CURRENT ISSUES IN GASTRIC CANCER EPIDEMIOLOGY (Abstract): Gastric cancer, one of the most common malignant tumors of digestive tract continues to be a major health problem by frequency, aggressiveness and low rate of cure in symptomatic stage. Although its incidence is decreasing (especially in the West), globally the gastric cancer is ranked fourth in incidence among cancers at various sites. Despite these developments, the gastric cancer mortality, overall declining globally, is high, especially in the West where even if diagnosed fewer cases of gastric cancer, TNM stages are advanced and have a poor prognosis. In contrast, in Japan, where the incidence is still high, the percentage of cases diagnosed at the stage of “early gastric cancer” has greatly increased, thus improving prognosis. Gastric neoplasia affects more men, age range 50-70 years, disadvantaged social classes and black race. In Romania the gastric cancer incidence is increasing over recent years, presenting variations across the country being more common in men compared with women, reaching a peak of incidence around age 60. Gastric cancer mortality in the world places Romania among the countries with average mortality. Gastric cancer prognosis remains extremely reserved, in close correlation with tumor stage at diagnosis, surgical treatment being the only possibility to provide improved survival, especially in the early stages. Improvement of survival rate in recent years is due to increased gastric resectability result of an earlier diagnosis, a more complex treatment and a closer monitoring of the population at risk. Keywords: GASTRIC CANCER, INCIDENCE, MORTALITY

Gastric cancer still remains one of the most common malignant tumors of digestive tract responsible for a mortality which remains high (1). Adeno-carcinoma accounts for over 95% of malignant gastric tumors tract, that is why the generic name of gastric cancer refers, in most cases, to adenocarcinoma, other gastric tumors (lymphoma, stromal tumors, sarcoma, carcinoid) being very rare (2, 3). Both main locations of gastric adenocarcinoma are proximal (cardial) and distal (noncardial).

Despite the decline of distal gastric cancer, the incidence of proximal tumors increased continuously since 1970 (4). These types of gastric tumors are prevalent in populations of different geographical regions, different races and from different socio-economic groups. There may also be differences in the genetic susceptibility, disease profile, clinical manifestations and prognosis, the differences related to differ-
ent locations of gastric cancer suggesting the hypothesis that they are distinct diseases with different pathologies (5).

Epidemiologically gastric cancer has two distinguishing features: variability of incidence and mortality rates in different countries and geographical areas and the downward trend of these indicators.

**GEOGRAPHICAL VARIATIONS OF GASTRIC CANCER**

In 2008, 988,000 people worldwide were diagnosed with gastric cancer, international incidence having wide variations. The highest incidence rate is recorded in East Asia (China, Japan, Korea, Mongolia), the rate being estimated at 42 cases per 100,000 masculine gender persons and 18 new cases per 100,000 women. A high incidence is recorded in Eastern Europe and South America, with more than 20 new cases per 100,000 men and 9 cases per 100,000 women. The lowest incidence is estimated in North and South Africa (6).

Difference in gastric cancer incidence and mortality is not only recorded in an international context, but also within the same country. In Japan, the gastric cancer remains the most common type of cancer in both men and women, the incidence of gastric cancer being the highest (100 cases per 100,000 inhabitants), here this neoplasia being the first cause of death (6). The high incidence of this disease in Japan has led to the development of efficient programs for early detection of gastric cancer. In Japan, gastric cancer is more common in northern areas (Miyagi) than the south (Fu Knoka). Distal tumors predominate in Japan contrasting with an increased incidence of proximal tumors in Western countries, although here in recent years, there has been an increase in the proportion of proximal gastric cancers. In the U.S. the decline of incidence was dramatic, gastric cancer becoming the 14th leading cause of death each year being estimated at 21,900 new cases per year and 13,500 deaths per year (7). Also, the same unevenness in the distribution of the disease is reported by American authors, the highest rates of mortality from gastric cancer being recorded in the northern states: Iowa, Michigan, New York, Connecticut compared to Georgia, Louisiana in the southern of United States (8). In 2008, the European Union has reported 83,000 new cases of gastric cancer, the incidence being of 18.9 new cases at 100,000 inhabitants per year, with rates 1.5 times higher in males with the top of incidence in the seventh decade of life. The highest rate of incidence was registered at Lithuanian men and Estonian women and the lowest in Sweden, an average incidence being registered in the UK (9).

The multicentre study conducted in Romania in 2003 by the Romanian Society of Digestive Endoscopy, which evaluated the prevalence of gastric cancer among adults reporting to specialized medical services has shown that the national prevalence of gastric cancer was 2.9 to illnesses at 100,000 people aged over 18, with high variations by region: 2.8‰ inhabitants in Moldova, 6.6‰ in Transylvania, 3.45‰ in the western region and 1.9‰ in Oltenia and Wallachia. Demographic peculiarities of gastric cancer patients were as follows: 66.4% were males compared with 33.6% women, 51.7% were from urban areas compared with 48.3% in rural areas, and the average age of patients was 63.07 ± 12.10 years. 95.5% of cases had at the time of diagnosis, advanced gastric cancer most commonly located in the gastric body.
(40.1%) and antrum (33.8%). According to Borrmann classification, 31.4% had type I polypoid, 32.1% type III ulceroc-infiltrative. Histological, according to Lauren classification, the most common histological type was intestinal type (63.8%). Early gastric cancer was diagnosed in 4.4% of patients (10).

**TEMPORAL TRENDS OF GASTRIC CANCER**

In 1930, gastric cancer was the leading cause of cancer mortality in Europe and the U.S. In the past 70 years the death rate declined dramatically in developed countries, especially due to the decrease of prevalence (11). However in the last 30 years the incidence of gastric adenocarcinoma at cardial level increased 5-6 times in developed countries.

Tumors in the cardial area are now nearly half of gastric cancers among men in the U.S. and UK. Also increased the incidence of esophageal adenocarcinoma whose main etiologic factors are represented by obesity, gastroesophageal reflux disease and Barrett's esophagus. Cardial adenocarcinomas share certain epidemiological characteristics of oesophageal adenocarcinoma (13).

In England the standardized incidence rate was reduced to more than half, from 30 cases per 100,000 male populations in the years 1975-1977 to 13 cases per 100,000 men in 2006-2008. The downward trend is similar for women too, being estimated at 14 cases per 100,000 women to 5 new cases per 100,000 women (14).

Gastric cancer was the first cause of cancer death in the world until 1980, when it was surpassed by lung cancer.

**DISTRIBUTION OF GASTRIC CANCER BY GENDER, ENVIRONMENT, AGE AND RACE**

Gastric neoplasm affects both sexes, but unevenly, the male / female ratio being of 2-3/1, with no significant difference between urban and rural areas, the incidence being certainly higher for vulnerable social categories.

Disease frequency increases significantly with age, the elderly being the most affected groups. Gastric cancer is an exception under age 30, after 40 years the frequency of disease increases reaching the maximum level after the age of 60.

In Romania, the average age of patients with gastric cancer is 68 years. Male / female ratio, regardless of histological form remains around 2.41 / 2.5 (15). By frequency indices, in our country gastric cancer ranks second among men neoplasia and third at women. In the world, Romania ranks seventh of gastric cancer in men and eleven among women (15).

Black race seems to be more frequently affected by the disease, recent statistics suggesting a ratio of 60/36 in favor of black population. Immigrants initially keep the risks of disease similar to those in origin countries, but these risks are modified in descendants, becoming similar to those from the area where they migrated, demonstrating the important role of environmental factors in the occurrence and progression of the disease.

Cardial carcinoma affects men 5 times more than women and 2 times the whites more frequently than the black race. More, proximal carcinoma incidence rate is relatively high in certain professional groups (14). An upward trend recorded the esogastic region carcinoma (6.18%) with reserved prognosis, decreasing age of onset,
predominantly diffuse infiltrative type, predominantly in men.

**PATHOLOGICAL CONSIDERATIONS ON GASTRIC CANCER**

Approximately 90% of gastric cancers are adenocarcinomas, divided into two categories: well differentiated or intestinal type and undifferentiated or diffuse type. Intestinal type correlates with gastric body gastritis, gastric atrophy and intestinal metaplasia, whereas the diffuse type is related to pangastritis without atrophy (16). Intestinal type is more common in men, black race and older age groups, while the diffuse type is about equally distributed by gender and is more common in young people. Intestinal type is predominant in high risk areas such as East Asia, Eastern Europe, South America and Central America (17). Diffuse type has a more uniform geographical spread. Reducing the incidence of intestinal type is based on the general decline of gastric cancer. In contrast, the incidence of diffuse type, especially the cell “in signet ring” increased.

For Romania, the report of histopathological types is represented by the intestinal carcinoma / diffuse carcinoma of approximately 1.7 / 1.8, i.e. 46-48% of intestinal type carcinoma and 27% diffuse type carcinoma, unclassified forms being of 25-27% (15).

After WHO histological types for Romania are: papillary carcinoma 4.6%, tubular carcinoma 26.1%, mucipar carcinoma 17.2%, carcinoma with “signet ring” cell 22% and undifferentiated carcinoma 29.9% (9).

By mode of histological differentiation, well-differentiated carcinoma accounts for about 23%, average differentiated carcinoma 18.6%, poorly differentiated carcinoma 28% and undifferentiated carcinoma 30%.

The most striking upward trend is manifested by poorly differentiated carcinoma. A retrospective study conducted in our country by the Ministry of Health in 2000 showed an increased incidence of poorly differentiated carcinomas in the “signet ring” as other forms with poor histological differentiation which recorded 57.9%.

An upward trend recorded the esogastic region carcinoma (6.18%) with reserved prognosis, decreasing age of onset, predominantly diffuse infiltrative type and predominantly in men.

In patients younger than 40 years, gastric carcinoma is most often diffuse, with high localization and low histological differentiation. The incidence of this form is currently about 1.92% (18).

An improvement in the prognosis of gastric cancer could be obtained by the discovery of neoplastic process in the “early carcinoma” stage due to endoscopic diagnostic techniques with histological confirmation. Thus, of all gastric cancers included in the study of authors from Cluj-Napoca, early carcinoma accounted for 5.1% of the total (11).

Intestinal metaplasia of different types is associated with gastric cancer in percentage of 11.5% and with duodenal ulcer in percentage of 4.8%. Intestinal metaplasia type III, colonic, represents between 8-12% of the total intestinal neoplasia, being found in approximately 3% of all gastric biopsies from patients with various symptoms, which were subjected to endoscopic biopsies.

Regarding the correlations between different types of dysplasia and gastric cancer types, was revealed that non metaplastic-dysplasia is found in 46.2% of diffuse-type gastric cancer, 7.7% of intestinal type cancers and 53.8% of intermediate type cancers.
Dysplasia of mucosa with intestinal metaplasia was found in 23.1% of diffuse-type cancers, 84.6% of intestinal type cancers and 30.6% of intermediate type cancers.

The causes which determine gastric cancer include genetic and environmental factors. Genetically are described the p53 genetic mutation, loss of heterozygosity (LOH) at APC locus, deletion or suppression of FHIT gene. Environmental factors include rich diet in salt, nitrates, chronic alcohol consumption, and previous gastric interventions.

*Helicobacter pylori* was considered by WHO as class I carcinogenic agent, the risk of detecting a malignant tumor of the distal portion of the stomach is 2-3 times higher in patients with Helicobacter pylori infection than in the control group.

**CONCLUSIONS**

Since 1980 the prevalence and mortality due to gastric cancer (particularly the distal localization) decreased significantly in all countries and in all ages of 2-7% per year and instead increased the number of patients with adenocarcinoma located at the esogastric junction and at the gastric initial portion.

Gastric cancer still remains a disease with extremely poor prognosis and increased mortality which is exceeded only by lung cancer mortality.

In general, the countries with high incidence of gastric cancer have a survival rate higher than the countries with low incidence. This association is based mainly on the difference in survival due to tumor localization in the stomach. Thus, tumors located in the cardial area have a worse prognosis than those in the pyloric antrum with a lower 5-year survival and increased perioperative mortality.

When the tumor is localized to the mucosa, 5-year survival is approximately 95%. In the U.S. few cancers are discovered at an early stage, which leads to decreased 5 years survival at fewer than 20%. Similarly, in European countries the survival varies between 10-20%.

Possibility to perform screening for early detection of cancer resulted in a significant decrease in mortality in high-risk areas. In Japan, where are used screening procedures very frequently, gastric cancer mortality has halved from 1970.

In Romania, gastric carcinoma does not tend to decrease the incidence seen in developed countries. Moreover, there are growing higher forms of aggression.

**REFERENCES**


**NEWS**

**NEW INSIGHT INTO MOLECULAR EPIDEMIOLOGY OF MRSA STRAINS IN ROMANIA**

A recent study by Székely and co. brings new information regarding methicillin-resistant *Staphylococcus aureus* strains (MRSA) circulating in Romania. The authors used pulsed-field gel electrophoresis (PFGE), spa typing and SCCmec typing to describe the clonal relations and virulence profiles of MRSA isolates from patients admitted to intensive care and surgical units, during 2010, in Mureș County Emergency Clinical Hospital. The study identified 25 pulsotypes clustering into 4 major clonal groups, named from A to D. The majority of MRSA isolates, included into clonal group A (82%), were associated with the successful HA-MRSA clone, spa type t030, which carried SCCmec type III and enterotoxin A genes. Group B was represented by 15 % of the strains, which were assigned to spa types t127, t015 and t321. These strains harbored SCCmec type IV and enterotoxin genes. Two strains that belonged to spa types t044 and t582 were included into clonal groups C and D, respectively. They were PVL-producing strains (Panton-Valentine leukocidin) and had genes encoding for enterotoxin G and SST-1 (toxic shock syndrome toxin). The remaining two strains were non-typeable by PFGE and belonged to spa type t034, which is characteristic for livestock-associated MRSA (LA-MRSA). These strains were isolated from community onset infections, harbored SCCmec type V and were negative for the searched exotoxins. The study concluded that most MRSA strains were clonally related and suggested an intrahospital origin, but also pointed out the danger of new emerging LA-MRSA strains. (Székely E, Man A, Mare A, Vas KE, Molnár S, Bila D, *et al*. Molecular epidemiology and virulence factors of methicillin-resistant *Staphylococcus aureus* strains in a Romanian university hospital. *Rev Rom Med Lab.* 2012; 20: 370-382).

*Teodora Vremera*