Recent Advances in Management of Gastric Cancer

An Essay

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Mohammed Ahmed Momtaz Haykal

Contents

List of Abbreviations

1	^{18}F-FDG PET/CT Scan	^{18} Fluorine Fluoro-2-Deoxy-d-Glucose Positron Emission Tomography/Computed Tomography
2	5-ALA	5-Aminolevulinic Acid
3	5-FU	5-Fluorouracil
4	ABCG2	ATP-binding Cassette Transporter G2
5	AGC	Advanced Gastric Cancer
6	AJCC	American Joint Committee on Cancer
7	ASPDA	Anterior Superior Pancreaticoduodenal Artery
8	BMI	Body Mass Index
9	CA	Cancer-related Antigen
10	CEA	Carcinoembryonic Antigen
11	CECT	Contrast Enhancement Computed Tomography
12	CHA	Common Hepatic Artery
13	CLE	Confocal Laser Endomicroscopy
14	CRT	Chemo-radiotherapy
15	CSC	Cancer Stem Cells
16	CT	Computed Tomography
17	DCF	Docetaxel, Cisplatin, 5- Fluorouracil
18	DG	Distal Gastrectomy
19	ECF	Epirubicin, Cisplatin, 5-Fluorouracil
20	ECL	Enterochromaffin-like Cells
21	ECX	Epirubicin, Cisplatin, Capecitabine
22	EGC	Early Gastric Cancer
23	EGFR	Epidermal Growth Factor Receptor
24	EGJ	Esophagogastric Junction
25	EMR	Endoscopic Mucosal Resection
26	ESD	Endoscopic Submucosal Dissection
27	EUS	Endoscopic Ultrasonography
28	FGFR2	Fibroblastic Growth Factor Receptor 2
29	FISH	Fluorescence in situ Hybridization
30	GC	Gastric Cancer
31	GDA	Gastroduodenal Artery
32	HDGC	Hereditary Gastric Cancer
33	HDL	Hepatoduodenal Ligament
34	HER2	Human Epidermal Growth Factor Receptor 2
35	HGF	Hepatocyte Growth Factor
36	ICC	Indigo Carmine Chromoendoscopy
37	IHC	Immunohistochemistry
38	IM	Intestinal Metaplasia
39	LADG	Laparoscopy-Assisted Distal Gastrectomy

40	LAG	Laparoscopy-Assisted Gastrectomy
41	LATG	Laparoscopy-Assisted Total Gastrectomy
42	LGA	Left Gastric Artery
43	LGEA	Left Gastro-epiploic Artery
44	lncRNA	long non-coding RNA
45	MDCT	Multidetector Row Computed Tomography
46	ME-NBI	Magnifying Endoscopy with Narrow-Band Imaging
47	miRNA	microRNA
48	MRI	Magnetic Resonance Imaging
49	MS	Microsurface structures
50	MV	Microvascular pattern
51	OTG	Open Total Gastrectomy
52	PDD	Photodynamic Diagnostics
53	PPG	Pylorus-Preserving Gastrectomy
54	PpIX	Protoporphyrin IX
55	RECIST	Response Evaluation Criteria in Solid Tumors
56	RGA	Right Gastric Artery
57	RGEA	Right Gastro-epiploic Artery
58	SEER	Surveillance, Epidemiology and End Results
59	SNP	Single Nucleotide Polymorphisms
60	SPEM	Spasmolytic Polypeptide-Expressing Metaplasia
61	TG	Total Gastrectomy
62	TLG	Totally Laparoscopic Gastrectomy
63	TNFA	Tumour Necrosis Factor-Alpha
64	TNM	Tumor Node Metastasis
65	TSG	Tumor Suppressor Gene
66	VEGF	Vascular Endothelial Growth Factor
67	WLE	White Light Endoscopy

List of Figures

List of Tables

Abstract

Gastric cancer is the second leading cause of death from malignant disease worldwide and most frequently discovered in advanced stages. Because curative surgery is regarded as the only option for cure, early detection of resectable gastric cancer is extremely important for good patient outcomes. Therefore, noninvasive diagnostic modalities such as evolutionary endoscopy and positron emission tomography are utilized as screening tools for gastric cancer. To date, early gastric cancer is being treated using minimally invasive methods such as endoscopic treatment and laparoscopic surgery, while in advanced cancer it is necessary to consider multimodality treatment including chemotherapy, radiotherapy, and surgery. Because of the results of large clinical trials, surgery with extended lymphadenectomy could not be recommended as a standard therapy for advanced gastric cancer. Recent clinical trials had shown survival benefits of adjuvant chemotherapy after curative resection compared with surgery alone. In addition, recent advances of molecular targeted agents would play an important role as one of the modalities for advanced gastric cancer.

Keywords:

gastric cancer; surgery; chemotherapy; radiotherapy; laparoscopic gastrectomy

Chapter 1
Introduction

Introduction

Gastric cancer (GC) is a major public health issue, and it is the fourth most common cancer and the second leading cause of cancer-related death. However, its incidence rates in different geographical regions are distinctly varied. Etiologically, gastric cancer is associated with *Helicobacter pylori* (*H. pylori*) infection, dietary and lifestyle factors, and genetics. ***(Ferlay et al., 2010)***

It is usually diagnosed at an advanced stage, and, consequently, the prognosis is dismal. Although surgery is the definitive therapy, rates of recurrence are high, creating the need for neoadjuvant or adjuvant therapy. These therapies have improved significantly the 5 year survival of these patients but not all patients benefit equally from these treatment options. The ability to predict patient response to specific therapies would be particularly valuable and would allow for the stratification of patients for personalized treatment strategies, likely with less toxicity. Recent advances have improved our understanding of gastric carcinogenesis with an unprecedented opportunity of developing novel therapeutic strategies. Exploring and validating tissue-based biomarkers are ongoing processes, which will certainly open new avenues for treating and improving the prognosis of patients with GC. (***Jemal et al., 2010)***

Despite modern advances in diagnostics, surgical techniques, radiation therapy, and chemobiologic therapy, gastric cancer remains a highly fatal disease. Based on SEER data, the 5-year relative survival for gastric cancer (all stages) from 2002–2008 is 27%. The presence of micrometastatic disease, even in apparent early stage disease, contributes to the poor overall survival and the need for improved chemotherapeutics. Most gastric cancers are adenocarcinoma histology (>90%). There has been a migration of gastric cancers over the past century. In the early 1900s most gastric cancers were distal and involved the gastric antrum and body. The incidence of distal gastric cancers has been declining steadily, whereas the incidence of proximal gastric cancers and esophagogastric junction (EGJ) cancers has risen. There has also been a corresponding increase in the number of adenocarcinomas of the distal esophagus. The rate of increase is alarmingly high and should be considered an epidemic. In regards to gastric, EGJ, and distal adenocarcinomas of the esophagus, their natural history, response to treatment, and prognosis are very similar suggesting a shared

pathogenesis. Some of the possible causes include infectious pathogens (ie, Helico bacter pylori); Barrett esophagus; and obesity. As the world continues to struggle with the obesity epidemic, there will continue to be an increase in these malignancies. ***(Wijnhoven et al., 1999)***

Surgical resection remains the primary therapy for gastric cancers when the goal of care is curative. More than 50% of gastric cancers have metastasized to regional lymph nodes at the time of surgery. The survival of the remaining patients with potentially curable, non-metastatic disease falls below 50% and 20% when the tumour invades through the muscularis propria and involves regional lymph nodes, respectively,prompting much effort to improve patient outcomes following gastrectomy. Survival rates are correlated with the degree of lymph node involvement. Five-year survival for N0 disease is around 50%, whereas survival for N3 disease is only 10%. The poor survival with advanced disease confirms the importance of developing more active systemic therapy, which can be incorporated into a multidisciplinary approach to improve outcomes. There is currently no agreed on approach (neoadjuvant vs adjuvant) for locally advanced gastric cancer. This is in part related to the numerous areas of controversy, which have not been addressed in large multicenter randomized controlled phase III trials. Some of the issues have arisen because classifications of gastric cancers and EGJ cancers have changed with time. In addition, this overlap has diluted the data pool because most of the major clinical trials have included a sizable population of distal esophageal, EGJ, and gastric cancers. In the most recent version of TNM staging system (version 7), EGJ and gastric cardia tumors (Siewert III, arise in cardia within 5 cm of EGJ and extend into esophagus or EGJ junction) are classified as esophageal cancer rather than gastric cancer. ***(Edge et al., 2010)***

The publication of two landmark trials in 2001 and 2006 established both post-operative chemo-radiotherapy (CRT) and perioperative chemotherapy (CT) as effective adjuvant treatment options, and both are currently accepted standards of care in the Western world. However, debate continues concerning the applicability of these trials to the Asian population, where there is the highest incidence of gastric cancer. (***Cunningham et al., 2010)***

Chapter 2

Anatomy

1. **Stomach parts**
2. **Arterial supply**
3. **Lymphatic drainage**
4. **Nerve supply**

Anatomy

The thoracic esophagus enters the abdomen via the esophageal hiatus of the diaphragm at the level of T10. The abdominal portion of the esophagus has a small intra-abdominal length (2-3 cm). The esophagogastric junction (cardia), therefore, lies in the abdomen below the diaphragm to the left of the midline at the T11 level. ***(Drake et al., 2013)***

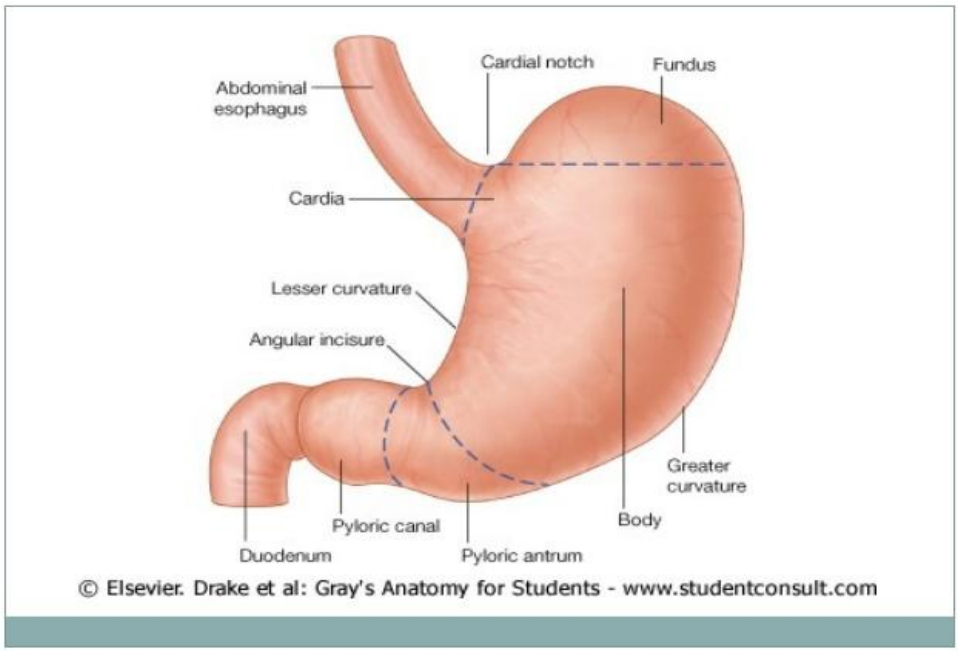

Figure 1: Stomach Anatomy ***(Drake et al., 2013)***

The cardiac notch (incisura cardiaca gastri) is the acute angle between the left border of the abdominal esophagus and the fundus of the stomach, which is the part of stomach above a horizontal line drawn from the cardia. The body (corpus) of the stomach leads to the pyloric antrum (at the incisura angularis). The pyloric antrum narrows toward the right to become the pyloric canal, surrounded by the pyloric sphincter, which joins the duodenum at the L1 level (transpyloric plane) to the right of the midline. ***(Agur et al., 1999)***

The anterior surface of stomach is related to the left lobe (segments II, III and IV) of the liver, the anterior abdominal wall, and the distal transverse colon. The posterior surface of the stomach is related to the left hemidiaphragm, the spleen, the left kidney (and adrenal), and the pancreas (stomach bed).The omental bursa (lesser sac) lies behind the stomach and in front of the pancreas; it communicates with the greater sac (main peritoneal cavity) via the omental (epiploic) foramen (of Winslow) behind the hepatoduodenal ligament (HDL; the free edge of the

lesser omentum).The convex greater curvature of the stomach starts at the left of the cardia and runs from the fundus along the left border of the body of the stomach and the inferior border of the pylorus. The concave lesser curvature starts at the right of the cardia as a continuation of the right border of the abdominal esophagus and runs a short distance along the right border of the body of the stomach and the superior border of the pylorus. The junction of the vertical and horizontal parts of the lesser curvature is called incisura angularis. Lesser curvature is shorter in length than the greater curvature. The stomach and the first part of the duodenum are attached to the liver by the hepatogastric ligament (the left portion of the lesser omentum) containing right and left gastric vessels, to the left hemidiaphragm by the gastrophrenic ligament, to the spleen by the gastrosplenic/gastrolienal ligament containing short gastric vessels, and to the transverse colon by the gastrocolic ligament (part of the greater omentum) containing epiploic (omental) vessels. Few peritoneal bands may be present between the posterior surface of the stomach and the anterior surface of the pancreas. Part of the greater omentum hangs like an apron from the transverse colon, with 4 layers of the peritoneum (often fused): 2 layers go downward from the stomach and then run upward to be attached to the transverse colon. ***(Gray et al., 2000)***

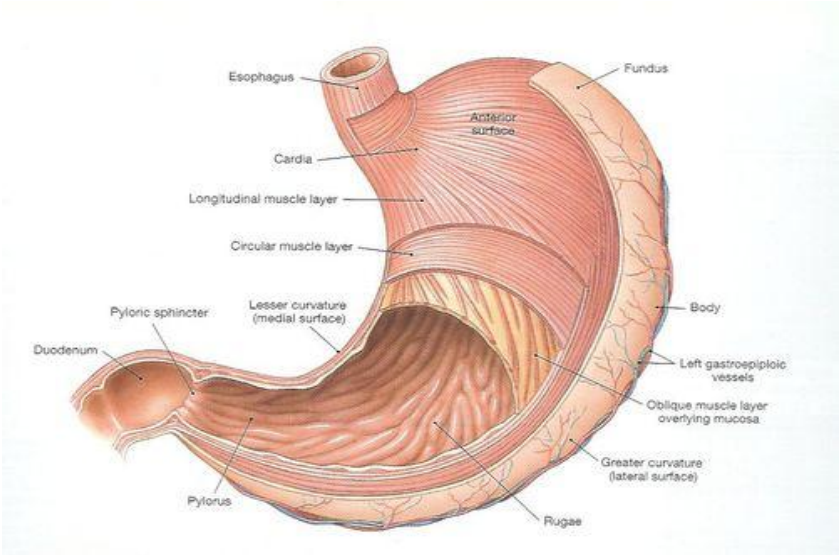

Figure 2: Musclar layers of stomach ***(Drake et al., 2013)***

Blood Supply

The celiac trunk (axis) arises from the anterior surface of the abdominal aorta at the level of L1. It has a short length (about 1 cm) and trifurcates into the common hepatic artery (CHA), the splenic artery, and the left gastric artery (LGA).The LGA runs toward the lesser curvature of the stomach and divides into an ascending branch (supplying the abdominal esophagus) and a descending branch (supplying the stomach).