# INTRODUCTION

Gastric cancer is the second most common cancer in the world after carcinoma of lung ***(Elbolkainy, 2005).*** With the highest incidence in areas such as Japan, Korea, South America, and Eastern Europe, the incidence is much lower in the United States with about (22.000) new cases per year. The overall incidence of gastric cancer in the United States is decreasing in the past 60 years. But cancers of the upper stomach and gastroesophageal junction are increasing ***(Noguchi, 2000)***.

In 1930, gastric cancer was the leading cause of cancer related deaths among American men. Since then, the death rate in men from gastric cancer in the United States has dropped from 28 to 5 per 100.000 people ***(Miaskowski, 1999)***. This form of cancer is (1.5-2.5) times more common in African American, and Native American people than in whites ***(Coial, 1996)***.

In Egypt the National Cancer Institute (NCI) reported that malignant tumours of stomach constitute (2.12%) of total malignancies, and (14.72%) of digestive organ malignancies. The cardia was the most frequent site (11.06%) of malignant gastric tumours ***(Mokhtar et al., 2007).***

Researchers have learned that some people are more likely than others to develop gastric cancer. It affects men twice as often as women. These tumours typically occur in people in their 60s and 70s, but can also occur in younger and older individuals. At this time, studies cannot explain why one person gets gastric cancer and another does not ***(Elbolkainy, 2005)***.

The vast majority of gastric cancers are classified as adenocarcinoma (95%) which are tumours arising from the inner mucosal lining of the stomach. Gastric cancer not classified, as adenocarcinoma comprise only (5-10%) of all gastric cancers. Theses cancers include lymphomas (4%), neuroendocrine tumours (carcinoids) (3%) and malignant gastrointestinal stromal tumours 2% ***(Rosai, 2004)***.

# AIM OF THE WORK

Registry of different types of primary malignant tumours of stomach received at the pathology department of Ain Shams University Hospital and Ain Shams Specialized Hospital during the last 5 years (from January 2001- December 2005), with full registration of clinico-pathological data from the patients' files.

# ANATOMY OF THE HUMAN STOMACH

The stomach is the most dilated part of alimentary canal. It lies between the esophagus and the duodenum (the first part of the small intestine). It is on the left side of the abdominal cavity, the fundus of the stomach lying against the diaphragm. Lying beneath the stomach is the pancreas, and the greater omentum hangs from the greater curvature ***(Bannister, 1995)***.

The stomach is divided into four sections, each of which has different cells and functions (Fig. 1). The sections are: (1) ***cardiac*** region, where the contents of the esophagus empty into the stomach 0.5 to 3.0 cm in width, that surrounds the esophagogastric junction; (2) ***fundus***, formed by the upper curvature of the organ; (3) ***body***, the main central region extend from the level of cardiac orifice to the level of the incisura angularis; and (4) ***pyloric*** region including ***antrum*** which is the lower region of the stomach where its begins to narrow, pylorus which extends from the incisura angularis to the proximal limit of the pyloric sphincter. The pylorus is the most tubular part of the stomach. The cavity of the pylorus is called the pyloric canal that facilitates emptying the contents into the small intestine. The stomach has two borders the superior concave lesser curvatures, which is suspended from the liver by lesser omentum, and inferior convex greater curvature from which hangs the greater omentum ***(Steven et al., 1997)***.

Two smooth muscle valves, or sphincters, keep the contents of the stomach contained. They are: 1) cardiac or esophageal sphincter, dividing the tract above, and 2) pyloric sphincter, dividing the stomach from the small intestine. In humans, the stomach has a volume of about 50 ml when empty. After a meal, it can expand to hold about 1 liter of food, but it can actually expand to hold as much as 4L ***(Kenneth, 2004)***.

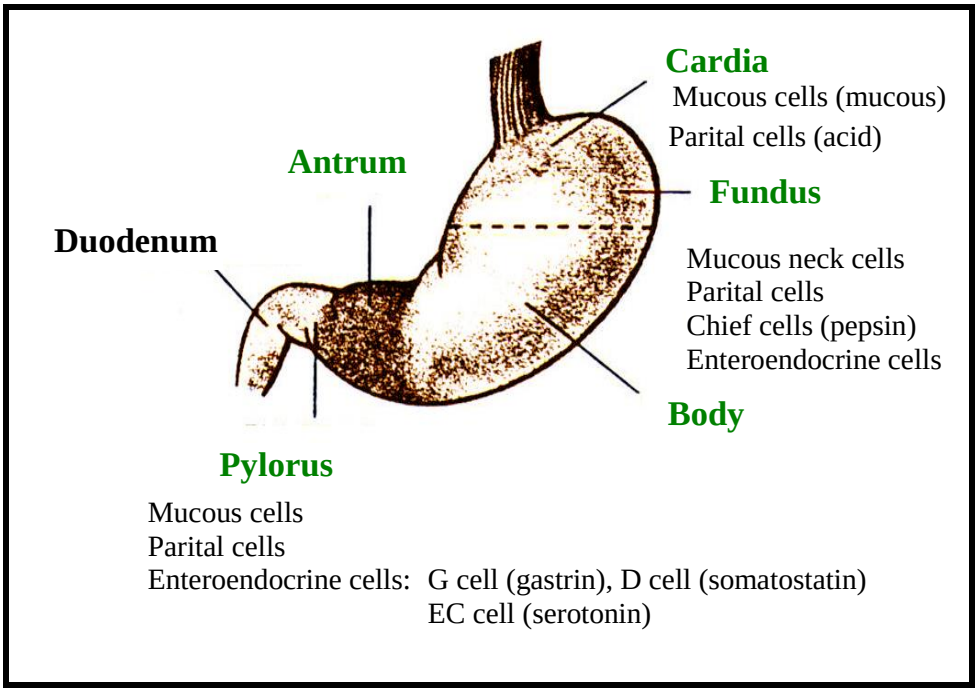


**Fig. (1):** Anatomy of the stomach.

# CLASSIFICATIONS OF PRIMARY MALIGNANT TUMOURS OF THE STOMACH

## WHO (2000) histological classification of gastric tumours

### *Epithelial tumours:*

Intraepithelial neoplasia-adenoma

Carcinoma

- Adenocarcinoma (intestinal – diffuse).
- Papillary adenocarcinoma.
- Tubular adenocarcinoma.
- Mucinous adenocarcinoma.
- Signet-ring cell carcinoma.
- Adenosquamous carcinoma.
- Squamous cell carcinoma.
- Small cell carcinoma.
- Undifferentiated carcinoma.
- Others.

Carcinoid (well differentiated endocrine neoplasm)

***Non-epithelial tumours:***

Leiomyoma

Schwanoma

Granular cell tumour

Glomus tumour

Leiomyosarcoma

GI Stromal tumour (GIST)

- Benign
- Uncertain malignant potential
- Malignant

Kaposi sarcoma

Others

Malignant lymphomas

- Marginal zone B-cell lymphoma of MALT-type
- Mantle cell lymphoma
- Diffuse large B-cel lymphoma
- Others

***(Fenoglio-Preiser et al., 2000)***

## Different classifications of gastric carcinoma:

Due to the high variability of the epidemiology, genetics, morphology, and biologic behavior of gastric carcinoma, many classification systems were in use.

Such as the ***Borrmann*** system ***(1926)*** which has 5 categories:

- Type I tumours are polypoid or fungating;
- Type II are ulcerating lesions surrounded by elevated borders;
- Type III have ulceration with invasion of the gastric wall;
- Type IV are diffusely infiltrating (i.e. linitis plastica);
- Type V cannot be classified.

***Stout (1953)*** classified gastric cancer into ulcerative, polypoid, linitis plastica, superficial spreading, multicentric, or no special type.

Another classification system, the ***Lauren*** system ***(1965),*** classified gastric cancer pathology as either an epidemic form (intestinal) or an endemic form (diffuse).

***Japanese Research Society for Gastric Cancer (1995)*** has classified gastric cancer in to 5 main types and 4 subtypes. The five main types are papillary adenocarcinoma, tubular adenocarcinoma, poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma.The four subtypes are well differentiated, moderately differentiated tubular adenocarcinoma and poorly solid, poorly non solid adenocarcinoma.

# PATHOLOGY OF DIFFERENT TYPES OF PRIMARY MALIGNANT TUMOURS OF STOMACH ACCORDING TO WHO CLASSIFICATION

## GASTRIC CARCINOMA

### Introduction:

Gastric carcinoma is a malignant epithelial tumour of the stomach mucosa with glandular differentiation. Adenocarcinoma is the most important microscopic variant of gastric carcinoma. It is makes up nearly 95% of gastric carcinoma and account for 3% of deaths from cancer. Adenocarcinoma of the stomach is the second most common cancer worldwide. In 2001, stomach cancer affected 850,000 people, of which 522,000 men and 328,000 women died of stomach cancer. According to data collected by the **WHO**, the top three causes of death from cancer are lung (17.8%), gastric (10.4%), and liver (8.8%) ***(Macdonald et al., 2001).*** Gastric adenocarcinoma occurs most frequently in men over 40 years old ***(El-Bolkainy et al., 2005)***. The incidence of this form of gastric cancer is extremely high in Japan, Chile, and Iceland. The incidence of gastric adenocarcinoma in the USA has declined over the years. The decrease may be related to reduce intake of salted and smoked foods, and increased vitamin C consumption. However, the incidence of adenocarcinoma in the high part of the stomach where it connects with the esophagus

has increased markedly, along with an increase in cancers of the lower esophagus ***(Noguchi et al., 2000)***.

***Crawford et al. (2007)*** mentioned that the location of gastric carcinoma within the stomach is as follows: pylorus and antrum (50-60%), cardia (25%), and the remainder, in the body and fundus.

In Egypt the ***National Cancer Institute*** (NCI) reported that malignant tumors of stomach constitute (2.12%) of total malignancies, and (14.72%) of digestive organ malignancies. The adenocarcinoma was the most common type of primary malignant tumours of stomach (glandular adenocarcinoma constitute 47.6%, and signet ring adenocarcinoma constitute 20.66% of total reported cases). The cardia was the most frequent site involved when stated in the reports ***(Mokhtar et al., 2007)***.

**Risk factors of gastric carcinoma include the following:**

- ***Environmental factors:***
  - ***Dietary factors:***

Dietary factors play a role in the development of adenocarcinoma of the stomach. These factors included a high intake of salt, a high intake of carbohydrates and consumption of smoked or cured meat or fish, pickled vegetables and chili peppers ***(Fenoglio-preiser et al., 2000)***.

An adequate intake of fruits and vegetables (which are rich in vitamine C) lowers the risk due to their antioxidant effects. A modest increase in risk has been reported with increased consumption of meat and a positive correlation with longer cooking time of meat has been reported (***Mansfield et al., 2003).***

- ***Socioeconomic status and smoking:***

Low socioeconomic status and cigarette smoking increase the risk of stomach cancer ***(Crawford, 1999).*** Smoking increases the risk of cardiac and non cardiac forms of stomach cancer ***(Gonzlez et al., 2003).*** Cigarette smoke contains many cancer causing agents. Cancer-causing agents (carcinogens) in tobacco smoke damage important genes that control the growth cells, causing them to grow abnormally or to reproduce too rapidly. In that way, smoking can help to cause stomach cancer ***(Michael et al., 2002)***.

People that smoke have twice the risk of stomach cancer compared to non smokers. The risk stays higher for 10-20 years after stopping smoking. If smokers have H.pylori infection, they may have as much as 17 times the risk of non smokers without H.pylori infection, because nicotine potentiates the vacuolating toxin activity of H.pylori in gastric cells, which might be relevant to the finding that smoking promotes atrophic gastritis and intestinal metaplasia in patients infected with H.pylori ***(Nakamura et al., 2002).***

- ***Host factors:***

  - ***Helicobacter pylori infection:***

Many studies have demonstrated a higher frequency of stomach cancer in people chronically infected with Helicobacter pylori. It is the main risk factor in about 80% or more of gastric cancer, most cases of intestinal type carcinoma ***(Scheiman and Cutler, 1999).***

H.pylori stimulates mucousal cell proliferation as shown by higher expression of nucleolar organizer regions and proliferating cell nuclear antigen in H.pylori infected mucosa. Cell proliferation markers decline when H.pylori is eradicated. The mitogenic effect of H.pylori is due to the organism production of urease which generates intraluminal ammonia, a compound known to stimulate cell proliferation. Increased cell proliferation results in an increase in the risk of mutations produced by carcinogenic agents. ***(Fenoglio-preiser et al., 2000)***

H.pylori infection is associated with increased neutrophils infiltration in the gastric mucosa and submucosa. Neutrophils are a known source of the carcinogenic oxygen based free radicals ***(Correa, 1995).*** H.pylori can also produce a vaculating cytotoxin named VacA. This cytotoxin is responsible for epithelial cell damage, also associates with gastric carcinogenesis ***(Soares et al., 1998).***

Certain strains produce a toxin encoded by the cytotoxin -associated gene A (cag A), which is a powerful stimulus for the production of interleukin 8 that recircuits and activates the neutrophils. Thus strains containing a gene (cag A) induce a greater degree of inflammation than strains lacking this gene. High serum antibody levels against the cagA strain is associated with increased risk of gastric cancer when compared to uninfected controls and persons with cagA-negative infection ***(Blaser et al*, *1995 and Liu and Crawford, 2004).***

H.pylori is a strong risk factor for noncardia gastric cancer but is inversely associated with the risk of gastric cardia cancer ***(Kamangar et al., 2006).***

- ***Treating pathological lesions:***

Treating pathological lesions of stomach or duodenal ulcer disease by removing part of stomach is associated with an increased risk of cancer developing in the remaining stomach, especially at least 15 years after surgery ***(Adachi et al., 2000).*** The rationale is that surgery alters the normal pH of the stomach which may in turn lead to metaplastic and dysplastic changes in luminal cells (***Neugut et al., 1996)***

- ***Chronic atrophic gastritis and intestinal metaplasia:***

Chronic atrophic gastritis and intestinal metaplasia, commonly precede and /or accompany intestinal type adenocarcinoma, particularly in high- incidence areas. H.pylori

associated gastritis is the common gastric precursor lesion. If gastritis persists, gastric atrophy occurs followed by intestinal metaplasia beginning a series of changes that may result in neoplasia, especially of intestinal type cancers ***(Reis et al., 1999 and Fenoglio-Preiser et al., 2000)***.

Gastritis and atrophy alter gastric acid secretion, elevating gastric P.H, changing the flora and allowing anaerobic bacteria to colonize the stomach. These bacteria produce active reductases that transform food nitrate into nitrite, an active molecule capable of forming nitrosamines and other related carcinogens ***(Fenoglio-Preiser et al., 2000).***

In contrast, diffuse gastric cancers often arise in a stomach lacking atrophic gastritis with intestinal metaplasia ***(Reis et al., 1999 and Fenoglio-Preiser et al., 2000)***.

There are two main types of intestinal metaplasia "complete" (also designated as small intestinal type or type I), and "incomplete" (type II and III). Different mucin expression patterns characterize the metaplasias. Complete intestinal metaplasia shows decreased expression of gastric (MUC1, MUC5AC and MUC6) mucins and expression of MUC2 an intestinal mucin. Incomplete intestinal metaplasia, gastric mucins are co-expressed with MUC2 mucin ***(Fenoglio-preiser et al., 2000)***.

- ***A prior diagnosis of pernicious anemia***

A prior diagnosis of pernicious anemia (a chronic progressive disease caused by the failure of body to absorb vitamin B-12), which associated with advanced autoimmune atrophic gastritis ***(McCane and Huther, 2002).***

- ***Peptic ulcers***

Some experts suggest that peptic ulcers in the stomach can lead to adenocarcinoma ***(Adachi et al., 2000).***

- ***Gastric polyps***

Gastric polyps may become cancerous and are thus removed. Adenocarcinoma of the stomach is particularly likely to develop in the adenometous polyps, if the polyps are larger than ¾ inch, or if several polyps exist ***(Schlemper et al., 1997).***

- ***Genetic factors:***

Slightly increased risk with blood group A, and family history of gastric cancer ***(Al Bolkainy, 2005).***