet ring cell”.

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**Figure 6 – Distribution according to gross aspect.**

**Figure 7 – Presence of ulceration on tumor surface.**

**Figure 8 – Tumor ulceration: (a) Gross aspect; (b) Microscopic aspect (HE staining, ×100).**

**Figure 9 – Distribution based on WHO classification.**
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Figure 10 – WHO tumor classification: (a) Tubular pattern (MUC1, ×100); (b) Papillary pattern (HE staining, ×100); (c) Mucinous pattern (Alcian Blue staining, ×100); (d) “Signet ring cells” pattern (Mucicarmine staining, ×100); (e) Undifferentiated pattern (Masson’s trichrome staining, ×100). Red arrows mark different characteristics of each pattern.

Table 1 – Association of histological patterns in Group 2

<table>
<thead>
<tr>
<th>WHO type</th>
<th>Tubular</th>
<th>M</th>
<th>P</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous (M)</td>
<td>7</td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Papillary (P)</td>
<td>2</td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Signet-ring cell</td>
<td>2</td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>16</td>
</tr>
</tbody>
</table>

WHO: World Health Organization.

Degree of differentiation

For those tumors with gland formation in which we included also the papillary aspects, the degree of differentiation was assessed in addition.

In Group 1, the glandular formation, present in 19 cases, showed most often (almost 60% of cases) a moderately differentiated aspect. In turn, in Group 2, the poorly differentiated aspect is dominating, being present in more than half of the cases with glandular formation of this group (17 cases). Well-differentiated aspects were observed rarely but twice as frequently in Group 2 as compared to Group 1 (Figure 11).

Figure 11 – Distribution based on the grade of differentiation of tubular and papillary forms.

Secretory phenotype (Goseki classification)

Another important feature of the tumoral cell population is the presence (or absence) of the secretory properties. The assessment scale used was that of Goseki et al. [14], which combine the tumoral architecture and secretory properties.

In Group 1, the distribution of the three most often observed Goseki types was almost even, however one should notice that Goseki patterns with secretory phenotype accounted for almost two-thirds of the cases.

In Group 2, excepting one case, all cases revealed secretory properties, three quarters of which presented glandular formation too (Figures 12 and 13).
Figure 12 – Goseki classification: (a) Goseki I (MUC1–, ×200); (b) Goseki II (MUC1+, ×100); (c) Goseki III (MUC1–, ×200); (d) Goseki IV (MUC1+, ×200).

Figure 13 – Distribution based on secretory phenotype.

Zhu classification

Last year, Zhu et al. tried to give a prognostic value to the wide heterogeneity of histological aspects of gastric carcinomas. In the first step, they assigned a score, in points, to each histopathological aspect recognized by WHO classification, according to the degree of differentiation. This primary score allowed further calculating a final general score of the tumor, by taking into consideration all its architectural patterns. Finally, from this obtained histological grading stage (H stage), a four steps scale was designed as follows: H1 (≤2 points), H2 (2–3 points), H3 (3–4 points), and H4 (4–5 points) [15].

Using this new score, we observed that, while in Group 1 more than half of tumors had a high H score, most of them H4, in Group 2 almost two-thirds of the tumors had lower H score, most of them H2 (Figure 14).

Figure 14 – Distribution based on Zhu score.

Gastric wall invasion (pT)

The studied tumors could be considered very aggressive, more than two-thirds of them being found beyond the muscular layer of the gastric wall (Figures 15 and 16d). All cases of Group 2 invaded at least muscular layer, the few cases with incipient invasion in the mucosal or submucosal layers being observed only in Group 1 (Figure 16, a and b).

The percentage of going beyond the muscular layer was of two-thirds of cases in Group 1 while in Group 2 it was slightly higher than eighty percent.

In turn, more than one-third of Group 1 tumors were found beyond the gastric wall in the neighboring tissues, while only less than 15% of Group 2 tumors reached the perigastric tissues (Figure 15).
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Invasion of particular parietal structures

Invasion of at least one of the parietal structures that could have prognostic value was identified in 18 of the 59 operated patients, meaning a significant percentage of more than one-third of the cases (Figure 17).

This phenomenon with prognostic value was more pregnant in Group 1, being encountered in around 42% of the cases, whereas in Group 2 it was identified in only a quarter of cases.

The invasion of blood vessels was the most frequently encountered in the entire series, but in a higher percentage in Group 1 than in Group 2 (Figures 17 and 18a).

The second parietal structure affected by the tumor invasion was the network of local nerve fibers, which was equally involved in the two groups (Figures 17 and 18b).

Lymphatic vessels invasion was the third as frequency of occurrence in the entire series, being found three times less often in Group 2 than in Group 1 (Figures 17 and 18c).

Regional lymph nodes invasion (pN)

Lymph node invasion was present in nearly two-thirds of all patients (Figure 19). In more than half of the cases, tumor extension involved between one and six lymph nodes placed along the lesser curvature at less than 3 cm from the primary tumor.

Figure 15 – Distribution of different degrees of gastric wall invasion.

Figure 16 – Tumor invasion in gastric wall layers: (a) Tumor in mucosa – pT1 (Masson’s trichrome staining, ×100); (b) Tumor in submucosa – pT1 (MUC1+ staining, ×100); (c) Tumor in the muscular layer – pT2 (α-SMA+, ×200); (d) Tumor in subserous layer – pT3 (HE staining, ×100). Red arrows: Tumor cells; Yellow arrows: Muscularis mucosae; Blue arrows: Serous layer.

Figure 17 – Frequency of different particular parietal structures invasion in the two groups.

Figure 18 – Lymph node invasion (pN): (a) No invasion; (b) Invasion of one lymph node; (c) Invasion of two lymph nodes; (d) Invasion of three lymph nodes.
Figure 18 – Tumor invasion in particular structures of gastric wall.

Figure 19 – Distribution of different degrees of regional lymph nodes invasion.

The secondary tumor proliferations in regional lymph nodes had an extensive appearance, destroying the normal follicular structures, which could be identified only isolated (Figure 20, blue arrow) under the lymph node capsule (Figure 20, yellow arrow).

Figure 20 – Lymph node extended invasion.

The differences between the two groups were not so significant, however lymph node involvement was more frequent in Group 1 than in Group 2 – 62.8% vs. 56.2%, respectively (Figure 19).

Distant metastases (pM)

Although most of investigated tumors proved an aggressive and invasive behavior, distant dissemination was recorded in only eight cases. One could notice that, in percentage, metastasis was 2.5 times higher in Group 1 than in Group 2 – 25% vs. 9.3%, respectively (Figure 21).

Figure 21 – Distribution of distant metastases.

TNM staging

The advanced parietal invasion, coupled frequently with regional lymph node involvement resulted in high scores in TNM staging system for most of the cases included in the study. More than 60% of the Group 1 cases were in stages III and IV had more whereas less than 60% of the Group 2 cases were in these stages. The difference of almost 10% concerning the advanced stages was influenced particularly by the higher percentage of stage IV tumors of Group 1 (Figure 22).

Figure 22 – Distribution of different TNM stages.

Tumor aggressiveness

The immunohistochemical analysis of tumoral proliferation became an important assessment tool of the tumor aggressiveness and prognosis [17].

Ki67 index

There are few data in the literature concerning the prognostic value of Ki67 proliferation index in gastric carcinoma. There were not yet devised standardized scales to
assess Ki67 index, the estimation of positive cells percentage being still done subjectively in most of cases because dedicated software for image analysis are not in the current usage of diagnostic pathology departments.

Using such software, we could calculate the exact values of Ki67 index and its variations (Figure 23). For the latter, we used more nuanced values stratification, with a threshold value between classes of “10%”.

Even the dispersion interval of index values was wider, the mean value of Ki67 index was lower in Group 1 than in Group 2 because more than 40% of the cases had an index lower than 0.3.

In Group 2, even the dispersion interval of index values was more narrowed, the mean value of Ki67 index was higher than in Group 1 because three quarters of the cases had an index higher than 0.3 and one quarter higher than 0.5 (Figures 24 and 25).

However, the difference between mean values was not so significant both being included in the interval 0.3–0.4.

**P53 index**

Gene mutations and altered expression of p53 protein are frequently encountered in human malignant proliferations including those of the stomach [18–22].

Using the above-mentioned software, we could calculate the exact values of p53 index (Figure 26) and its variations too. The situation was somehow different as compared to the design of Ki67 score because not all cases showed positivity for p53. Therefore, the first class of the score scale included all negative cases and so the index value was “0”, value that was taken into consideration when statistical indices were computed.
Thus, dispersion interval of index values was very wide in both groups. Group 1 had a lower mean value of the p53 index and a more restricted interval where most of values were concentrated (Figure 27).

Group 2, in turn, had a wider interval where most of values were concentrated and a higher mean value of the p53 index. One should notice that the percentage of cases expressing p53 was significantly higher in Group 2 as compared with Group 1 – 50% vs. 32%, respectively and also that the percentage of cases with p53 index higher than 0.25 was two-fold higher in Group 2 than in Group 1 (Figure 28).

Tumor necrosis

Microscopic examination revealed also the presence of necrotic areas within the tumor masses, accompanied sometimes by hemorrhagic foci (Figure 29).

These intratumoral necrotic areas were slightly more often observed in Group 1 tumors, but without exceeding one-third of the cases (Figure 30).

Discussion

The comparative analysis of the clinical, morphological and behavioral parameters allowed us to delineate individual profiles for the two types of gastric carcinomas, profiles presented below and summarized in Table 2.

Thus, tumors showing only one histological pattern within the tumor mass were usually found in older men, showed no clear-cut predilection for any of the stomach segments even though the antro-pyloric region was most commonly affected, expressing both as wall infiltration and protrusion in the lumen, in both cases with associated tumor surface ulceration. From the histological point of view, they usually showed an undifferentiated pattern followed by a tubular/glandular pattern, usually moderately differentiated and secretory.

Positivity for Ki67 was present in all cases but with index values lower than 0.3 in more than 40% of the cases and p53 expression was rare.

The necrotic phenomenon, whether macroscopically visible on the tumor surface or microscopically identifiable within the tumor mass, was also a common observation. The biological behavior was an aggressive one, with complete gastric wall invasion in two-thirds of cases, frequent tumor emboli in intraparietal vascular structures, invasion into regional lymph nodes representing almost a rule, behavior reflected in the large proportion of stages III and IV as determined by the TNM system.

On the other hand, tumors with two dominant histological aspects within the tumor mass, usually revealed a younger patient, not infrequently a woman who had a tumor located almost exclusively in the antro-pyloric region, with predominantly infiltrative pattern and ulcerations on the flat surface of the tumor.

The dominant histological pattern was the tubular/glandular one, but most often poorly differentiated, with secretory phenotype, often accompanied by mucinous areas. Necrotic phenomena were present, as already mentioned, but more rarely than in the group with monomorphic tumors.

The biologic behavior was somewhat less aggressive, completely invading the wall but not exceeding the serous layer, with rare invasion of particular parietal structures, usually in blood vessels and perineural, more reduced lymph node invasion but with distant metastases twice as common as in the other type. Overall, TNM staging was more “gentle” than in the other group.

Positivity for Ki67 was present in all cases and with index values higher than 0.3 in three quarters of the cases and p53 expression was more frequent and with higher mean values than in the group of tumors showing only one histological pattern.
The difficulty, not to say the impossibility, to obtain data concerning the evolution after the hospitalization period put us in the awkward position of not being able to comparatively assess the outcome in the two groups of tumors and to compare our results with the literature.

A final observation resulted from the summarizing table is that not always and, unfortunately, in many situations the statistical test did not validate the differences between the two types of tumors revealed by the charts. We think that the explanation is the size of the studied series; larger groups would most probably express more statistically validated differences.

However, from histological point of view and even assessed on small series, the two architectural types of gastric carcinoma have different profiles.

### Table 2 – Clinical, pathological and behavioral profiles of the two types of gastric carcinoma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (One morphological aspect)</th>
<th>Group 2 (Two morphological aspects)</th>
<th>χ² correlation test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Men (72%)</td>
<td>More than 40% women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [years]</td>
<td>&gt;60 – many &gt;70</td>
<td>&lt;60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td>&lt;1/3 AP-R</td>
<td>Almost exclusively AP-R</td>
<td></td>
<td>0.113</td>
</tr>
<tr>
<td>Borrmann</td>
<td>Infiltrated 40% then fungating</td>
<td>Infiltrated &gt;50% then fungating</td>
<td></td>
<td>0.406</td>
</tr>
<tr>
<td>Ulceration</td>
<td>2/3rd of cases</td>
<td>More than 1/2 of cases</td>
<td></td>
<td>0.869</td>
</tr>
<tr>
<td>WHO classification</td>
<td>Mainly UD</td>
<td>Mainly T usually PD</td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Then T mainly MD</td>
<td>Then MUC</td>
<td></td>
<td>0.147</td>
</tr>
<tr>
<td>Goseki classification</td>
<td>Secretary &gt;60%, poor gland formation 60%</td>
<td>Secretary, mostly with gland formation</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Zhu classification</td>
<td>Mainly H4</td>
<td>Mainly H2</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ki67</td>
<td>Almost even distribution of index classes</td>
<td>75% with index &gt;0.3 Mean value slightly higher than in Group 1</td>
<td></td>
<td>0.332</td>
</tr>
<tr>
<td>P53</td>
<td>Expressed more rarely – around 1/3 of cases</td>
<td>Expressed more often – 50% of cases Mean value higher than in Group 1</td>
<td>0.499</td>
<td></td>
</tr>
<tr>
<td>Intra tumoral necrosis</td>
<td>Present in more than 1/3rd of cases</td>
<td>Present slightly lesser than in Group 1</td>
<td>0.671</td>
<td></td>
</tr>
<tr>
<td>pT</td>
<td>2/3rd pT3 and more than Group 2</td>
<td>More pT3 + pT4 than Group 1</td>
<td></td>
<td>0.153</td>
</tr>
<tr>
<td></td>
<td>Predominant pT3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasion of parietal structures</td>
<td>Frequently – 41% Mainly in blood vessels</td>
<td>Only 25% Blood vessels and perineural</td>
<td>0.138</td>
<td></td>
</tr>
<tr>
<td>pN</td>
<td>Present – 2/3rd of cases</td>
<td>Present – less in Group 1 but &gt;50%</td>
<td></td>
<td>0.425</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Rarely</td>
<td>Twice more frequently than in Group 1</td>
<td>0.117</td>
<td></td>
</tr>
<tr>
<td>TNM</td>
<td>All stages. 2/3rd III and IV</td>
<td>All stages. Less III and IV than Group 1 but &gt;50%</td>
<td>0.959</td>
<td></td>
</tr>
</tbody>
</table>


Although there are independent studies that have shown that the mixed type gastric tumor is a reality and not a rare one, accounting for over 25% of all gastric cancers and, moreover, that it has a more severe prognosis than pure types [8–10, 23, 24], on one hand taking into account the classifications that include this entity in routine practice is still far from becoming a common practice.

### Conclusions

The type of tumors with two dominant histological aspects present simultaneously is a reality that cannot be argued, which the authors of classifications have seen and try its individualization within the evaluation systems of gastric malignant epithelial neoplasia. Our results outlined a draft of the morphological and biological profile, which proves to be different from that of mono-morphic tumors, profile which needs to be completed and validated.

### Conflict of interests

The authors declare that they have no conflict of interests.

### Contribution note

All authors have contributed equally to this work.

### References

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Received: March 4, 2015
Accepted: December 16, 2015

[References: 24]