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Immunohistochemical Profile of Mucins in Gastric Carcinoma

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1. Introduction

Gastric cancer represents the second leading cause of cancer related death (after lung cancer) despite a global decline in both its incidence and mortality since the late half of the 20th century (Kelley & Duggan, 2003; Zheng et al., 2008). This type of cancer continues nowadays to be a major health problem due to the slow decrease in incidence in Asia and its high mortality in the western countries (Roukos et al., 2002). The overall prognosis is reserved, depending on the TNM stage in the moment of diagnosis and somewhat on its histological type (Lauren, 1965).

Based on morphological characteristics focused on gland formation and histogenetic background, gastric adenocarcinomas are divided into intestinal and diffuse types using the Lauren classification system (Lauren, 1965), or as differentiated and undifferentiated using the Nakamura classification system (Nakamura et al., 1968). Intestinal-type adenocarcinoma is considered to be equivalent to differentiated adenocarcinoma and the diffuse-type to the undifferentiated adenocarcinoma.

These different types of gastric carcinomas express particular biological behaviours. Helicobacter pylori infection leads to the development of chronic atrophic gastritis and intestinal metaplasia (Byrd et al., 1997). Usually the intestinal-type gastric carcinoma arises on the background of intestinal metaplasia (Stemmermann, 1994; Tahara, 1993), and, by contrary, the diffuse-type on the background of gastric mucosa without intestinal metaplasia (Nakamura et al., 1968). The diffuse-type, as classified according to the Lauren system (non-solid type of poorly differentiated adenocarcinoma and the signet-ring cell carcinoma according to a Japanese classification system) (Japanese Gastric Cancer Association, 1996), do not show glandular formation, can be further divided into two subtypes. In the first one, the tumor is predominantly composed of signet-ring cells (>50%) (signet-ring cell carcinomas) and in the other one, the adenocarcinoma contains few signet-ring cells (<50%) (non-signet ring cell carcinomas). Although these histological types can usually be distinguished using standard stainings, new advances in histochemical and immunohistochemical reactions using gastric and small intestinal cell markers determined emerging of gastric cancer classification into different phenotypes, according to mucin expression (Tatematsu et al., 1990).

Much effort is being carried out to identify markers with biological and therapeutical significance in gastric cancer. Mucins are expressed by various epithelial cell types, both normal and malignant. Mucins, high-weight glycoproteins, represent major components of the mucus layer which protects the gastric epithelium against chemical and mechanical aggressions (Corfiefd et al., 2000; Moniaux et al., 2001). In humans, at least 14 genes were identified, coding proteins of mucins, called MUC1, MUC2, MUC3, MUC4, MUC5AC, MUC5B, MUC6, MUC7, MUC8, MUC9, MUC11, MUC12, MUC13 and MUC16 (Pinto-de-Sousa et al., 2002; Silva et al., 2002). They are classified into two groups: membrane bound including MUC1, MUC3A, MUC3B, MUC4, MUC12, MUC13 and MUC 17, and secreted or gel forming including MUC2, MUC5AC, MUC5B and MUC6 (Fowler et al., 2001). All these mucins present common structural characteristics, but are distinct in their tandem repeat peptides. Abnormal expression of mucins has been reported to accompany cancer development, influence cellular growth, differentiation, transformation, adhesion, invasion and immune surveillance (De Bolos et al., 1995).

MUC1 is involved with cell signaling, immuno-regulation and inhibition of cell-cell and cell-matrix adhesion (Rakha et al., 2005; Wesseling et al., 1996). MUC1 cytoplasmic domain has been observed to interact with β-catenin through a similar mode found in E-cadherin, by this way inhibiting the formation of E-cadherin- β-catenin complex (Yamamoto et al., 1997). By this action, MUC1 may participate in tumor cell detachment, invasion and metastases, being associated with aggressive tumor behavior and poor prognosis. There have been reported interactions between MUC1 and members of EGFR family (Rahn et al., 2001). The cytoplasmic domain has a role of signaling mediator of tyrosine kinase receptors (phosphorylated MUC1-Grb2/SOS complex) (Schroeder et al., 2001). MUC1 is present on the apical surface of secretory epithelia, but in the malignant tissues is variable in amount and cellular localization (Pandey et al., 1995). The high aberrant MUC1 expression in tumors leads to antigenically recognizable epitopes on the MUC1 molecules and stimulation of the immune response, making MUC1 a potential immunotherapeutic target (Gendler, 2001).

MUC2 and MUC5AC are important proteins for producing the mucus that protects and lubricates epithelial surfaces. MUC2 is the major secretory glycoprotein expressed abundantly by intestinal and airway epithelium (Gum et al., 1994). Its expression is a common feature of all mucinous carcinomas derived from different organs, including stomach, colon, breast and prostate, acting as a potential prognostic marker (Utsunomiya et al., 1998; Yamashita et al., 1993; Zhang et al., 1998).

MUC5AC is found mainly in the mucosal layer of the cardia, fundus and antrum of the stomach, with the role of epithelia protection (Ho et al., 1995). Tumor phenotypes are classified on the basis of the expression of various markers, such as CD10 as a marker for the brush border on the luminal surface of enterocytes, mucin 2 (MUC2) as a marker of intestinal goblet cells, MUC5AC or human gastric mucin (HGM) as a marker of surface gastric epithelium (foveolar cells) and MUC6 as a marker for pyloric glands (Namikawa & Hanazaki, 2010).

CD10 and MUC2 are considered diagnostic markers of the intestinal phenotype and MUC5AC, HGM and MUC6 are markers of the gastric phenotype. Gastric cancer phenotypes can be classified into four groups, depending on the combination of mucin expression: intestinal type, gastric type, combined type and unclassified type (Shiroshita et al., 2004).

Intestinal metaplasia can be divided into incomplete (precancerous lesion), consisted by the presence of goblet cells in the gastric gland, and complete (not a precancerous lesion),

consisted by the presence of both enterocytes and goblet cells (Kawachi et al., 1974; Segura & Montero, 1983; Tosi et al., 1993). Based on the type of intestinal metaplasia, there are four phenotypes of gastric cancer: complete intestinal type, incomplete intestinal type, gastric type and unclassified type. The complete intestinal type is positive for CD10 and MUC2, and negative for MUC5AC. The incomplete intestinal phenotype is positive for CD10 and MUC5AC, or positive for MUC2 alone. The gastric type is positive for MUC5AC, and negative for CD10 and MUC2. Unclassified phenotypes are negative for CD10, MUC2, MUC5AC and MUC6. This classification based on mucin phenotype is important for assessing the biological behavior of gastric carcinomas and different therapeutic options (Namikawa & Hanazaki, 2010).

Gastric-type mucins are mucins specific to the gastric mucosa, although differentiated gastric adenocarcinomas change their mucin phenotype as they grow and invade deeper into the gastric wall. Recent reports reveal an incidence of 7.9-23.9% for the gastric-type differentiated adenocarcinomas among early gastric cancers (Kabashima et al., 2002; Koseki et al., 2000; Matsuoka et al., 2003). This type of early cancer tends to form larger tumors and exhibit higher rates of submucosal invasion in comparison with the intestinal-type (Matsuoka et al., 2003).

Gastric- and intestinal-types of differentiated gastric adenocarcinoma present differences in terms of their biological behavior. Usually, gastric-type tumors show scirrhous infiltration and intestinal-type carcinomas show a solid growth inside the wall (Oda et al., 2003; Shimoda et al., 1991). Some authors reported a significantly poorer prognosis in patients with advanced gastric cancer presenting gastric-type tumors vs. intestinal-type carcinomas, associated with increased malignant potential in the early phase of invasion and metastasis (Tajima et al., 2001). Koseki et al. (2000) have reported a significantly higher incidence of lymphatic invasion, venous invasion, and lymph node metastasis in the gastric-type. For these reasons, even in the early phase of the gastric-type, the decision to perform endoscopic mucosal/submucosal resection or minimal surgical procedures as a curative treatment should be carefully taken (Namikawa & Hanazaki, 2010).

The undifferentiated gastric adenocarcinoma show no clinicopathological differences between gastric and intestinal phenotypes. However, gastric-types present different growth patterns compared with intestinal-type tumors (Kabashima et al., 2005), showing a tendency to spread through the middle layer of the mucosa.

Recent studies have reported a different genetic background of patients with differentiated gastric adenocarcinomas for gastric-type compared to intestinal-type (Endoh et al., 2000; Fiocca et al., 2001; Matsuoka et al., 2003; Sugai et al., 2004). Overexpression of p53 protein is a common feature in differentiated adenocarcinoma (in both gastric- and intestinal phenotypes), but is rare in undifferentiated carcinoma (Matsuoka et al., 2003; Sugai et al., 2004). Data suggest that differentiation to gastric gland cells is related to the presence of microsatellite instability (MSI), whereas differentiation to intestinal epithelial cells is related to mutations in APC gene (Endoh et al., 2000; Tajima et al., 2006; Yamazaki et al., 2006).

Usually, the phenotype of gastric cancer tends to imitate the surrounding mucosa, with gastric-type cancers arising in areas expressing gastric-type or mixed-type mucins (Kabashima et al., 2000). Intestinal metaplasia surrounding gastric-phenotype of differentiated adenocarcinoma seems to be immature or incomplete, compared with gastric-intestinal or intestinal phenotype (Egashira et al., 1999).

Pinto-de-Sousa et al (2002) showed that the mucin phenotype is associated with the tumor site. In the study of Toki et al (2010), the signet ring cell carcinomas and non-signet ring cell

carcinomas were most frequently encountered in the upper or middle segments of the stomach. Over 95% of the advanced gastric cancers had either a G or GI phenotype. Pinto-de-Sousa et al (2002) studied the mucin phenotypes of 23 diffuse-type adenocarcinomas and showed that the MUC5AC expression rate in these tumors was significantly higher than that in the unclassified and expansive adenocarcinomas. Reis et al (1997), studying the expression of MUC5AC in early gastric cancers, demonstrate at least some G phenotype cells in the initial stages of the tumors.

Some studies show that the expression rates of the GI and I phenotypes in the cases of undifferentiated advanced gastric cancers were encountered in over half of the cases (Baresi et al., 2006; Tajima et al., 2001; Toki et al., 2010). Studies reported that the progression of the signet ring cell carcinomas was associated with a phenotype shift from the G-type to the I-type in order to progress to the deep layer (Bamba et al., 2001; Tian et al., 2007; Yamachika et al., 1997; Yamagishi et al., 2004). It is also suggested that the morphological features of the signet ring cells change and are subsequently classified as non-signet ring cell carcinomas during tumor progression (Toki et al., 2010).

In the present research we aimed to assess the profile of mucins in gastric carcinomas through immunohistochemical reactions using anti- MUC1, MUC2, and MUC5AC monoclonal antibodies. The purpose of this study is to compare the expression of mucins with clinicopathological factors and outcome of patients.

2. Material and method

From the total of 256 patients (186 males and 79 females), diagnosed clinically and histopathologically with gastric cancer in the period 1998-2002 that underwent surgical interventions in the Departments of Surgery of the Emergency County Clinical Hospital Timisoara, there were 67 patients selected. A prospective study was performed on this group, regarding the evolution and aggressiveness of gastric cancer, on a period of 5 years. Surgical interventions, performed with curative or palliative intention, were not preceded by chemotherapy or radiotherapy. The patients or their relatives were contacted periodically, on the phone or by medical letter, at 6-month intervals, survival being monitored on a variable period, between one month and 68 months. Patients who died postoperatively through various complications, or due to other conditions, were excluded from the study. Clinical and morphological (macroscopic and microscopic) data were collected for each case. Gastric carcinomas were classified and interpreted according to the evaluation protocol recommended by the American Joint Committee on Cancer (AJCC) and International Union against Cancer (UICC).

Survival time was calculated from the month of surgery until the month of death or confirmation of survival, and survival rate was represented by the percentage of survivals at the end of the interval monitored (in years and months). Out of the total of cases included in the prospective study, 6 patients died at variable intervals, between 7 and 26 months, due to other medical causes, being excluded from the study.

Immediately after excision, specimens were fixed in 10% neutral buffered formalin, embedded in paraffin wax, cut into 3 µm paraffin sections and stained with haematoxylin and eosin (HE) for routine light microscopy. For immunohistochemical staining, additional 3 µm thick sections were cut from paraffin-embedded tissue and placed on poly-L-lysine-coated glass slides. For the determination of mucin phenotypes, immunostaining was done for MUC 1 (monoclonal antibody Ab-5, MH1, Thermo Scientific), MUC2 (monoclonal

antibody Ab-2, M53, Thermo Scientific) and MUC5AC (monoclonal antibody Ab-1, 45M1, Thermo Scientific). Immunohistochemistry used the UltraVision Detection System, HRP/DAB (Ready-To-Use). The nuclear counterstaining was accomplished using Mayer's hematoxylin. According to their immunoreactivity, the cases were classified in 2 categories:

- negative cases (negative or positive immunoreactions in less than 5% of cells examined);
- positive cases (positive immunoreactions in more than 5% of cells examined).

Statistical analysis was performed using STATA 9.2 software (Statacorp, Texas, USA). Frequencies and percentages are shown for categorical data. Chi-square test was used to compare categorical data. Survival time was calculated as the time from cancer diagnosis to death, censoring at the date of last contact. The Kaplan-Meier method was used to compute 5-year survival rates and disease-specific survival curves were drawn. Differences between survival curves were determined by log-rank test. Survival analysis was performed using a Cox proportional hazards model. A *P*-value <0.05 was considered statistically significant, and hazard ratios (HR) with their respective 95% confidence interval (CI) were calculated.

3. Results

The final group consisted of 61 patients (43 males and 18 females) who presented ages between 30 and 80 (average age = 59.34 years). The main clinicopathological features of cases of gastric cancer investigated are presented in Table 1. In the peritumoral mucosa, MUC1 reactivity was detected in specialized glands of the gastric body (Fig. 1), in the pyloric glands (Fig. 2), and at the level of the antrum, in surface mucous cells and mucous neck cells.

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

Table 1. Clinicopathological characteristics of gastric cancers studied

MUC5AC is expressed strongly in the foveolar epithelium of gastric antrum and body (Fig. 3 and Fig. 4). MUC2, an intestinal-type mucin, was identified only on foci of intestinal metaplasia of gastric mucosa (in goblet cells – Fig. 5).

The expression of mucins in gastric carcinomas studied is heterogeneous and includes mucins synthesized normally by the gastric mucosa, as well as intestinal mucins expressed "de novo". We identified 41 cases with positive immune reactions for MUC1 (67.2%), 25 cases with positive reactions for MUC2 (40%), and 43 cases for MUC5AC (70.5%) (Graphic 1).

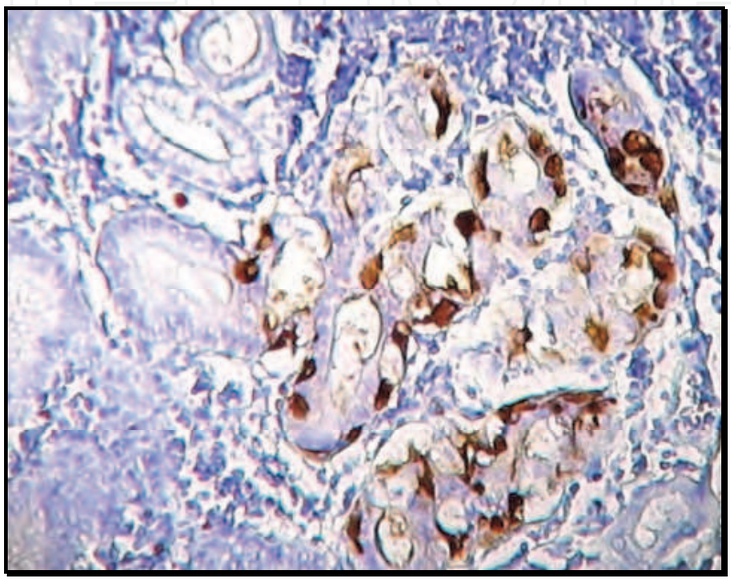


Fig. 1. MUC1-positive immunoreaction in specialized glands of the gastric body. DABx200.

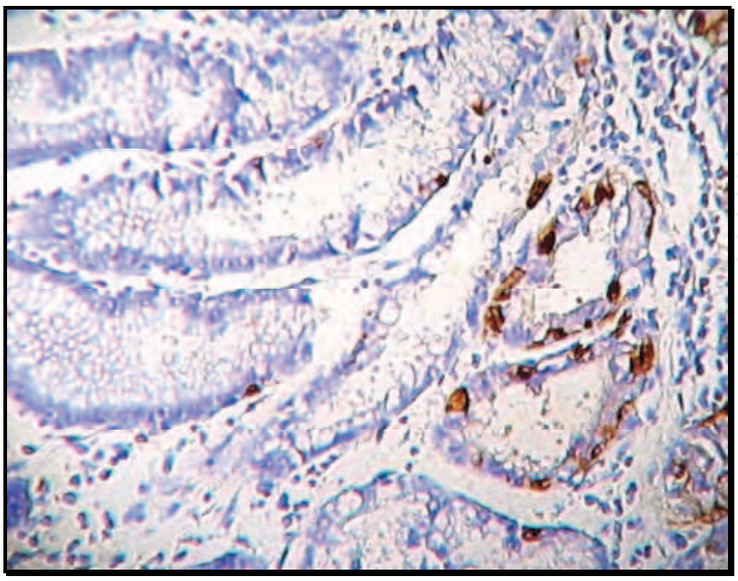


Fig. 2. MUC1 positive immunoreaction in pyloric glands. DABx200.

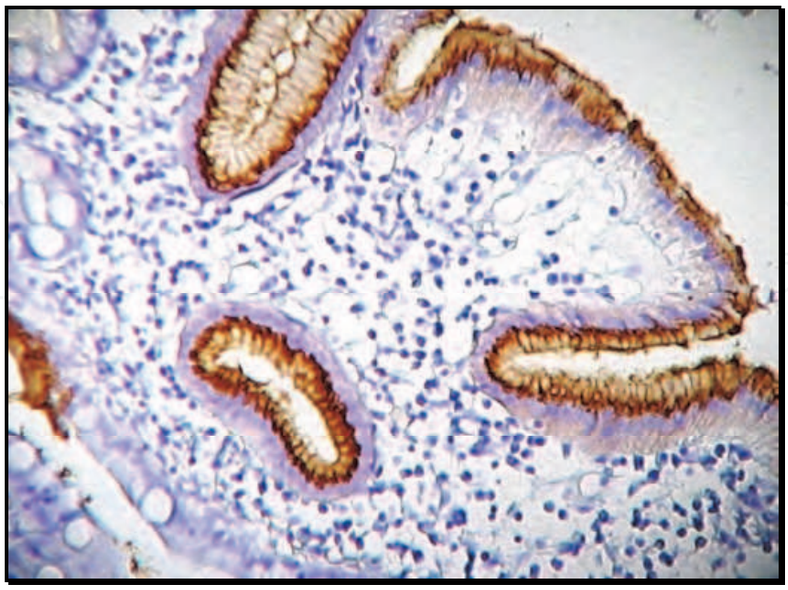


Fig. 3. MUC5AC-intensely positive immunoreaction in the gastric foveolar epithelium. DABx200.

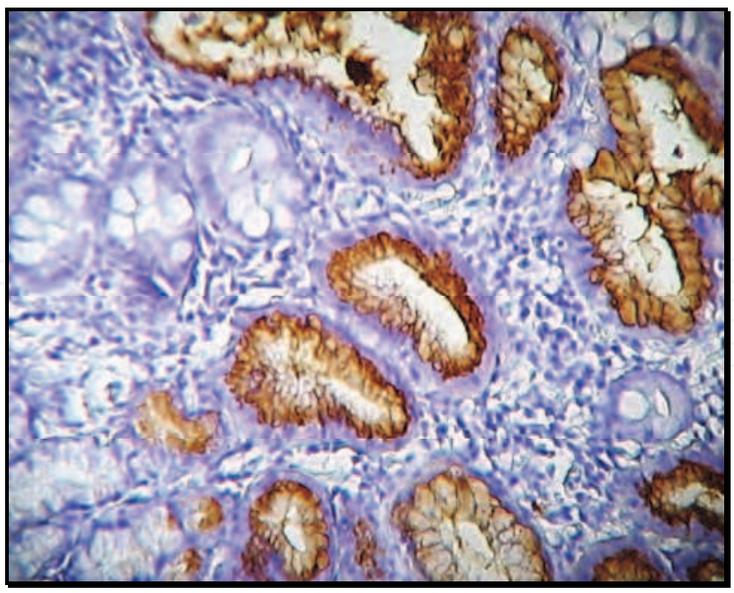


Fig. 4. MUC1-positive secretion in gastric glands; negative metaplastic foci. MUC1 immunoreaction, DABx200.

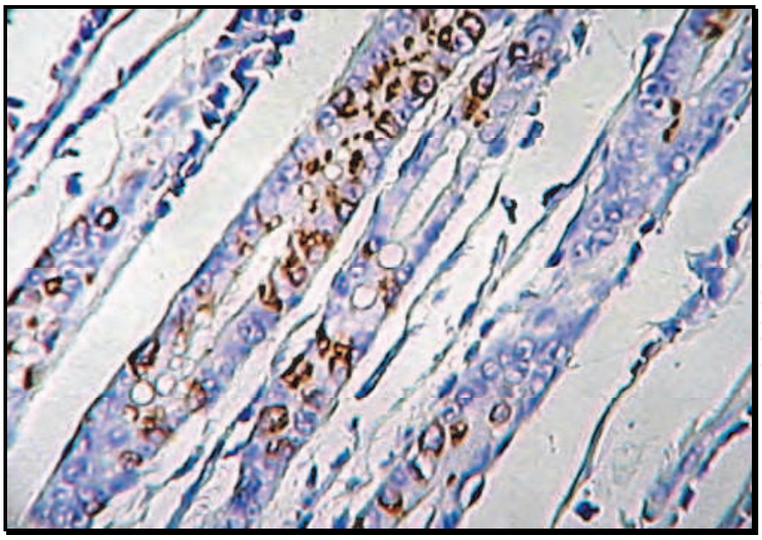
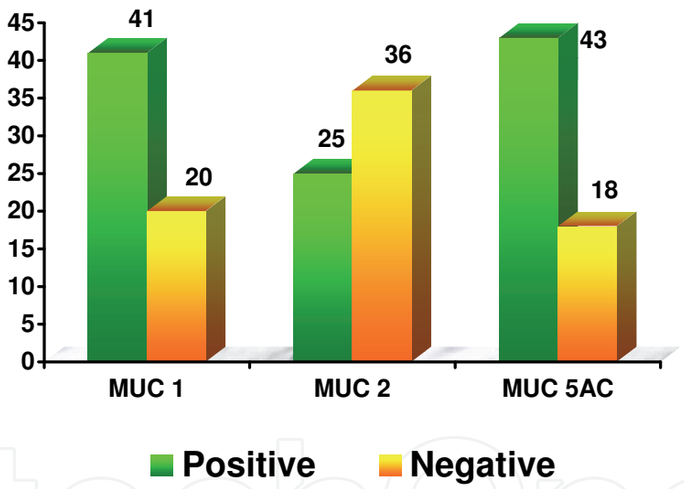


Fig. 5. MUC2-positive immunoreaction on foci of intestinal metaplasia. DABx200.



Graphic 1. Expression of mucins in gastric carcinomas

3.1 Immunohistochemical expression of MUC1 in gastric carcinomas

MUC1 antigen is expressed in most cases at the apical pole of cells and intraluminally (Fig. 6), and occasionally diffusely intracytoplasmatic (Fig. 7).

Our results do not show a relationship between the expression of MUC1 and gender of patients, but reveal greater immunopositive results in patients with ages over 61 (78.1%) in comparison with patients under 60 (55.2%) (P=0.057 borderline statistical significance) (Table 2). According to the location of tumors, we noted MUC1 positive immunoreactions in 64.5% of antral carcinomas, in 73.3% of body carcinomas, in 70% of carcinomas extended in the entire stomach, in 66.7% of carcinomas developed on the gastric stump and in 50% of carcinomas of the cardia.

Clinicopathological factors		MUC1		P
		- n=20	+ (%) n=41	
Gender	Males	13	30 (69.8%)	0.511
	Females	7	11 (61.1%)	
Age	≤ 60 years	13	16 (55.2%)	0.057
	≥ 61 years	7	25 (78.1%)	
Location	Antrum	11	20 (64.5%)	0.956
	Body	4	11 (73.3%)	
	Pangastric	3	7 (70%)	
	Cardia	1	1 (50%)	
	Gastric stump	1	2 (66.7%)	

Table 2. Relationship between gender of patients, age of patients and MUC1 expression

Classifying the tumors studied according to Lauren, we observed the greater frequency of MUC1-positive immune reactions (without reaching statistical significance) in carcinomas with glandular differentiation (73.7% - Fig. 8) (Table 3). The diffuse type of carcinoma became positive in 53% of cases (Fig. 9), and for the mixed type we obtained an intermediate value (66.7%).

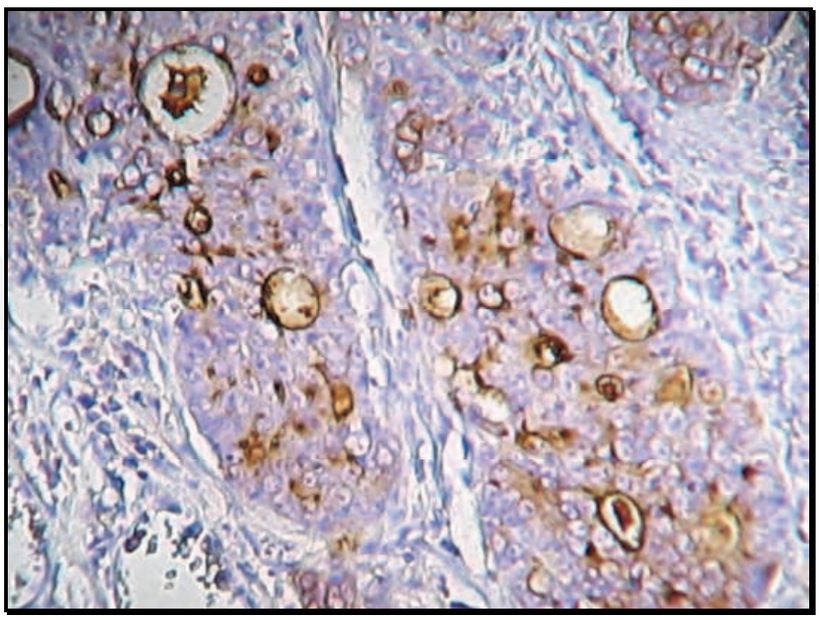


Fig. 6. MUC1-positive immunoreaction intra luminally and at the apical pole of malignant cells. DABx200.

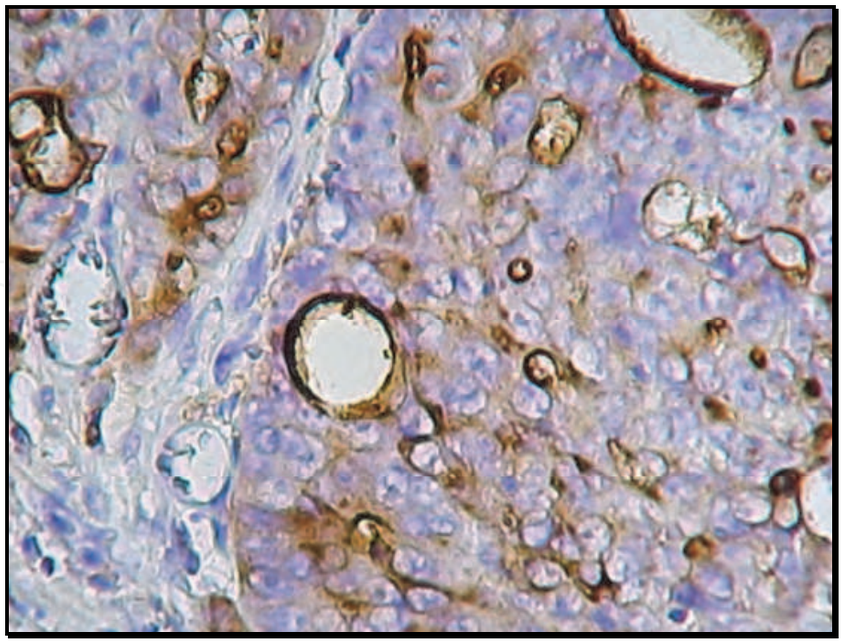


Fig. 7. MUC1 synthesis at the apical pole and intracitoplasmatical. MUC1 immunoreaction, DABx400.

Classifying the tumors studied according to Lauren, we observed the greater frequency of MUC1-positive immune reactions (without reaching statistical significance) in carcinomas with glandular differentiation (73.7% - Fig. 8) (Table 3). The diffuse type of carcinoma became positive in 53% of cases (Fig. 9), and for the mixed type we obtained an intermediate value (66.7%).

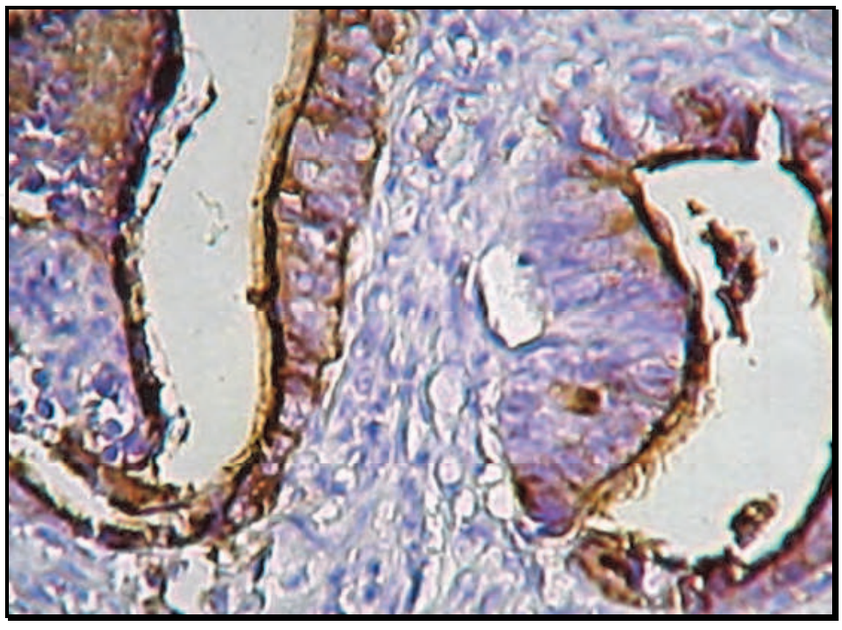


Fig. 8. Intestinal type of gastric carcinoma. MUC1 immunoreaction, DABx400.

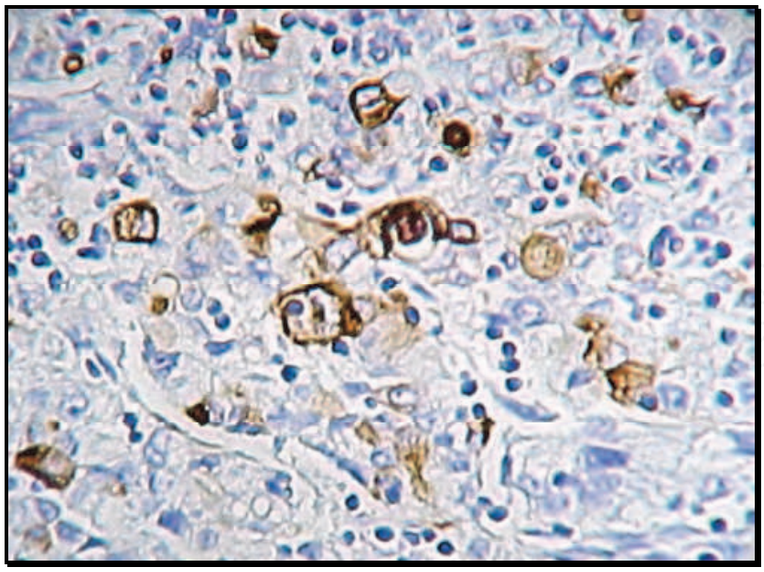


Fig. 9. Diffuse type of gastric carcinoma. MUC1 immunoreaction, DABx400.

From the histological forms, tubular and papillary adenocarcinomas (Fig. 10) became positive in a great number of cases (78.6% and 80%). For the mucinous adenocarcinoma we encountered 62.5% positive cases. The poorly differentiated forms, such as signet-ring cell carcinoma and anaplastic carcinoma (Fig. 11 and 12), expressed MUC1 in 53% and 33.3% of cases. In our study, the differences in MUC1 expression between various histological types were not statistically significant.

Clinicopathological factors		**MUC1**		**P**
		- n=20	**+ (%) n=41**	
Lauren classification	Intestinal type	10	28 (73.7%)	0.318
	Diffuse type	8	9 (53%)	
	Mixed type	2	4 (66.7%)	
Histological type	TA	6	22 (78.6%)	0.265
	PA	1	4 (80%)	
	MA	3	5 (62.5%)	
	SRCC	8	9 (53%)	
	AC	2	1 (33.3%)	
Tumor grade	G1	0	2 (100%)	0.468
	G2	8	12 (60%)	
	G3	12	27 (69.2%)	
Lymphovascular invasion	Present	13	25 (65.8%)	0.761
	Absent	7	16 (69.6%)	

TA-tubular adenocarcinoma; PA-papillary adenocarcinoma; MA-mucinous adenocarcinoma; SRCC-signet-ring cell carcinoma; AC- anaplastic carcinoma

Table 3. Relationship between the histological type, tumor grade, lymphovascular invasion and expression of MUC1

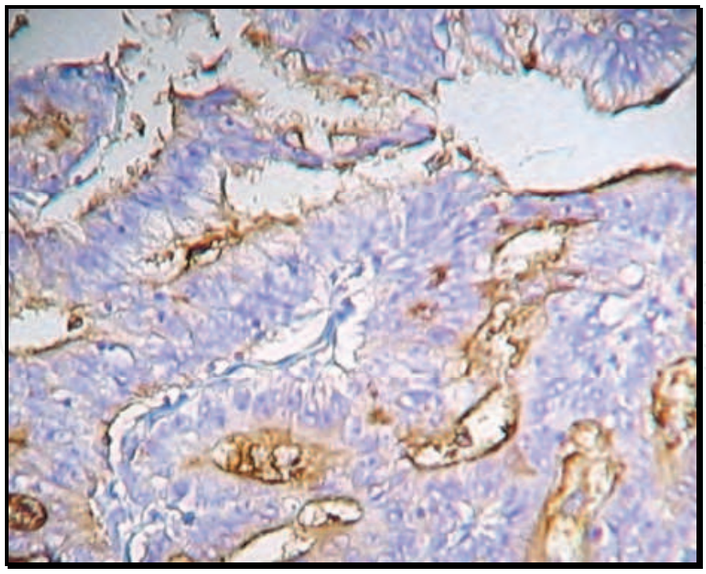


Fig. 10. Papillary adenocarcinoma. MUC1 immunoreaction, DABx200.

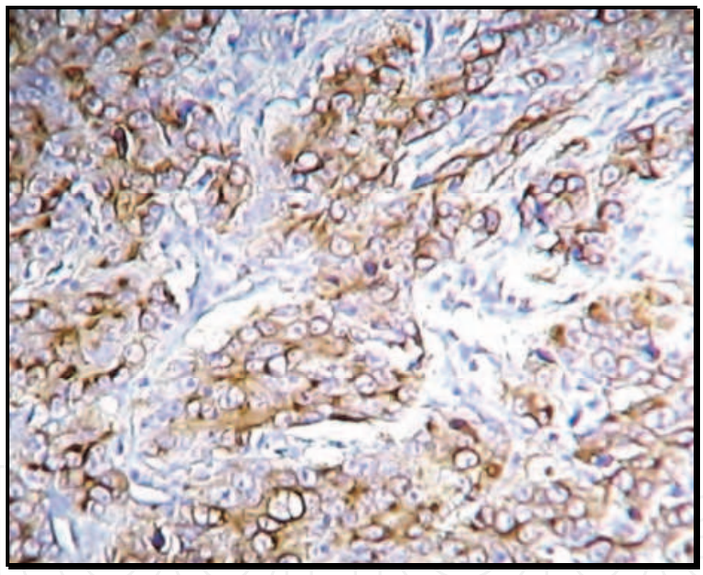


Fig. 11. Anaplastic carcinoma. MUC1 immunoreaction, DABx200.

The immunohistochemical expression of MUC1 is not correlated with the tumor histological grade and lymphovascular invasion. G1 carcinomas became positive for MUC1 in 100% of cases, but the result obtained could be influenced by the small number of cases included in this category.

From our data does not result a correlation between the MUC1 positive immune reaction and the level of tumor invasion (pT stage), the presence of distance metastases (pM stage) and pTNM staging (Table 4). However, we noted a largerer number of positive immunoreactions in cases with lymph node metastases (31 carcinomas – 72.1%) in comparison with tumors without metastases (10 cases – 55.6%), although not reaching statistical significance.

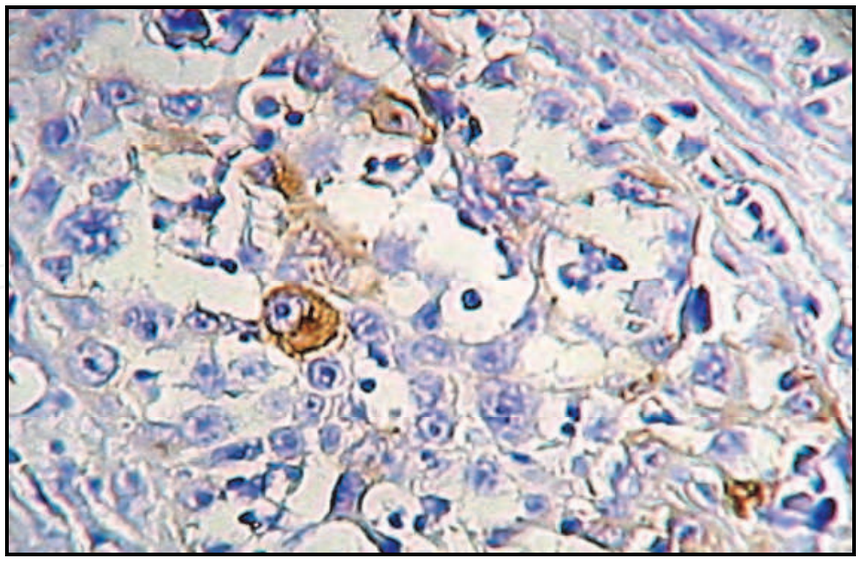
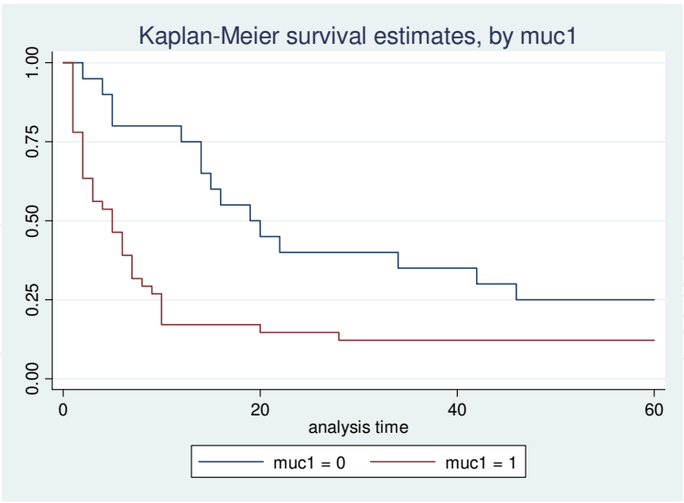


Fig. 12. Anaplastic carcinoma. MUC1 immunoreaction, DABx400.

Our results regarding survival of patients at 5 years demonstrate the role of MUC1 over-expression as a prognosis factor in gastric carcinomas. Patients with carcinomas which became positive for MUC1 survived significantly less than patients with MUC1 negative carcinomas (12.2% vs. 25% at 5 years) (P=0.0047) as shown in Graphic 2.

Clinicopathological factors		**MUC1**		**P**
		- n=20	**+ (%) n=41**	
pT	Tis	0	1 (100%)	0.870
	T1	1	3 (75%)	
	T2	3	6 (66.7%)	
	T3	7	10 (58.8%)	
	T4	9	21 (70%)	
pN	N0	8	10 (55.6%)	0.636
	N1	5	11 (68.7%)	
	N2	6	17 (74%)	
	N3	1	3 (75%)	
pM	M0	16	31 (66%)	0.702
	M1	4	10 (71.4%)	
pTNM	0	0	1 (100%)	0.884
	IA	1	2 (66.7%)	
	IB	1	4 (80%)	
	II	2	5 (71.4%)	
	IIIA	3	8 (72.7%)	
	IIIB	2	6 (75%)	
	IV	11	15 (57.7%)	

Table 4. Relationship between TNM staging and expression of MUC1

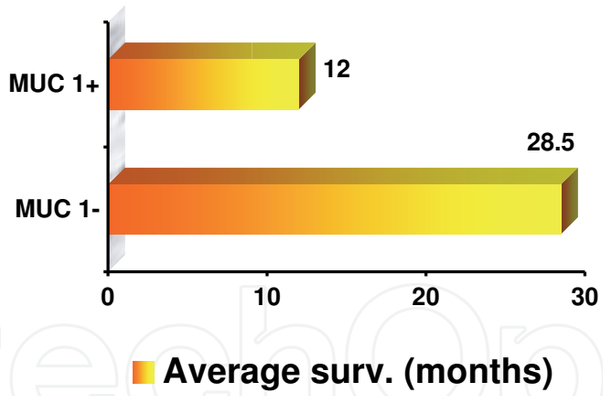


Muc1 = 0 (negative expression); Muc1 = 1 (positive expression)

Graphic 2. Survival at 5 years according to the MUC1 expression

A significant difference was also obtained by calculating the average survival in months, in the postoperative period, between the two types of patients (Graphic 3):

- for patients with MUC1-positive carcinomas: 12 months;
- for patients with MUC1-negative carcinomas: 28.5 months.



Graphic 3. Average survival of patients according to the MUC1 expression

Patients with MUC1 positive carcinomas were about two times more likely to die than those with MUC1 negative carcinomas (HR=2.30; 95%CI: 1.24-4.26; *P*=0.008).

3.2 Immunohistochemical expression of MUC2 in gastric carcinomas

Positive immunoreaction for MUC2 was observed only in malignant cells (intracytoplasmic) and in goblet cells from foci of intestinal metaplasia of gastric peritumoral mucosa (Fig. 13). We did not note the synthesis of MUC2 in epithelial cells of the normal gastric mucosa.
From the results obtained we conclude the absence of a relationship between the age and gender of patients and the immunohistochemical expression of MUC2 (Table 5).

According to the tumor location we noted MUC2 positive immunoreactions in 41.9% of antral carcinomas, 40% of gastric body carcinomas, 30% of pangastric carcinomas, and 25% of carcinomas developed on the gastric stump. We noted the tumors developed at the level of the cardia which expressed MUC2 in 100% of cases, suggesting the existence of a possible correlation between the overexpression of MUC2 and the cardial location of gastric carcinomas, but these data needs further confirmation by a larger number of cases.

Clinicopathological factors		MUC2		P
		- n=36	+ (%) n=25	
Gender	Males	25	18 (41.9%)	0.830
	Females	11	7 (38.9%)	
Age	≤ 60 years	18	11 (37.9%)	0.644
	≥ 61 years	18	14 (43.7%)	
Location	Antrum	18	13 (41.9%)	0.483
	Body	9	6 (40%)	
	Pangastric	7	3 (30%)	
	Cardia	0	2 (100%)	
	Gastric stump	2	1 (25%)	

Table 5. MUC2 expression and clinicopathological factors in gastric cancer

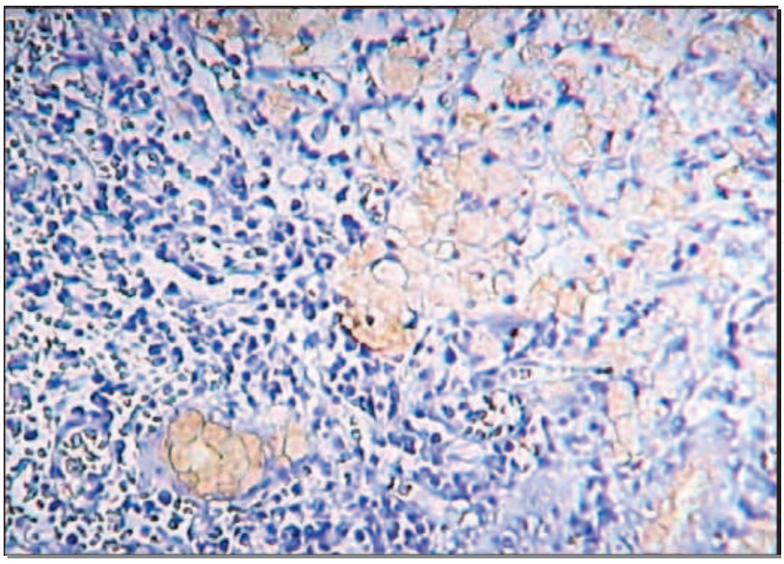


Fig. 13. Intracytoplasmic synthesis of MUC2 in tumoral cells and metaplastic foci. MUC2 immunoreaction, DABx100.

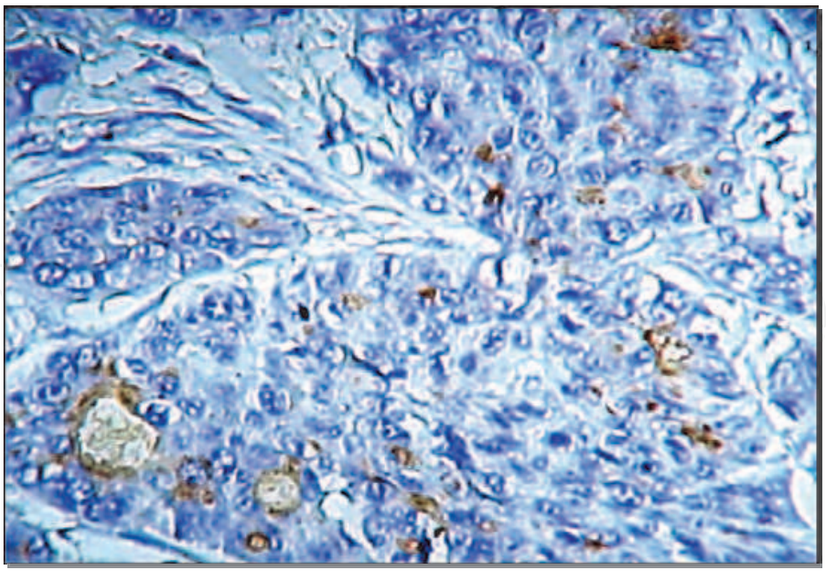


Fig. 14. Intestinal-type of gastric carcinoma. MUC2 immunoreaction, DABx100.

According to the Lauren classification, we noticed a greater immune positivity in intestinal-type carcinomas (47.4% - Fig. 14) and in mixed-type carcinomas (50%), in comparison with diffuse-type carcinomas (23.5% - Fig. 15) (Table 6), but without reaching statistical significance.

Clinicopathological factors		MUC2		P
		- n=36	+ (%) n=25	
Lauren classification	Intestinal type	20	18 (47.4%)	0.225
	Diffuse type	13	4 (23.5%)	
	Mixed type	3	3 (50%)	
Histological type	TA	17	11 (39.3%)	0.052
	PA	3	2 (40%)	
	MA	1	7 (87.5%)	
	SRCC	13	4 (23.5%)	
	AC	2	1 (33.3%)	
Tumor grade	G1	1	1 (50%)	0.859
	G2	11	9 (45%)	
	G3	24	15 (38.5%)	
Lymphovascular invasion	Present	22	16 (42.1%)	0.819
	Absent	14	9 (39.1%)	

TA-tubular adenocarcinoma; PA-papillary adenocarcinoma; MA-mucinous adenocarcinoma; SRCC-signet-ring cell carcinoma; AC- anaplastic carcinoma

Table 6. MUC2 expression and clinicopathological factors in gastric cancer

Overexpression of MUC2 is correlated (P=0.052 borderline statistical significance) with mucinous adenocarcinoma as histological form, being identified in 87.5% of cases (Fig. 16). From histological forms that are associated most rarely with the secretion of MUC2, we should mention the signet-ring cell carcinoma (23.5%). The data obtained are not suggestive

for a relationship between the tumor histological grade or lymphovascular invasion and the immunohistochemical expression of MUC2.

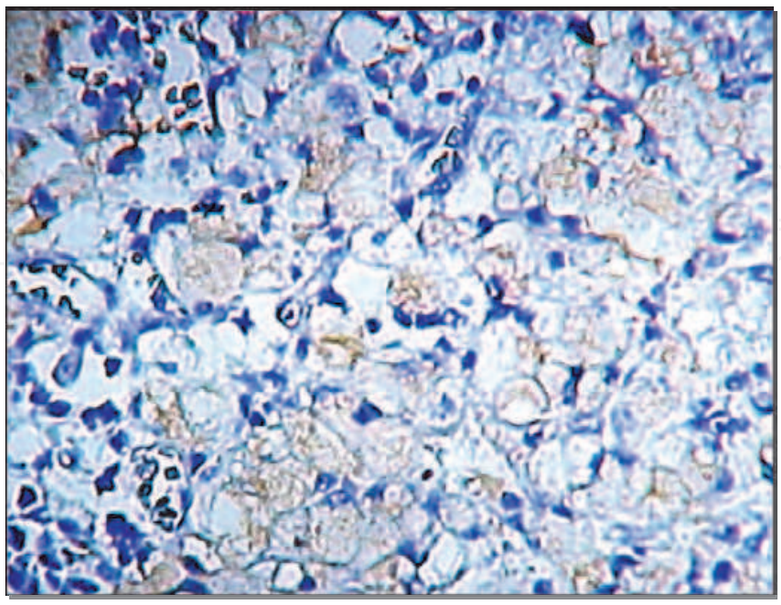


Fig. 15. Diffuse type of gastric carcinoma. MUC2 immunoreaction, DABx200.

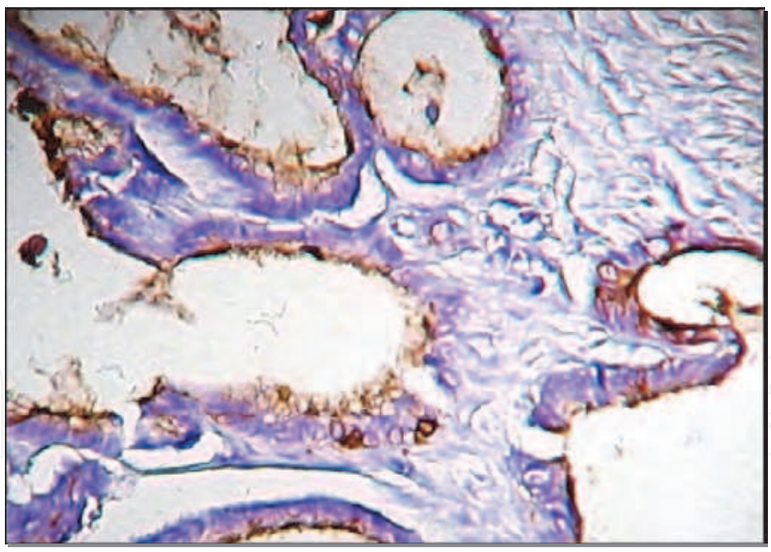


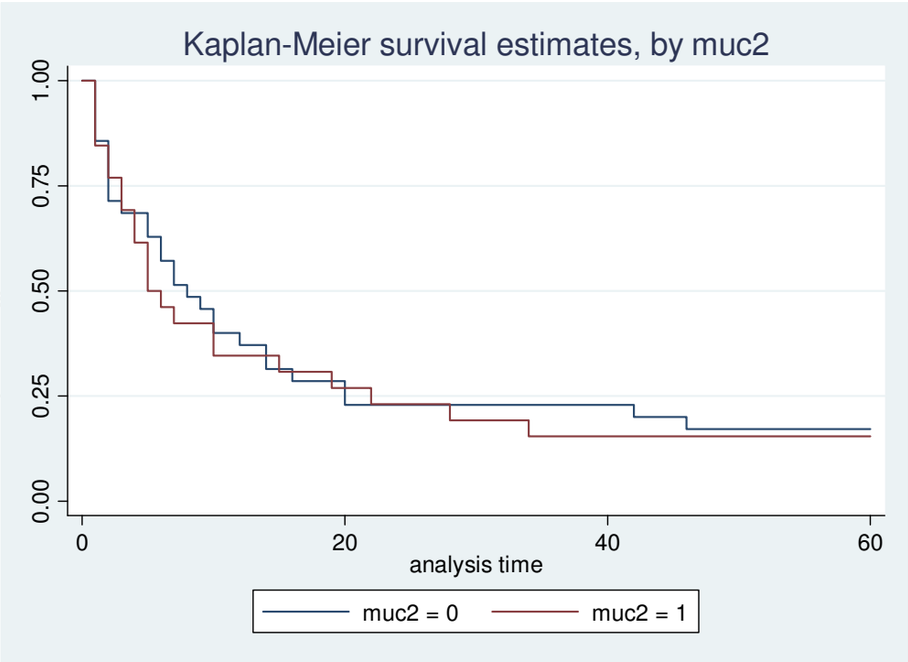
Fig. 16. Mucinous adenocarcinoma. MUC2 intensely positive immunoreaction, DABx200.

Based on the results obtained, we cannot point to the existence of a relationship between the pT, pN, pM, and pTNM factors, and the MUC2 immunoreaction in the gastric carcinomas examined (Table 7).

The immunohistochemical expression of MUC2 does not influence survival at 5 years of patients (16% for MUC2 positive patients vs. 16.7% for MUC2 negative patients) (P = 0.7568) (Graphic 4).

Clinicopathological factors		MUC2		P
		- n=36	+ (%) n=25	
pT	Tis	1	0 (0%)	0.927
	T1	2	2 (50%)	
	T2	5	4 (44.4%)	
	T3	10	7 (41.2%)	
	T4	18	12(40%)	
pN	N0	10	8 (44.4%)	0.953
	N1	10	6 (37.5%)	
	N2	14	9 (39.1%)	
	N3	2	2 (50%)	
pM	M0	28	19 (40.4%)	0.871
	M1	8	6 (42.9%)	
pTNM	0	1	0 (0%)	0.988
	IA	2	1 (33.3%)	
	IB	3	2 (40%)	
	II	4	3 (42.9%)	
	IIIA	6	5 (45.4%)	
	IIIB	5	3 (60%)	
	IV	16	10 (38.5%)	

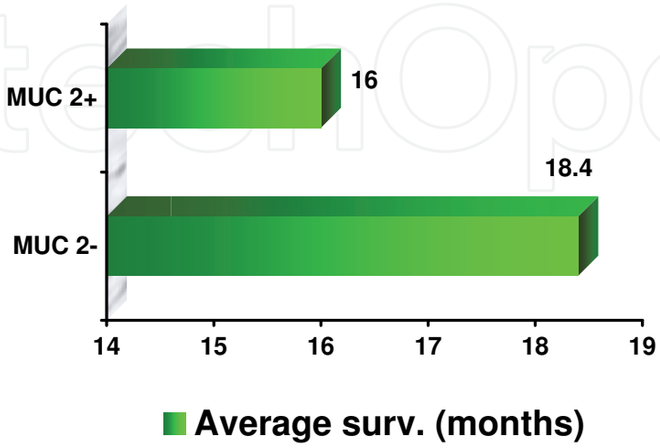
Table 7. Expression of MUC2 and clinicopathological factors in gastric cancer



Muc2 = 0 (negative expression); Muc2 = 1 (positive expression)

Graphic 4. Survival at 5 years according to expression of MUC2

Average survivals calculated in months show the lack of correlation between the prognosis of patients and the immunohistochemical expression of MUC2 (16 months for patients with MUC2-positive carcinomas, and 18,4 months for patients with MUC2-negative carcinomas) (Graphic 5).



Graphic 5. Average survival of patients according to expression of MUC2

3.3 Immunohistochemical expression of MUC5AC in gastric carcinomas

Immunohistochemical reactions performed with the anti-MUC5AC antibody have demonstrated the strong expression of the foveolar epithelium of the gastric antrum and body (Fig. 17), as well as in the cytoplasms of malignant cells from 43 gastric carcinomas (70.5% - Fig. 18).

The results obtained do not show a relationship between the age or gender of patients and the expression of MUC5AC (Table 8).

Clinicopathological factors		MUC5AC		P
		- n=18	+ (%) n=43	
Gender	Males	12	31 (72.1%)	0.672
	Females	6	12 (66.7%)	
Age	≤ 60 years	9	20 (69%)	0.804
	≥ 61 years	9	23 (71.9%)	
Location	Antrum	6	25 (80.6%)	0.137
	Body	5	10 (66.7%)	
	Pangastric	4	6 (60%)	
	Cardia	2	0 (0%)	
	Gastric stump	1	2 (66.7%)	

Table 8. Expression of MUC5AC and clinicopathological factors in gastric cancer

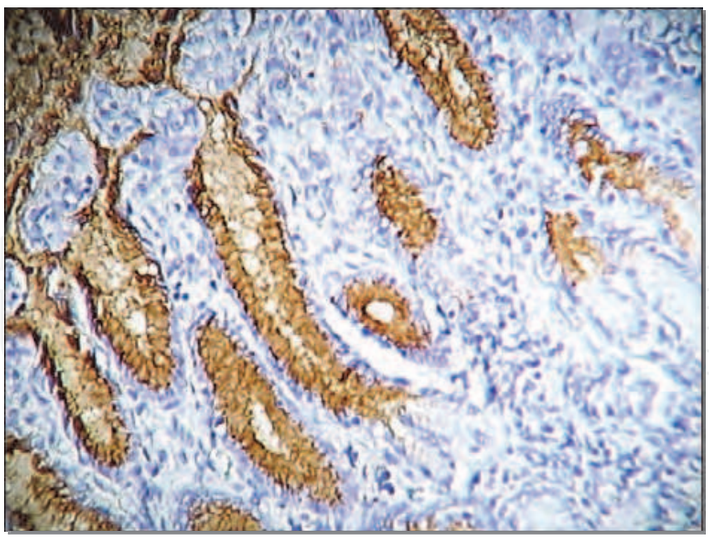


Fig. 17. MUC5AC intensely positive immunoreaction in the gastric foveolar epithelium. DABx100.

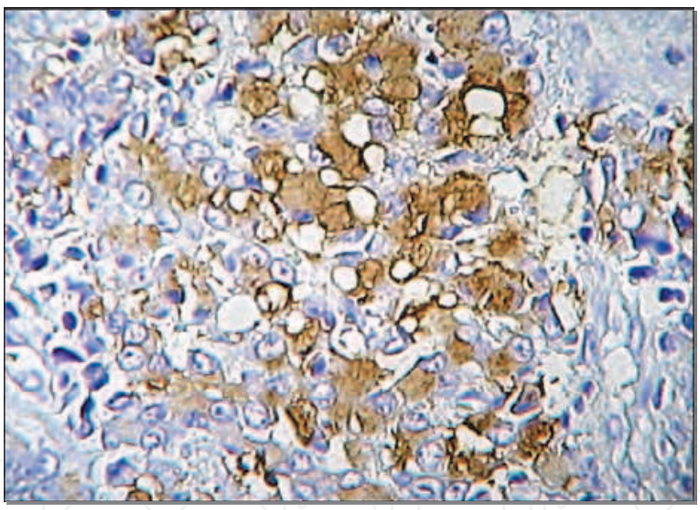


Fig. 18. MUC5AC immune reactivity in the cytoplasm of malignant cells. DABx200.

Analysis of MUC5AC according to location of tumors demonstrated the most frequent immunoreactivity of the antibody in antral carcinomas (80.6%) (without statistical significance). We identified positive immunoreactions in 66.7% of gastric body carcinomas, 60% of pangastric carcinomas and 66.7% of carcinomas developed on the gastric stump. Cardial tumors did not express the MUC5AC antigen.

The diffuse type of gastric carcinoma, as well as the signet-ring cell carcinoma, presented in a very high percentage (88.2%) MUC5AC positive immunoreactions (Tab. 9 – Fig. 19). Our results seem to show that MUC5AC is expressed mostly in the signet-ring cell carcinoma, but the differences between the histological subtypes did not reach statistical significance. According to the tumor histological grade, we noted 50% positive reactions in well-differentiated carcinomas, 70% positive reactions in moderately differentiated carcinomas

and 71.8% in poorly differentiated carcinomas. We noted no relationship between the lymphovascular invasion and the expression of MUC5AC.

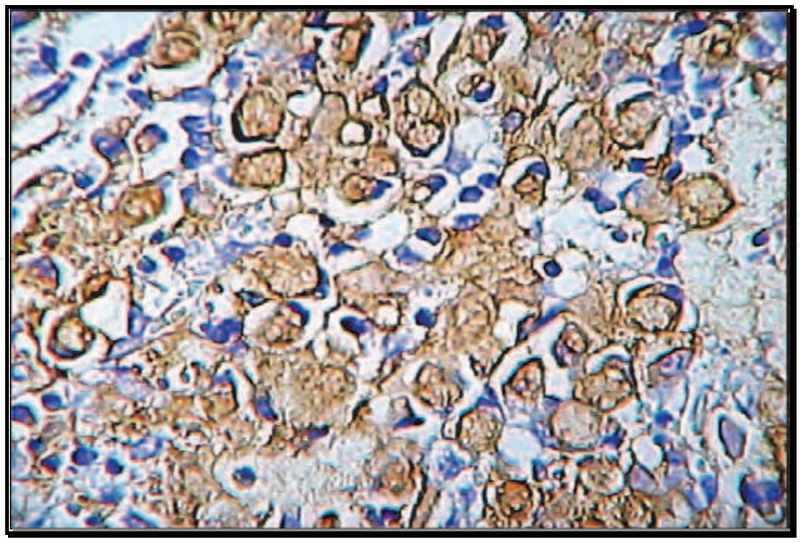


Fig. 19. Gastric signet-ring cell carcinoma. MUC5AC immunoreaction, DABx400.

Clinicopathological factors		MUC5AC		P
		- n=18	+ (%) n=43	
Lauren classification	Intestinal type	14	24(63.2%)	0.165
	Diffuse type	2	15 (88.2%)	
	Mixed type	2	4 (66.7%)	
Histological type	TA	20	18 (64.3%)	0.082
	PA	2	3 (60%)	
	MA	3	5 (62.5%)	
	SRCC	2	15 (88.2%)	
	AC	1	2 (66.7%)	
Tumor grade	G1	1	1 (50%)	0.958
	G2	6	14 (70%)	
	G3	11	28 (71.8%)	
Lymphovascular invasion	Present	12	26 (68.4%)	0.649
	Absent	6	17 (73.9%)	

TA-tubular adenocarcinoma; PA-papillary adenocarcinoma; MA-mucinous adenocarcinoma; SRCC-signet-ring cell carcinoma; AC- anaplastic carcinoma

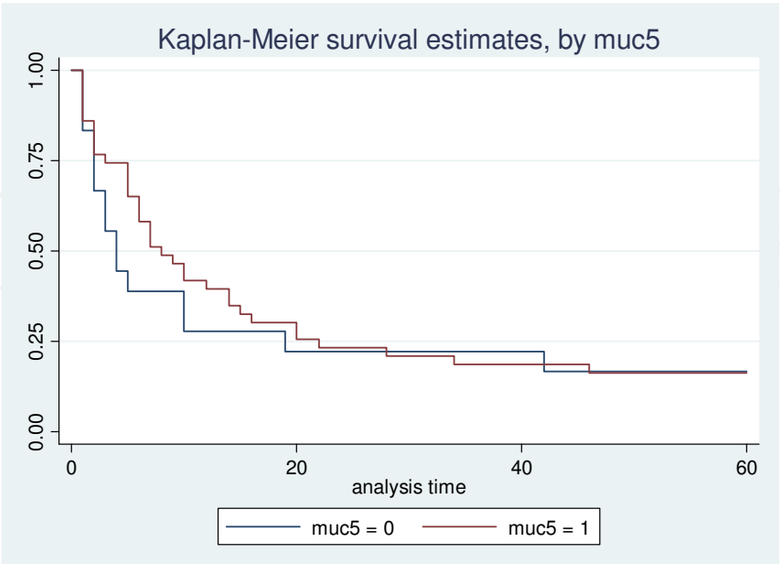
Table 9. Expression of MUC5AC and clinicopathological factors in gastric cancer

Our results, similar with those obtained in analyzing MUC2, did not show the existence of a correlation between the level of tumor invasion, the presence of lymph node or distant metastases, the pTNM stage and the immunohistochemical expression of MUC5AC (Table 10).

Clinicopathological factors		MUC5AC		P
		- n=18	+ (%) n=43	
pT	Tis	0	1 (100%)	0.489
	T1	1	3 (75%)	
	T2	2	7 (77.8%)	
	T3	3	14 (82.4%)	
	T4	12	18 (60%)	
pN	N0	5	13 (72.2%)	0.992
	N1	5	11 (68.8%)	
	N2	7	16 (69.6%)	
	N3	1	3 (75%)	
pM	M0	14	33 (70.2%)	0.930
	M1	4	10 (71.4%)	
pTNM	0	0	1 (100%)	0.985
	IA	1	2 (66.7%)	
	IB	1	4 (80%)	
	II	2	5 (71.4%)	
	IIIA	4	7 (63.6%)	
	IIIB	2	6 (75%)	
	IV	8	18 (69.2%)	

Table 10. Expression of MUC5AC and clinicopathological factors in gastric cancer

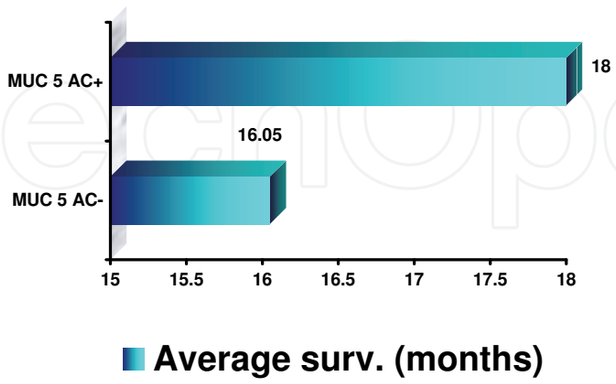
The expression of MUC5AC does not constitute a prognostic factor in our study, the survival rate at 5 years being 16.3% for MUC5AC positive patients vs. 16.7% for MUC5AC negative patients (P = 0.5334; Graphic 6)



Muc5AC = 0 (negative expression); Muc5AC = 1 (positive expression)

Graphic 6. Survival at 5 years according to the expression of MUC5AC

The average survival rates, calculated in months, were of 18 months for patients with MUC5AC-positive carcinomas and 16.05 months for patients with MUC5AC-negative carcinomas, the two values being relatively close (Graphic 7).



Graphic 7. Average survival rate (in months) according to the expression of MUC5AC

4. Discussions

The genes of mucins are expressed in normal cells and tissues. The stomach offers a very good example of expressing mucins. MUC1 can be identified in mucous cells of the surface epithelium and neck of glands at the level of the antrum, but also in the pyloric and oxyntic glands in the gastric body (Ho et al., 1995; Pinto-De-Sousa, 2002). The MUC5AC mucin is expressed strongly in the foveolar epithelium of the antrum and body and MUC5AC is limited to mucous neck cells of gastric body glands and pyloric glands of the antrum (Ho et al., 1995; Pinto-De-Sousa, 2002; Silva et al., 2002). The expression of mucins in gastric carcinomas is heterogeneous, including mucins synthesized normally by the gastric mucosa (MUC1, MUC5AC and MUC6), as well as intestinal mucins synthesized de novo (MUC2) (Baldus et al., 1998; Ho et al., 1993; Reis, 1997, 1998). Some authors suggested that the heterogeneous pattern of expression would offer information regarding the evolution of various forms of gastric cancer.

The progression of tumorigenesis involves abnormalities in the expressions of cyclins and other cell-cycle related genes (Ioachim, 2008). Abnormalities have been found for cyclins D1, A, E and their co-operating partners (cyclin-dependent kinase), that promote cell cycle progression (Handa et al., 1999; Ioachim, 2008). These progressive factors can be inhibited by blockers, such as p21, p27 and p57, p16, p15 and p18. Key regulators of progression through the G1 phase of the cell cycle are cyclin D1, cyclin E, p53, p21 and p27 (Gamboa-Dominguez et al., 2007; Mrena et al., 2006). Sugai et al. (2010), analyzing 190 gastric intramucosal differentiated-type cancers have suggested that the cellular mucin phenotypes are dependent on distinct cell cycle-related alteration. It was proposed a novel carcinogenesis model that relies on the mucin phenotype. Based on abnormalities of cell-cycle related proteins, overexpressions of p53 and cyclin A characterize gastric phenotype cancers, whereas overexpression of p27 is associated with the development of intestinal-phenotype cancers and overexpression of cyclin A with the mixt phenotype cancers.

Mucin and mucin O-glycosylation have attracted attention for their role in the adhesion of bacteria, cell-cell adhesion, and cancer cell metastization (Hollingsworth & Swanson, 2004).

The expression of mucins is often altered in cancer, with frequent aberrant glycosylation, resulting immature structures and exposure of the peptide backbone (Ferreira et al., ;Reis et al., 1998). These structures are useful markers of premalignant and malignant cells. Gomez et al (Gomes et al., 2009) have studied the pattern of expression of UDP-N-acetyl-D-galactosamine: polypeptide N-acetylgalactosaminyltransferase-6 (ppGal NAc-T6) in gastric mucosa, intestinal metaplasia and gastric carcinoma. ppGal NAc-T6 was expressed in normal mucosa (both antrum and body region), in 52% of the cases with intestinal metaplasia and had a heterogeneous expression in gastric carcinomas, being present in 79% of case. Its expression in gastric carcinomas was associated with venous invasion.

In our study we aimed to evaluate the profile of mucins in gastric carcinomas in the study group, through immunohistochemical reactions, using monoclonal anti-MUC1, MUC2, and MUC5AC antibodies. The purpose of the study is to compare the expression of mucins with clinicopathological factors and with the outcome of patients. In accordance with other works (Pinto-De-Sousa, 2002), the data obtained show that the immunohistochemical expression of mucins is associated with some characteristics of differentiation in gastric carcinomas. We noted the alteration of the profile of normal gastric mucins and the overexpression of intestinal mucin in the various forms of cancer.

In the peritumoral mucosa, the MUC1 immunoreactivity was detected in the specialized glands of the gastric body, in the pyloric glands, and at the level of the antrum (in surface mucous cells and neck mucous cells). Amongst the carcinomas studied we identified 41 cases with positive immunoreactions for MUC1, representing 67.2%. Using two specific monoclonal antibodies, Pinto-de-Sousa (2002) obtained positive reactions in 89% of cases with HFMG1 antibody and 50 of cases with SM3 antibody (which recognizes only the non-glycosylated forms of MUC1). Generally, the immunoreactivity for MUC1 varies in different studies between 24.3% and 100% (Gürbüz et al., 2002). The MUC1 antigen was expressed in most cases at the apical pole of cells and intraluminally, and occasionally diffusely intracytoplasmatic. Our results do not show a relationship between the expression of MUC1 and the gender of patients or the location of tumors, but reveal a greater immune positivity in patients with ages over 61 (78.1%), in comparison with patients under 60 years of age (55.2%) (borderline statistical significance).

Classifying the tumors studied, according to Lauren, we noticed a greater frequency of MUC1 positive immunoreactions in carcinomas with glandular differentiation (73.7%), although without reaching statistical significance. Concordant results were obtained by Gürbüz Y et al. (2002), Lee HS et al. (2001), Machado JC et al. (2000), Reis CA et al. (1998), Utsunomiya T et al. (1998). The diffuse type of carcinoma became positive in 53% of cases, and for the non-classifiable type we obtained an intermediate value (66.7%). Reis CA et al. (1998) note the significant association between the immune reactivity of SM3 and the non-classifiable gastric carcinoma.

In our study, the differences in MUC1 expression between various histological types were not statistically significant. Also, in the study of Pinto-De-Sousa et al (2002), the expression of HMFG1 and SM3 antibodies was not correlated with histological forms of gastric cancer.

The immunohistochemical expression of MUC1 is not correlated with the tumor histological grade and lymphovascular invasion. The G1 carcinomas became positive for MUC1 in 100% of cases, but the result obtained could be influenced by the small number of cases included in this category.

No correlation results from our study between the MUC1 immunoreaction and the level of tumor invasion (pT stage), the presence of distance metastases (pM stage) and pTNM

staging. We noted, however, a greater number of positive immune reactions in cases with lymph node metastases (31 carcinomas – 72.1%), in comparison with tumors without lymph node metastases (10 cases – 55.6%), but without statistical significance. The correlation between MUC1 positivity and the presence of lymph node metastasis was observed by Zhang HK et al. (2004), together with the association between MUC1 and the advanced age of patients with gastric tumors of large dimensions.

In epithelial cancer cells, MUC1 is over-expressed, aberrantly glycosylated with short oligosaccharides and also loses its apical polarization and becomes expressed over the entire cell surface (Hilkens et al., 1992; Kim & Gum, 1996; Lloyd et al., 1996; Wesseling et al., 1996). MUC1 is an endogenous ligand of galectin-3 (an apoptosis inhibitor) in cancer cells (colon cancer), the interaction occurring via binding the galectin-3 to the oncofetal Thomsen-Friedenreich carbohydrate (TF) antigen on MUC1 (Yu et al., 2007). The increased expression of MUC1 and TF antigen are both associated with high metastatic potential of the cancer cell and poor prognosis (Nakamori et al., 1994). Over-expression of MUC1 promotes tumor cell release from primary tumor sites by inhibiting E-cadherin-mediated cell-cell and integrin-mediated cancer extracellular matrix interactions (Kondo et al., 1998). Thus, MUC1 may promote the formation of cancer cell aggregates/emboli and prolong the survival of disseminated cells in the circulation and contributes to cancer cell haematogenous dissemination (Zhao et al., 2010).

The role of MUC1 in invasion and metastasis has been shown in different models. The cytoplasmic tail of MUC1 was reported to enhance the invasion in breast cancer cells expressing wild-type GSK-3β and β-catenin (Lillehoj et al, 2003), suggesting possible interactions between these proteins. MUC1 expression is associated with increased steady-state levels of β-catenin in the cytoplasm and nucleus of breast carcinoma cells by blocking the GSK-3β-mediated phosphorylation of β-catenin, and preventing proteosomal degradation (Schroeder et al., 2003). It is possible that the cytoplasmic tail of MUC1 enables interaction between different regulators or alternatively might compete for or sequester β-catenin. In some cell types, the MUC1 cytoplasmic tail is also involved in the transcriptional activation of β-catenin-TCF-binding sites and transcriptional activation of cyclin D1 (Huang et al., 2005). MUC1 may play an antiapoptotic role in response to cellular stresses by stimulating Akt and the antiapoptotic protein Bcl-X to attenuate genotoxin-induced apoptosis (Raina et al., 2004). Recent reports suggest that this MUC1-mediated carcinogenesis is likely through the TGF-α signaling pathway (Pochampalli et al., 2007).

MUC1 is immunogenic in its hypoglycosylated form expressed on tumors, and the tumor-bearing patients generate both cellular and humoral immune responses to this antigen (Coronella-Wood & Hersh, 2003; Vlad et al., 2004). High levels of anti-MUC1 antibodies are associated with a better prognosis in some adenocarcinomas (Kurtenkov et al., 2007; Silk & Finn, 2007), an observation that has made MUC1 an attractive candidate for vaccines against these malignancies. Prophylactic vaccination is the most desirable strategy to prevent malignant diseases. Several vaccine trials involving MUC1 have been conducted, but none have resulted in therapeutically beneficial immune responses (Silk & Finn, 2007). Identification and understanding of the host factors that influence naturally occurring immune responses is an important prerequisite to successfully designing a vaccine that would induce therapeutic responses.

For MUC1 there are significant interindividual differences in naturally occurring antibody responses (Cramer et al., 2005). Recent studies in humans have shown that immune responsiveness to a variety of antigens- infectious agents, vaccines, autoantigens, including

some tumor-associated antigens- are associated with particular GM and KM allotypes, hereditary antigenic determinants of γ and κ chains, respectively (Kameda et al., 1998; Pandey, 2001; Pertovaara et al., 2004). Pandey et al. (2008) have studied 169 Caucasian subjects with gastric cancer that were allotyped for several GM and KM markers. Their results have revealed that GM 3 23 5,13 phenotype is highly significantly associated with MUC1 IgG levels; subjects with this phenotype had lower antibody levels compared with those having other phenotypes. This phenotype had an interactive effect with KM phenotypes on the levels of IgG antibodies to this antigen. Association of non- GM 3 23 5,13 phenotypes with high responsiveness to MUC1 could aid in identifying subjects who are more likely to benefit from MUC1-based vaccines. For individuals with the low responder phenotype, MUC1 could be fused with appropriate adjuvants, such as heat shock proteins, in order to conceive a vaccine that could potentially generate high antibody responses in the majority of population (Li et al., 2006; Pandey et al., 2004).

In accordance with Reis CA et al (1998) and Baldus SE at al (1998), our results regarding the survival of patients at 5 years prove the association between the overexpression of MUC1 and the worse prognosis. Patients with carcinomas which became positive for MUC1 survived at 5 years significantly less (12.2%) than patients with MUC1-negative carcinomas (25%). A significant difference was also obtained by calculating, in months, the average survival in the postoperative period: for patients with MUC1-positive carcinomas – 12 months; for patients with MUC1-negative carcinomas – 28.5 months.

The results regarding the prognostic role for the immunohistochemical expression of MUC1 are contradictory. Studying a group of 94 gastric carcinomas, Pinto-De-Sousa et al. (2002) did not observe a relationship between MUC1 and the prognosis of patients.

The immunohistochemical reactions performed with the anti-MUC5AC antibody demonstrated a strong expression in the foveolar epithelium of the antrum and gastric body, as well as in the cytoplasms of malignant cells in 43 gastric carcinomas (70.5%).

The results obtained do not show a relationship between the age or gender of patients and the expression of MUC5AC. The analysis of MUC5AC according to the location of tumors demonstrated a frequent immunoreactivity of the antibody in antral carcinomas (80.6%), but without reaching statistical significance. Cardial tumors did not express the MUC5AC antigen.

The diffuse type of gastric carcinoma, as well as "signet-ring" cell carcinoma, presented in a very high percentage (88.2%) MUC5AC-positive immune reactions. Our results seem to show that MUC5AC is expressed mostly in the signet-ring cell carcinoma, but the differences between the histological subtypes did not reach statistical significance. The association between the expression of MUC5AC and the diffuse type carcinoma is mentioned also by other authors (Pinto-De-Sousa et al., 2002), suggesting keeping certain features of tumor differentiation in the gastric mucosa. Some studies signal the strong correlation between the immunoreactivity of MUC5AC and the tumors with infiltrative growth pattern (Gürbüz et al., 2002). This association reflects the modality of growth and invasion in diffuse type carcinomas.

We did not note a relationship between the tumor histological grade, the lymphovascular invasion and the expression of MUC5AC. Our results did not show the existence of a correlation between the level of tumor invasion, the presence of lymph node or distance metastases, the pTNM stage, and the immunohistochemical expression of MUC5AC.

In accordance with Pinto-De-Sousa`s results (2002), the expression of MUC5AC in our study does not constitute a prognostic factor, survival rates at 5 years being of 16.3% for patients

with MUC5AC-positive carcinomas, and 16.7% for patients with MUC5AC-negative carcinomas. In the studies of Reis CA et al. (1998) and Hatori & Kushima (2002), the expression of MUC5AC was much frequently observed in incipient gastric carcinomas (100%) in comparison with advanced carcinomas (58.6%). The authors conclude that all gastric carcinomas are characterized by a "gastric" phenotype in the first stages of tumorigenesis. The average survival rates, calculated in months, were of 18 months for patients with MUC5AC-positive carcinomas, and 16.05 months for patients with MUC5AC-negative carcinomas, the two values being relatively close.

Several papers have described the relationship between mucin and pancreatic cancer, de novo expression of MUC5AC frequently occurring in intraductal papillary mucinous tumors and pancreatic adenocarcinoma (Kanno et al., 2006; Kim et al., 2002), while Takikita et al. (2009) reported that borderline statistically significant associations are seen between MUC5AC positivity and shorter survival time in patients with pancreatic cancer. Yamazoe S et al. (2010) demonstrated that suppression of MUC5AC reduced adhesive, invasive and metastatic potential of pancreatic cancer cell lines. MUC5AC might contribute to the progression of pancreatic cancer by inducing adhesiveness and invasiveness in extracellular matrix via VEGF overexpression.

Immune positivation for MUC2 was observed in our study only in malignant cells (intracytoplasmic) and in goblet cells in foci of intestinal metaplasia of peritumoral gastric mucosa. We did not note the MUC2 synthesis in epithelial cells of the normal gastric mucosa. Our results show that MUC2 intestinal mucine is expressed aberrantly in 25 gastric carcinomas (40% of cases).

Tumors developed at the level of the cardia expressed MUC2 in 100% of cases, suggesting the existence of a possible correlation between the overexpression of MUC2 and the cardial location of gastric carcinomas, but these data needs further confirmation by a larger number of cases.

According to the Lauren classification, we noted a greater immune positivation in intestinal-type carcinomas and mixed-type in comparison with diffuse-type carcinomas, but without reaching statistical significance.

In accordance with results of other studies (Pinto-De-Sousa et al., 2002; Reis et al., 2000), overexpression of MUC2 is correlated significantly (borderline statistical significance) with mucinous adenocarcinoma, being identified in 87.5% of cases. Overexpression of MUC2 was also described in colonic, pancreatic, mammary and ovarian mucinous carcinomas (Hanski et al., 1997). Immunoreactivity of MUC2 is tightly correlated with the presence of goblet cells. This fact suggests that the predominant cellular population in mucinous carcinoma consists of goblet cells.

Choi JS et al (2009) have studied human mucin gene expression and mucin phenotypes in mucinous and non-mucinous gastric carcinomas. Mucin gene expression profiles differed in nucinous vs. non-mucinous tumors. MUC2 was related distinctively to mucinous carcinomas and was expressed in 95.5% of these tumors, whereas it was observed in only 33.4% of non-mucinous carcinomas, suggesting that MUC2 is closely related to the mucinous histology and that it may play a role in the histogenesis of mucinous gastric carcinomas. MUC2 is expressed in normal colonic and small intestinal mucosa, but is not expressed in normal gastric mucosa. When intestinal metaplasia occurs in the stomach, MUC 2 is expressed in the goblet cells. In this study, mucinous gastric carcinomas were characterized by MUC1 negativity, MUC2 positivity, MUC5AC negativity, and MUC6 negativity compared with non-mucinous tumors. Mucinous carcinomas were categorized as

intestinal mucin phenotype in 60.9%, mixed phenotype in 34.6%, and gastric phenotype in 2.3%. Patients who had the gastric or mixed phenotype had a shorter median survival than patients who had the intestinal phenotype, although the survival curves were not significantly different.

Data obtained in our study are not suggestive for a relationship between the tumor histological grade or lymphovascular invasion and the immunohistochemical expression of MUC2. Based on the results obtained, we cannot state the existence of a relationship between the pT, pN, pM, pTNM factors and the MUC2 immunoreaction in the gastric carcinomas examined.

The immunohistochemical expression of MUC2 does not influence survival at 5 years of patients, survival rates at 5 years being of 16% for patients with MUC2-positive carcinomas and 16.7% for patients with MUC2-negative carcinomas. Average survivals calculated in months show the lack of correlation between the prognosis of patients and the immunohistochemical expression of MUC2 (16 months for patients with MUC2-positive carcinomas and 18.4 months for patients with MUC2-negative carcinomas).

Immunohistochemical evaluation of the pattern of mucins can be considered an important method of interpretation and understanding of various clinical and pathological entities of gastric cancer. The expression of the intestinal mucin MUC2 was shown much more frequently in carcinomas located at the level of the cardia (100%), in comparison with antral tumors (41.9%), gastric body tumors (40%), pangastric tumors (30%), or tumors developed at the level of the gastric blunt (25%). This result suggests that cardial tumors are diagnosed and resected in advanced pTNM stages. In accordance with Ho and colab. (28), the data obtained in our study confirm the hypothesis according to which the heterogeneous expression of mucins and the "de novo" synthesis of non-gastric mucins correspond to advanced stages of gastric cancer.

Gastric carcinomas located at the level of the antrum express MUC5AC in a significantly greater proportion (80.6%) in comparison with tumors of the gastric body (66.7%), pangastric (60%) or cardial (0%). This high percentage could be due either to the slightly more advanced tumor stage in comparison with proximal carcinomas, either to the high frequency of diffuse-type carcinomas, located in the distal stomach.

5. Conclusions

The immunohistochemical evaluation of the pattern of mucines can be considered as an important method of interpreting and understanding the various clinical and pathological entities of gastric cancer.

The immunohistochemical expression of mucines is correlated with the histological type of gastric carcinoma (MUC1 with carcinomas with glandular differentiation, MUC2 with the mucinous carcinoma, and MUC5AC with the diffuse type of gastric carcinoma and the ring cell carcinoma). Our results suggest the different carcinogenesis of these histological types.

In our study, the immunohistochemical expression of MUC1 constitutes an important prognostic factor, survival at 5 years of patients with MUC1-positive carcinomas being significantly lower than survival at 5 years of patients with MUC1-negative carcinomas. Patients with MUC1 positive carcinomas were about two times more likely to die than those with MUC1 negative carcinomas.

The results obtained show that the immunohistochemical expressions of MUC2 and MUC5AC do not constitute prognostic factors in assessing the patients with gastric cancers.

According to the immunoreactivity of MUC2, the gastric mucinous carcinoma develops from a cellular population consisting predominantly of goblet cells.
The data obtained in our study confirms the hypothesis according to which the heterogeneous expression of mucines and the "de novo" synthesis of non-gastric mucines correspond to advanced stages of gastric cancer.

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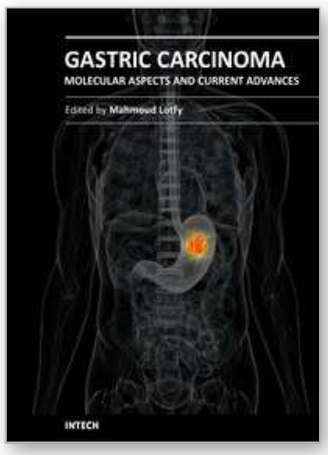

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Gastric cancer is one of the most common tumors worldwide. It has a heterogeneous milieu, where the genetic background, tumor immunology, oxidative stress, and microbial infections are key players in the multiple stages of tumorigenesis. These diverse factors are linked to the prognosis of the gastric cancer and the survival of gastric cancer patients. This book is appropriate for scientists and students in the field of oncology, gastroenterology, molecular biology, immunology, cell biology, biology, biochemistry, and pathology. This authoritative text carefully explains the fundamentals, providing a general overview of the principles followed by more detailed explanations of these recent topics efficiently. The topics presented herein contain the most recent knowledge in gastric cancer concerning the oncogenic signaling, genetic instability, the epigenetic aspect, molecular features and their clinical implications, miRNAs, integrin and E-cadherin, carbohydrate-associated-transferases, free radicals, immune cell responses, mucins, Helicobacter-pylori, neoadjuvant and adjuvant therapy, prophylactic strategy for peritoneal recurrence, and hepatic metastasis.

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