

Clinical, Histological and Prognosis Correlations in Diagnosis and Treatment of Gastric Cancer

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ABSTRACT: Purpose The study authors have proposed to highlight the main epidemiologic and prognostic aspects of digestive malignancies in the Dolj county population, justifying the need for permanent and detailed estimate of this phenomenon. **Methods** The authors of the study have proposed to outline a descriptive epidemiological panel, characteristic for the population groups at risk of developing gastric cancers and establishing clinical factors (tumor location, disease stage, type of surgery) and histological factors (histopathological type, degree of tumor differentiation) with prognostic significance having as landmark, survival rate at 5 years or disease-free survival of 5 years. **Results** The study was conducted on a sample of 458 patients with gastric tumors endoscopically detected, histologically confirmed and treated between 2000-2010. The epidemiological study allowed us to outline the descriptive epidemiological panel characteristic for the group of patients at risk of developing gastric cancer. Analysis of correlation between clinical parameters and histopathological parameters reached statistical threshold in multivariate statistical analysis of the localization of tumor, disease stage and histological type ($p < 0.0001$) and the degree of differentiation of gastric carcinomas ($p < 0.005$). Multivariate statistical analysis has detected statistically significant differences in terms of survival rate at 5 years ($p > 0.001$) and free interval of disease at 5 years ($p > 0.001$), depending on the location of the tumor, correlated with other clinical factors (disease stage, type of surgery) and histological factors (histopathological type, tumor differentiation grade), which allowed us to outline clinical, histological and prognostic groups. **Conclusions** Defining the clinical, histological and prognostic groups, allows an accurate assessment of patient prognosis from the time of randomization and initiation of treatment, type of surgery in advanced loco-regional, reconvered to operability, after neoadjuvant polychemotherapy being dictated by the location of the tumor (1/3 superior vs. 1 / 3 medium vs. 1/3 lower stomach).

KEYWORDS: gastric cancer, descriptive epidemiology, the survival rate at 5 years, disease-free survival of 5 years, prognostic groups

Introduction

Globally gastric cancer ranks fourth, after lung cancer, breast cancer and colorectal cancer and is the second leading cause of cancer death [1-4]

In Romania, the incidence and mortality of gastric cancer experienced a gradual decline, ranging from 33.14 / 18.77 per 100,000 inhabitants in 1995 to 15.9 / 15.2 per 100,000 people in 2008, areas with increased mortality were eastern and western Transylvania (Covasna, Harghita, Timis, Arad, Bihor), Bucharest and Teleorman County [1-4].

Data reported in various epidemiological studies confirms that the peak incidence of gastric carcinomas age is within a range of 50-70 years, gastric cancer is rarely met under the age of 40 years [1-4].

The incidence is higher in men, with a ratio of 2:1 in favor of males. [5].

Surgical treatment is the only potentially curative treatment in operable stages respective IB-III, total gastrectomy is indicated in tumors localized in the middle and upper third of the stomach, and subtotal gastrectomy in tumors localized in the lower third of the stomach, associated with lymph node dissection in both situations D1 + D2 [16-23]. Adjuvant treatment consists in the administration of chemo-radiotherapy (45 Gy / 25 fr / 33 days, 1.8 Gy / fr + 2 cycles of FUFOL: 5-FU 400 mg / sqm + folinic acid 20 mg / sqm, D1-4, 33-35) followed by adjuvant polychemotherapy 3 cycles of FUFOL regimen (5-FU 425 mg / sqm + folinic acid 20 mg / sqm D1-5 / 28) [24-27].

The therapeutical standard in locally advanced stages, consists of 2-4 cycles of neoadjuvant polychemotherapy (ECP protocol: Epirubicin 50 mg/sqm, Cisplatin 60 mg/sqm and

5-fluorouracil 200 mg/sqm/ day in 3 weeks), followed by radical surgery (total gastrectomy with extended lymphadenectomy D1 + D2) and chemo-radiotherapy (45 Gy/ 25 fr/ 33 days, 1.8 Gy/fr + 2 cycles of FUFOL: 5-FU 400 mg / sqm + folinic acid 20 mg / sqm, D1-4, 33-35) [29-33] The prognosis of gastric cancer patients is reserved, with a low survival rate, which is due to late diagnosis, most cases presenting in advanced stages, as well as reduced efficacy of therapeutic methods with the emergence of local recurrence, hardly responsive to treatment [42 - 45].

Materials and Methods

The authors have proposed to make a retrospective observational study, longitudinal, for a period of six years, between 2005-2010, in the most representative county of the South-West district of Oltenia region, respectively Dolj County, where its geographical profile, socio-economic and population characteristics (customs, traditions, lifestyle) can be included in an analytical study, epidemiologic and clinical of gastric malignancies.

The study was conducted on patients hospitalized in the Gastroenterology Clinic, Internal Medicine and Surgery Clinics of the Clinical Emergency County Hospital Craiova, where they were diagnosed after performing upper gastrointestinal endoscopy with sampling biopsies in order to confirm malignancy, then patients are taken into evidence and treated in the Medical Oncology Clinic of the Clinical Emergency County Hospital Craiova. The data used in statistical interpretation were collected from the cancer patients statistical sheet ONC 1 and evidence sheet of the cancer patient ONC2.

In the epidemiological study, we aimed to outline the characteristic epidemiological demographic panel group of patients at risk of developing gastric cancer, the analysis is performed on a sample of 458 patients diagnosed with gastric cancer and confirmed between 2005-2010, monitored parameters being the analysis of the distribution of patients by sex, age, origin and detection of risk factors involved in gastric cancer etiopathogeny.

In the clinical study data analysis was also performed on the batch of 458 hospitalized patients and investigated in the Surgery and Gastroenterology Clinics of Clinical Emergency County Hospital Craiova and histopathological diagnosis of gastric carcinoma

was established in the Laboratory of Pathology of the same hospital, between 2005-2010.

The authors analyzed the distribution of patients in relation to the symptoms at admittance, disease stage at presentation and the type of surgery that was performed with the aim of splitting clinical factors with prognostic significance, evaluation of the therapeutical results are interpreted in terms of survival rate at 5 years and interval free of disease at 5 years.

In the histopathological study we aimed to detect factors with histological and prognostic impact and establishing clinical, histological and prognostic correlations having as parameters for reporting the location of the tumor and the stage of disease correlated with histopathological type and degree of tumor differentiation, the therapeutic results are reported to the international standard parameters, respectively, 5-year survival rate and disease free interval of 5 years.

Statistical analysis was performed using Microsoft Excel software and SPSS version 17.0, results were considered statistically significant at $p < 0.05$.

In the statistical processing of data obtained from epidemiological study, clinical and histopathological evaluation of the results was performed after a 5-year follow-up period, the authors having as a benchmark, the detection, of two primary objectives:

-in the epidemiological study it was aimed to establish the characteristic demographic epidemiological panel of patients with increased risk of developing gastric cancer;

-in the clinical and histopathological study it was aimed to identify clinical factors with prognostical significance and establishing correlations with histological and prognostic factors with the purpose of defining the impacting factors in the prognosis of patients registered with this pathology tumor.

Results

Epidemiological investigation of gastric carcinomas

In this study, the authors have proposed to analyze the distribution of gastric cancer patients in relation to sex, age and area of origin of the patients.

Analysis of the incidence of gastric cancer in the Dolj county has up showed a relatively balanced distribution for Craiova and other geographic regions (North, Southeast, Southwest) of Dolj County.

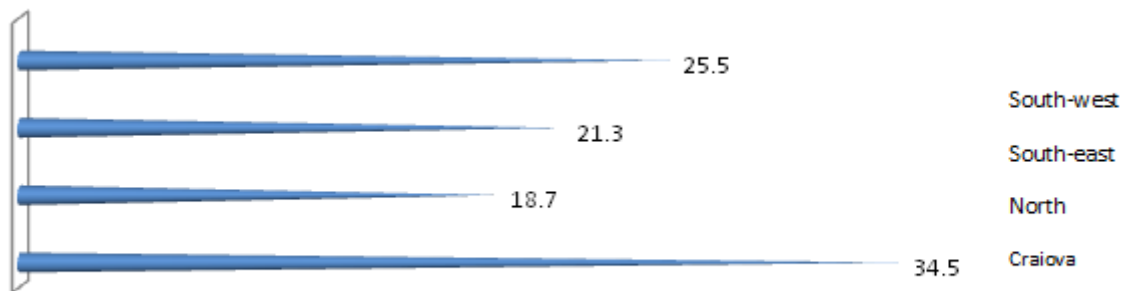


Fig.1. The incidence of gastric cancer in based on geolocation

Compared to a retrospective study over the period 1981-1993, the peak incidence has passed from the age group 55-64 years to 65-74 years. In the current study, increased incidence of gastric cancer is progressive until around the age

group 65-74 years (37% of gastric cancers), and the number of new cases decreases after the age of 75 years, the decline being slow but steady (Fig.2).

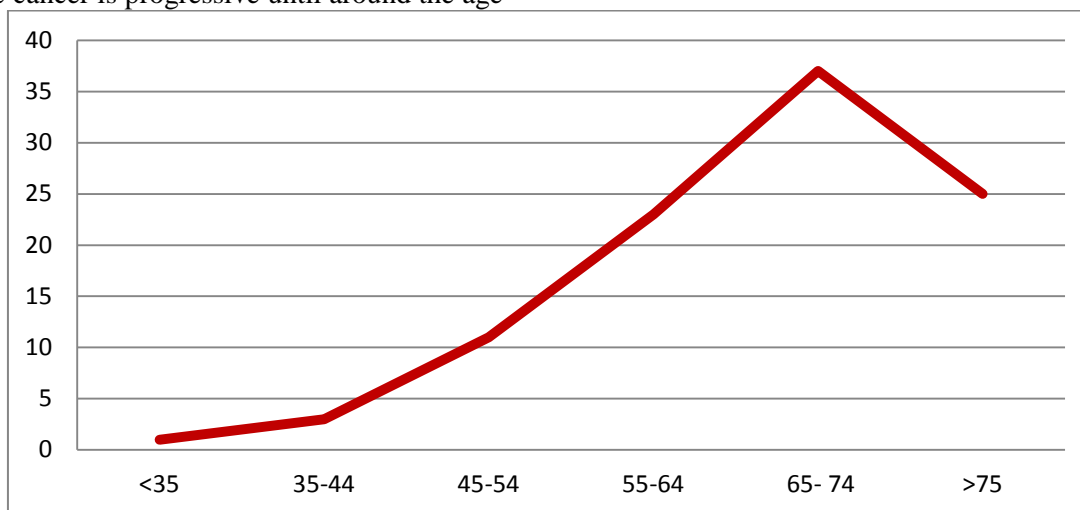


Fig.2. Distribution of gastric cancer based on age

Regarding distribution by area of origin (urban/rural), gastric cancer incidence has not registered significant differences between the two backgrounds, slightly higher values being recorded for rural areas (253 patients, 55.24%) vs. urban environment (205 patients, 44.75%) (Table 1).

The most commonly affected are male patients - 305 cases (66.66%), with a ratio of 2: 1 in favor of males (Table 2).

Table 1. Distribution by area of residence (urban/rural) of gastric cancer.

Area	Number of patients (%)
Rural	253 patients (55,24%)
Urban	205 patients (44,75%)

Table 2. Distribution by sex of gastric cancer

Sex	Number of patients (%)
Male	305 patients(66,66%)
Female	153 patients (33,34%)

The study authors have proposed to detect the risk factors involved in the etiopathogenesis of gastric cancers, the data being collected from evidence sheet ONC 1 of hospitalized patients in Medical Oncology Clinic of the Clinical Emergency County Hospital Craiova, with focus on the medical history of patients, respectively surgical interventions practiced for gastric ulcers and Helicobacter pylori infection involvement in this condition and the conditions of life and

work, especially on the diet of oncological patients.

From this study we observed that the main risk factors involved in the etiopathogeny of patients diagnosed and treated with gastric cancer were:

- Nutritional factors: eating meat or salted fish, as well as insufficient food preparation and lack of refrigeration, increased consumption of nitrates, low consumption of fat and protein and low diet in vitamins A and C.

- iatrogenic factors: previous stomach surgery, especially for gastric ulcer.

- infectious factors: *Helicobacter pylori* detected with predilection gastric neoplasm with intestinal type, neoplasms located mainly at the lower third of the stomach.

Following the epidemiological study we were able to shape a demographic epidemiological panel characteristic for the group of patients at risk of developing gastric cancer, including elderly men, in the decade VI-VII of life, with origin in rural areas with a history of peptic ulcer, *Helicobacter pylori* positive or salted fish meat eaters with insufficient food preparation and lack of refrigeration and low diet in fat, protein, vitamins A and C.

Clinical and histopathological study of gastric carcinomas

The study was conducted on a total of 458 hospitalized patients and investigated in the Surgery and Gastroenterology Clinics of the Clinical Emergency County Hospital Craiova, who were histologically diagnosed with gastric carcinoma in the Laboratory of Pathology at the same hospital between 2005-2010.

The study authors have proposed to analyze the distribution of patients in relation to the symptoms the patients presented at admission, disease stage at presentation and the type of surgery, with the aim of detecting clinical factors with prognostic value.

The analysis of symptoms at admission revealed that the main subjective symptoms, which were the reason for referral to a doctor, were: abdominal pain (148 cases, 32.31%), nausea and vomiting (110 cases, 24.01%), epigastric pain (102 cases, 22.27%) and abdominal discomfort (98 cases, 21.39%).

Endoscopic assessment was major criteria for inclusion in the group of cases analyzed, enabling the assessment of two parameters, namely the location of the tumor and histopathological analysis of the type and degree of tumor differentiation.

Depending on the tumor location, in 205 (44.75%) cases of gastric carcinoma, tumor formation was located in the lower third of the stomach, in 161 (35.15%) cases were located in the middle third of the stomach, in 65 (14.19%) cases the tumors were located in the upper third of the stomach, in 5 (1.09%) cases of gastric carcinoma, tumor formation was located in the gastric stump (for patients who underwent subtotal gastrectomy for gastric ulcer) and in 22 (4.8%) cases tumor location could not be ascertained.

In terms of histopathology, from the total of 458 gastric carcinomas, most cases were of intestinal type tumors (370 cases, a percentage of 80.78%) (Table 3).

In relation to the degree of tumor differentiation, both intestinal carcinomas, as well as the diffuse type, they were in most cases, poorly-differentiated tumors (Table 4)

Table 3. Distribution by histopathological type of gastric carcinomas

Gastric carcinoma	intestinal	diffuse	total
Nr. cases/ Percentage	370 (80.78%)	88 (19.22%)	458

Table 4. Correlation with the degree of differentiation of gastric carcinomas

Nr. cases /Percentage	Well-differentiated	Moderate-differentiated	Poorly differentiated	Total casesi
Intestinal type carcinoma	27 (7.29%)	147 (39.72%)	196 (52.97%)	370
Diffuse type carcinoma	24 (27,27%)	23 (26,13%)	41(46,59%)	88

Also imaging evaluation by CT scan with contrast agent of the abdomen and pelvis allowed to establish the loco-regional and distant extension of the disease. Thus, in all cases diagnosed with gastric cancer during this period only 4.8% of the cases (22 patients) were identified in a localized stage, which is a curable phase of the disease, compared to 88.86% of cases (patients 407) discovered in an advanced

stage of the disease. The worst is that the percentage of patients diagnosed metastatic disease (hepatic metastasis and peritoneal) exceeded the percentage of patients diagnosed curable stage disease, which is understandable considering the lack of specific symptoms and late symptoms of this neoplastic location (Table 5).

Table 5. Distribution of gastric carcinomas according to tumor stage

Disease stage	Nr. Cases (%)
Localized	22 patients(4,8%)
Advanced	407 patients (88,86%)
Metastatic (M1HEP,PER)	29 patients (6,33%)

After the clinical study we can sustain the predominant symptom was dyspeptic abdominal syndrome with abdominal pain, nausea and vomiting, which allowed endoscopic and imaging diagnosis of gastric carcinomas, mostly in advanced loco-regional with localized tumors, especially at level 1/ 3 lower part of the stomach.

Histological and prognostic factors analysis, respectively histopathological type and degree of differentiation in order to realize clinical, histological and prognostic correlations (histopathological type and degree of differentiation based on tumor location, disease stage and type of surgery) was performed on 352 pieces gastrectomy.

In 22 patients diagnosed with localized and curable stage of disease, tumor formation was detected endoscopically, being located in the lower third of the stomach, initially a subtotal gastrectomy with local lymphadenectomy was performed.

From the 407 patients diagnosed at an locally advanced stage therapy consisted of administration neo-adjuvant polychemotherapy 2-4 cycles (Epirubicin 50mg / sqm + Cisplatin 60 mg / sqm iv + 5-fluorouracil 200 mg / sqm IV /21 days) with imaging reevaluation to establish the operability reconversion, which was possible in 330 cases. Of the 330 pieces of gastric resection, in 51 cases the tumor was

located in the upper 1/3 and in 111 cases in the lower third of the stomach, in all cases, a total gastrectomy with local lymphadenectomy was practiced and in 168 cases the tumor was located in the lower third of the stomach and a subtotal gastrectomy with lymphadenectomy was performed.

Thus, of the 352 pieces of gastric resection, in 51 of 65 cases the tumor originated in the upper stomach 1/3 and a total gastrectomy was performed, in 111 of 161 cases in which the tumor originated in the middle 1/3 stomach a total gastrectomy was also practiced, and in 190 of 205 cases in which the tumor originated in the lower third of the stomach a subtotal gastrectomy was performed. We can state that the conservative intervention or subtotal gastrectomy was practiced in most cases (190 cases, 53.97%), in which the tumor had originated in the lower third of the stomach, being classified as locally advanced by imaging methods at presentation (168 cases advanced loco-regional stage curable vs. 22 cases). Radical intervention was practiced in 46.02% of cases (162 patients), and the tumor was detected by endoscopic imaging in a locally advanced stage, having in most cases originated in middle1/3 of the stomach (111 cases the middle 1/3 vs. 51 cases in upper 1/3 stomach) (Tables 6 and 7).

Table 6. Distribution of gastric carcinomas according to tumor location and type of surgery

Total	Tumor location	Type of surgery	Nr. patients (%)
Curable Stage	1/3 lower	Subtotal Gastrectomy	22 patients(6,2%)

Locally Advanced Stage 330 patients	1/3 upper 1/3 middle 1/3 lower	Total Gastrectomy Total Gastrectomy Subtotal Gastrectomy	51 patients(14,48%) 111 patients(31,53%) 168 patients (47,72%)
Total			352 patients

Table 7. Type of surgery depending on the location and stage of the disease

Surgery type	Tumor location	Disease stage	Nr. patients (%)	Total patients
Subtotal Gastrectomy	Lower third	Curable Locally advanced	22 patients (6,2%) 168 patients (47,72%)	190 patients (53,97%)
Total gastrectomy	Upper third Middle third	Locally advanced Locally advanced	51 patients (14,48%) 111 patients (31,53%)	162 patients (46,02%)
Total				352 patients

The analysis of the histopathological type was conducted on 352 pieces of gastrectomy, most cases, respectively 284 (80.68%) being intestinal type tumors located mainly in the lower third of the stomach (187 cases in lower 1/3 vs. 97 cases middle 1/3 of the stomach) and classified mostly by endoscopic imaging in a locally advanced stage of the disease (168 cases

cases advanced stage vs. 19 cases curable stage) and 68 tumors were histologically diffuse type carcinomas, mostly localized in the upper third of the stomach (51 cases upper third vs. 14 cases middle 1/3 vs. 3 cases, lower 1/3 of the stomach), also detected by endoscopic imaging and classified locally advanced stage of the disease (Table 8).

Table 8. Distribution of histopathologic type depending on tumor location

Histopathological type	Tumor location	Nr. cases	Total number of gastrectomy pieces	Total number of gastrectomy pieces
Intestinal type	Lower 1/3	187 cases	Locally advanced stage (168 cases)	284 patients (80,68%)
	Middle 1/3	97 cases		
Diffusetype	Upper 1/3	51 cases	Locally advanced	68 patients (19,31%)
	Middle 1/3	14 cases		
	Inferior 1/3	3 cases		
Total				352 patients

Most cases, as it resulted in histopathological type analysis, overall, were poorly differentiated tumors; 196 such cases (69.01%) of the total 284 intestinal carcinomas were poorly differentiated tumors and were diagnosed in locally advanced stages, having originated in the lower third of

the stomach, and 41 cases (60.29%) of the 68 carcinomas were diffuse type, poorly differentiated tumors, originating in upper third of the stomach and also detected and classified by endoscopic imaging in locally advanced stages of the disease (Table 9).

Table 9. Correlation with histopathological type of tumor differentiation grade

Histopathological type 352 pieces of gastric resection	Poorly differentiated tumors	Tumor location	Disease stage	Nr total cases
Intestinal type	196 (69,01%)	Lower 1/3	Locally advanced	284
Diffuse type	41 (60,29%)	Upper 1/3	Locally advanced	68

It was analyzed the correlation between clinical parameters (location of gastric tumors, stage of disease and type of surgery) and histopathological parameters (histopathological type and differentiation degree of tumor) which showed up a statistically significant correlation between tumor location, disease stage and histology ($p < 0.0001$) and the degree of differentiation of carcinomas of the stomach ($p < 0.005$).

Thus, gastric tumors originating in lower third of the stomach are more commonly associated with intestinal type (intestinal type carcinomas 187 vs. 3 cases of diffuse type carcinomas) and are poorly differentiated tumors, detected and classified by endoscopic imaging, in most cases in locally advanced stages of the disease (168 cases advanced stage vs. 22 cases localized stage), where it was possible to revert to operability, after

neoadjuvant polychemotherapy and a subtotal gastrectomy being practiced.

Gastric tumors originated in upper third of the stomach were associated with diffuse type (51 cases) and are poorly differentiated tumors, endoscopic detected and classified into locally advanced stage of the disease, where it was possible to revert to operability, post-neoadjuvant polychemotherapy with total gastrectomy being practiced.

Tumors originating in middle third of the stomach are associated with intestinal type (97 intestinal carcinomas vs. 14 diffuse type carcinomas) and are moderately differentiated tumors, endoscopic detected and classified in a locally advanced stage of the disease, and it was possible to revert the operability, after neoadjuvant polychemotherapy with total gastrectomy being practiced (Table 10).

Table 10. Correlation between tumor location, disease stage, histopathological type and degree of tumor differentiation

Location	Upper third	Middle third	Lower third	Total
Histopathological type $p < 0,0001$				
Diffuse	51	14	3	68
Intestinal type	-	97	187	284
Histopathological degree $p < 0,005$				
INTESTINAL				
G3 intestinal	-	9	187	196
G2 intestinal	-	75	-	75
G1 intestinal	-	-	-	0
DIFFUSE				
G3 diffuse	51	14	3	68
G2 diffuse	-	13	-	13
G1 diffuse	-	-	-	0
Total	51	111	190	352

After the clinical and histopathological study we established a statistically significant correlation between clinical factors (tumor location, disease stage and type of surgery) and the histopathological factors (histopathological type and degree of tumor differentiation), tumors detected endoscopically, located in the upper 1/3 of the stomach being diffuse type carcinomas, poorly differentiated and classified

into locally advanced stages, where it was possible to revert to operability, after neoadjuvant polychemotherapy with total gastrectomy being practiced.

Tumors originating in the lower third of the stomach are poorly differentiated, intestinal type carcinomas, mostly classified by imaging methods as locally advanced stage of the disease, where it was possible to revert to

operability, after neoadjuvant polychemotherapy, with subtotal gastrectomy being practiced.

Tumors originating in the middle third of the stomach were intestinal type carcinomas, moderately differentiated, most of them being classified at presentation in locally advanced stages of the disease, where it was possible to revert to operability, after neoadjuvant polychemotherapy with a subtotal gastrectomy being practiced.

Conservative surgery, respectively subtotal gastrectomy was practiced in most cases (190

cases, 53.97%) and in all situations in which endoscopic tumor origin has been detected in the lower third of the stomach, histologically confirmed as intestinal type carcinomas (187 cases vs. 3 diffuse type carcinomas) and in most cases they were classified as locally advanced stage of the disease (168 cases in the advanced stage vs. 22 cases in localized stage), but it was possible to revert operability after neoadjuvant polychemotherapy (2-4 series), reconversion which was spotted and established by imaging techniques (Table 11).

Table 11. Correlation between clinical factors (tumor location, disease stage and type of surgery) and histopathological factors (type and degree of differentiation histopathologic tumor)

Tumor location	Disease stage	Histopathological type	Tumor differentiation degree	Type of surgery	Nr. patients 352 patients
Upper third of the stomach	Locally advanced stage	Intestinal	Poorly differentiated	Total gastrectomy	51 patients
Middle third of the stomach	Locally advanced stage	Intestinal	Moderate differentiated	Total gastrectomy	111 patients
Lower third of the stomach	Curable stage	Diffuse	Poorly differentiated	Subtotal gastrectomy	22 patients
	Locally advanced stage	Diffuse	Poorly differentiated	Subtotal gastrectomy	168 patients

Furthermore, in order to establish the impact of the clinical and histopathological factors in the prognosis of patients, the study authors analyzed the results of treatment depending on the location of the tumor, only in the group of patients endoscopically identifiable and enclosed in locally advanced stage of the neoplastic disease, where the treatment was similar (neoadjuvant polychemotherapy followed by surgery), statistically significant batch number which allowed the type of surgery efficacy analysis dictated by the location of the tumor. The authors have proposed analyzing the prognosis of patients, imaging employed in locally advanced stages, in the three locations neoplastic (upper 1/3 vs. middle 1/3 vs. lower 1/3 of the stomach), to find out the impact of surgery, dictated by location of the tumor, in terms of survival rates and disease-free interval.

They were thus excluded statistical errors due to a comparative analysis between two groups of unequal numbers, including localized stage (22 cases) vs. advanced loco-regional disease (330 cases) as the default would not have allowed a comparative analysis of the real efficacy of the

two therapeutic regimens if administered in localized vs. advanced loco-regional stages of neoplastic disease.

Because the location of the gastric tumor involves different histopathological types and degrees of differentiation, it results that histopathological type and degree of tumor differentiation are two parameters important in assessing tumor progression and patient outcomes, which are considered independent factors of prognosis for gastric cancers.

Reporting therapeutic results was made after a post-treatment follow-up period of 5 years, having as reference the parameters of international standard in reporting the results of therapeutic, respectively 5-year survival rate and disease free interval of 5 years.

Subsequently, based on demonstrating statistically significant correlation between clinical factors (tumor location, disease stage and type of surgery) and histopathological factors (type and degree of differentiation histopathologic tumor), clinical, histological and prognostic groups can be defined.

Disease free survival of 5 years

Loco-regional and distance recurrence rate, was analyzed in patients who were included by imaging investigations in locally advanced disease stage, reconverted to operability, i.e. 330 patients, where it was possible to analyze the histopathological factors for the gastric resection pieces.

Overall therapeutic failure rate was 33.03% (109 patients) after a disease-free interval of 7 months, and when reporting data after a 5-year follow-up period, was recorded the death of these patients.

From 111 patients who were found with intestinal type carcinomas, moderate differentiated, located in the medium 1/3 of the stomach, in which total gastrectomy was performed there was recorded a resumption of loco-regional evolution of the disease at the tumor bed at 38 patients (34.23%), recorded the data in reporting the death of patients. It can be argued that the practice of total gastrectomy in these patients has secured control of the disease with decreased loco-regional recurrence rate definite and eliminating the risk of developing secondary determinations remotely, hard responsive to treatment.

From the 168 patients who were found with intestinal type carcinomas, poorly differentiated, localized to the lower third of the stomach, subtotal gastrectomy was performed and there was recorded, a reduced rate of loco-regional recurrence in the gastric stump, 11,90% (20 patients), but when reporting data was being recorded, patients were dead.

Multivariate statistical analysis, of the disease-free interval to 5 years, showed up statistically significant differences depending on the location of the tumor ($p > 0.001$).

Recurrence rate, recorded as remote failures (secondary determinations of the liver and peritoneum) was statistically significantly superior (100%) patients, who had endoscopically detectable tumors having originated in the upper third of the stomach, confirmed histologically as diffuse type carcinomas, poorly differentiated and enclosed by imaging techniques in loco-regional advanced stages of the disease, but were reconverted to operability after neoadjuvant polychemotherapy with total gastrectomy being practiced.

Recurrence rate, recorded as loco-regional failures in the gastric stump, was statistically significantly lower in 168 patients with endoscopically detectable tumor originating in the lower third of the stomach, histologically confirmed as intestinal type carcinomas, poorly differentiated and enclosed by imaging techniques in advanced loco-regional disease stage, but were reconverted to operability after neoadjuvant polychemotherapy with subtotal gastrectomy being practiced (11.90%).

Recurrence rate, recorded as loco-regional failures in the tumor bed was statistically significantly reduced (34.23%) in 111 patients with endoscopically detectable tumor which originated in the middle 1/3 of the stomach, confirmed histologically as intestinal type carcinomas, poorly differentiated and enclosed by imaging techniques in locally advanced stage of the disease, but who were reconverted to operability after neoadjuvant polychemotherapy with total gastrectomy being practiced, which provides local and distant control of the disease (Table 12).

Table 12. Therapeutic failures rate

Tumor location	Nr. Patients (%)	Therapeutic failures rate
Upper third	51 patients (14,19%)	51 patients (100%)
Middle third	111 patients (35,15%)	38 patients (34,23%)
Lower third	168 patients (44,75%)	20 patients (11,90%)

It can be clearly outlined that the prognosis of patients reported to the free interval of disease at 5 years rate, depends on the location of the tumor correlated with other clinical factors with prognostic value (stage of disease, type of surgery) and histological factors (histopathological type and grade tumor differentiation).

Patients who have tumors located in the upper stomach 1/3, confirmed histologically as diffuse type carcinoma, poorly differentiated that have been reconverted the operability and underwent total gastrectomy have a poor prognosis.

Patients with favorable prognosis are patients with tumor located in the lower third of the

stomach, histologically confirmed as intestinal type carcinoma, poorly differentiated, with subtotal gastrectomy being practiced after reconverting to operability.

Intermediate prognosis is reserved for patients with tumor located at the middle third of the stomach, histologically confirmed as intestinal type carcinomas, moderately differentiated who underwent total gastrectomy, after reversion to operability, that provided local and distant control of the disease, certified by reduced rate of local recurrence and by the absence of distant disease progression.

Reported to the rate of disease-free interval, practicing total gastrectomy is imposed as a mandatory criterion for approaching locally advanced tumors, located in the upper third and middle third of the stomach.

Five year overall survival

The mortality rate was also analyzed for patients who were classified by imaging techniques in locally advanced stages of the disease and that it was possible to reconvert the operability after neoadjuvant polychemotherapy, respectively 330 patients, where it was possible to analyze histopathological factors on the gastric resection pieces (histologic type and grade of tumor differentiation).

Overall mortality rate was 46.6%, when reporting data, after a 5-year follow-up period, 154 patients were registered as dead, after a median interval of 11 months. Death occurred in all 109 patients who experienced therapeutical failures, hardly responsive to second line palliative polychemotherapy (including Taxanes regimes).

Also, death occurred in 45 patients who had tumors located in the middle third of the stomach, confirmed histopathologically as intestinal type carcinoma, moderately differentiated, in locally advanced stages, reconverted to operability, with total gastrectomy being practiced and that when reporting data, the patient's death was registered, through local recurrence at the tumor bed, developed late in the disease (median

interval 11 months), hardly responsive to second line polychemotherapy.

Multivariate statistical analysis, of the survival rate at 5 years has detected statistically significant differences in mortality according to the location of the tumor, correlated with other clinical factors (stage of disease, type of surgery) and histological factors (histopathological type, degree of tumor differentiation) ($p > 0.001$).

The mortality rate was statistically significantly superior in the 51 patients with endoscopically detected tumors, originating in the upper third of the stomach, histologically confirmed as diffuse type carcinomas, poorly differentiated and enclosed by imaging techniques in locally advanced stage of the disease, but who were reconverted to operability after neoadjuvant polychemotherapy with total gastrectomy being practiced (100%).

The mortality rate. was statistically significantly lower in 168 patients with endoscopically detected tumors, originating in the lower third of the stomach, histologically confirmed as intestinal type carcinomas, poorly differentiated and enclosed by imaging techniques into locally advanced stages of the disease, but were reconverted to operability after neoadjuvant polychemotherapy with subtotal gastrectomy being practiced (20 patients, 11.90 %).

The mortality rate was also reduced (74.77%) in 111 patients with endoscopically detected tumors, originating in the middle third of the stomach, histologically confirmed as intestinal type carcinomas, moderately differentiated and enclosed by imaging techniques into locally advanced stage of the disease but who were reconverted to operability after neoadjuvant polychemotherapy with total gastrectomy being practiced.

In this group death occurred in 83 patients. (38 patients who developed therapeutic failures, 45 patients died of local recurrence developed late in the disease) (Table 13).

Table 13. The survival rate at 5 years

Tumor location $p > 0.001$	Nr. Patients (%)	Mortality rate
Upper third	51 patients (14,19%)	51 patients (100%)
Middle third	111 patients (35,15%)	83 patients (74,77%)
Lower third	168 patients (44,75%)	20 patients (11,90%)

It can be clearly outlined that the prognosis of patients reported to the survival rate at 5 years varies depending on the location of the tumor correlated with other clinical factors with prognostic value, respectively, disease stage, type of surgery and the histological factors respective histopathological type and tumor grade differentiating.

Patients who have tumors located in the upper stomach 1/3, confirmed histologically as diffuse type carcinoma, poorly differentiated that have been reconverted the operability and underwent total gastrectomy have a poor prognosis.

Patients with favorable prognosis, are patients with tumor located in the lower third of the stomach, histologically confirmed as intestinal type carcinoma, poorly differentiated, with subtotal gastrectomy being practiced after reconverting to operability.

Intermediate prognosis is reserved for patients with tumor located at the middle third of the stomach, histologically confirmed as intestinal type carcinomas, moderately differentiated who underwent total gastrectomy, after reversion to operability, that provided local and distant control of the disease, certified by reduced rate of local recurrence and by the absence of distant disease progression.

Reported to the mortality rate, total gastrectomy practice is required as mandatory criterion approach for tumors located in the upper 1/3 and medium 1/3 of the stomach.

After analyzing the survival rate at 5 years and free interval of disease at 5 years, we can shape clinical, histological and prognostic groups based on correlations statistically significant established between clinical factors with prognostic value (tumor location, disease stage, type of surgery) and histo-prognostic factors (histopathological type, tumor differentiation grade), prognosis of patients being analyzed through the two international standardized parameters respectively 5-year survival rate and disease free interval of 5 years.

Good prognosis group includes patients with endoscopically detected tumors located in the lower third of the stomach, histopathologically confirmed with intestinal type carcinomas, poorly differentiated, employes by imaging techniques in locally advanced stage of the disease, reconverted to operability after neoadjuvant polychemotherapy with practicing a subtotal gastrectomy with local lymphadenectomy, with a statistically

significant lower rate of therapeutic failures, mortality and low postoperative morbidity.

The intermediate prognostic group includes patients with tumor endoscopically detected, originating in middle third of the stomach, histologically confirmed with with intestinal type carcinomas, moderately differentiated, employed by imaging techniques in locally advanced stage of the disease, reconverted to operability after neoadjuvant polychemotherapy, with total gastrectomy with local lymphadenectomy being practiced, that ensures a statistically significantly superior local control rate with loco-regional recurrences reduced and eliminates the risk of developing secondary determinations at distance, but with increased postoperative morbidity.

The group with poor prognosis, includes patients with endoscopically detected tumors located in the upper third of the stomach, histologically confirmed with diffuse type carcinoma, poorly differentiated, employed by imaging techniques in locally advanced stage of the disease, reconverted to operability after neoadjuvant polychemotherapy, with total gastrectomy with local lymphadenectomy being practiced, with a rate of therapeutic failures and mortality statistically significantly increased and with increased postoperative morbidity.

Compared to mortality and disease-free interval of 5 years, total gastrectomy practice, imposes itself as a mandatory criterion approach to tumors located in the upper and middle third of the stomach.

In our study, the most frequent location of gastric cancer was in the lower third of the stomach respectively the antro-pyloric region that has favorable prognosis, followed by the upper and middle third of the stomach.

Discussions

According to data from the World Health Organization and The Globocan Project in Romania gastric cancer mortality, ranks fourth, after lung cancer, breast cancer and colorectal cancer and is the second leading cause of cancer death [1-4].

There is a significant geographic variability, of gastric cancers, the highest incidence rates being recorded in East Asia, South America and Eastern Europe, and the lowest in the United States and Western Europe.

In Romania, the incidence and mortality of gastric cancer experienced a gradual decline, ranging from 33.14 / 18.77 per 100,000 inhabitants in 1995 to 17.0 / 6.6 per 100,000

inhabitants in 2002, and 15.9 / 15.2 per 100,000 people in 2008, areas with increased mortality were eastern Transylvania (Covasna, Harghita), western Transylvania (Timis, Arad, Bihor), Bucharest and Teleorman County [1-4] ..

There has also been registered a peak incidence in the patient age ranging between 30 and 87 years, with a mean of 65.08 years. The progressive increase in the incidence of gastric carcinoma with age is consistent with the data reported in various epidemiologic studies, according to which its maximum is in the range 50-70 years, gastric cancer is uncommon under the age of 40 years [1-4]

The incidence is higher in males, the data reported in magazines quoted a ratio of 2: 1 in favor of males. [5].

Incorrect eating habits, food preferences or refined culinary preparation, incorrect diet makes a primary risk factor that can influence digestive cancer.

Polysaccharides undigested from plant form together with lignin, dietary fiber, with hypoglycemic and cholesterol lowering role and in the development of flora fermentation, but the effect that maintains their protective role in gastric cancers is the effect of absorption of toxic or potentially carcinogenic substances.

Other factors with potential gastric protection, inquired at present are coumarins, lactones, glutathione, ellagic acid, quercetolul, resveratrol, triterpens [6-8]

Excessive drinking causes important metabolic and immunological disorders and can act as an antifolate with alteration of methylation reactions and methionine metabolism whose role is demonstrated in the process of carcinogenesis [6-8].

Tobacco contains at least two secondary amine respectively pyrrolidine, and piperidine. During smoking they dissolve in the saliva and in the stomach they are converted to nitrosamines, whose role in carcinogenesis is known [6-8].

The association between *Helicobacter pylori* infection and intestinal type gastric carcinoma is based on an analysis of 11 case-control studies, which revealed the association of this infection in 70-90% of cases investigated, while Eurogast Study Group concluded that *Helicobacter pylori*, confers a risk 6 times higher for intestinal type gastric carcinoma.

In the literature, the reported data reveals a correlation between gastric mucosal lesions (gastric atrophy, intestinal metaplasia, and dysplasia type) and intestinal type gastric

carcinoma with favorable prognosis (64.59% intestinal type carcinoma vs. 23.52% diffuse carcinoma) [6-8] .

Patients with gastric cancer, however, have a poor prognosis and a low survival rate, which is due to late diagnosis, early gastric cancer is asymptomatic in 80% of cases, or is accompanied by minor and uncommon symptoms such as asthenia, minimum pain in the form of embarrassment / abdominal discomfort, weight loss, anorexia, abdominal pain, nausea, vomiting, early satiety.

Most cases present with advanced disease, and depending on the location of the primary tumor we can meet dysphagia (cardial gastric cancer), vomiting and belching (antral gastric cancer), early satiety, ascites and jaundice are characteristic signs of advanced stages of the disease, and hematemesis is only present in 10-15% of patients.

In metastatic disease, the peritoneal disseminations in the pelvis can be palpated by rectal examination (Blumer sign), extent of disease in the liver may show clinically as hepatomegaly, lymph node metastases in the supraclavicular (sign Virchow-Troiser) and left axillary regions (sign Iris) and the presence of subcutaneous nodules around the navel (Sister Mary Joseph sign), is a sign of tumor invasion along the falciform ligament. There are also a number of paraneoplastic syndromes that may accompany gastric cancer, the most common being: achantosis nigricans (55%), polymyositis, dermatomyositis, erythema circinate, pemphigoid, dementia, cerebellar ataxia, idiopathic venous thrombosis, ectopic Cushing syndrome or carcinoid syndrome, Lesser-Trelat syndrome.

Sometimes gastric cancer may begin with complications such as intestinal obstruction by primary tumor or peritoneal metastasis or gastric perforation.

The balance of the disease before treatment imposes the obligation to perform laboratory investigations, endoscopic and imaging as it follows: tumor markers (carcinoembryonic antigen and CA19-9), abdominal radiography with contrast (viewing mobility loss of the gastric wall, filling defects, ulceration images) endoscopy (accompanied by biopsy from pathologic lesions considered the benchmark standard in confirming the diagnosis of gastric cancer), computed tomography of the thorax, abdomen and pelvis (real appreciation of the local and distant extension of the disease) [9-15].

Treatment of localized disease

Early gastric cancer limited to the mucosa allows endoscopic resection of the tumor lesion histologically confirmed as non-ulcer and with size ≤ 2 cm.

Surgery represents the only treatment with curative potential, in operable stages, respectively IB-III, with the condition of absence of metastasis and obtaining resection margins in safety oncological limits, at a distance of at least 6 cm of the primary tumor and the surgical technique is dictated by the location of the primary tumor.

Total gastrectomy is indicated in tumors localized to the middle and upper third of the stomach, but in tumors with proximal location, if you can get a limited margin of oncological safety resection in 6 cm, between the tumor and the esogastric junction esogastric a subtotal gastrectomy can be practiced.

Subtotal gastrectomy is indicated in tumors located in the lower third of the stomach. Lymph node dissection extension grade, according to current TNM classification recommendations (Sixth Edition) includes the removal of a minimum of 15 lymph nodes. But according to data reported in the literature, D2 dissection with excision of lymph node level N1 and N2 is superior level is superior to D1.

Wu et al, have reported a superior survival rate in the case of para-aortic lymph nodes dissection, plus D2 (D3) dissection as compared to D1 + D2.

JCOG 9501 study reported an equivalent survival between D2 dissection and D3 + D2, but with greater morbidity for extensive procedure.

Standard consensus is that D1 + D2 dissection should be the standard procedure in patients with good performance index that could tolerate this enlarged intervention. Splenectomy is indicated for tumors in the region proximal gastric near the great curvature and bottom, for splenic hilar lymph nodes removal. [16-23].

Adjuvant treatment consists in the administration chemo-radiotherapy (45 Gy / 25 fr / 33 days, 1.8 Gy / fr + 2 cycles of FUFOL: 5-FU 400 mg / sqm + folinic acid 20 mg / sqm, D1-4, 33-35) followed by adjuvant polychemotherapy treatment FUFOL 3 cycles (5-FU 425 mg / sqm + folinic acid 20 mg / sqm D1-5 / 28) - Mc Donald protocol [24-27].

Treatment of advanced disease

A randomized study of MRC UK has shown that multi-agent neoadjuvant and adjuvant chemotherapy (in both cases, three cycles with

epirubicin 50 mg/sqm cisplatin 60 mg/sqm and continuous infusion with 5-fluorouracil (F) 200 mg/sqm/ day), improved survival at 5 years 36.3 vs. 23.0% in the case of surgery alone.

A randomized study of North American Intergroup has shown that five cycles of neoadjuvant polychemotherapy 5-fluorouracil / Leucovorin, during and after radiotherapy (45 Gy / 25 fractions / 5 weeks) resulted in an overall improvement of 15% survival rate at 5 years, and the maximum benefit is obtained with enlarged lymph node dissection D1 + D2. The results of meta-analyses reported in journals, have shown a reduced benefit in terms of survival at 5 years, in case of adjuvant chemoradiotherapy and apparently greater benefit was observed in five studies from Asia [hazard ratio 0.74, confidence interval (CI) of 95% from 0.64 to 0.85], compared to the 14 studies conducted outside of Asia (relative risk 0.90, 95% CI 0.85 to 0.96). Statistically it has been demonstrated that the median survival is 27 months for surgery exclusive vs. 36 months in the adjuvant setting and survival at 5 years without adjuvant therapy is 4.5% vs. 5-year survival with adjuvant therapy > 5% (> 10%).

Thus, the therapeutical standard, in the locally advanced stages consists of 2-4 cycles of neoadjuvant polychemotherapy protocol (ECP: epirubicin 50 mg/sqm cisplatin and 60 mg/sqm and 5-fluorouracil 200 mg/sqm / day to 3 weeks), followed radical surgery (total gastrectomy with extended lymphadenectomy D1 + D2) and chemo-radiotherapy (45 Gy/25 fr/ 33 days, 1.8 Gy / fr + 2 cycles of FUFOL: 5-FU 400 mg / sqm + folinic acid 20 mg / sqm, D1-4, 33-35). Although neoadjuvant chemo-radiotherapy offers a greater chance of radical surgery, it remains experimental, and its value has not been confirmed in randomized comparative studies [29-33].

Treatment of inoperable locally advanced disease

Patients with inoperable, gastric cancer, locally advanced, benefits of palliative polychemotherapy, chemoradiotherapy with neoadjuvant cisplatin and etoposide following induction chemotherapy with cisplatin, 5-FU and leucovorin addresses locally advanced squamous carcinomas of the esogastric junction but has not demonstrated statistically significant prolongation of survival. [34 = 37]

Treatment of recurrent and metastatic disease

Patients with stage IV disease benefit from palliative polychemotherapy regimens

containing a platinum-based agent and a fluoropyrimidine, but it still remains controversial the need of a triple regimen, but it has been demonstrated that the ECF regimen (Epirubicin, Cisplatin, 5-Fluorouracil continuous infusion) is the most efficient.

However, a meta-analysis demonstrated a benefit by adding an anthracycline to the double regimen.

Docetaxel increases the effectiveness of 5-FU/cisplatin regimen, but it has a higher toxicity, neutropenia was reported in 29% of patients. A randomized Phase-II study showed that weekly administration of docetaxel in combination with cisplatin and 5-fluorouracil infusion or Capecitabine has similar efficacy and reduced toxicity.

Irinotecan in combination with 5-fluorouracil/ leucovorin, has an activity similar to 5-fluorouracil/ Cisplatin.

A recent study of NCRI in the UK showed that the EOX regimen with the use of capecitabine (X) instead of 5-fluorouracil (F) and oxaliplatin (O) instead of cisplatin (C) was associated with a longer overall survival rate (11.2 versus 9.9 months, HR 0.80, 95% CI 0.66 to 0.97; $P = 0.02$), and the rate of venous thromboembolism was significantly reduced by the introduction of oxaliplatin (7.6% compared to 15.1%, $p = 0.0003$).

A recent meta-analysis demonstrated that in the double or triple regimens in advanced gastric cancer, overall survival rate obtained after the administration of capecitabine is superior to that associated with 5-Fluorouracil infusion.

Irinotecan improves survival rates in gastric cancer and cancer of the esogastric junction, in advanced stage (median survival 4.0 vs. 2.4 months, HR 0.48, 95% CI 0.25 to 0.92; $P = 0.023$). In patients with recurrent disease, radiotherapy (hipofractionated) is recommended to control bleeding, obstruction or pain.

Also, palliative resection is indicated for the relief of complications respectively obstruction, bleeding and perforation. [38-40].

It has been demonstrated that the addition of trastuzumab to polychemotherapy using cisplatin + fluoropyrimidine in patients with HER2-positive gastric cancer, determined clinical improvement and a statistically significant higher response rate, median progression-free survival and median overall survival (13.8 versus 11.1 months, HR 0.74, 95% CI 0.60 to 0.91; $P = 0.0048$).

The use of cetuximab, bevacizumab and panitumumab in combination with polychemotherapy remains experimental [41].

Data gathered from the literature shows that patients with gastric cancer present a poor prognosis, with a reduced survival rate, in early gastric cancer survival is about 90% at 5 years and overall survival at 5 years is 10-15%, which is due on one hand to late diagnosis, as well as reduced efficacy of therapeutic methods.

Thus, despite the constant efforts of diagnosis and treatment, 5-year survival of patients with locally advanced/ metastatic gastric cancer is low (5-15%).

Only 20% of patients present with resectable disease, and of these 80% present risk of loco-regional or distant recurrence, even after curative resection. [42-45]. Factors associated with poor prognosis are:

- advanced age
- weight loss >10%
- proximal location of the tumor
- low differentiation grade
- more than 4 lymph nodes invaded
- aneuploidy

Among these prognostic factors mentioned multifactorial analysis of published studies found that gastric wall infiltration and lymph node metastases and therefore regional lymphadenectomy extension, are the most significant in terms of efficacy of treatment outcomes and therefore the prognosis of patients [42-45].

Regional profile of Dolj county, both by geographic and demographic characteristics provides support to undertake epidemiological studies.

Analysis of the incidence of gastric cancer in the Dolj county has up showed a relatively balanced distribution for Craiova, the other geographic areas (North, Southeast, Southwest) of Dolj county.

Following the epidemiological study we were able to shape descriptive demographic panel, characteristic for the group of patients at risk of developing gastric cancer, including elderly men, in the decade VI-VII of life, with origin in rural areas with a history of peptic ulcer *Helicobacter pylori* positive associated with intestinal type, or salted fish meat eaters, with bad food preparation and lack of refrigeration and diet low in fat, protein, vitamins A and C.

The clinical and histopathological study was conducted on a total of 458 confirmed gastric cancer patients, diagnosed and treated in the Medical Oncology Clinic of the Clinical

Emergency County Hospital Craiova, between 2005-2010.

Analysis of symptoms at admission revealed that the main cause of presenting at a doctor, was a painful abdominal dyspeptic syndrome (148 cases, 32.31%), endoscopically being detected tumors predominantly in the lower third of the stomach (205 cases, 44.75% in the lower third of the stomach vs. 161 cases 35.15%, in the middle third of the stomach vs. 65 cases 14.19%, in the upper third of the stomach).

Unspecific and late symptoms of gastric cancers, explains the late diagnosis of the disease, most patients being enclosed by imaging investigations in locally advanced stages of the disease (407 patients, 88.86% advanced stage vs. 22 patients, 4.8% localized stage).

In terms of histopathology, the vast majority of cases were tumors of the intestinal type (370 cases, 80.78% vs. 88 cases, 19.22%, tumors with diffuse type), and both types of carcinoma, the intestinal type, as well as the diffuse type have in most cases poorly-differentiated tumors (196 cases of intestinal type tumors 52.97% vs. 41 cases, 46.59% of diffuse type tumors).

Analysis of clinical, histological and prognostic correlations (tumor location, disease stage, type of surgery, histopathologic type and degree of differentiation) was conducted on 352 pieces of resected gastric tumors, where it was possible to analyze histopathological factors (histopathological type, degree of tumor differentiation) in order to establish a correlation with clinical factors (tumor location, disease stage, type of surgery).

Radical intervention, respectively, total gastrectomy has been practiced for all situations in which endoscopic tumor origin was detected in the upper third and middle third of the stomach (162 cases, 46.02%), mostly confirmed histologically as intestinal type carcinomas (97 cases vs. 51 diffuse type carcinomas in the upper third of the stomach vs. 14 diffuse type carcinomas in the middle third of the stomach), poorly differentiated (51 tumors originate in the upper third of the stomach) and moderate differentiated (111 tumors originating in the middle third of the stomach) and enclosed by imaging techniques in locally advanced stages of the disease, but reconverted to operability after neoadjuvant polychemotherapy, reversion established imaging techniques.

Subtotal gastrectomy with local lymphadenectomy, has been practiced in most cases (190 cases, 53.97%), respectively 22

patients diagnosed in a curable stage and 168 patients in locally advanced stages of the disease, reconverted to operability, after neoadjuvant polychemotherapy, the tumor in both cases having origin in the lower third of the stomach, intestinal type carcinomas, poorly differentiated.

Analyzing the correlation between clinical parameters (location of gastric tumors, stage of disease and type of surgery) and histopathological parameters (histological type and degree of differentiation), have reached statistical significance in multivariate analysis of the location of the tumor, disease stage and histology ($p < 0.0001$) and the degree of differentiation of carcinomas of the stomach ($p < 0.005$).

Based on statistically significant correlations demonstrated between clinical factors (tumor location, disease stage and type of surgery) and histopathological factors (type and degree of differentiation of the tumor) we can define the clinical, histological and prognostic groups.

Multivariate statistical analysis has detected statistically significant differences in terms of survival rate at 5 years ($p > 0.001$) and free interval of disease at 5 years ($p > 0.001$), depending on the location of the tumor, correlated with other clinical factors (disease stage, type of surgery) and histological factors (histopathological type, tumor differentiation grade).

After analyzing the survival rate at 5 years and free interval of disease at 5 years, we have outlined the clinical, histological and prognostic groups based on correlations statistically significant established between clinical factors with prognostic value (tumor location, disease stage, type of surgery) and histoprognostic factors (histopathological type, tumor differentiation grade), the prognosis of patients being analyzed in terms of the two international standard parameters, respectively 5-year survival rate and disease free interval of 5 years.

Good prognosis group includes patients with endoscopically detected tumors located in the lower third of the stomach, histopathologically confirmed with intestinal type carcinomas, poorly differentiated, enclosed by imaging techniques in locally advanced stage of the disease, reconverted to operability after neoadjuvant polychemotherapy with practicing a subtotal gastrectomy with local lymphadenectomy, with a statistically significant lower rate of therapeutic failures, mortality and low postoperative morbidity.

The intermediate prognostic group includes patients with tumor endoscopically detected, originating in middle third of the stomach, histologically confirmed with intestinal type carcinomas, moderately differentiated, employed by imaging techniques in locally advanced stage of the disease, reconverted to operability after neoadjuvant polychemotherapy, with total gastrectomy with local lymphadenectomy being practiced, that ensures a statistically significantly superior local control rate with loco-regional recurrences reduced and eliminates the risk of developing secondary determinations at distance, but with increased postoperative morbidity.

The group with poor prognosis, includes patients with endoscopically detected tumors located in the upper third of the stomach, histologically confirmed with diffuse type carcinoma, poorly differentiated, employed by imaging techniques in locally advanced stage of the disease, reconverted to operability after neoadjuvant polychemotherapy, with total gastrectomy with local lymphadenectomy being practiced, with a rate of therapeutic failures and mortality statistically significantly increased and with increased postoperative morbidity.

Compared to mortality and disease-free interval of 5 years, total gastrectomy practice, imposes itself as a mandatory criterion approach to tumors located in the upper and middle third of the stomach.

In our study, the most frequent location of gastric cancer was in the lower third of the stomach, respectively the antro-pyloric region, which were tumors with favorable prognosis, followed by tumors located in the middle third and upper third of the stomach, our study results being consistent with those reported in the literature.

Conclusions

The study conducted by analyzing data collected from the records of the Medical Oncology Clinic of the Clinical Emergency County Hospital Craiova, allowed the following conclusions:

Epidemiological research and statistics analysis has detected a growing incidence of gastric malignancies during the study showing that gastric cancer is a significant public health problem.

Analysis of the incidence of gastric cancer in Dolj county has up showed a relatively balanced distribution for Craiova and the other geographic areas (North, Southeast, Southwest) of Dolj

The descriptive demographic panel, characteristic for the group of patients at risk of developing gastric cancer, includes elderly men, in the decade VI-VII of life, with origin in rural areas with a history of peptic ulcer *Helicobacter pylori* positive associated with intestinal type, or salted fish meat eaters, with bad food preparation and lack of refrigeration and diet low in fat, protein, vitamins A and C.

Unspecific and late symptoms explain the late diagnosis of the disease, most patients being enclosed by imaging techniques in locally advanced stages of the disease (407 patients, 88.86%). The study highlights the importance of early diagnosis and the objective of establishing prevention strategies, screening and surveillance of patients with gastric cancer.

The balance of the disease before treatment imposes the obligation to perform laboratory investigations, endoscopic and imaging as it follows: tumor markers (carcinoembryonic antigen and CA19-9), abdominal radiography with contrast (viewing mobility loss of the gastric wall, filling defects, ulceration images) endoscopy (accompanied by biopsy from pathologic lesions considered the benchmark standard in confirming the diagnosis of gastric cancer), computed tomography of the thorax, abdomen and pelvis.

Gastric tumors originating in lower third of the stomach are more commonly associated with intestinal type (intestinal type carcinomas 187 vs. 3 cases of diffuse type carcinomas) and are poorly differentiated tumors, detected and classified by endoscopic imaging, in most cases in locally advanced stages of the disease (168 cases advanced stage vs. 22 cases localized stage), where it was possible to reconvert to operability, after neoadjuvant polychemotherapy and a subtotal gastrectomy being practiced.

Gastric tumors originated in upper third of the stomach were associated with diffuse type (51 cases) and are poorly differentiated tumors, endoscopic detected and classified into locally advanced stage of the disease, where it was possible to reconvert to operability, post-neoadjuvant polychemotherapy with total gastrectomy being practiced.

Tumors originating in middle third of the stomach are associated with intestinal type (97 intestinal carcinomas vs. 14 diffuse type carcinomas) and are moderately differentiated tumors, endoscopic detected and classified in a locally advanced stage of the disease, and it was possible to reconvert the operability, after

neoadjuvant polychemotherapy with total gastrectomy being practiced.

Radical intervention, total gastrectomy with local lymphadenectomy, has been practiced for tumors located in the upper and middle third of the stomach, confirmed histologically in most cases, as intestinal type carcinomas, poorly differentiated (upper third of the stomach) and moderately differentiated (middle third of the stomach), enclosed by imaging techniques into locally advanced stage of the disease stage, where it was possible to reconvert to operability after neoadjuvant polychemotherapy.

Subtotal gastrectomy with local lymphadenectomy has been practiced for tumors located in the lower third of the stomach, being intestinal type carcinomas, poorly differentiated, in locally advanced stage of the disease, where it was possible to reconvert to operability after neoadjuvant polychemotherapy.

Analysis of correlation between clinical parameters (gastric tumor location, disease stage and treatment given) and histopathological parameters (histological type and degree of differentiation), reached the threshold statistical significance in multivariate statistical analysis, localization of tumor, disease stage and histology ($p < 0.0001$) respectively the degree of differentiation of gastric carcinoma ($p < 0.005$).

The prognosis of patients was analyzed in the patients group, enclosed in locally advanced stage of the disease, 330 patients, where we analyzed the gastric resection pieces, and detected histopathological factors (histopathological type, tumor differentiation grade) for the three neoplastic locations (upper 1/3 vs. middle 1/3 vs. lower 1/3 of the stomach), considering that type of surgery is dictated by the location of the tumor in the stomach.

Based on the statistically significant correlation demonstrated between clinical factors (tumor location, disease stage and type of surgery) and histopathological factors (type and degree of differentiation histopathologic tumor) we could define the clinical histological and prognostic groups.

Multivariate statistical analysis has detected statistically significant differences in terms of 5-year survival rate ($p > 0.001$) and disease-free interval of 5 years ($p > 0.001$), depending on the location of the tumor, in correlation with others clinical factors (stage of disease, type of surgery) and histological factors (histopathological type, tumor differentiation grade).

After analyzing the 5-year survival rate and disease-free interval of 5 years we have outlined the clinical, histological and prognostic groups based on demonstrated statistically significant correlations between clinical factors with prognostic value (tumor location, disease stage, type of surgery) and histological and prognostic factors (histopathological type, tumor differentiation grade).

Good prognosis group includes patients with endoscopically detected tumors located in the lower third of the stomach, histopathologically confirmed with intestinal type carcinomas, poorly differentiated, employed by imaging techniques in locally advanced stage of the disease, reconverted to operability after neoadjuvant polychemotherapy with practicing a subtotal gastrectomy with local lymphadenectomy, with a statistically significant lower rate of therapeutic failures, mortality and low postoperative morbidity.

The intermediate prognostic group includes patients with tumor endoscopically detected, originating in middle third of the stomach, histologically confirmed with with intestinal type carcinomas, moderately differentiated, employed by imaging techniques in locally advanced stage of the disease, reconverted to operability after neoadjuvant polychemotherapy, with total gastrectomy with local lymphadenectomy being practiced, that ensures a statistically significantly superior local control rate with loco-regional recurrences reduced and eliminates the risk of developing secondary determinations at distance, but with increased postoperative morbidity.

The group with poor prognosis, includes patients with endoscopically detected tumors located in the upper third of the stomach, histologically confirmed with diffuse type carcinoma, poorly differentiated, employed by imaging techniques in locally advanced stage of the disease, reconverted to operability after neoadjuvant polychemotherapy, with total gastrectomy with local lymphadenectomy being practiced, with a rate of therapeutic failures and mortality statistically significantly increased and with increased postoperative morbidity.

In relation to mortality and disease-free interval of 5 years, total gastrectomy practice, imposes itself as a mandatory criterion approach to tumors located in the upper third that have poor prognosis and middle third of the stomach that have intermediate prognosis.

In relation to mortality and disease-free interval of 5 years, subtotal gastrectomy

practice, imposes itself as a mandatory criterion approach for tumors located in the lower third of the, that have a favorable prognosis.

In our study, the most frequent location of gastric cancer was in the lower third of the stomach, respectively the antro-pyloric region, which were tumors with favorable prognosis, followed by tumors located in the middle third and upper third of the stomach.

Defining the clinical, histological and prognostic groups, allows an accurate assessment of patient prognosis from the time of randomization and initiation of treatment, type of surgery in locally advanced, reconverted to operability, after neoadjuvant polychemotherapy being dictated by the location of the tumor (upper third vs. middle third vs. lower third of the stomach).

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