

IMMUNOHISTOCHEMICAL EXPRESSION OF HER-2/neu RECEPTORS IN GASTRIC CARCINOMA

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By

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ABSTRACT

Cancer of the stomach shows increasing rates of mortality and morbidity in the world. Gastric adenocarcinoma is the second leading cause of cancer specific mortality worldwide and efforts intended for prevention and early detection of gastric carcinoma are effective and yet important

HER-2/neu amplification and overexpression are currently attracting attention, as these factors can be used as both prognostic and predictive marker. Alteration of HER-2/neu has been implicated in the carcinogenesis and is frequently observed in a variety of tumors.

This study aimed to evaluate HER-2/neu expression in gastric carcinomas and the correlation between its expression and the clinicopathological characteristics of tumors was evaluated.

This study included thirty cases of primary gastric carcinoma from patients who underwent radical or partial gastric resection which were referred to pathology department at Kasr El-Aini hospitals and a private laboratory between January to December 2007

The age of the cases is ranged between 30 and 76 years with a mean age 53 years. Thirteen cases were females and 17 cases were males.

Key Words:

Anatomy of the stomach, Histology of the stomach, Gastric carcinoma, Immunohistochemistry of gastric carcinoma

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List of Abbreviations

ABC: Avidin-Biotin Complex
AJCC: American Joint Committee on Cancer
APUD: Amine precursor uptake and decarboxylation
CISH: Chromogenic insitu hybridization
CK: Cytokeratine
COX-2: Cyclooxygenase 2
CSA: Catalyzed Signal Amplification
EGF: Epidermal growth factor
FISH: Fluorescence insitu hybridization
GSCs: Gastric stump cancers
H&E: Hematoxylin and Eosin
HER-2: Human epidermal growth factor receptor -2
H. pylori: Helicobacter pylori.
HRP: Horseradish peroxidase
IARC: International Agency for Research on Cancer
IHC: Immunohistochemistry
LSAB: Labeled Streptavidin Biotin
Mab: Monoclonal antibodies
MUC: Mucinous adenocarcinoma
N.C.I: National Cancer Institute
NSCLC: Non-small cell lung carcinoma
NSE: Neuron-specific enolase
PAP Method: Peroxidase anti-peroxidase method
PGC: Papillary gastric carcinoma
SCC: Squamous cell carcinoma
SmCC : Small cell carcinoma
SRC: Signet ring cell carcinoma
WHO: World Health Organization

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Introduction

Gastric cancer is one of the most common tumors and remains the second leading cause of cancer mortality in the world (**Kelley & Duggan, 2003**). The interaction of both environmental and gastric factors contributes to the etiology and pathogenesis of these aggressive cancers, mainly smoking and alcohol consumption, besides dietary habits and bacterial infection by *Helicobacter pylori* in gastric cancer (**Tahara, 2004**).

More than 95% of the gastric carcinoma consists of adenocarcinomas. (**Parkin et al., 2001**) which has been classified by **Laurén (1951 and refined 1965)** into two main histological types, intestinal and diffuse, its incidence has markedly decreased in some countries, such as United States and England. But it remains inordinately high in others such as Japan, Chile and Italy (**Keller, 2002**).

Gastric carcinoma is extremely rare below the age of 30 years; thereafter it increases rapidly and steadily to reach the highest rates in the oldest age groups, both in males and females. The intestinal type rises faster with age than the diffuse type; it is more frequent in males than in females. Diffuse carcinoma tends to affect younger individuals, mainly females. (**De Vries et al., 2007**).

Molecular genetic analyses have indicated that transformation of normal epithelial cells into a cancer is a multi- step process associated with the progressive accumulation of abnormalities in DNA repair genes, tumor suppressor genes, oncogenes, cellular growth factors, surface receptors, and cellular adhesion molecules(**Marmor et al.,2004**).Structural and functional alterations of human epidermal growth factor receptor -2 (HER-2 /neu) also known as c-erbB-2 proto-oncogene have been reported in different steps of carcinogenesis including initiation, promotion and progression (**Schlessinger,2000**).

Survival of patients with advanced gastric cancer treated with palliative chemotherapy remains low. New therapies are urgently needed. A better understanding of the molecular basis of cancer has contributed to the development of rationally designed molecular targeted therapies, which interfere with the signaling cascades involved in cell differentiation, proliferation, and survival (**Wagner et al., 2006**).

HER-2 proto-oncogene is located at chromosome 17q21, Alteration of which has been implicated in the carcinogenesis and is frequently observed in a variety of tumors. **(Pauletti et al., 2000)**. HER-2/neu amplification and overexpression are currently attracting attention, as these factors can be used as both prognostic and predictive marker **(Hofmann et al., 2007)**. It is remarkable to consider that cellular transmembrane receptor contents might be good biological markers for selecting candidates for possible therapy by an HER-2/neu- targeting strategy. Favorable clinical results with anti HER-2/neu antibodies in breast cancer have led to the analysis of HER-2/neu expression in other solid tumors **(Vogel et al., 2002)**.

HER-2/neu has been reported in 10-35 % of gastric carcinomas **(Dursun et al., 1999, Kuraoka et al., 2003, Park et al., 2006 and Raziee et al., 2007)**, the intestinal type shows higher prevalence of HER-2/neu expression in contrast to diffuse type **(Raziee et al., 2007)**.

The prognosis of patients with gastric cancer depends on several clinical and pathological variables, such as age of onset, gastric wall invasion, tumor location, lymph node involvement, and systemic metastases **(Siewert et al., 1999)**. However, there are conflicting results in studies of HER-2/neu with regard to HER-2/neu relationship to prognosis in gastric cancer patients **(Park et al., 2006)**. **Dursun et al. (1999)** reported that although a higher incidence of HER-2/neu expression was found in advanced carcinomas however, there was no significant association between its positivity and depth of invasion, tumor size, and lymph node metastasis. **Satiroglu-Tufan et al. (2006)** revealed a significant association between HER-2/neu positivity and stage III-IV tumors. Some authors revealed that HER-2/neu expression in gastric carcinomas has been related to their aggressive clinical behavior and poor survival rate **(Tsugawa et al., 1993, Chariyalertsak et al., 1994 and García et al., 2003)**.

AIM OF THE WORK

In this study, the expression of HER-2/neu receptors was investigated in gastric carcinomas and the correlation between HER-2/neu expression with histopathological features of gastric carcinoma and its association with other prognostic factors was evaluated.

Review of Literature

The anatomy of the human stomach:

The stomach is a hollow, distensible organ with a mean volume of 1,500 cc that resides in the upper abdomen. The stomach is divided into three major segments the cardia, the fundus and the body. The cardia surrounds the superior opening of the stomach. The rounded portion superior to the body and to the left of the cardia is the fundus and rests just below the left hemidiaphragm (*Mostafa et al., 2006*).

The body of the stomach is bordered superiorly by the fundus and distally by the antrum. The region of the stomach that connects to the duodenum is the pylorus. It has two parts, the pyloric antrum, which connects to the body of the stomach, and the pyloric canal, which leads into the duodenum (*figure 1*). The pylorus communicates with the duodenum of the small intestine via the pyloric sphincter (valve). This valve regulates the passage of chyme from stomach to duodenum and it prevents backflow of chyme from duodenum to stomach (*Tortora and Grabowski, 2002*). The medial and lateral curvatures of the stomach are known as the lesser and greater curvatures respectively. (*Ian & William, 2005*).

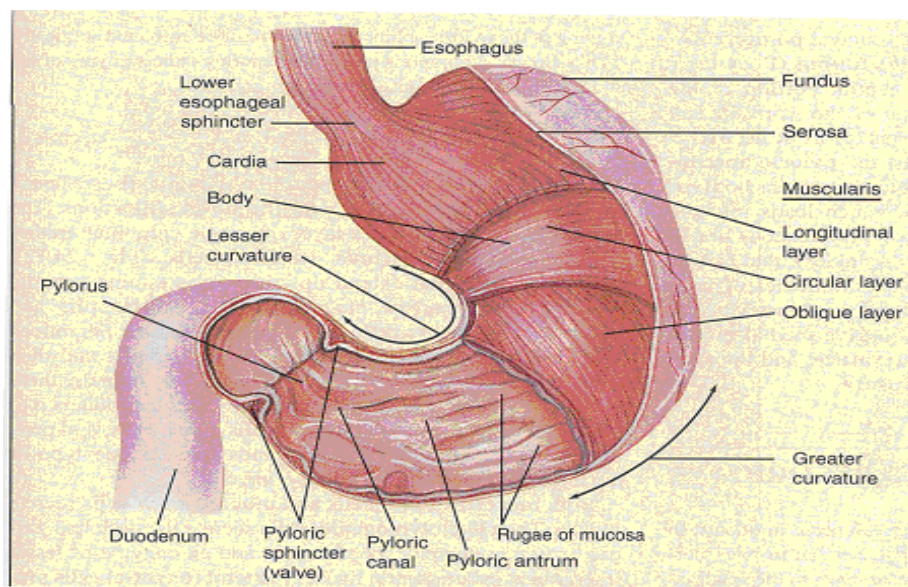


Fig. (1) Gastric Anatomy
(*Tortora and Grabowski, 2002*)

Normal Histological Features:

The five gross gastric regions: cardia, fundus, body, antrum and pylorus show correspondence to the three major microscopic types of gastric mucosa: cardiac, fundic and pyloric (antral), with transitional areas in between. The gastric mucosa consists of surface epithelium, gastric pits and gastric glands. All gastric glands have two major components: foveolar (crypt, pit) and secretory portion. The foveolae represent the most important area of genesis of gastric carcinoma (**Owen, 1997**). The differences among the various types of gastric mucosa depend on the relative proportions between foveolae and secretory portions and the microscopic composition of the latter. The gastric glands extend from the muscular mucosa to the stomach lumen via gastric pits. The foveolar cells lining the surface and gastric pits are identical throughout the stomach. Glands differ in different regions of the stomach. Gastric pits occupy approximately 25% of the mucosa. Pits lie parallel to one another. These are separated by the lamina propria. There is more lamina propria separating the pits than between the glands (**figure (2)**) (**Lewin et al., 1992**).

In normal gastric biopsy degree of pits and glandular separation should be the same throughout the biopsy (**Sarbia et al., 2002**).

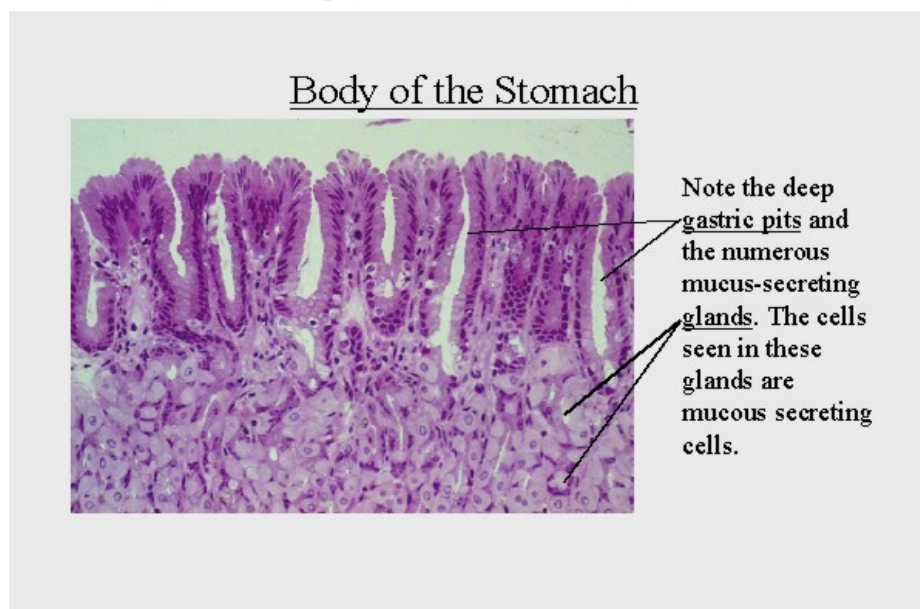


Fig.(2) Gastric Histology
(Tortora and Grabowski, 2002)

The **cardiac glands** are predominantly mucus secreting glands surrounding the entrance of the esophagus. The mucous secreting cells (goblet cells) line the luminal surface of the stomach, gastric pits and gastric glands (**Fielding & Hallissey, 2005**). Glands are less coiled than in the antral glands. These glands have wide lumina and shallow pits than the antropyloric pits. This zone may contain a few APUD cells that synthesize monoamines. In the transitional area, where this zone is continuous with the fundic zone, a few parietal cells may be present (**Chandrasoma et al., 2000**).

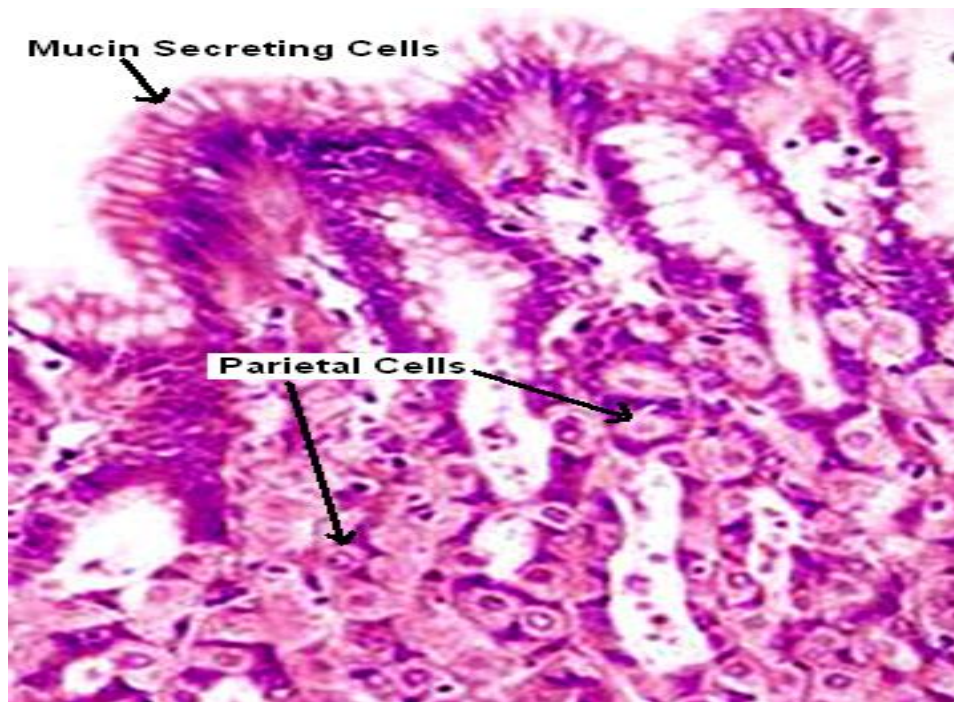


Fig.(3) Gastric cells(Menard, 2004)

The **fundic glands**, proper gastric glands or principal gastric glands are responsible for the secretion of gastric acid. The term oxyntic (Greek: acid- forming) is also used as an indicator of this glandular zone. The mucosa here is much deeper than in the cardiac zone and contains a greater number of glands. Each principal gastric gland is composed of four kinds of cells. (**Snell, 2000**).The **parietal cells**