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Gastric Cancer: Clinical Features, Screening, Diagnosis, Treatment, and Prevention

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Abstract

The objective of this article is to highlight the clinical features, screening, diagnosis, treatment, and prevention of gastric cancer (GC). Early GC is often asymptomatic leading to frequent delays in diagnosis. Weight loss and persistent abdominal pain are the most common symptoms at initial diagnosis. The diagnosis of GC typically involves a combination of endoscopy, biopsy, and imaging studies. Endoscopic resection techniques are emerging as successful treatment options for early GC. Treatment options for advanced GC include surgery and chemotherapy. The first line chemotherapy for advanced GC consists of doublet therapy with a combination of platinum and fluoropyrimidines. Trastuzumab, a monoclonal antibody, is used in the treatment of human epidermal growth factor 2 positive GCs. Antiangiogenic agents and immunotherapy are also useful in the treatment of GC. Currently there are no GC screening guidelines in the United States, but they exist in other regions where there is increased prevalence of GC. Prevention strategies for GC include *Helicobacter pylori* eradication and adoption of a healthy diet consisting of fruits and vegetables.

Keywords: Gastric cancer, Clinical features of gastric cancer, Diagnosis of gastric cancer, Gastric cancer screening, Treatment of gastric cancer, Gastric cancer prevention, Gastric adenocarcinoma

1. Introduction

Globally, gastric cancer (GC) is the fifth most common cancer and the fourth most common cause of cancer-related mortality.[1] In 2020, the estimated global incidence of GC was 11.1 per 100,000 with an associated mortality of 7.7 per 100,000.[2] Eastern Asian countries, such as Japan, Korea, and China, showed the highest age-standardized incidence rates of GC. In the United States, GC is the fifteenth most common cancer.[3] Risk factors of GC include salt preserved foods, food items containing N-nitroso compounds, tobacco use, alcohol consumption, and infections such as *Helicobacter pylori*. Given the high global rates of incidence and mortality related to GC, the aim of this article will be to highlight the clinical features, screening, diagnosis, treatment, and prevention of GC.

2. Clinical features

Early GC is often asymptomatic leading to delayed presentation and diagnosis. However, weight loss and abdominal pain are the common presenting symptoms. Vague epigastric abdominal pain is a persistent complaint in early disease and the frequency and severity of pain worsens with disease progression. Weight loss can be due to decreased oral intake secondary to anorexia, abdominal pain, or early satiety, as well as increased metabolic demands and inflammatory responses. Additional symptoms include nausea, vomiting,

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anorexia, dysphagia, melena, and early satiety. Less than 20 % of cases present with overt gastrointestinal bleeding in the form of melena or hematemesis.[4] However, patients may present with symptoms of symptomatic anemia due to slow bleeding from the gastric malignancy. Advanced GC can promote a hypercoagulable state and give rise to venous thromboembolism.

Physical exam is often unremarkable in early stages of GC, but the most common findings are cachexia and signs of bowel obstruction. Often a palpable mass is not appreciated on exam but the patient may experience epigastric pain. Patients may present with hepatomegaly, jaundice and ascites as the liver is the most common site of metastasis. Associated elevations in liver enzymes would also be seen, particularly alkaline phosphatase. Patients with lymphatic involvement can have periumbilical nodules (Sister Mary Joseph's node), enlargement of the left supraclavicular lymph nodes (Virchow's node) and left axillary lymph nodes (Irish node).[5,6] Additionally in the presence of metastasis one could appreciate left ovarian enlargement suggesting Krukenberg tumor or cul-de-sac mass on rectal exam (Blumer's shelf).[7,8] GC causing obstruction at the esophagogastric junction can mimic manometry findings of achalasia. This phenomenon is called pseudo-achalasia and endoscopy findings can be used to distinguish it from achalasia.[9] In rare cases, patients can present with linitis plastica, a condition in which diffuse gastric tumor burden results in poor wall distensibility.

Although relatively rare, paraneoplastic syndromes can present in some cases of GC. This may present as disseminated intravascular coagulation, polyarteritis nodosa, microangiopathic hemolytic anemia, Trousseau's syndrome, and membranous nephropathy.[10-13] Leser-Trélat sign and acanthosis nigricans are the most common dermatological paraneoplastic findings. Leser-Trelat sign involves a sudden outbreak of multiple seborrheic keratoses. There are no standardized diagnostic criteria; it's colloquially defined by an increase in the number/size of these keratoses.[14] Acanthosis nigricans is characterized by thickened, darkened skin or mucous membranes. It often affects skin fold such as in the back of the neck, and is characterized by velvety, brownish-black, hyperkeratotic plaques.[15]

3. Screening

Routine screening for GC is not performed in the United States (US) due to the overall lower incidence of GC in the US population. Current screening modalities are labor-intensive and not cost-effective in areas with low incidence of GC. While mass screening has been recommended for certain populations in geographic areas associated with a high risk of developing GC, this remains a controversial topic. Given that the incidence of GC varies in different geographic regions, each region might be served by specific surveillance strategies that are based on studies of populations at risk. For example, in Japan population-based screening consisting of radiographic and endoscopic methods are recommended for individuals aged 50 and older.[16] Double contrast barium swallow is the preferred radiographic method for GC screening as it is cost-effective and has shown to reduce GC related mortality in the Japanese population.[17] However, studies have shown that endoscopic screening can reduce GC mortality by 67 % compared with radiographic screening and is now being recommended in conjunction with radiography.[18] The British Society of Gastroenterology suggests endoscopic screening to be considered in individuals aged ≥50 years with multiple risk factors for gastric adenocarcinoma such as male, smokers, pernicious anemia and in those with a first-degree relative with GC.[19]

Given these variations in the current evidence, Kim et al. proposed the use of the following algorithm.[20] Patients who are first or second-generation immigrants from regions with a high incidence of GC (such as East Asia, Russia, or South America) or with family history of GC should undergo screening esophagogastroduodenoscopy (EGD) at the age of 50. Further endoscopic surveillance is recommended based on initial EGD findings as detailed below:

1. Individuals without family history of GC and negative for intestinal metaplasia (IM) and *H. pylori* (Hp) infection: no follow up
2. Individuals without family history of GC, who test positive for Hp but negative for IM, should receive Hp eradication therapy with repeat EGD in 3–5 years. If no IM is detected in the repeat EGD, no further follow-up is required whereas if the patient has IM, surveillance EGD every 1–2 years is recommended.
3. Individuals with positive family history of GC or IM, should undergo Hp eradication therapy if Hp positive, followed by surveillance EGD every 1–2 years.

Additional prospective studies will be needed to generate definitive guidelines for GC screening in the US.

4. Diagnosis

When GC is suspected, EGD with biopsy is the procedure of choice for diagnosis due to the high sensitivity and specificity. EGD allows direct visualization of the neoplasia, assessment of the extent of mucosal involvement, and biopsy of suspicious lesions. A single biopsy is about 70 % accurate in diagnosing GC, but when 7 biopsies are performed the sensitivity increases to 99 %.[21] Therefore, for a malignant appearing ulcer, at least 7 biopsies of the heaped-up edges and base is recommended.[22] If there is high suspicion of gastric malignancy and the first endoscopy does not confirm the diagnosis, endoscopy should be repeated.

The Paris classification uses morphologic appearance to classify superficial gastric lesions into type 0-I (elevated or polypoid), type 0-II (flat or superficial) and type 0-III (excavated).[23] This classification system is most helpful in assessing the endoscopic resectability of a lesion. Early GC is limited to the mucosa and submucosa and is amenable to endoscopic resection. Early GC carries a more favorable prognosis compared to advanced GC due to low risk of lymph node metastasis and potential for early resection.[24] The Borrmann classification uses gross macroscopic appearance to classify GCs into four subgroups: polypoid (type I), fungating (type II), ulcerating (type III), and diffusely infiltrating carcinoma (type IV). This classification system has been shown to predict prognosis in advanced GCs and help guide treatment strategy.[25]

Techniques such as chromoendoscopy, magnification endoscopy, and narrow band imaging (NBI) can be utilized to provide more detail to suspicious lesions. Chromoendoscopy is an endoscopic technique in which stains like Indigo Carmine are used to highlight the mucosal architecture and improve the detection of early GCs and premalignant lesions compared to standard white light endoscopy.[26] Magnification endoscopy includes an adjusting focusing mechanism that allows the endoscopist to enlarge the image to view lesions in more detail. NBI is a technique that uses filtered light with wavelengths 415 ± 30 nm (blue) and 540 ± 30 nm (green). Peak light absorption of hemoglobin at these wavelengths highlights the mucosal vascular patterns. Studies have shown that combining NBI and magnification endoscopy with white light endoscopy can increase both sensitivity and specificity of GC diagnosis.[27-29]

Brush cytology is another diagnostic technique in which nylon fiber bristles are rubbed against the mucosal surface of a suspicious lesion to collect samples for cytopathology analysis. GCs infiltrate the submucosa and deeper layers. Hence, brush cytology may be inadequate as it only assesses the mucosal surface layer. When used alone, brush cytology has been shown to be inferior to endoscopic biopsy, however, several studies have shown that the combination of biopsy and brush cytology increases diagnostic accuracy.[30,31]

Endoscopic ultrasonography (EUS) can be used to assess depth of tumor invasion and presence of perigastric lymph nodes and is a valuable tool in the diagnosis and staging of GC.[32] The accuracy of EUS guided T-staging ranges from 60 % to 90 % whereas N-staging is not as accurate.[33] Further staging will always require radiographic imaging as EUS cannot evaluate the presence and extent of metastasis. Additionally, EUS with fine needle aspiration or core needle biopsy can aid in cytopathological analysis of suspicious lesions as well as help with staging through evaluation of lymph nodes.

Radiologic examination can also be helpful in diagnosis of GC. Double contrast barium studies can assist in identifying lesions and determining whether they have features that warrant endoscopic evaluation. The primary advantages to this study are that it is relatively cost effective to EGD and is noninvasive. Barium swallow can help demonstrate ulceration and invasion into the gastric wall and surrounding tissue and organs, but even in the presence of these features one will still require EGD for diagnosis. Evaluation with computed tomography (CT) can help visualize primary tumors but is more frequently used for GC staging by estimating the extent of tumor invasion and identifying local and distant metastasis. MRI may also be used, but CT is the most frequently used modality for staging GCs.[34] Some studies have shown that CT gastrography may aid in early diagnosis of GC with sensitivity of 73 %–76 % but cannot yet be recommended as a screening tool.[35] 2-Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography - computed tomography (PET-CT) can detect distant metastases involving the skeleton, liver, lungs, adrenals, and ovaries.[36] However, FDG-PET is not routinely recommended for staging of GC as the determination of FDG avidity of diffuse-type GC is challenging.[37]

There are currently no serum markers that show high sensitivity and specificity for GC diagnosis. Studies have shown that tumor markers such as carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9), cancer antigen 242 (CA 242), cancer antigen 72-4 (CA 72-4), and alpha-fetoprotein (AFP) may correlate with the tumor, node, metastasis (TNM) staging but do not have high sensitivity to aid in diagnosis.[38] Specifically, CEA and CA 19-9 have

shown to be more useful in monitoring recurrence of GC in patients with high preoperative levels of the markers.[39] Pepsinogen is being studied as a marker for GC screening. The inflamed gastric mucosa in the setting of Hp infection causes an elevation in serum pepsinogen I and II levels but decreases the ratio of pepsinogen I to pepsinogen II (due to a relatively higher elevation in pepsinogen II). The progression from normal gastric mucosa to atrophic gastritis closely correlates with the stepwise reduction in the ratio of pepsinogen I to pepsinogen II.[40]

5. Treatment

The primary curative treatment of GC is surgical resection. The 5-year survival rates of GC in the US from 2010 to 2016 were 70 %, 32 %, and 6 % in the setting of localized disease, regional and distant metastasis respectively.[41] Chemotherapy is a valuable aid to surgery in the neoadjuvant, perioperative, and postoperative roles. Palliative treatment options should be considered in addition to chemotherapy to alleviate symptoms in patients who are not candidates for curative treatment.

Endoscopic techniques are emerging as a successful treatment option for early GC with low risk for lymph node metastasis. The two endoscopic techniques are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). During EMR, a lifting solution is injected into the submucosal space to separate the mucosa from the muscularis propria for removal of the lesion while minimizing injury to the deeper layers. ESD involves the use of an electrocautery knife to dissect through the submucosa to allow en-bloc removal of a relatively larger lesion compared to an EMR. ESD has shown an improved histologically complete resection rate and lower local recurrence compared to EMR, however, has a higher rate of perforation.[42] In 2015, 90 % of endoscopic resection for early GC in Japan was performed via ESD, widely replacing EMR.[43] Currently in the United States, ESD is considered superior to EMR for resecting lesions larger than 1 cm and is considered first line therapy for visible endoscopically resectable superficial gastric neoplasia. According to the American Gastroenterological Association (AGA), the absolute indications for ESD include well differentiated or moderately differentiated adenocarcinoma $\leq$2 cm in size without ulceration.[44] Even though ESD allows resection of larger lesions, there is a notable increase in lymph node metastasis with malignant lesions $\geq$4 cm.[45] Therefore, endoscopic resection should only be performed only when the likelihood of lymph node metastasis is extremely low.

Surgery is indicated for curative treatment of localized disease and potentially palliative treatment in advanced and metastatic disease. Surgery should be attempted for treatment of GC unless the malignancy is unresectable due to distant metastasis, major vascular invasion, linitis plastica, or severe comorbid illness that contraindicates surgery.[46,47] Total gastrectomy is typically reserved for lesions in the upper third of the stomach and the diffuse type of GC. Proximal tumors of the stomach have higher rates of recurrence with partial gastrectomy as opposed to total gastrectomy due to preserved lymph nodes along the lesser curvature of the stomach.[48] Partial gastrectomy can be considered for lesions in the distal two thirds of the stomach.[49] When comparing partial and total gastrectomy there is no difference in 5-year survival rates, however, quality of life after partial gastrectomy has shown to be superior to total gastrectomy.[49,50]

Lymph node dissection is classified into D1 (perigastric lymph nodes), D2 (D1 and celiac nodes), and D3 (D2 and paraaortic lymph nodes).[51] D3 is not typically performed as it has been shown that there was no benefit when compared to D2 resection.[52] When positive nodes are found beyond the boundaries of a D2 resection, long term survival is very poor suggesting that it has advanced to a more systemic disease.[53] It has been heavily debated on whether D1 or D2 is more appropriate. The Japanese consensus is that D2 resection is more appropriate and has shown overall improved survival rates. One British study that compared D1 and D2 lymphadenectomy showed no significant difference in overall survival at 5 years and showed a significantly higher in hospital mortality in the D2 arm.[54] In addition, a Dutch study reported no significant difference in overall survival and posted a higher rate of complication and postoperative death following D2 resection.[55] However, after a mean 15-year follow, D2 resection was associated with lower locoregional recurrence and GC related deaths.[56] Most recent consensus opinion in Western countries now recommends D2 resection that is carried out in specialized high volume surgical centers.[57]

Neoadjuvant chemotherapy has shown a clear benefit in patients with locally advanced GC planned for resection. The MAGIC trial performed in the UK looked at patients with gastric, gastroesophageal, or distal esophageal cancer and then compared surgery alone to surgery following neoadjuvant chemotherapy. In patients with stage 2 and 3 GCs that were treated with six cycles of ECF (epirubicin, cisplatin and 5-fluorouracil), there was an improvement in the 5-year overall survival rate from 23 % to 36 %.[58] In addition, following chemotherapy the

resected tumors were significantly smaller and less advanced in the neoadjuvant group. The ECF regimen was recently compared to the FLOT regimen (fluorouracil, leucovorin, oxaliplatin, and docetaxel). FLOT was associated with a greater median overall survival and three-year overall survival.[59] However, it was associated with higher rates of complications such as diarrhea, neutropenia, infections, and neuropathy. Despite the adverse effects, FLOT is the recommended chemotherapy regimen in patients without significant comorbidity with locally advanced GC.

For patients who have undergone curative gastrectomy without neoadjuvant therapy, adjuvant therapy is recommended versus surgery alone. However, the PRODIGY trial showed that neoadjuvant therapy may be of benefit in comparison to adjuvant therapy. In this study, the neoadjuvant arm showed an increased three-year progression-free survival (66 versus 60 %, HR 0.70, 95 % CI 0.52–0.95) but no overall survival benefit.[60] S-1 (a combination of tegafur, gimeracil, and oteracil) monotherapy is a proven regimen after curative surgery with D2 lymphadenectomy. Five-year overall survival was significantly better with S-1 for one year when compared to surgery alone.[61] Combined therapy with S-1 and docetaxel may provide better outcomes than S-1 alone but are associated with more frequent adverse events.[62] As of now, current guidelines do not recommend the addition of radiotherapy to adjuvant or neoadjuvant chemotherapy.

When patients present in the unresectable stage, treatment goals are symptomatic relief, improving quality of life and survival. Chemotherapy should be offered to patients who have good functional status. It has shown to be effective in increasing overall survival when compared to supportive care alone, showing an increase in median survival from 4 months to 11 months.[63] In addition, initiation of chemotherapy in unresectable disease has shown to have an improved or prolonged high quality of life for a minimum of 4 months when compared to supportive care alone.[64] It has also displayed the ability to decrease the size of the tumor to allow curative surgery.[65]

First line chemotherapy consists of doublet therapy with a combination of platinum and fluoropyrimidines.[57] Cisplatin and oxaliplatin may both be used but differ in side effect profiles. The addition of docetaxel to the 5-fluorouracil and cisplatin doublet was associated with higher overall survival, however, combination therapy adds significant toxic effects including febrile neutropenia.[66] The UK REAL-2 trial revealed that the EOX regimen (epirubicin, oxaliplatin, and capecitabine) was found to be non-inferior to cisplatin-based therapy and demonstrated longer median overall survival (11.2 versus 9.9 months).[67] In addition, this regimen had fewer side effects and greater ease of administration. In patients with previously treated GC, second line chemotherapy typically includes taxane or irinotecan.[68] Although there is an increase in overall survival, the increase is minimal, and the benefit is questionable. Hence, treatment should be tailored to the patient taking into account response to first line chemotherapy.

Trastuzumab, a monoclonal antibody which binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER-2), has been showing promise in the treatment of HER-2 positive GC. Increased expression of the HER-2 oncogene is relatively common among GCs and is associated with poor outcomes and more aggressive disease.[69] In the ToGA (Trastuzumab for Gastric Cancer) study, patients were treated with trastuzumab in addition to cisplatin and fluoropyrimidine. This resulted in a median overall survival of 13.8 versus 11.1 months in those treated with cisplatin and fluoropyrimidine alone.[70] As a result, it is recommended that HER-2 tumor testing should be performed for all patients with advanced GC and if positive should be offered combination chemotherapy and an HER-2 targeted agent.[71]

Newer therapies are now being used as second line agents that include anti-angiogenic agents and immunotherapy. Ramucirumab is an anti-vascular endothelial growth factor 2 receptor antibody that can be used alone or in addition to paclitaxel for previously treated advanced GC. Programmed cell death inhibitors (PD-1) such as pembrolizumab and nivolumab have also shown evidence of increased overall survival in patients with chemo-refractory GC. Response to this therapy measured by CT scan proves to be higher in patients with mismatch repair deficiency or microsatellite instability.[72]

6. Prevention

Consumption of fruits and vegetables has a significant impact in reducing the risk of developing GC. Larsson et al. conducted a prospective study in Sweden for 7.2 years which found an inverse association between vegetable consumption and risk of GC, while no significant association was observed for fruit consumption.[73] However, a meta-analysis published by Wang et al. revealed that consumption of fruits (but not vegetables) had a significant impact on reducing the risk of developing GC (fruits: standardized rate ratio [SRR], 0.90; 95 % CI, 0.83–0.98; heterogeneity, 0.450; vegetables: SRR, 0.96; 95 % CI,

0.88–1.06, heterogeneity, 0.150).[74] Results from a recent meta-analysis by Ferro et al. 2020 revealed a significant reduction in the risk of developing GC associated with consumption of approximately six portions of citrus and non-citrus fruits and 10 portions of vegetables per day (fruits: OR, 0.76; 95 % CI, 0.64–0.90; I^2, 59.7 %; vegetables: OR, 0.68; 95 % CI, 0.56–0.84, I^2, 74.5 %; fruits and vegetables: OR, 0.61; 95 % CI, 0.49–0.75; I^2, 75.5 %).[75] Consumption of more vegetables was also associated with a significant reduction in the risk of developing cardia compared to non-cardia GC. Collectively, most of the evidence collected suggests that consumption of fruits and vegetables has a significant role in reducing the risk of developing GC.

The use of non-steroidal anti-inflammatory medications (NSAIDs) has been shown to decrease the risk of developing GC. NSAIDs may be protective via their capacity to inhibit the cyclooxygenase (COX) pathway. Cheng et al. reported increased expression of COX cells in gastric adenocarcinoma compared to normal mucosal cells.[76] A 2009 meta-analysis that evaluated the outcomes of aspirin and non-aspirin NSAID use on the risk of developing both cardia and non-cardia GC revealed that the risk of non-cardia GC decreased with the use of aspirin ($p = 0.0032$). Similar findings were obtained for those using non-aspirin NSAIDs, although the results were only borderline significant ($p = 0.050$). However, the risk of developing GC was reduced in the group who used both aspirin and nonaspirin NSAIDs when compared to non-users.[77] A similar meta-analysis published by Tian et al. reported similar results and confirmed that NSAIDs are associated with a decreased risk of developing GC.[78] Additionally, reproductive hormones in women provided protection and reduced the risk of developing GC.[79]

Early diagnosis of Hp and use of appropriate eradication therapy is imperative in the prevention of GC. Hp infection is the strongest known risk factor for development of GC and has been recognized as a class 1 carcinogen.[80] GC predominantly develops in patients infected with Hp and specifically affects those with features such as gastric atrophy, corpus-predominant gastritis, or IM.[81] It is thought that Hp infection triggers a cascade of chronic inflammation that ultimately leads to gastric atrophy predisposing an individual to develop adenocarcinoma. The risk is thought to be increased based on the extent of mucosal damage and atrophy. Several studies have shown the reduced incidence of GC with the eradication of Hp in infected individuals without premalignant lesions.[82,83] The Taipei global consensus concluded that eradication therapy should be offered to all individuals infected with Hp to prevent GC.[84] They additionally recommended that vulnerable subjects should be tested and mass screening and eradication of Hp should be considered in populations at higher risk of GC.

7. Conclusion

The diagnosis of GC often presents a challenge due to its asymptomatic nature in the early stage, leading to delay in diagnosis. Routine screening for GC is not performed in the United States due to low incidence. Diagnosis typically involves endoscopy with biopsy, and assessment of endoscopic resectability. In the early stages, GC can be treated by endoscopic resection techniques, while advanced cases are managed by surgical resection, and chemotherapy. In addition to *H. pylori* eradication, NSAID use and consumption of fruits and vegetables are showing promise in GC prevention. Further research is essential to aid timely diagnosis, and to refine treatment of GC and preventive measures.

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