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Review Article

Gastric Cancer Screening; Current Modalities and Strategies

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Abstract

Gastric cancer is one of the most common cancers worldwide being the 5th most common cancer and the 4th leading cause of cancer death. The most common type of gastric cancer is adenocarcinoma and is divided into two types; cardia and non-cardia gastric cancer. The incidence of non-cardia gastric cancer is declining due to the better detection and treatment of H. pylori which is one of its main risk factors. On the other hand, the incidence of the cardia type is rising due to the increase rate of obesity and gastroesophageal reflux disease. Worldwide, mass screening for gastric cancer is not currently implemented due to its variable incidence and cost effectiveness especially in low-risk countries. However, some countries with high incidence of gastric cancer have developed national screening programs which have led to better detection and reduction in mortality. There are different modalities that are approved for screening including upper endoscopy and photofluorography. Additionally, a few serum biomarkers have also been developed for screening which have promising results.

Keywords: Gastric Cancer; Screening, Gastric Cancer Screening; Gastric Cancer Prevention; Universal Screening in Gastric Cancer.

Introduction

Gastric cancer (GC) is one of the most common cancers worldwide. In the year 2020, there were 1,089,103 new cases of GC worldwide, ranking it the 5th cancer (CA) after breast, lung, colorectal and prostate [1]. It was also the 4th leading cause of cancer death after lung, colorectal and liver [1]. In the United States (US), there were 26,259 new cases of GC in 2020 (1.2% of all cancers) with 11,413 deaths (1.9% of all cancer deaths) [2]. The incidence of GC in the US is declining with the age-standardized incidence rate of 5.5 and 3.3 in males and females per 100,000 population in 2016 compared to 9.4 and 7.7 in 1975, respectively [3]. Nevertheless, it continues to be a considerable burden on cancer deaths.

The major type of GC is adenocarcinoma which is subdivided anatomically into cardia and non-cardia subtypes [4]. It is also classified histologically into intestinal and diffuse type. The intestinal type (gland-forming) is characterized by tumour cells that adhere to each other and develops through a cascade of mucosal changes (Correa Cascade) that starts from chronic non-atrophic gastritis and progresses to atrophic gastritis (AG), gastric intestinal metaplasia (GIM) and finally dysplasia and GC [5]. On the other hand, the diffuse type is characterized by Discohesive cells that develop due to loss of adhesion molecules, allowing them to spread and invade without forming glands.

As mentioned previously, the incidence of GC has been declining globally, which is believed to be partly due to better recognition of the predisposing risk factors including Helicobacter pylori (Hp) infection, dietary and environmental factors [6]. This decline is mainly in the distal or non-cardia GC and is probably related to treatment of Hp infection. However, the proximal or

cardia type is slowly rising due to the increasing rates of obesity and gastroesophageal reflux disease which are believed to be contributing factors [6].

There is wide variation in the incidence of GC geographically. High-risk regions include Eastern Asia, Eastern Europe, and South America. On the other hand, the incidence of GC is lower in Northern America and Africa [6]. Despite the low incidence in the US and the overall decline in GC rates, it is important to know that it has a very low 5-year survival rate at 32% [7]. This suggests that most of the cases are likely being diagnosed at an advanced stage resulting in a poor prognosis. Some countries with high incidence rate such as Japan and Korea, have implemented national screening protocols. This has helped in early detection, leading to higher rates of early gastric cancer (EGC) with a more favourable prognosis and lowering the mortality rate with one study from Japan reporting over 50% of resected GC in Japan to be EGC compared to 20% in the US [8].

Given the low incidence of GC in the US, universal screening is not considered cost effective, but screening is recommended in high-risk groups with precancerous lesions [9].

In this review, we present the current modalities available for GC screening and discuss their role in different screening protocols. Furthermore, we review other methods of screening that are being developed and/or studied.

Screening Modalities

A comprehensive online search of PubMed using the keywords "gastric", "cancer", "screening" in different combinations was made. Relevant articles published in English between January 2000 and January 2022 were included.

Radiographic imaging

Photofluorography (upper gastrointestinal series with a barium meal) can be used to screen for GC and may identify lesions at different locations in the stomach with different morphological patterns including polypoid, infiltrative/scirrhous or ulcerative [10]. It was first introduced in Japan in the 1960s as a screening tool for GC but subsequently became part of the national screening program for GC in all adults aged 40 and older in 1983 [11]. Initial data from observational studies reported a sensitivity ranging from 60% to 80% and a specificity of 80% to 90% for detection of GC with a 40% to 60% reduction in GC mortality [11]. More recent studies from South Korea reported a first-round screening sensitivity and specificity of 38.2% and 96% respectively, while a study from Japan reported an incidence screening sensitivity of 0.885 and specificity of 0.891 [12-13]. (Table 1).

Upper endoscopy

Upper endoscopy allows direct visualization of the stomach and the ability to take biopsies for histological evaluation. It was incorporated in South Korea in 1999 as part of the national screening program for GC as an alternative to photofluorography and in 2016 was added to the updated Japanese guidelines for GC screening [14]. Cases-control studies from Japan and South Korea have reported a 30% to 47% reduction in GC mortality by endoscopic screening done at 1 to 4 years interval and specifically in the 40-74 years old age group [15-16]. Endoscopy has a higher sensitivity for GC screening compared to photofluorography with a Korean study showing a first-round screening sensitivity of 69.4% and specificity of 96% [12]. Another study from Japan, showed a first-round screening sensitivity of 0.995 and a specificity of 0.851 [13] see in (Table 1).

Modality	Sensitivity	Specificity	Reference
Photofluorography	38% - 85%	89% - 96%	12, 13
Upper endoscopy	69% - 99%	85% - 99%	12, 13
PGI	55%	79%	30
PGI + PGI: PGII	70%	79%	30
G-17	50%	83%	42
sTims-3 + PGI: PGII	86%	91%	46
TFF3	80% - 81%	43% - 81%	47, 48
TFF3 + PGI + PGI: PGII	87.5% - 90%	36%	48

Table 1: Sensitivity and specificity of GC detection modalities

Endoscopically, gastric atrophy is characterized by loss of gastric rugae, mucosal pallor and increase visibility of the mucosal blood vessels. Moreover, the atrophic border acts as a line that can delineate between atrophic and non-atrophic mucosa. On the other hand, GIM appears as an area of irregular surface with elevated grey-white plaques surrounded by patchy pale and pink mucosa [17]. Several systems have been validated to assess the degree and stage of gastric atrophy and GIM histologically, including the updated Sydney system, Operative Link for Gastritis Assessment (OLGA) and Operative Link on Gastric Intestinal Metaplasia (OLGIM) systems [17-18]. They recommend taking at least five biopsy samples (the lesser and greater curvature of the antrum, incisura angularis and the lesser and greater curvature of the corpus) to allow mapping of the stomach, then the histological changes are arranged into groups of progressively increasing severity and higher risk of GC. Furthermore, endoscopic classification systems have also been developed to assess gastric atrophy and GIM including the Kimura–Takemoto system and the Endoscopic Grading of Gastric Intestinal Metaplasia (EGGIM) score, respectively, with the latter using enhanced endoscopic imaging to assess the degree of GIM [17].

Several studies have reported improved detection of precancerous gastric lesions or EGC with image-enhanced endoscopy (IEE) compared to white light endoscopy (WLE). Chromoendoscopy (CE) using indigo carmine and acetic acid has been shown to be superior to WLE in detection of EGC with a sensitivity of 87.0% vs 56.5%, respectively, as well better ability in horizontal border delineation of differentiated-type EGC (93% vs 47.9%) [19-20]. Narrow band imaging (NBI) has been reported to be superior to WLE in identifying GIM with a recent meta-analysis showing a significantly higher detection rate of GIM (78% vs 38%), however, there was no statistically significant difference between the modalities in detecting dysplasia [21].

Magnifying endoscopy with NBI (M-NBI) can allow visualization of the microanatomy of the gastric mucosa [22]. Blue light crest (BLC) is a bluish-white line that reflects on the crest of the gastric epithelial surface when examined with M-NBI and has been associated with GIM [23]. A meta-analysis evaluating BLE that included 3 studies with 247 patients and 721 lesions showed both a sensitivity and a specificity of 0.90 in diagnosing GIM [23]. Marginal turbid band (MTB) is an enclosing white turbid band on the gastric epithelial surface that is also visualized with M-NBI and has been associated with IM [24]. A prospective study form South Korea evaluating MTB and BLC in GIM reported that both were highly indicative of GIM with MTB likely representing early GIM while BLC appearing with progression and with more severe disease [24].

Additionally, the vessel plus surface (VS) classification system, is based on the microvascular and micro surface patterns of gastric lesions identified on M-NBI and is a well-accepted system to aid in diagnosing superficial (0-II) cancers and the delineation of the margins of EGC [25]. Studies have showed that M-NBI has a higher accuracy and specificity in diagnosing cancer in depressed gastric mucosal lesions less or equal to 10 mm in size compared to conventional WLE (90.4% vs 64.8% and 94.3% vs 67.9%, respectively), and it reached 96.6% accuracy, 95.0% sensitivity, and 96.8% specificity when combined with WLE [26]. M-NBI has also been reported to have a greater sensitivity and reproducibility than CE in the diagnosis of minute gastric lesions equal or less than 5 mm in diameter [27]. Despite the evidence of IEE's usefulness in the detection of GIM and EGC, it is not widely available and requires trained endoscopists to recognize mucosal patterns which can limit its utility.

Serum Pepsinogen test

Pepsinogen (PG) is a precursor of pepsin, synthesized by the gastric mucosa and converted to pepsin by gastric acid which helps in the digestion of protein. It has two isozymes, PGI which is released from the chief cells of the gastric body and fundus and PGII which is released from the entire stomach [28-29]. A low serum PG and low PGI/PGII ratio have been associated with gastric atrophy and GIM which are predictors of GC [30], with the cut offs of PGI <= 70 ng/ml and PGI/PGII ratio <= 3 being associated with increased risk of AG and GC [14]. Initial studies reported a serum PG sensitivity of 40% to 80% in detecting GC, but the specificity was <80% [31]. A meta-analysis and a systematic review of 31 studies including 2,265 AG patients and 1,520 GC patients reported a low PGI sensitivity and specificity of 46% and 93%, respectively in detecting AG and 55% and 79%, respectively, in detecting GC [30]. The combination of PGI and PGI:PGII ratio did slightly better with a sensitivity and specificity of 79% and 89% in AG and 70% and 79% in GC, however, the studies deemed to have high heterogeneity [30].

In 2018, the updated Japanese guidelines did not recommend PGI and PGI/PGII ratio as markers for GC screening due to lack of sufficient evidence [31]. A recent cross-sectional study from China which evaluated asymptomatic patients with different Hp status for AG and GC, found that different cut off values for PGI and PGI/PGII ratio in patients with different Hp status groups better predicted gastric atrophy, severe atrophy and GC compared to using the same cut off for all patients [32]. Nevertheless, several factors can influence the serum concentration of PG in addition to Hp including smoking, alcohol intake and different geographic regions which can be limiting factors to its use [28].

Hp serology

Hp antibody testing as a sole screening tool for GC has low sensitivity and specificity in detecting GC [14]. Some studies have investigated the use of certain Hp virulence factors such as CagA, VacA, GroEL, OMP and HP0305It as markers of high-risk individuals who are at risk of progression of precancerous gastric lesions and development of GC [33-34]. However, larger studies are needed to further explore their potential role in screening for GC.

ABC method

Miki et al, proposed the ABC method to screen for GC risk by combining serum anti-Hp IgG antibody (antibody tier of >10 U/ml defined as a positive results) and the PG method (serum PGI <=70 ng/ml and PGI/PGII ratio <=3 defined as a positive result) and classified subjects into 4 groups: Group A [Hp(−)PG(−)], Group B [Hp(+)PG(−)], Group C [Hp(+)PG(+)], and Group D [Hp(−)PG(+)] [35]. Group A and B were classified as low risk for developing GC and group C and D as high risk, where group A can be excluded from further endoscopic follow up while groups B, C and D will require regular endoscopic follow up every 3 years, 2 years and annually, respectively [35].

Multiple studies have evaluated the ABC method and have shown that there is an increased risk of developing GC as the groups go from A to D [36-39]. Ikeda et al, reported a 20-year prospective study of 2446 subjects who were evaluated by the ABC method

and demonstrated a significant increase in the cumulative incidence of GC in groups B, C and D compared to A [39]. The study also showed a significantly increased multivariable-adjusted risk of GC in Group B with a hazard ratio (HR) 4.08 and a combined HR of 11.1 in Groups C and D. These results remained significant even after adjusting for age, sex, body mass index, smoking status and salt intake [39].

However, there have been some concerns that individuals who have lost their Hp antibody after the infection had been eradicated would be falsely misclassified in group A even though they are at a higher risk of developing GC compared to non-infected individuals [40]. The combined Hp antibody and PG method was not recommended for GC screening in the updated Japanese guidelines in 2018 due to the lack of data on its effect on reduction in GC mortality [31].

Gastrin 17

Gastrin 17 (G-17) is a hormone secreted by the stomach mainly by the gastric antral chief cells and stimulates the parietal cells to secrete gastric acid. In addition, it helps maintaining the growth and proliferation of the gastric mucosa and reflects its functional status [28]. G-17 level can be affected by inflammation and/or atrophy of the gastric mucosa [28]. Some studies have evaluated its role as a marker of gastric malignancy with one study from China reported higher levels of G-17 in GC compared to healthy individuals, however, the sensitivity was low at 50% [41].

G-17 has also been evaluated in combination with other biomarkers as part of a panel [GastroPanel® test: biomarker panel of PGI, PGII, G-17, Hp IgG ELISA] to assess the presence of gastric atrophy and GC [42-43]. A multi-phase study including a cross sectional phase, a prospective follow up phase and a risk prediction model analysis reported that all five biomarkers (especially PGII, PGI/PGII ratio and Hp IgG +] were associated with the presence of precancerous gastric lesions or GC at enrollment [42]. Moreover, the follow up analysis showed that both a low and a high PG-17 levels were associated with a higher risk of developing GC, suggesting a J-shaped association. Finally, in the risk prediction model analysis, combing all five biomarkers lead to improved prediction ability beyond the traditional risk factors of age, sex, smoking, family history of GC, and upper gastrointestinal symptoms for detecting precancerous gastric lesions at enrollment (Improved C-statistic from 0.580 to 0.811, $P<0.001$) [42]. A more recent study from Finland, evaluated the accuracy of the new-generation GastroPanel® test in detecting gastric atrophy in dyspeptic patients and found a 92.4% agreement with histological diagnosis [43].

Other biomarkers

The role of the following biomarkers and tests as potential modalities for GC screening and for detection of GC and its precancerous lesions requires further evaluation in large scale studies.

- Carbohydrate Antigen 72-4 (CA72-4) has been evaluated in combination with PGI, PGI/PGII ratio and G-17 for the detection of EGC and was found to have high sensitivity and specificity with area under the curve (AUC) of 0.883, which was significantly higher than that of any of the biomarkers separately [44].
- T cell immunoglobulin and mucin domain molecule 3 (Tim-3) is a tumour immune checkpoint molecule that is expressed by inflammatory cells and a number of tumour tissues. In GC, Tim-3 expression is upregulated in immune cells which can be reflected by changes in the concentration of its soluble form (sTims-3) that is shed from immune cells [45]. A study from China found that the level of sTims-3 was significantly higher in GC and benign gastric disease compared to healthy controls. Additionally, the combination of sTims-3 and PGI/PGII had a sensitivity of 86.44% and a specificity of 91.78% for the diagnosis of GC [45].
- Serum trefoil factor 3 (TFF3) is a protein expressed by goblet cells in the intestines and in gastric metaplastic tissue. A few studies have evaluated its role in the detection of GC with one study from Japan reported both a sensitivity and specificity of 81% [46]. A more recent study demonstrated a higher sensitivity (87.5%) for detection of EGC when TFF3 was combined with PGI + PGI: PGII [47].
- MicroRNAs are small cellular RNAs that have a role in regulating cell proliferation, differentiation, and invasion. Dysregulation in these RNAs have been implemented in a few cancers including GC [48]. A few studies have evaluated the expression profiles of microRNA and their role in screening for GC as they can be detected peripherally in body fluids [49-50]. A meta-analysis of 107 studies reported a relatively low diagnostic performance of single microRNA for GC with AUC 0.84, while combining multiple-miRNAs assay improved the diagnostic accuracy significantly to 0.92 [49].

Finally, several tests that involve circulating proteins and mutations in cell-free tumour DNA (Cancer SEEK) and cancer-specific methylation patterns (Pan Seer) are currently being investigated in clinical trials as potential screening tools for GC detection [51-52].

Screening Strategies

There has been controversy about implementing universal screening for GC due to its variable incidence worldwide. Some countries with high incidence, such as Japan and South Korea, have implemented national screening programs which have resulted in higher detection of EGC and reduction in mortality from GC

[15-16]. On the other hand, countries with low incidence of GC such has US and Northern Europe, have not implemented such programs due to not being cost effective and only recommended screening in high-risk groups [9]. (Table 2)

The national screening program in Japan currently recommends screening starting at age 50 years with upper endoscopy with repeat testing every 2-3 years [28]. Meanwhile, in South Korea, the national screening program recommends that screening with upper endoscopy to be done at 2 years interval in patients between the age of 40 to 74 years old [28]. The above programs have resulted in a higher proportion of EGC in Japan (50%) and South Korea (46-67%) compared to Europe (15%) in patients who are diagnosed with GC [53]. China has multiple screening programs that target individuals in high-risk rural areas and recommend screening at age 40 to 69 [28]. The British Society of Gastroenterology (BSG) guideline has recommended against the use of non-invasive biomarkers in screening for GC, however, it recommended to consider endoscopic screening for individuals who are 50 years or older with multiple risk factors for GC (male, smokers, pernicious anaemia) especially if there is a family history of a first-degree relative with GC with follow up endoscopy every 3 years if extensive AG or GIM is present [54].

In the US, universal screening is not recommended due to the low incidence of GC with concerns of such program being not cost effective. A few studies have evaluated the cost effectiveness of GC screening [55-56]. Saumoy et al, conducted a decision analytic Markov model to evaluate the cost effectiveness of non-cardia GC screening in the US population and found that upper endoscopy with biopsies initiated at the time of screening colonoscopy followed by continued surveillance only when indicated by the identified pathology was cost effective for non-Hispanic blacks, Hispanics, and Asians, but not for non-Hispanic whites [55]. Furthermore, Shah et al, reported that endoscopic GC screening was cost effective for Asian Americans ages >=50 years with continued surveillance when indicated [56].

In 2020, the American Gastric Association (AGA), released guidelines for the management of incidentally found GIM and recommended a shared decision approach to repeat endoscopy in 1 year for risk stratification in patients with GIM who have 1) high risk of developing GC [extensive and/or incomplete histological type], 2) family history of gastric cancer in a first -degree relative and 3) overall increased risk of GC (racial/ethnic minorities and immigrants from high incidence region) [9].

Conclusion

GC continues to be one of the most common cancers worldwide contributing to a significant number of cancer deaths annually. Its incidence has been declining globally likely due to better detection and management of its risk factors. There has been controversy about universal screening for GC due to the wide geographic variation in its incidence with concerns of cost effectiveness in low-risk regions. Several high-risk regions have implemented national screening programs for GC which have led to increase in EGC detection and decrease in GC mortality. Currently, photofluorography and upper endoscopy are the two main screening modalities with evidence for GC reduction. Additionally, the use of IEE to complement endoscopic evaluation has been shown to be superior to WLE and its use is advised if available by multiple studies. Moreover, a few serum biomarkers and tests have been investigated for GC screening with promising results, however, they are not currently endorsed by the major societies or screening guidelines due to lack of strong evidence. Further studies are needed to evaluate their role as potential markers for GC screening in the future.

Country	Starting Age	Modality	Frequency
Japan	50	Endoscopy	Every 2-3 years
South Korea	40	Endoscopy	Every 2 years
China	40-69 in individuals in high-risk rural areas	Endoscopy	Within 3 years if severe chronic active gastritis, severe GIM and low-grade intraepithelial neoplasia
Britain (BSG)	50 with multiple risk factors*	Endoscopy	Every 3 years if extensive AG or GIM is present
United States (AGA)	Any individual with GIM who is high risk for GC**, or at overall increased risk of GC***	Endoscopy	Within 1 year for risk stratification, then surveillance every 3-5 years based on shared decision-making.
*__Risk factors:__ male, smokers, pernicious anemia, especially if there is a family history of a first-degree relative with GC; **GIM with high risk of GC: Incomplete GIM, extensive GIM and family history of GC; ***__Overall increased risk of GC:__ Racial/ethnic minorities, Immigrants from high incidence regions			

Table 2: GC Screening Protocols

Conflicts

No conflicts of interest or financial interests to disclose.

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