Introduction

In 2012, there were ~140 000 new cases of gastric cancer diagnosed across all European countries, making it the sixth commonest cancer diagnosis and the fourth commonest cause of cancer-related death, being responsible for ~107 000 deaths annually ***(Ferlay et al., 2013)***.

Despite a gradual decline in the worldwide incidence of gastric cancer, there has been a relative increase in the incidence of tumors of the oesophago-gastric junction and gastric cardia. The peak incidence is in the seventh decade, and the disease is approximately twice as common in men as in women. There is a marked geographic variation, with the highest rates reported in East Asia, South America and Eastern Europe and the lowest rates in the United States and Western Europe ***(Forman et al., 2006)***.

Gastric cancer is the 14th most common cancer in Egypt representing 1.8% of cases in both sexes ***(Alieldin, 2014)***.

The median age of gastric cancer in the Egyptians is 56 years ***(MOH, 2007).*** The incidence rises with age and 55% of cases occur between 50 and 70 years of age ***(Freedman et al., 2014)***.

Factors that increase risk of stomach cancer include: Infection with Helicobacter pylori, a diet high in salty and

smoked foods, a diet low in fruits and vegetables, eating foods contaminated with aflatoxin fungus, family history of stomach cancer, long-term stomach inflammation, pernicious anemia, smoking and stomach polyps ***(Mayo clinic, 2013)***.

There are two distinct types of gastric adenocarcinoma, intestinal (well-differentiated) and diffuse (undifferentiated), which have distinct morphologic appearance, pathogenesis, and genetic profiles. The morphologic differences are attributable to intercellular adhesion molecules, which are well preserved in intestinal-type tumors and defective in diffuse carcinomas ***(Shah et al., 2011)***.

The symptoms of gastric cancer are often nonspecific, frequently leading to diagnosis at an advanced stage. Early symptoms such as vague gastrointestinal distress, episodic nausea, vomiting, and anorexia. The most common symptoms at diagnosis are abdominal pain and weight loss. Symptoms also vary by the location of the primary lesion. Dysphagia occurs predominantly among patients with proximal cancer localization. Nausea and vomiting are more common among patients with nonproximal cancer. Early satiety can be especially prominent among patients with linitis plastica type of disease ***(Holland, 2003).***

Initial investigations include physical examination, blood count and differential, liver and renal function tests, endoscopy

and contrast-enhanced computed tomography (CT) scan of the thorax and abdomen ± pelvis. Positron emission tomography (PET) imaging, if available, may improve staging through an increased detection of involved lymph nodes/metastatic disease. However, it may be uninformative in some patients, especially those with mucinous tumors ***(Degraff et al., 2007).***

Endoscopic ultrasound (EUS) is helpful in determining the proximal and distal extent of the tumors and provides further assessment of the T and N stages, although it is less useful in antral tumors ***(Nath et al., 2008).***

The TNM classification should be recorded and the corresponding stage determined according to the seventh edition of the Union for International Cancer Control (UICC), American Joint Cancer Committee (AJCC) ***(Edge et al., 2010).***

Multi-disciplinary treatment planning is mandatory. The core membership of the multi-disciplinary team should include surgeons, medical and radiation oncologists, gastroenterologists, radiologists and pathologists, as well as dieticians and nurse specialists if available ***(ESMO Annals of Oncology 24, 2013).***

The three main treatment options for gastric cancer are surgery, chemotherapy, and radiation. Endoscopic resection

followed by close surveillance is the preferred option for early stage T1N0 ***(Kitano et al., 2007)***.

Survival benefit for postoperative chemotherapy, chemoradiotherapy, and neoadjuvent chemotherapy in case of pathologic T > 2 and/or node positive gastric cancer patients has been established, and chemotherapy should contain 5-fluorouracil and cisplatin or their analogs capecitabine and oxaliplatin ***(Zhibing et al., 2013).***

In metastatic gastric cancer patients, chemotherapy with cisplatin-5-fluorouracil or capecitabine as the most widely used drugs. Addition of anti-HER2 antibody trastuzumab to first-line chemotherapy for patients overexpressing HER2 receptor and addition of the anti VEGFR-2 antibody in second line improves overall survival and progression-free survival when compared to chemotherapy alone ***(Liu et al., 2010).***

Prognosis depends greatly on stage but overall is poor (5-yr survival: < 5 to 15%) because most patients present with advanced disease. If the tumor is limited to the mucosa or submucosa, 5-yr survival may be as high as 80%. For tumors involving local lymph nodes, survival is 20 to 40%. More widespread disease is almost always fatal within 1 year ***(Cabebe et al., 2014).***

Aim of the Work

The aim of this work is explore the best management options across the continuum of care for patients at Ain Shams University Hospitals by retrospectively analyzing various clinico-epidemiological factors in gastric cancer patients and correlate them to clinical outcome; these factors are either patient or disease ones, while outcome include both clinical benefit parameters and encountered toxicities.

Epidemiology

Gastric cancer is one of the most common cancers worldwide ***(Jemal et al., 2011).*** Approximately 22,220 patients are diagnosed annually in the United States, of whom 10,990 are expected to die ***(Siegel et al., 2014).***

The worldwide incidence of gastric cancer has declined rapidly over the recent few decades ***(Zhu, 2012).***

Almost one million new cases of stomach cancer were estimated to have occurred in 2012 (952,000 cases, 6.8% of the total), making it the fifth most common malignancy in the world, after cancers of the lung, breast, colorectum and prostate. More than 70% of cases (677,000 cases) occur in developing countries (456,000 in men, 221,000 in women), and half the world total occurs in Eastern Asia (mainly in China). Age-standardized incidence rates are about twice as high in men as in women, ranging from 3.3 in Western Africa to 35.4 in Eastern Asia for men, and from 2.6 in Western Africa to 13.8 in Eastern Asia for women. Stomach cancer is the third leading cause of cancer death in both sexes worldwide (723,000 deaths, 8.8% of the total). The highest estimated mortality rates are in Eastern Asia (24 per 100,000 in men, 9.8 per 100,000 in women), the lowest in Northern America (2.8 and 1.5, respectively). High mortality rates are

also present in both sexes in Central and Eastern Europe, and in Central and South America ***(GLOBOCAN, 2012).***

Estimated Incidence, Mortality and Prevalence Worldwide in 2012 shown in table (1) ***(GLOBOCAN, 2012).***

Table (1): Estimated Incidence, Mortality and Prevalence Worldwide in 2012 ***(GLOBOCAN, 2012).***

Estimated numbers (thousands)	Men			Women			Both sexes		
	Cases	Deaths	5-year prev.	Cases	Deaths	5-year prev.	Cases	Deaths	5-year prev.
World	631	469	1031	320	254	507	952	723	1538
More developed regions	175	107	372	99	68	193	275	175	565
Less developed regions	456	362	659	221	186	315	677	548	974
WHO Africa region (AFRO)	10	10	14	9	8	12	19	18	26
WHO Americas region (PAHO)	52	39	84	34	26	54	85	65	138
WHO East Mediterranean region (EMRO)	15	13	19	9	8	11	23	21	31
WHO Europe region (EURO)	98	75	136	64	51	86	162	126	222
WHO South-East Asia region (SEARO)	60	56	54	30	28	29	91	83	82
WHO Western Pacific region (WPRO)	396	276	724	175	134	315	571	410	1039
IARC membership (24 countries)	232	148	449	124	86	226	355	234	675
United States of America	13	7	20	8	5	12	21	12	32
China	283	221	419	122	104	175	405	325	594
India	43	41	31	20	18	14	63	59	45
European Union (EU-28)	51	35	74	31	23	45	82	58	119

Gastric cancer is the sixth most common cancer in Europe, with more than 139,000 new cases diagnosed in 2012 (4% of the total). In Europe (2012), the highest World age-standardized incidence rates for gastric cancer are in Belarus for men and Albania for women; the lowest rates are in Sweden for both men and women. UK gastric cancer incidence rates are estimated to be the fifth lowest in males in Europe, and fourth lowest in females ***(Ferlay et al., 2013).***

Much of decrease in incidence of gastric cancer can be attributed to declining prevalence of Helicobacter pylori infection (a major cause of stomach cancer), and increased fresh food in the diet (and use of refrigeration rather than salting for food preservation). This overall trend masks a rise in incidence of cancers in the cardia over the last 30 years in many developed countries, particularly in males, although rates have begun to decline in England since the late 1990s ***(Jemal et al., 2011).***

The age of onset of developing gastric cancer in Chinese population is younger than that in the West. In the United States, risk factors for non-cardia gastric cancer include male gender, non-white race, and older age ***(Schlansky, 2011).***

Estimated age-standardised rates (World) per 100,000 are as shown in figure (1) ***(GLOBOCAN, 2012).***

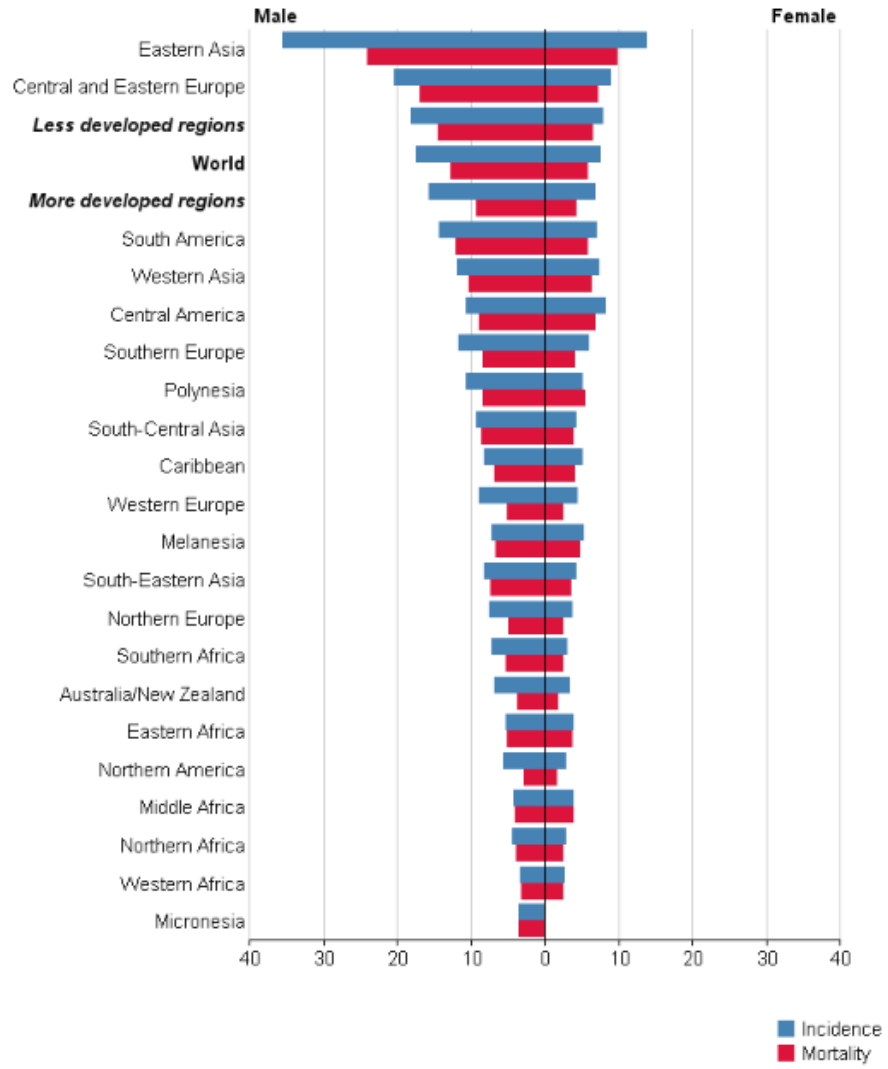

Figure (1): Figure (1.0) Estimated age-standardised rates (World) per 100,000 ***(GLOBOCAN, 2012).***

A dramatic shift in the location of upper GI tract tumors has occurred in the United States. Changes in histology and location of upper GI tract tumors have also been observed in some parts of Europe. The proximal lesser

curvature, cardia, and the EGJ are the most common sites of gastric cancer in Western countries. It is possible that in the coming decades these changing trends will also occur in South America and Asia ***(Jemal et al., 2010).***

Most gastric cancers (around 95%) are adenocarcinomas which may be further classified into intestinal and diffuse type. Intestinal adenocarcinomas are associated with a history of atrophic gastritis, have better survival and are associated with older patients, whereas the diffuse adenocarcinomas are more common, with poorer survival and occur more frequently in women and people with blood group A ***(Souhami et al., 2005).***

In Egypt; Incidence rates per 100 000 populations of individuals in Lower, Middle, and Upper Egypt for males and females were as follow ***(Ibrahim et al., 2014):***

Table (2): Incidence rates/100,000 population in Lower, Middle, and Upper Egypt: males.

	Crude rate	**Age of standardized age**	**%**
Lower Egypt 2009-2011	1.4	2.0	0.98%
Middle Egypt 2009	1.7	2.5	1.53%
Upper Egypt 2008	2.4	3.8	2.48%

Table (3): Incidence rates/100,000 population in Lower, Middle, and Upper Egypt: females.

	Crude rate	Age of standardized age	%
Lower Egypt 2009-2011	2.3	3.2	1.73%
Middle Egypt 2009	1.2	1.8	1.25%
Upper Egypt 2008	1.9	3.1	1.6%

In Aswan, 2008 there were 25 cases per 100 000 populations where males: Females ratio 1.3:1 respectively, with mean age 61.4 in males and 59.1 in females. Age Specific Incidence Rates of Stomach Cancer per 100,000 Population, Aswan, 2008 (25 cases) ***(Cancer registry, Aswan, 2008).***

Subsite	**Distribution**
Pylorus	5 (55.6%)
Cardia, NOS	2 (22.2%)
Fundus of stomach	1 (11.1%)
Overlapping lesion	1 (11.1%)
Total (known subsites)	9 (100%)
Pathological Diagnosis	
Mentioned	13 (52.0%)
Not mentioned	12 (48.0%)
Adenocarcinoma	7 (53.8%)
Signet ring cell carcinoma	3 (23.1%)
Malignant lymphoma	2 (15.4%)
Stromal sarcoma	1(7.7%)
Total	13 (100%)
Localized	3 (17.6%)
Regional (direct)	2 (11.8%)
Regional (lymph node)	2 (11.8%)
Distant	8 (47.1%)

In ElMinia, 2009 there were 64 cases per 100 000 populations where males: Females ratio 1.5:1 respectively, with mean age 49.8 in males and 54.2 in females.

Subsite	Distribution
Known subsite	3 (4.7%)
Unknown subsite	61 (95.3%)
Body of stomach	1 (33.3%)
Gastric antrum	1 (33.3%)
Greater curvature of stomach	1 (33.3%)
Total (known subsites)	3 (100.0%)
Pathological Diagnosis	
Mentioned	20 (30.3%)
Not mentioned	44 (69.7%)
Adenocarcinoma	9 (45.0%)
Carcinoma, NOS	2 (10.0%)
Carcinoma, anaplastic	1 (5.0%)
Signet ring cell carcinoma	1 (5.0%)
Other	5 (25%)
Total	20 (100%)
Stage at diagnosis	
Mentioned	17 (26.6%)
Not mentioned	47 (73.4%)
Localized	10 (58.8%)
Localized (direct)	3 (17.6%)
Regional (lymph nodes)	1 (5.9%)
Regional (direct + lymph nodes)	2 (11.8%)
Distant	1 (5.9%)
Total	17 (100%)

Crude and Age Specific Incidence Rates of 64 Stomach Cancer case per 100,000 Population by sex (Cancer registry, El-Minia, 2009).

Screening and Prevention

The value of screening in asymptomatic individuals for gastric cancer remains controversial (***Leung et al., 2008).*** Annual mass screening for gastric cancer has been granted in some countries with a high incidence of gastric cancer (such as Japan, Chile and Venezuela), with the aim of detecting gastric cancer in its earliest stages when there is better prognosis ***(Chisato et al., 2008).***

Screening to detect gastric cancer at its early stages can be done for large masses of the population (mass screening) or for individuals at high risk (opportunistic screening). Although the value of screening mass populations for gastric cancer remains controversial, it has been provided in some countries with high incidence of gastric cancer, such as Japan, Venezuela, and Chile. In contrast, in countries with low incidence of gastric cancer, such as the United States, this strategy is costly and unwarranted. In low-risk regions, only people with certain conditions may benefit from gastric cancer screening, including older individuals with chronic gastric atrophy or pernicious anemia, and patients who have had gastric polyps, partial gastrectomy, FAP, and hereditary nonpolyposis colon cancer ***(Karimi et al., 2014).***

Screening may be done using markers of atrophy in the stomach (a precursor lesion of gastric cancer), such as

serum pepsinogens; or serum antibodies to H. pylori, the main risk factor for gastric cancer; or examining the stomach mucosa using methods such as barium photofluorography or endoscopy ***(Croswell et al., 2010).***

Serum pepsinogen tests were imported for gastric cancer mass screening for identifying individuals with atrophic gastritis who are at high risk for gastric cancer. Gastritis leads to increased serum concentrations of pepsinogen I and II. As the severity of gastric atrophy advances, replacement of chief cells by pyloric glands occurs, the concentration of pepsinogen II concentration remains elevated. Meanwhile the concentration of pepsinogen I decreases. Patients with extensive atrophic gastritis, as suggested by low serum pepsinogen I concentrations and low serum pepsinogen I/II ratios, can then be offered screening with upper endoscopy ***(Lomba et al., 2012).***

Serum PG measurement for mass screening of gastric cancer enabled achieving high recruitment for gastroendoscopy in intended individuals, a favorable detection rate of gastric cancer and, in particular, an extremely high proportion of early-stage gastric cancer in all the detected cancers ***(Miki et al., 2009).***

Serum trefoil factor 3 (TFF3), a small stable molecule expressed in the goblet cells of the small and large intestine and in gastric intestinal metaplasia, may be a better marker for

gastric cancer than serum pepsinogen. In one study, the sensitivity and specificity for detection of gastric cancer were both 81 percent with TFF3 compared to 45 and 88 percent for pepsinogen ***(Aikou et al., 2011).*** The combination of pepsinogen and TFF3 may provide even higher sensitivity for gastric cancer. Serum TFF3 may be even a better predictor of gastric cancer than the PG test, while the combined testing of serum PG and TFF3 could further improve the efficacy of gastric cancer screening ***(Huang et al., 2014).***

An effective screening program should have the following characteristics: the disease should be common in the population; otherwise the individual benefit will not offset the risk, cost, and inconvenience of screening the rest of the population. In addition, the diagnostic test(s) used should be safe, simple, inexpensive, and reliable, and effective treatment should be available ***(Cho et al., 2013).***

Screening recommendations for high-risk individuals include elderly patients with atrophic gastritis or pernicious anemia, those who have undergone partial gastrectomy, those with a sporadic gastric adenoma, patients with familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer, and immigrant ethnic populations from countries with high rates of gastric cancer ***(Hamashima et al., 2008).***