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CLINICOPATHOLOGICAL ANALYSIS OF GASTRIC CANCER

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ABSTRACT:
GASTRIC CANCER (CRC) REPRESENTS ONE OF THE MOST COMMONLY DIAGNOSED CANCERS WORLDWIDE. THE TREATMENT STRATEGY FOR GASTRIC TUMORS HAS CHANGED DURING THE LAST DECADES WITH THE USE OF MOLECULAR PROGNOSTIC FACTORS AND ADEQUATE COMBINATION THERAPIES. CURATIVE THERAPY INVOLVES SURGICAL RESECTION, MOST COMMONLY REPRESENTED BY A TOTAL OR SUBTOTAL GASTRECTOMY WITH AN ACCOMPANYING LYMPHADENECTOMY. MANY STUDIES HAVE INVESTIGATED THE CORRELATION BETWEEN HISTOPATHOLOGICAL CHARACTERISTICS IN GASTRIC CANCER AND PATIENT DATA, DISEASE-SPECIFIC CRITERIA, AND OVERALL OUTCOME. IDENTIFYING PREDICTIVE AND PROGNOSTIC MARKERS IS AN IMPORTANT STEP TO IMPROVE CURRENT TREATMENT APPROACHES AND TO EXTEND SURVIVAL. THEREFORE, WE RETROSPECTIVELY ANALYZED THE CLINICOPATHOLOGICAL CHARACTERISTICS AND PROGNOSTIC FACTORS AFFECTING THE SURVIVAL RATE OF PATIENTS WITH GASTRIC CANCER.

KEY WORDS: CLINICOPATHOLOGICAL FACTORS, GASTRIC CANCER, PROGNOSIS, SURVIVAL.

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INTRODUCTION

Although 70 years ago gastric cancer was the most common neoplasm, the incidence and mortality have decreased dramatically in recent years[10]. At the beginning of the 21st century, we witness a substantial change in the global trends compared to the first estimates in 1975. In 2012 were diagnosed approximately one million new cases (952,000 cases), making it the fifth frequent cancer in the world (6.8% of the total) after lung, breast, colorectal, and prostate[11]. Currently, gastric cancer is the second leading cause of death from cancer in both genders worldwide after lung and liver malignancies (723,000 deaths, 8.8% of the total)[12].

The two main locations of gastric cancer are proximal (cardia) and distal (non-cardia). Even though the incidence of distal gastric cancer is continuously decreasing, the incidence of proximal tumors has been steadily increasing since the 1970s, especially in men in Western countries[13].

Gastric tumors can predominate in populations of different races, socioeconomic groups, and geographical regions because there are large differences in genetic susceptibility, pathological profile, clinical manifestations, and prognosis.

Over the past 3 decades, mortality in gastric cancer has declined significantly in many regions of the world[14]. It has been found that in countries with an increased incidence of gastric cancer the survival rate is higher than in countries where its incidence is lower due to the variable location of the tumor in the stomach[15]. Also, the presence of screening programs for early detection of gastric cancer in high-risk areas (like in Japan) has led to a decrease in mortality more than half since the early 1970s[16]. Tumors located near the pylorus have a better prognosis than those found in the gastric cardia, with a higher 5-year survival rate and lower periprocedural mortality rate[17]. If the tumor is limited to the mucosa, survival at 5 years is around 71% and decreases to 4% in the case of metastasis[18].

One of the reasons for the poor overall survival rate is that gastric cancers are frequently discovered in advanced stages. The stage of cancer together with the race (Asians have a better prognosis) and tumour location (proximal tumors) have a major effect on the

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prognosis of a patient. This shift to a more aggressive pattern and the inability to detect cancer early limit progress in improving survival in gastric cancer.

The purpose of this study was to identify clinicopathological features that influence the prognosis of patients operated for gastric cancer.

MATERIAL AND METHODS

CASE SELECTION

The present retrospective-observational analytical study enrolled between 1 January 2012 and 31 December 2017 a total of 107 patients aged 40–87 years who were diagnosed with gastric cancer and underwent surgery in the 2nd Surgical Department of the Emergency County Hospital of Craiova. Surgical interventions performed, with curative or palliative intentions, were not preceded by chemotherapy or radiotherapy. The preoperative informed consent about the surgical procedure and use of the resected tissue for research and other ethically acceptable purposes was obtained from all individual participants included in the study. 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 (IUCC). The analysis of the potential prognosis factors have included in this study parameters regarding the patient (sex, age), as well as parameters regarding the tumor (the macroscopic aspect according to the Borrmann's classification, the histological type according to the WHO and Lauren's classifications, the histopathologic grading, the tumoral localization, the stage of the disease, pT, pN and pM parameters, according to the TNM and AJCC classification).

Histopathological examination

The tumoral fragments were formalin-fixed and paraffin-embedded (FFPE). Histopathological examination was performed in the Department of Pathology of the Emergency County Clinical Hospital of Craiova. Due to formalin-induced cross-linking of proteins, FFPE tissues present a particular challenge for proteomic analysis.

Morphological evaluation of tumor extension (pT)

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 (IUCC).

T – Primary Tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria, high-grade dysplasia

T1 Tumour invades lamina propria, muscularis mucosae, or submucosa

T1a Tumour invades lamina propria or muscularis mucosae

T1b Tumour invades submucosa

T2 Tumour invades muscularis propria

T3 Tumour invades subserosa

T4 Tumour perforates serosa (visceral peritoneum) or invades adjacent structures [a, b, c]

T4a Tumour perforates serosa

T4b Tumour invades adjacent structures [a, b]

a. The adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

b. Intramural extension to the duodenum or esophagus is classified by the depth of greatest invasion in any of these sites including the stomach.

c. Tumour that extends into gastrocolic or gastrohepatic ligaments or greater or lesser omentum, without perforation of visceral peritoneum, is T3.

Morphological evaluation of lymphonodular metastases (pN)

Microscopic examination of resection pieces allowed identifying the lymph nodes in the perigastric adipose tissue.

The pN stage was quantified according to the TNM system, recommended by the AJCC/UICC, in which:

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1 to 2 regional lymph nodes
N2 Metastasis in 3 to 6 regional lymph nodes
N3 Metastasis in 7 or more regional lymph nodes
N3a Metastasis in 7 to 15 regional lymph nodes
N3b Metastasis in 16 or more regional lymph nodes

Evaluation of distance metastases (M)

M0 No distant metastasis

M1 Distant metastasis[1]

1. Distant metastasis includes peritoneal seeding, positive peritoneal cytology, and omental tumour not part of the continuous extension

Stage 0:	Tis	N0	M0
Stage IA:	T1	N0	M0
Stage IB:	T1	N1	M0
	T2	N0	M0
Stage IIA:	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB:	T1	N3a	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA:	T2	N3a	M0
	T3	N2	M0
	T4a	N1-2	M0
	T4b	N0	M0
Stage IIIB:	T1-2	N3b	M0

	T3-4a	N3a	M0
	T4b	N1-2	M0
Stage IIIC:	T3-4a	N3b	M0
	T4b	N3a-3b	M0
Stage IV:	any T	any N	M1

Table 1 - Pathological TNM staging of gastric cancer as per Union for International Cancer Control (UICC), 8th Edition (2017)

STATISTICAL ANALYSIS

The data from the patients were entered into an anonymized Excel file and analyzed by descriptive statistics and logistic regression analysis using the Microsoft Excel module in the Microsoft Office Professional Plus (Word, Excel) 2019 Version 16.45 for Mac and MedCalc program for Windows 10 Ver. 18.11.6. Quantitative data were summarized as mean and standard deviation (SD) after confirming Gaussian distribution or median and range for non-parametric variables. All qualitative data were represented with percentage and absolute numbers.

A literature search was performed and our results were compared to those available in the literature.

RESULTS

The clinical and histopathological study enrolled 107 human subjects who were diagnosed with gastric cancer and underwent surgery in the 2nd Surgical Departments of the Emergency County Hospital Craiova. Three-quarters of the patients were 60 or older. The mean age at diagnosis was 65.9 years with a standard deviation of 10,2 years. There was no significant difference between genders age (p=0.55; male: 65,5 years, female 66,8 years).

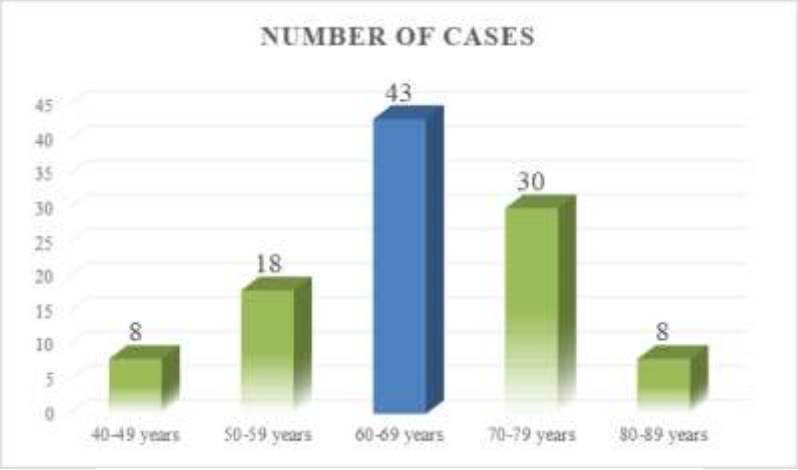

Figure 1 Distribution of patients according to age groups

Gastric carcinomas were are far more common in men than in women with an M / F ratio of 1,97. Analyzing the distribution of patients according to urban and rural areas, we noticed that there was a significant difference between the number of urban and rural residents.

The main clinicopathological features of cases of gastric cancer investigated are presented in Table 2.

Clinicopathological factors	No. of cases
Men	71
Women	36
Rural	69
Urban	38
Eso-cardia	6
Body	67
Pangastric	2
Antrum	30
Gastric stump	2
pTis/T1/T2/T3/T4	0/0/12/70/25
pN0/N1/N2/N3	28/31/11/37
pM0/M1	98/9

Table 2 – Clinicopathological features of gastric cancer studied

Patients were admitted to the hospital for a wide variety of symptoms that did not always suggest a disease involving the gastrointestinal tract. Only 14% of the patients had characteristic symptoms.

Tumor location was defined as the part of the stomach which contained the bulk of the tumor, as described in pathology reports. The body was the part in which gastric cancer was most frequently found, with more than half of the cases (62,6%). These tumors have all classical macroscopic features. Significant percentages were found also in the antrum and eso-cardial region. Only 2 patients had gastric stump cancer.

As for macroscopic features, all of the gastric lesions examined were classified as one of the four major macroscopic appearances of advanced gastric carcinoma (Borrmann's classification, 1926).

Macroscopic appearance		Number of cases	%
Early gastric cancer	Type 0 - llb (Flat)	0	0
Advanced gastric cancer	Type I (Polypoid)	10	9,3
	Type II (Ulcerated)	31	29
	Type III (Ulcerous-infiltrative)	52	48,6
	Type IV (*Diffusely-infiltrative*)	14	13,1
Total		107	100

Table 3 - Macroscopic aspects of gastric carcinomas

The most frequently (48,6%) observed macroscopic aspect has mixed morphology with both infiltrative and ulcerative components. The exophytic tumor, protruding from the surface of the gastric mucosa, with an irregular shape, was the least common with only 10 cases.

Examination of surgical specimens allowed accurate assessment of the extension of the tumor in the depth of the gastric wall. One argument of the aggressiveness of the analyzed

tumors is represented by the fact that almost 90% of cases in our study had aspects of tumor invasion beyond the muscularis mucosae.

The evaluation of local lymph node invasion (pN status) was performed on all patients. Secondary cellular proliferation in regional lymph nodes has been often extensive in the lymph node parenchyma with the destruction of normal follicular structures. Only 28 patients do not have metastatic abdominal adenopathies.

The prognostic of a gastric tumor is conditioned not only by the depth of the invasion into the gastric wall but also by the interception of other components of the wall. During the microscopic examination, it is important to evaluate the invasion into blood vessels, intraparietal lymph vessels, and nerves, their invasion being often encountered in advanced cases with a poor prognosis.

The tumours in our study exhibit a biologically aggressive phenotype, which is highlighted by the table below.

Invasion	Present	Absent	Indeterminate
Blood vessels	45	48	14
Intraparietal lymph vessels	41	47	18
Perineural	50	41	16

Table 4 - Invasion in the components of the gastric wall

In most cases, the gastric tumours were accompanied by important acute inflammatory reactions with hyperemic vessels, leukocyte marginations, lymphoplasmocytic and granulocytic inflammatory infiltrate, and fibrin deposits. Only 15 gastric tumors had minimal inflammation. Tumor necrosis is associated with poor clinical outcomes in many malignancies. The tumors in our study were very aggressive, with almost 80% of them being associated with a significant degree of necrosis.

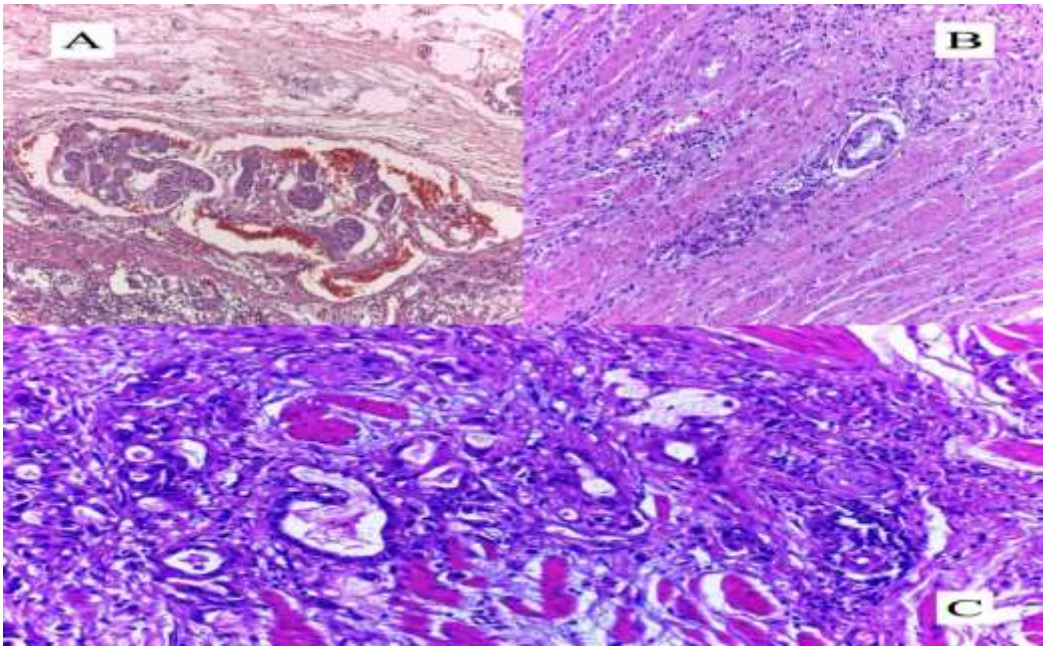

Figure 2 Tumor invasion in adjacent structures related to the gastric wall A. Vascular invasion (Hematoxylin-eosin stain, X10) B. Lymphatic invasion (Hematoxylin-eosin stain, X20) C. Perineural invasion (Hematoxylin-eosin stain, X20)

As we have shown above, most of the gastric tumours had a local and regional aggressive phenotype, which was also confirmed by the fact that approximately 8% of the patients have metastasis at CT scan. Liver and peritoneal metastases were identified in 9 patients. Only one patient had ovarian metastases.

The TNM Classification of Malignant Tumors (TNM), first published largely as a clinical classification by the Union for International Cancer Control (UICC) in 1966 is now a globally recognized standard for classifying the extent of the spread of cancer. It is also used by the American Joint Committee on Cancer (AJCC) and the International Federation of Gynecology and Obstetrics (FIGO).

TNM stage	Number of cases	%
Stage IA	0	0
Stage IB	7	6,5
Stage IIA	25	23,4
Stage IIB	19	17,8
Stage IIIA	17	15,9
Stage IIIB	18	16,8
Stage IIIC	12	11,2
Stage IV	9	8,4
Total	44	100

Table 5 - Invasion in the components of the gastric wall

The classification system used for the anatomic-pathological study was the WHO classification (2019).

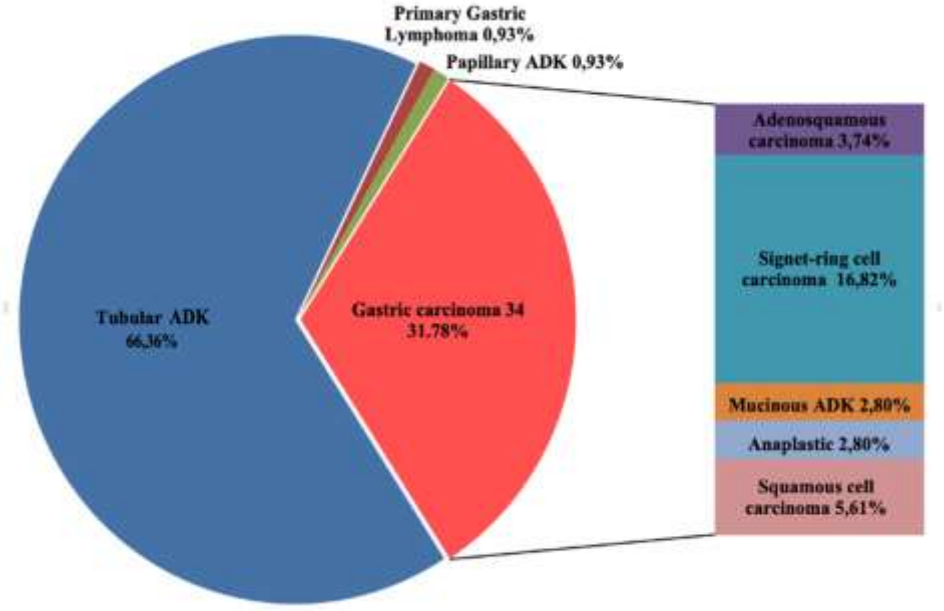

Figure 3 Distribution of the main histopathological types of gastric cancer

According to this classification system, almost 70% of the microscopic aspects were tubular adenocarcinomas. The other patterns were found in lower percentages: poorly cohesive with signet-ring cell carcinomas (16,8%) and squamous cell carcinoma (5,6%).

Since its establishment in 1965, the Laurén classification of gastric cancer has been the most commonly used and the most studied classification for gastric adenocarcinoma because the tumoral types have important clinical differences and are very useful in assessing

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prognosis. This system describes tumors based on microscopic configuration and growth patterns.

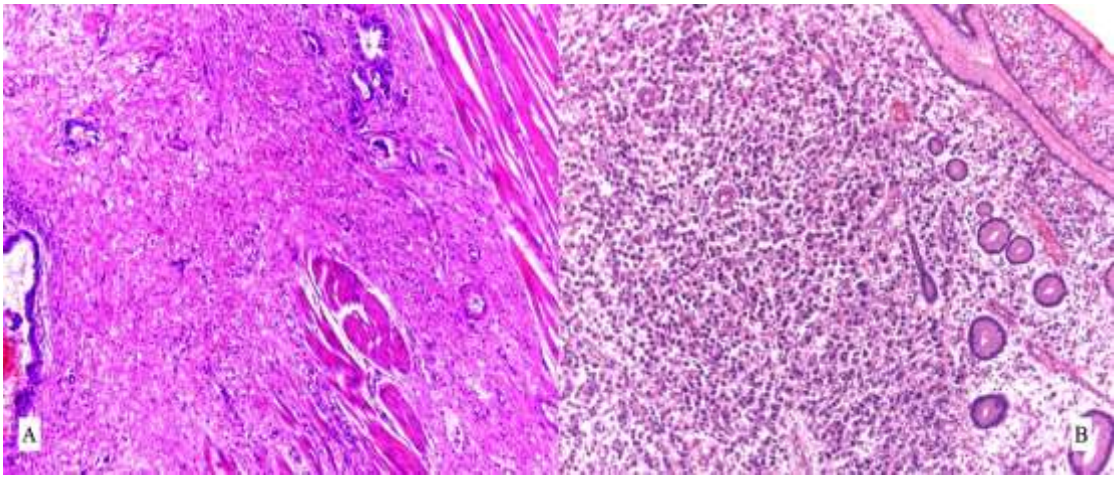

Figure 4 A. Intestinal type gastric adenocarcinoma (Hematoxylin-eosin stain, X10) B. Diffuse type gastric adenocarcinoma (Hematoxylin-eosin stain, X10)

More than half of the tumors were included in the intestinal type described by Lauren followed in order by the diffuse type. Only four patients presented an indeterminate type.

Correlations between the TNM stage and various clinicopathological features are listed in table 6.

	IA	IB	IIA	IIB	IIIA	IIIB	IIIC	IV
Men	-	4	15	10	12	15	10	5
Women	-	3	10	9	5	3	2	4
Median age	-	67,6	65,2	66,1	69,2	67	64,7	59,6
Rural	-	3	16	14	13	10	6	7
Urban	-	4	9	5	4	8	6	2
Esocardia	-	-	1	1	1	-	-	3
Body	-	7	15	12	8	11	8	6
Pangastric	-	-	1	-	1	-	-	-
Antrum	-	-	6	6	7	7	4	-
Gastric stump	-	-	2	-	-	-	-	-
Intestinal	-	6	16	10	12	12	6	5
Diffuse	-	1	7	8	4	6	6	3
PGL	-	-	-	1	-	-	-	-
Indeterminate	-	-	2	-	1	-	-	1
Tubular ADK	-	6	17	11	12	12	7	6
Papillary ADK	-	-	-	-	1	-	-	-
Adenosquamous carcinoma	-	-	-	-	1	1	1	1
SRCC	-	1	6	4	2	3	1	1
Mucinous ADK	-	-	-	2	-	1	-	-
Anaplastic	-	-	2	-	1	-	-	-
SCC	-	-	-	1	-	1	3	1
G1	-	2	1	-	-	-	-	-
G2	-	4	9	4	3	5	2	2
G3	-	1	12	14	13	12	8	7
G4	-	-	3	1	1	1	2	-

Abbreviations: PGL = primary gastric lymphoma, SRCC = signet-ring cell carcinoma

Table 6 Correlation between TNM stage and clinicopathological factors

We observed in our study that the advanced stages had a slight predominance of women. There was no correlation between the male sex and the TNM stage. The age of the patients in our study and TNM stages were inversely related, the patients in stage IV having the lowest median age. Tumors developed in the body of the stomach, the intestinal and diffuse types are frequently encountered in all TNM stages. The adenosquamous carcinoma and primary gastric squamous cell carcinoma were found in advanced stages of the disease. As expected, well-differentiated tumors (G1) are observed in the early stages of the disease (IB and IIA). Tumors with lower degrees of differentiation presented a diffuse distribution in all TNM stages.

DISCUSSIONS

Gastric cancer (GC) is one of the most common malignancies worldwide despite the fact incidence rates have decreased in the last few decades in most parts of the world[19].

Our study enrolled 71 males (66,4 %), and 36 females (33,6%). The male / female ratio is consistent with the previous studies that indicate a frequency greater than 6 times in males than in women with cardial cancer and twice in non-cardial cancers. The reasons for these differences are not clear, exposure to the environment or the workplace factors may play a role. For example, men are smokers in a higher proportion than women, although the lifetime risk of developing *stomach cancer* is *higher* also in countries where men and women share the same smoking habits. Alternatively, those differences in incidence may reflect physiological differences, estrogen may protect against the development of gastric cancer. In women, delayed menopause and increased fertility can reduce the risk, while anti-estrogen drugs, eg tamoxifen may increase gastric cancer rates. These hormones can protect during women's reproductive years, but their effect is diminished after menopause. This explains the 10-15 year gap after their male counterparts.

The mean age at diagnosis was 65.9 years and a standard deviation of 10,2 years, Also, the data from the literature showed a small incidence of gastric carcinoma under the age of 30, with a global peak between 65 and 74 years. Studies in Romania showed the same tendency, 63 being the average age at the time of diagnosis, significantly lower than in developed countries. In the USA, for example, the average age at the time of diagnosis is 69 years. Approximately 6 from 10 people diagnosed with gastric cancer each year are older than 65 years.

Almost 70% of the patients were from rural areas. The data in our study are consistent with those in the literature that highlighted the incidence of gastric cancer in patients with low social-economic status and low levels of education and hygiene[20].

Studies in Romania have shown an inverse ratio of patient distribution, predominantly those in the urban areas[21].

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Regarding the localization of the neoplasm, the body has represented the predominant localization for both sexes, being encountered in approximately 65% of the cases. At 30 patients (28%) tumors were located in the antrum. Most cancers of the stomach are gastric antrum cancer, although the incidence of gastroesophageal junction carcinoma is increasing gradually[22]. While the incidence of proximal tumours is increasing in the "western world", distal tumours continue to be predominant in Japan.

Concerning the macroscopic aspect of tumors, according to Borrmann's classification, for the studied group, the ulcerative-infiltrative type was predominant (48,6%), followed by the ulcerative type (29%). We found that 13,1% of patients with gastric cancers had Borrmann type IV gastric cancer, an incidence rate similar to that observed in other studies[23]. Patients with vegetative (type I) tumours have the most favorable prognosis, while the patients with infiltrative tumours (type III and IV) have a significantly less favorable prognosis. Borrmann type IV gastric cancer typically presents as an advanced stage tumor, with serosa-exposure and metastasis to the lymph nodes, as well as peritoneal dissemination.

Depending on the histological aspects at the tumour invasion level, 90% of cases in our study presented aspects of T3 and T4 lesions. The survival of carcinomas limited to the mucosa was significantly better in comparison to the neoplasms invading the submucosa[24]. It varies according to the T and N stage, being around 85–90% in T1 tumors and around 15–20% in T4 tumors and node-positive patients[25]. The lymph node metastases were present in 79 cases. The number of positive nodes best defines the prognostic influence of metastatic lymph nodes in gastric cancer. Survival estimates based on the number of involved nodes are better represented when at least 15 nodes are examined[26].

According to the WHO classification system, almost 70% of the microscopic aspects were tubular adenocarcinomas and 16,82% signet-ring cell carcinoma. In the WHO classification, the most common type of gastric cancer is tubular adenocarcinoma, followed by the papillary and mucinous types. In literature, the papillary ADK was associated with a worse prognosis[27].

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In another study, the WHO classification appeared to be an independent prognostic factor[28].

More than half of the tumors (62,6%) were included in the intestinal type described by Lauren followed in order (32,7%) by the diffuse type. The ratio of intestinal and diffuse types varies between countries and continents. In European countries, the intestinal type is currently more common. It tends to occur more often in the distal stomach, in high-risk areas, and it is often preceded by a long-standing precancerous lesion. The diffuse type prevails among young patients[29]. The prognostic relevance of Laurén's classification is still controversial.

Correlations between TNM stage and clinicopathological factors showed that the patients in stage IV had the lowest median age. In some studies, the young patients paradoxically present a less favorable prognosis because the malignity suspicion rarely appears and they are diagnosed in the advanced stage. As expected, well-differentiated tumors (G1) are observed in the early stages of the disease (IB and IIA).

CONCLUSIONS

Gastric cancer continues to be one of the leading causes of cancer-related death, its mortality rates have remained relatively unchanged over the past 30 years. Literature studies offer controversial data related to factors that influence prognosis in gastric cancer. Finding new predictive models generate important information allowing a logical evolution in the surgical and pathologic understanding and therapy for gastric cancer.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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