1. Introduction

Malignancies associated with the upper gastrointestinal (GI) tract are reported to be extremely lethal. Most patients with gastric cancer (GC) in the United States are symptomatic and already have complex untreated disease at the time of presentation. GC in general, is a senile malignancy (cancer of the aged) and is reportedly twice as common in blacks as in whites. Routine screening is not extensively performed, except in countries, which have a very high incidence of GC, such as Japan, Venezuela, and Chile. The three most common primary malignant gastric neoplasms are adenocarcinoma (95%), lymphoma (4%), and malignant GIST (Gastrointestinal stromal tumor)(1%). Fortunately, dedicated research into its pathogenesis and detection of new risk factors, treatment, and advanced endoscopic techniques have led to early diagnosis of GC in the modern era.

2. Adenocarcinoma

Adenocarcinoma of the gastric epithelium is the most common form of malignancies of the gut (90% of cases). Carcinoma of the connective tissue (sarcoma) and lymphatics (lymphoma) is reportedly less common. Adenocarcinomas (Figures 1, 2) most commonly occur in the gastric cardia (31%), followed by the antrum (26%), and body of the stomach (14%). The 5-year overall survival rate is 25.7%, which has not changed drastically over the past 30 to 40 years. Surgery remains the mainstay of treatment for GC, the survival can be improved with multimodal approach.
Figure 1. Showing A. CT image of Linitis plastic (arrows denotes a thickened gastric wall). B. endoscopic image. C. illustration of linitis plastic. Picture courtesy: John Hopkins Medicine- Gastroenterology and Hepatology department. ‘An introduction to Gastric cancer’, 2012.

Figure 2. Showing A. the Endoscopic image of an ulcerating adenocarcinoma. B. Ulcerating adenocarcinoma, pictorial representation. Picture courtesy: John Hopkins Medicine- Gastroenterology and Hepatology department. ‘An introduction to Gastric cancer’, 2012.
2.1. Incidence and prevalence

GC is one of the most common cancers worldwide, causing almost 738,000 deaths annually. The incidence of GC varies widely, both globally and within individual country. High-incidence has been reported from parts of Latin America, Eastern Asia, Europe and the Middle East [1]. The overall incidence rates are different, but they are increased among certain ethnic and racial groups, such as Hispanics and African-Americans [2] in the US. More recently, for reasons unknown, a growing rate in the incidence of GC has been reported among young adults in the US [3]. The incidence of early GC (EGC), as well as the percentage of gastric adenocarcinomas that are EGCs, vary depending on the population: In Japan and Eastern Asia, up to one-half of resections for gastric adenocarcinoma represent EGC. In Japan, the proportion rose from 15 to as high as 57 percent with the introduction of routine screening programs; In Korea, 25 to 30 percent of gastric adenocarcinomas are EGCs [4]; In Western countries, EGCs account for 15 to 21 percent of gastric adenocarcinomas [4]

GC tends to occur 1.5 to 2.5 times more frequently in African Americans, Hispanic Americans, and Native Americans than whites. GC occurs at a median age of 69 years for men and 73 for women [5], and has an elevated incidence in groups of lower socioeconomic status. In the US, an estimated 21,130 new cases of GC were diagnosed in 2009, with 10,620 deaths [2]. According to the Surveillance Epidemiology and End Results (SEER) [5] (2000–2006) database, only 24% of GCs are confined to the stomach (localized); 31 to 32% of newly diagnosed cases have spread beyond the stomach into the peripheral lymph nodes (regional) or other organs (distant), respectively [5]. GC predominantly affects men compared to women, at a ratio of 2:1. On the basis of SEER 2002-2006 data, the age-adjusted incidence of GC is 7.9 per 100,000 men and women per year [5]. In younger patients, tumors are more often of the diffuse variety and tend to be large, aggressive, and more poorly differentiated, sometimes infiltrating the entire stomach (linitis plastica). The 5-year OS (overall survival) rate is 25.7%, which has not changed significantly over the past 30 to 40 years [5]. Surgical intervention is still the only available option to effectively cure GC, and endurance could be improved with multimodal therapy.

2.2. Etiology

Gastric adenocarcinoma is a multifactorial disease. It is observed that when people migrate from a place with high incidence to a place with low incidence the occurrence of cancer in new generations is lesser. This suggests an unknown environmental factor contributing to the development of GC. It is widely believed that consumption of salt-preserved and smoked food is associated with onset of GC. Achlorhydric stomach predisposes to growth of bacteria wherein nitrate is converted into nitrite, a proven carcinogen. Bacteria may be introduced exogenously through the ingestion of partially decayed foods, which are consumed generously worldwide by the lower socioeconomic classes. Serial endoscopic examinations of the stomach in patients with atrophic gastritis have documented replacement of the usual gastric mucosa by intestinal-type cells. This process of intestinal metaplasia may lead to cellular atypia and eventual neoplasia. The theoretical sequence of development of gastric adenocarcinoma is illustrated in figure 3 [7].
2.3. *Helicobacter pylori* [7, 8]

*Helicobacter pylori* has been classified as a group 1 (i.e. definite) carcinogen by the World Health Organization (WHO) report. Recent lines of evidence showed that persistent *H. pylori* infection increases the risk of GC in patients to about three-fold. Patients with history of gastric ulcers are more likely to develop GC as compared to uninfected individuals, (incidence ratio 1.8, 95% confidence interval 1.6 to 2.0), and patients with a history of duodenal ulcer are at decreased risk for GC (incidence ratio 0.6, 95% CI 0.4 to 0.7). *H. pylori* causes chronic gastritis, loss of gastric acidity, and bacterial growth in the gastric antrum. The effect of *H. pylori* eradication on the subsequent risk for GC in high-incidence areas is under investigation.
2.4. Epstein-Barr virus

EBV, a virus belonging to the herpesviridae family of DNA viruses is reported to be associated with the development of late stages of cancer. EBV accounts for ~10% of all GCs.

2.5. Genetic factors

Numerous genetic abnormalities have been implicated in the development of GC, and most of them are aneuploid. Genetic abnormalities in the tumor suppressor gene \textit{p53}, and \textit{COX-2} are the two most common causes observed among the sporadic cases of GC. More than two thirds of GCs have deletion or suppression mutations in the \textit{p53} message.

2.6. Fruits, vegetables and fiber

Consumption of fruits and vegetables, especially fruits is believed to protect against GC. Case-control studies from Europe, Asia, and North America have shown that intake of fruits and vegetables could confer protection against GC, reducing the risk by ~40 percent for fruits, and ~30 percent for vegetables for the highest versus lowest categories of intake, respectively. Diets low in vitamin C show the strongest association with GC. The protection attributed to consumption of vegetables and fruits is most likely related to vitamin C content, which is believed to lower the formation of carcinogenic N-nitroso compounds in the gut. However, cooked vegetables do not show the equal degree of protection as uncooked vegetables.

2.7. Other factors

Prospective investigations have highlighted the importance of intake of cereal fibers in alleviating the risk of development of diffuse type GC, but not the intestinal type. Individuals with blood group A are reported to develop ~20 percent increased risk of GC than those with group O, B, or AB [6]. Interestingly, excessive body weight and obesity are associated with an increased risk of development of GC [9]. According to a study, the strength of association between body weight and cancer increased with increasing BMI. Several studies have investigated the relationship between tobacco smoking and GC. A meta-analysis of 40 different investigations has estimated that the risk was increased by ~1.5 to 1.6-fold and was higher in men. A prospective study found that, compared with non-smokers, active smokers were at increased risk for cancer at the gastric cardia (HR 2.9, 95% CI 1.7, 4.7), and gastric noncardia (HR 2.0, 95% CI 1.3, 3.2) [10]. Finally, regular use of NSAIDs has been inversely associated with the risk of distal gastric adenocarcinoma [11, 12].

2.8. Premalignant conditions of the stomach

Certain premalignant conditions of the stomach are reported to predispose to the development of GC. A study conducted in Tokyo and Japan involving 1900 cases has shown that the prevalence of certain premalignant conditions (figure 4) is associated with the development of EGC. Atrophic gastritis is by far the most commonly reported precancerous condition of the stomach predisposing to development of GC.
Figure 4. Showing the premalignant lesions of the stomach (Source: Swartz’s principles of surgery, 9th edition. September 2009)

<table>
<thead>
<tr>
<th>Precancerous lesion</th>
<th>Number of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polyp</td>
<td>10</td>
<td>0.53</td>
</tr>
<tr>
<td>Adenoma</td>
<td>47</td>
<td>2.47</td>
</tr>
<tr>
<td>Chronic ulcer</td>
<td>13</td>
<td>0.68</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>1802</td>
<td>94.84</td>
</tr>
<tr>
<td>Verrucous gastritis</td>
<td>26</td>
<td>1.37</td>
</tr>
<tr>
<td>Stomach remnant</td>
<td>2</td>
<td>0.11</td>
</tr>
<tr>
<td>Aberrant pancreas</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total 1900</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
2.9. Molecular pathogenesis of GC

Almost half of the intestinal types of GCs is associated with mutations in tumor suppressor genes. *TP53* is one key regulatory molecule that protects cells in the chronic inflammatory stress microenvironment, and any event leading to the loss of *TP53* expression by LOH (i.e. Loss Of Heterozygosity or mutational inactivation) culminates in frequent gastric alterations and development of GC, occurring in >60% of invasive tumors [13]. Another molecular factor associated with GC is the *c-met* oncogene expression that is reportedly amplified in 19% of intestinal type and 39% of diffuse type of GCs. Especially, expression of 6.0 kb *c-met* transcript is associated with more advanced disease stage at the time of presentation. Likewise, there are other molecular mechanisms suggested for GC. *k-ras* mutations are detected in intestinal metaplasia, dysplasia and invasive cancers. *TP73* is found to be either overexpressed or not expressed at all. Over expression of *p73* and the oncogenic isoform *Delta Np73* suppresses *p73* transcriptional and apoptotic activity in gastrointestinal cancer cells and increases intracellular β-catenin levels, an effect that is inhibited in the presence of wild-type but not mutant *p53*. Loss of expression has been reported via epigenetic mechanisms in EBV-associated GCs [14]. Mutations in APC (adenomatous polyposis coli) gene are identified in significantly more intestinal-type than diffuse-type GCs (33 versus 13 percent). These mutations are also found in *H. pylori*-associated dysplasia and intestinal metaplasia [14]. Loss of *TFF1* (trefoil factor family1) expression has been observed in intestinal metaplasia of the incomplete type and in GCs. The trefoil factor family (TFF) of proteins comprises a group of gastrointestinal peptides that are involved in the protection of the mucous epithelium. Cell cycle regulatory molecules — Cyclin E and cyclin-dependent kinase inhibitor 1B (CDKN1B, p27) are the two important cell-cycle regulators that take part in G1/S transition. Cyclin E overexpression is a frequent event in GCs, and might be an indicator for malignant transformation of dysplasia, and/or tumor aggressiveness following development of an invasive cancer. E-cadherin, a key protein on cell surfaces responsible for intercellular connections, is absent in diffuse type of carcinoma enabling tumor cells to invade and metastasize.

2.10. Pathology

Dysplasia, the earliest stage in the development of cancer, is regarded as the precursor of GC. Mildly dysplastic cases are followed up with endoscopic surveillance plus *H. pylori* eradication. Nonetheless, severely dysplastic cases need gastric resection if tumor is widespread or multifocal; or may need Endoscopic Mucosal Resection (EMR) if the tumor is localized.

2.11. Early and late GC

Early GC is defined as adenocarcinoma limited to the mucosa and submucosa of the stomach, irrespective of lymph node status. Late GC defined as a gastric carcinoma that has invaded the muscle wall. It is the stage at which the tumor is commonly diagnosed in the US. Different types of Early GCs (EGC) have been illustrated in figure 5.
2.12. Gross morphology and histologic subtypes

Morphologically, there are four varieties of GCs: polypoid, fungating, ulcerative, and scirrhus. In polypoidal and fungating, the bulk of the tumor mass is found intraluminally. In case of ulcerative and scirrhous type the bulk of the tumor is found in the wall of the stomach. Whilst polypoid type of tumors are not ulcerated, fungating tumors are elevated intraluminally, and ulcerated. As the name implies, ulcerative variety morphologically resembles ulcers. On contrary, the scirrhous tumors tend to infiltrate the entire thickness of the stomach and cover a very large surface area. Scirrhous tumors involve the entire stomach and have a very poor prognosis. This is classically described as ‘Linitis plastica’ or leather bottle appearance which is characterized by loss of distensibility of the gastric wall. Regarding the anatomic location of GC, in the US, 30% of GCs originate in the distal, 20% arise in the mid portion, and 37% originate in the proximal third of the stomach. The remaining 13% involve the entire stomach.

2.13. Histology

Histologic characterization of the GC is important as histologic type and the depth of invasion are the most important prognostic indicators. There are many histologic classifications of GC. The histologic classification described by WHO involves: Adenocarcinoma (papillary, tubular, mucinous, signet-ring), adenosquamous, squamous, small cell, undifferentiat-
ed, and others. Further, there is a Japanese classification which is similar to the one described by WHO, but more descriptive. There is also a Lauren classification which classifies GCs into intestinal (53%), diffuse (33%), and unclassified (14%) GC types.

2.14. Pathologic staging

Prognosis depends on the pathologic stage of the disease, and TNM (i.e. tumor-node-metastasis) (Table 1) staging is the most widely used system based on the depth of tumor invasion, extent of lymph node metastases [38], and presence of distant metastases. This system was initially developed by the American Joint Committee on Cancer and the International Union Against Cancer, and has undergone several modifications since then.

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Regional lymph nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>TX Regional lymph node(s) cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>T0 No regional lymph node metastasis</td>
</tr>
<tr>
<td>Tis</td>
<td>Tis Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria</td>
</tr>
<tr>
<td>N0</td>
<td>N0 No regional lymph node metastasis</td>
</tr>
<tr>
<td>T1</td>
<td>T1 Tumor invades lamina propria, muscularis mucosae, or submucosa</td>
</tr>
<tr>
<td>N2</td>
<td>N2 Metastasis in 3-6 regional lymph nodes</td>
</tr>
<tr>
<td>T1a</td>
<td>T1a Tumor invades lamina propria or muscularis mucosae</td>
</tr>
<tr>
<td>N3</td>
<td>N3 Metastasis in seven or more regional lymph nodes</td>
</tr>
<tr>
<td>T1b</td>
<td>T1b Tumor invades submucosa</td>
</tr>
<tr>
<td>N3a</td>
<td>N3a Metastasis in 7-15 regional lymph nodes</td>
</tr>
<tr>
<td>T2</td>
<td>T2 Tumor invades muscularispropria</td>
</tr>
<tr>
<td>N3b</td>
<td>N3b Metastasis in 16 or more regional lymph nodes</td>
</tr>
<tr>
<td>T3</td>
<td>T3 Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures</td>
</tr>
<tr>
<td>T4</td>
<td>T4 Tumor invades serosa (visceral peritoneum) or adjacent structures</td>
</tr>
<tr>
<td>T4a</td>
<td>T4a Tumor invades serosa (visceral peritoneum)</td>
</tr>
<tr>
<td>M0</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>T4b</td>
<td>T4b Tumor invades adjacent structures</td>
</tr>
<tr>
<td>M1</td>
<td>M1 Distant metastasis</td>
</tr>
</tbody>
</table>

Table 1. TNM Classification for Gastric Cancer
A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified T4. The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

A intramural extension to the duodenum or esophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.

◊ A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.


Table 2. Anatomic stage/prognostic groups

<table>
<thead>
<tr>
<th>Criteria</th>
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1. High probability of en bloc resection

2. Tumor histology:
   a. Intestinal type adenocarcinoma
   b. Tumor confined to the mucosa
   c. Absence of venous or lymphatic invasion

3. Tumor size and morphology:
   a. Less than 20 mm in diameter, without ulceration
   b. Less than 10 mm in diameter if Paris classification IIb or IIc

(Extended criteria)

4. Mucosal tumors of any size without ulceration

5. Mucosal tumors less than 30 mm with ulceration

6. Submucosal tumors less than 30 mm confined to the upper 0.5 mm of the submucosa without lymphovascular invasion

Table 3. The criteria for EMR/ESD
2.15. Spread

GC initially infiltrates the submucosa and invades through the muscle wall into the fat of the omentum. Transcoelomic spread of the tumor cells is possible through peritoneal fluid when serosa is involved. Such metastases may involve to rectovesical pouch or ovary (Krukenberg tumor). Microscopic satellite nodules may be formed some distance away from the main mass by involvement through submucosal lymphatics. Lymphatic spread is responsible for the involvement of the nodes around the stomach. Also, when tumor spreads to involve left supraclavicular nodes, it is known as Virchow’s nodes.

2.16. Clinical features

Most patients, who are diagnosed with GC in the US are in advanced stage III or IV disease at the time of diagnosis. GCs, when surgically curable and superficial, usually produce no symptoms. The clinical manifestations also depend on the anatomical location of the tumor. Large tumors which are present in the fundus and body may simply manifest with occult blood loss. In contrast, tumors of the antrum will delay gastric emptying and lead to anorexia, early satiety, and eventually the features of gastric outlet obstruction. Tumors of the proximal stomach can also involve the distal esophagus and present with dysphagia. As the cancer becomes more extensive, patients might complain of slight upper abdominal distress varying in intensity from a vague, postprandial fullness to a severe, sturdy pain. Symptoms are generally nonspecific and most frequently include abdominal pain, weight loss, nausea, decreased food intake due to anorexia and early satiety. Weight loss consequences from inadequate calorie intake rather than increased catabolism and may be attributable to nausea, anorexia, abdominal pain, early satiety, and dysphagia.

Abdominal pain tends to be epigastric in nature. Dysphagia is a common symptom in cancers involving proximal stomach or at the esophago-gastric junction. Other symptoms include nausea, early satiety, symptoms of gastric outlet obstruction. Occult gastrointestinal bleeding with or without iron deficiency anemia is not uncommon. Postprandial vomiting suggests pyloric obstruction. Nearly 25% of patients have a history of gastric ulcer, stressing the importance of eradication of *H. pylori* infection.

Patients may also present with signs or symptoms of distant metastatic disease. Since GC can spread through lymphatics, the physical examination may reveal a left supraclavicular adenopathy (a Virchow’s node) which is the most common physical examination finding of metastatic disease, a periumbilical nodule (Sister Mary Joseph’s node), or a left axillary node (Irish node). Peritoneal spread can present with an enlarged ovary (Krukenberg’s tumor) or a mass in the cul-de-sac on rectal examination (Blumer’s shelf). Ascites can also be the initial indication of peritoneal carcinomatosis. A liver mass that can be palpable may indicate metastases. Paraneoplastic manifestations may include skin findings such as rapid appearance of diffuse seborrheic keratoses (sign of Leser-Trelat) or acanthosis nigricans, which is characterized by velvety and darkly pigmented patches on skin folds. Other signs are: microangiopathic hemolytic anemia, membranous nephropathy, hypercoagulable states (Trousseau’s syndrome) and polyarteritis nodosa.
2.17. Tumor markers and screening

There is no single marker that has been identified as the marker of GC. A study conducted in Japan reported that screening program for GC has limited value. For the same reason, there are no recommendations for screening the cancer. Some of the high risk factors have been identified though. These include elderly patients with atrophic gastritis, pernicious anemia, patients with partial gastrectomy, patients with FAP/HNPCC (familial adenomatous polyposis / hereditary nonpolyposis colorectal cancer), patients with sporadic gastric adenoma. Periodic upper GI endoscopy can be of little benefit to those who are considered to be at risk. Recently, KAI1/CD82 has been researched as a possible marker for the cancer, but results are inconclusive [15]. Annexin II [16] and S100A6 proteins have shown promising results in predicting prognosis as these two proteins are associated with tumor invasion, metastasis, TNM stage and poor prognosis. Similarly PIWI protein and ADAM17 glycoprotein correlate with cancer occurrence, development and metastasis [17, 18].

2.18. Serologic markers

Serum levels of carcinoembryonic antigen (CEA), the glycoprotein CA 125 antigen (CA 125), CA 199, and CA 724 may be elevated in patients with GC [19, 20]. Nevertheless, low rates of sensitivity and specificity stop the use of any of these serologic markers as diagnostic tests for GC. Some GCs may mark elevated serum levels of α-fetoprotein (AFP); which are referred to as α-fetoprotein producing GCs [21-22]. A subset, hepatoid adenocarcinomas of the stomach, has a histologic appearance that is analogous to that of HCC. Regardless of morphology, AFP-producing GCs are aggressive and associated with a poor prognosis.

2.19. Investigations and preoperative evaluation

- Patients >45 years of age who have new-onset dyspepsia, as well as all patients with heart burn and alarm symptoms (dysphagia, weight loss, recurrent vomiting, evidence of bleeding, or anemia) or with a family history of GC should have timely upper endoscopy and biopsy if a mucosal lesion is noted by endoscope.

- All patients in whom GC is one of the differential diagnoses should undergo endoscopic and biopsy procedures. If the biopsy is negative and suspicion for cancer is high, the patient should be re-endoscoped and more aggressively biopsied.

- In some patients with gastric tumors, upper GI series can be useful in planning treatment. Although a good double-contrast barium upper GI examination is sensitive for gastric tumors (up to 75% sensitive), endoscopy has become the gold standard for the diagnosis of gastric malignancy.

2.20. Endoscopy

Tissue identification and anatomic localization of the primary tumor are best accomplished by upper gastrointestinal endoscopy. The early usage of upper endoscopy in patients presenting with gastrointestinal complaints may be related with a higher rate of finding of early GCs. En-
doscopy allows a close inspection of the mucosa, which is generally the only way to detect early GC. The presence of dysplasia, however, should always be regarded as significant because it could be a sign of malignant transformation, or presence of adjacent malignancy.

The diagnosis of a particularly aggressive form of diffuse-type GC, called "linitis plastica", can be cumbersome with endoscopy owing to the nature of these tumors to infiltrate into the submucosa and muscularis propria, and hence, biopsies of superficial mucosal may be false negative. For this reason, a combination of strip and bite biopsy technique should be used when there is a suspicion of diffuse type GC.

2.21. Ultrasonography

Ultrasonography of the abdomen may be helpful for assessing the spread of GC. It may detect evidence of lymphadenopathy but can be particularly precious in detecting metastases within the liver. A number of studies advocate that endoscopic ultrasound has an accuracy of 90% in defining the depth of invasion within the stomach itself. It is also sensitive to wall thickening and will detect diffuse carcinomas, and carcinomas associated with peripheral lymph nodes.

2.22. Barium studies

Barium studies can make out both malignant gastric ulcers and infiltrating lesions. However, false-negative barium studies can occur in as many as 50% of cases. Thus, in most settings, upper endoscopy is the chosen initial diagnostic test for patients in whom GC is suspected.

The only scenario where barium study may be superior to upper endoscopy is in patients with linitis plastica. The decreased distensibility of the stiff, "leather-flask" appearing stomach is more obvious on radiography, while the endoscopic image may appear relatively normal.

2.23. Positron emission tomography scanning

Whole-body PET scanning uses a principle whereby tumor cells preferentially amass positron-emitting $^{18}$F-fluorodeoxyglucose. This modality is most helpful in the evaluation of distant metastasis in GC but can also useful in loco-regional staging. PET scan is most useful when combined with spiral CT (PET-CT) and should be considered before major surgery in patients with predominantly high-risk tumors or multiple medical co morbidities.

2.24. Abdominopelvic CT scan

Dynamic computerized tomography (CT) imaging is generally performed early during preoperative assessment after a diagnosis of GC is made. CT is widely available and noninvasive. It is best suited in evaluating widely metastasized disease, especially hepatic or adnexal metastases, ascites, or distant nodal spread. Patients who have CT-defined visceral metastatic disease can evade unnecessary surgery, although biopsy confirmation is recommended because of the risk of false-positive findings. Peritoneal metastases and hematoge-
nous metastases smaller than 5 mm are often missed by CT, even using modern CT techniques [23].

2.25. Endoscopic ultrasonography [24-27]
Endoscopic ultrasonography (EUS) is considered to be the most reliable nonsurgical method available for evaluating the depth of invasion of primary gastric cancers, particularly for early (T1) lesions. The precision of EUS for differentiation of individual tumor stages (T1 to T4) ranges from 77 to 93%, with the experience of the operator markedly influencing these rates.

2.26. PET scan
The role of positron emission tomography (PET) using 18-fluorodeoxyglucose (FDG) in preoperative staging of GC is rapidly developing. From the standpoint of loco-regional staging, integrated PET/CT imaging may assist in the confirmation of CT-detected malignant lymphadenopathy [28]. The main advantage of PET is that it is more sensitive than CT for the detection of distant metastases [29, 30]. An important caution is that the sensitivity of PET scanning for peritoneal carcinomatosis is only approximately 50% [31]. Thus, PET is not a satisfactory replacement for staging laparoscopy.

2.27. Chest imaging
A preoperative chest x-ray is recommended in patients with GC [32]. However, the sensitivity for metastases is limited, and a chest CT scan is preferred (particularly for patients with a proximal GC) if the detection of intrathoracic disease would modify the treatment plan.

2.28. Staging laparoscopy
Laparoscopy, while more invasive than CT or EUS, has the advantage of directly visualizing the liver surface, the peritoneum, and local lymph nodes. Between 20 and 30 percent of patients who have disease that is beyond T1 stage on EUS will be found to have peritoneal metastases in spite of having a negative CT scan [34]. Particularly among patients with advanced (T3 or 4) primary tumors, performance of a diagnostic laparoscopy may alter management (typically by avoiding an unnecessary laparotomy) in up to one-half [35]. As noted previously, the sensitivity of PET scans for the detection of peritoneal carcinomatosis is only about 50%. Another advantage to laparoscopy is the chance to perform peritoneal cytology in patients who have no visible evidence of peritoneal spread. In most (but not all) series this is a poor prognostic sign, even in the absence of overt peritoneal dissemination, and predicts for early peritoneal relapse. Diagnostic laparoscopy should also be performed in patients who are being considered for neoadjuvant therapy.

2.29. Preoperative evaluation
The rationale of the preoperative evaluation is to primarily stratify patients into two clinical groups: those with loco-regional, potentially resectable (stage I to III) disease and those with systemic (stage IV) involvement.
2.30. Treatment (EGC)

Treatment options available for early GC (EGC) are endoscopic resection, gastrectomy, antibiotic therapy to eradicate *H. pylori* and adjuvant therapies. Endoscopic resection is achieved either by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). The criteria for EMR or ESD are outlined in the table: 2 [36, 37]:

Even though *en bloc* resection of the tumor mass has the ideal outcome following mucosal resection, when it fails gastrectomy is the option. Gastrectomy is the most widely practiced treatment modality for GC with a very high five-year survival rates [39-44]. Recently laparoscopic gastrectomy is gaining popularity with high success rates observed in several centers [40, 41, 45-50].

*Anti-*H.*pylori* therapy: As noted above, *H. pylori* is declared as a definite carcinogen. Its occurrence is associated with cancer recurrence necessitating its eradication [51]. According to a randomized trial and a case series, eradication of *H. pylori* following endoscopic resection of EGC is found to be associated with reduced risk of metachronous cancers [52].

*Adjuvant therapy:* The adjuvant therapy with either systemic chemotherapy, radiotherapy, or intraperitoneal chemotherapy following treatment for EGC is not completely established especially for patients with node-negative cancer. On the other hand, for all patients with positive nodes, adjuvant therapy is recommended irrespective of T stage.

2.31. Treatment of invasive GC

The only curative treatment for GC is surgical excision of tumorous mass [53, 54]. Usually abdominal exploration is considered with the curative intent unless there is doubt regarding dissemination, vascular invasion, patient has a medical contraindication for surgery, or a neoadjuvant therapy is considered.

*Linitis plastica:* In ~5 percent of GC, most of the stomach wall or sometimes the entire stomach wall is infiltrated by malignancy resulting in a rigid thickened wall called linitis plastica. It is more prevalent in younger population [55]. Sometimes this form of cancer represents spread from lobular breast cancer, and is associated with poor prognosis [56, 57]. As there will be nodal involvement frequently, complete excision is the goal even though surgeons consider it to be a contraindication to curative resection.

*Total versus subtotal gastrectomy:* Total gastrectomy is in vogue for the treatment of invasive GC, even though endoscopic resection is performed for superficial cancers. To note, total gastrectomy is indicated for lesions in the proximal (i.e. upper third) of the stomach, and distal lesions (lower two-thirds) require subtotal gastrectomy with resection of adjacent lymph nodes. Importantly, the patients presenting with large mid gastric or infiltrative lesions like linitis plastica require total gastrectomy.

*Proximal and esophagogastric junction tumors:* The precise guidelines for surgical excision of proximal tumors are complex. Those tumors that do not invade the esophagogastric junction (EGJ) are managed by either a total or a proximal subtotal gastrectomy. Most surgeons prefer total gastrectomy for the following reasons: 1. The incidence of reflux esophagitis is ex-
Extremely low following Roux-en-Y reconstruction performed during total gastrectomy compared to those who have undergone proximal subtotal gastrectomy in whom roughly one third patients had reflux esophagitis. 2. It is highly unlikely to remove the lymph nodes along the lesser curvature following proximal subtotal gastrectomy. This may make the metastases escape from surgery.

Degree of lymph node dissection: Again this is the controversial area in the surgical management of GC. Japanese surgeons routinely perform extended lymphadenectomy, which may partially account for the better survival rates among Asian series as compared to Western series [58]. ‘Extended lymphadenectomy’ refers to either a D2 or D3 nodal dissection.

D1, D2, and D3 terminologies: Japanese surgeons have divided the draining lymph nodes of stomach into 16 stations: stations 1-6 are perigastric, remaining 10 are located side by the major vessels, posterior to pancreas and along the aorta. D1 lymphadenectomy involves limited dissection of only the perigastric lymph nodes. D2 lymphadenectomy involves extended lymph node dissection encompassing removal of nodes along the hepatic, left gastric, celiac and splenic arteries and splenic hilum (stations 1 to 11). D3 lymphadenectomy involves super extended lymph node dissection. In short it is the D2 lymphadenectomy along with resection of nodes within portahepatis and periaortic regions (referred to as stations 1 to 16). Others use the term to denote a D2 dissection plus periaortic nodal dissection (PAND) [59].

Factors in favor of extended lymphadenectomy are, removing more number of nodes accurately stages the disease extent and failure to remove these nodes leaves behind the disease in nearly one third of patients [60]. This would explain the better stage specific survival rates in Asian patients.

Factors against the extended lymphadenectomy are, higher incidence of associated morbidity and mortality especially if splenectomy if done so as to achieve extended lymphadenectomy. Also, most of the randomized trials have shown low survival benefits which discourage surgeons to go for extended lymphadenectomy.

In summary, considering the impact of D2 lymphadenectomy on disease specific survival, most of the cancer hospitals perform D2 as compared to D1 dissection. National Comprehensive Cancer Network has published its treatment guidelines, according to which D2 node dissection is better than D1 dissection. Considering the higher rates of operative mortality in randomized trials, the choice of surgery is at the discretion of the surgeon. D2 lymphadenectomy that preserves pancreas and spleen provides superior staging benefit at the same time avoiding excess morbidity. If splenectomy performed during resection of gastric tumors not adjacent to or invading the spleen or the pancreatic tail will increase the morbidity and mortality without improving the survival [61]. Hence splenectomy is not recommendable unless the tumor has extended directly.

2.32. Adjuvant chemoradiotherapy

It is apt to consider adjuvant radiation therapy as nearly 80 percent of patients who succumb to GC would have experienced local recurrence. Also, three randomized trials (Inter-
group 0116, CALGB 80101 and ARTIST trials) have shown significant survival benefit for postoperative combined chemoradiation therapy compared to surgery alone following resection of GC [63].

Neoadjuvant/Perioperative chemotherapy: prior to operating for a locally advanced malignancy, neoadjuvant therapy if used will help to 'downstage' the disease process. Two of the three large trials (MAGIC, French FNLCC/FFCD, EORTC trial 40954) compared surgery alone and surgery with neoadjuvant chemotherapy showed a significant survival benefit for this approach [62, 64, 65].

2.33. Adjuvant chemotherapy

There are more than 30 trials which compared adjuvant systemic chemotherapy to surgery alone. The overall results were negative. Few of the trials to name are Japanese S-1 trial, CLASSIC trial.

2.34. Prognosis

Unless treatment is instituted, the doubling time for EGC is of the order of several years indicating a very stable biologic state compared to a doubling time of less than a year for advanced cancer [66]. A very interesting Nomogram has been developed based on various clinical and pathological statuses by Kim’s group for predicting the disease-free survival probability [67]. With the treatment on, the overall five year survival rate is more than 90 percent [68]. According to a Korean study, long term survival rate was 95 percent in patients without nodal involvement; 88% with one to three nodes involved; 77% with more than 3 nodes involvement.

3. Conclusion

Adenocarcinoma is the commonest type of GC. It is one of the top 10 causes of death in USA, twice more common in blacks. Infection with H.pylori, consumption of salt-preserved and smoked foods, achlorhydric stomach are few of the important insults for the development of GC. E-cadherin, a key protein on the cell surface responsible for intercellular connections, is absent in diffuse type of carcinoma enabling tumor cells to invade and metastasize. TNM staging is the most widely used system for staging the disease. As there are no screening tests available for diagnosis of GC, patients usually present in the stage 3 or 4 cancer. Early Gastric Cancer is treated with Endoscopic resection, gastrectomy, antibiotic therapy to eradicate H.pylori and adjuvant therapies. Surgery is the mainstay of treatment for invasive GC. Adjuvant chemoradiotherapy is essential as 80% treated cases develop local recurrence. With the treatment being initiated the prognosis is better as the overall five year survival rate becomes more than 90 percent.
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References


