Gastric cancer screening

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INTRODUCTION

Gastric cancer is one of the most common cancers worldwide [1]. However, there are significant differences in the incidence of gastric cancer by region. The value of screening asymptomatic individuals for gastric cancer is controversial even in areas with a relatively high incidence of gastric cancer [2]. This topic will review the screening of gastric cancer. The epidemiology, risk factors, pathology, pathogenesis, clinical features, diagnosis, and management of gastric cancer are discussed in detail, separately. (See "Epidemiology of gastric cancer" and "Risk factors for gastric cancer" and "Clinical features, diagnosis, and staging of gastric cancer" and "Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging" and "Early gastric cancer: Treatment, natural history, and prognosis" and "Surgical management of invasive gastric cancer" and "Adjuvant and neoadjuvant treatment of gastric cancer" and "Gastric cancer: Pathology and molecular pathogenesis".)

SCREENING MODALITIES

The two main modalities for gastric cancer screening are upper endoscopy and contrast radiography.

Upper endoscopy — Upper endoscopy allows for direct visualization of the gastric mucosa and for biopsies to be obtained for diagnosing precancerous lesions such as gastric atrophy, intestinal metaplasia, or gastric dysplasia in addition to gastric cancer. Although it is more

invasive and has a higher cost, upper endoscopy is also more sensitive for diagnosing a variety of gastric lesions as compared with alternative diagnostic strategies. (See 'Test performance' below.)

Contrast radiography — Double-contrast barium radiographs with photofluorography or digital radiography can identify malignant gastric ulcers, infiltrating lesions, and some early gastric cancers. However, false-negative barium studies can occur in as many as 50 percent of cases [3]. In early gastric cancer, the sensitivity of a barium study may be as low as 14 percent [4]. The one scenario in which a 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 the radiographic study, and the endoscopic appearance may be relatively normal. (See "Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging", section on 'Upper endoscopy' and "Clinical features, diagnosis, and staging of gastric cancer", section on 'Upper endoscopy with biopsy'.)

Other tests — While other modalities of screening for gastric cancer or its precursors have been proposed, further studies are needed to support their use.

Serum pepsinogen — A low serum pepsinogen I concentration and a low serum pepsinogen I/II ratio are suggestive of the presence of atrophic gastritis, a risk factor for gastric cancer. Serum pepsinogen testing has therefore been proposed to identify higher risk individuals who could benefit from gastric cancer screening with upper endoscopy [5-10]. However, in a pooled meta-analysis of 27 population-based screening studies and 15 studies in selected high-risk groups (eg, atrophic gastritis) that included approximately 300,000 individuals, the pooled sensitivity and specificity of serum pepsinogen (pepsinogen I level ≤70 ng/mL and serum pepsinogen I/II ratio <3) for gastric cancer were only 77 and 73 percent in population-based studies and 57 and 80 percent in selected high-risk groups [5].

Serum trefoil factor 3 — Serum trefoil factor 3 (TFF3) is a small stable protein expressed in the goblet cells of the small and large intestine and in gastric intestinal metaplasia. In one study, the sensitivity and specificity of serum TFF3 for detection of gastric cancer were both 81 percent compared with 45 and 88 percent, respectively, for serum pepsinogen (pepsinogen I level ≤70 ng/mL and serum pepsinogen I/II ratio <3) [11]. The combination of pepsinogen and TFF3 may provide even higher sensitivity for gastric cancer [12]. Prospective studies are needed to compare the performance of TFF3 with upper endoscopy and to establish its diagnostic utility.

MicroRNAs — At least three microRNAs (miRNAs), miRNA-421, miRNA 18a, and miR-106a, are highly expressed in gastric cancers and are detectable in peripheral blood and gastric aspirates [13-15]. Assays for multiple miRNAs may further improve diagnostic accuracy [16]. However,

additional studies are needed to define the role of these miRNAs as biomarkers for gastric cancer.

Multianalyte blood tests — An early study examining combinations of tumor-specific circulating proteins and mutations in cell-free DNA in the blood (CancerSEEK) suggests promise for early detection of potentially resectable gastric cancer (sensitivity 75 percent with a high degree of specificity) [17]. However, to establish clinical utility and demonstrate that early diagnosis of gastric cancer using this assay saves lives, prospective trials in large populations will be required.

COMPARISON OF SCREENING METHODS

Test performance — Although upper endoscopy and contrast radiography have not been directly compared, studies suggest that endoscopic screening may be a more sensitive test for screening for gastric cancer [18-22]. A population-based study in South Korea included 2,690,731 individuals who underwent screening for gastric cancer with either upper endoscopy or an upper gastrointestinal (GI) series [23]. Gastric cancer detection rates were 2.61 and 0.68 per 1000 screenings, respectively. The sensitivity rates for upper endoscopy versus upper GI series in detecting gastric cancer were 69 and 37 percent, respectively. Both studies had a specificity of 96 percent. The sensitivity of upper endoscopy in detecting a localized gastric cancer was also significantly higher as compared with upper GI series (68 versus 32 percent). In total, 2067 interval cancers occurred within one year of a negative upper GI series and 1083 cancers occurred after a negative upper endoscopy, but there was no difference in interval cancer rates (1.2 per 1000 screenings for both groups).

Effectiveness — Although some observational studies suggest that screening in areas of high gastric cancer incidence has contributed to the detection of cancer in early stages and an overall decline in gastric cancer mortality, there are no data from large randomized trials demonstrating lower gastric cancer-related mortality in screened populations [18,24-31]. In addition, lead time bias, length bias, and selection bias must be considered when appraising the overall effectiveness of screening demonstrated in observational studies. In a retrospective cohort study of 19,168 gastric cancer patients in Korea, endoscopy-screened patients and patients screened with upper GI series were significantly more likely to be diagnosed with localized gastric cancer as compared with never-screened patients (odds ratio 2.1, 95% CI 1.9-2.3 and 1.2, 95% CI 1.1-1.4, respectively) [31]. However, this study did not include data as to which patients were symptomatic or had undergone evaluation outside of the screening program for evaluation of symptoms.

Screening for gastric cancer may be cost-effective for high-risk subgroups, but not low-risk populations [32,33]. A cost-effectiveness analysis found that in a high-risk group of Chinese men ages 50 to 70 years (standardized incidence of gastric cancer of 25.9 per 100,000 population), screening with upper endoscopy every two years was highly cost-effective ($28,836 per quality-adjusted life-years saved [32]). By contrast, averting one gastric cancer death in men in the United States, assuming an incidence of gastric cancer of <10 per 100,000 population, would cost approximately $247,600, which does not compare favorably with other generally accepted cancer screening interventions. (See "A short primer on cost-effectiveness analysis".)

SCREENING STRATEGIES

Screening for gastric cancer is controversial, and recommendations for screening differ based on the incidence of gastric cancer.

Universal screening — Universal or population-based screening for gastric cancer has been implemented in some countries with a high incidence of gastric cancer (eg, Japan, Korea, Venezuela, and Chile) [18-20]. However, the recommended screening modality and intervals vary. As examples:

- In Japan, population-based screening for gastric cancer is recommended for individuals older than 50 years with conventional double-contrast barium radiograph with photofluorography every year or upper endoscopy every two to three years [21,34,35].
- In Korea, upper endoscopy is recommended every two years for individuals aged 40 to 75 years [35-37].

The optimal interval for screening has not been established in randomized trials. A two-year interscreen interval is supported by at least one study that evaluated the mean sojourn time (MST) for gastric cancer (ie, the asymptomatic period during which a cancer can be detected through screening tests before typical symptoms develop) in a cohort of 61,000 Korean men voluntarily attending a cancer screening program and rescreened by endoscopy [38]. A total of 91 incident cases were found during 19,598,598 person-years of follow-up, and the MST for gastric cancer was 2.4 years (95% CI 1.9-3.0). Of note, the MST was shorter in individuals 40 to 49 years of age (1.3 years, 95% CI 1.0-1.7) than the MST in those 50 to 59 years of age or 60 to 69 (3.2 and 3.7, respectively).

At least some data suggest that the screening interval may be widened to a three-year rather than a two-year interval without significantly decreasing the proportion of gastric neoplasms that can be adequately treated by endoscopic methods [39-41]. However, intervals longer than

three years may be associated with a greater risk of more advanced stage cancer at diagnosis. As an example, in a retrospective cohort study of 2485 patients with gastric adenocarcinoma in Korea, as compared with individuals who underwent annual screening for gastric cancer, the risk of advanced cancer was higher in individuals who underwent screening at four- or five-year intervals (four-year interval odds ratio [OR] 2.5, 95% CI 1.4-4.5, five-year interval OR 2.2, 95% CI 1.3-3.7), but not in individuals who underwent screening at two- or three-year intervals [39]. In subgroup analysis, individuals with a family history of gastric cancer and individuals in their 60s were more likely to be diagnosed with a higher stage of gastric cancer if upper endoscopies were performed every three years as compared with annually (family history of gastric cancer OR 2.68, 95% CI 1.3-5.7, gastric cancer in 60s OR 2.09, 95% CI 1.0-4.3).

Selective screening of high-risk subgroups — In areas of low gastric cancer incidence, screening for gastric cancer with upper endoscopy should be reserved for specific high-risk subgroups [42-53]. The intensity of screening should be based upon an appraisal of the magnitude of risk in each patient, their suitability for treatment should a lesion be detected, and their willingness to accept the uncertain benefits and risks of a screening program. Whether eradication of *H. pylori* can reverse or reduce the risk that precursor lesions will progress is unclear [54-61].

Individuals at increased risk for gastric cancer include those with the following:

- Gastric adenomas
- Pernicious anemia
- Gastric intestinal metaplasia
- Familial adenomatous polyposis
- Lynch syndrome
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome

Specific recommendations for gastric cancer screening in these individuals are discussed separately. (See "Gastric polyps", section on 'Management' and "Gastric intestinal metaplasia", section on 'Endoscopic surveillance in selected patients' and "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency", section on 'Determining the underlying cause of vitamin B12 deficiency' and "Juvenile polyposis syndrome" and "Familial adenomatous polyposis: Screening and management of patients and families", section on 'Upper gastrointestinal tumors' and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management", section on 'Gastric cancer'.)

Importantly, high-risk patients from families with hereditary diffuse gastric cancer are not good candidates for screening because of the propensity of these tumors to arise beneath an intact mucosa and elude radiographic and endoscopic detection. Instead, prophylactic gastrectomy should be strongly considered in these individuals. (See "Hereditary diffuse gastric cancer" and "Surgical management of hereditary diffuse gastric cancer".)

PREVENTION

Helicobacter pylori eradication — In several regions of high gastric cancer incidence, routine screening and eradication for *H. pylori* has been implemented or is being evaluated to decrease rates of gastric cancer [62]. There are limited data that suggest that screening for *H. pylori* in asymptomatic healthy individuals in areas of high gastric cancer incidence may decrease the risk of gastric cancer [63-66]. Successful eradication of *H. pylori* infection in first-degree relatives with gastric cancer has been demonstrated to significantly reduce the risk of a subsequent gastric cancer in areas of high cancer incidence [67]. This was illustrated in a randomized trial in South Korea in which 1838 individuals with *H. pylori* infection and a first-degree relative with gastric cancer were assigned to receive either eradication therapy or placebo. During a median follow-up of 9.2 years, gastric cancer developed in significantly fewer patients in the *H. pylori* treatment group as compared with the placebo group (1.2 versus 2.7 percent; HR 0.45).

In areas of low gastric cancer incidence, there is no role for routine screening of asymptomatic, average risk, healthy individuals for *H. pylori* in order to decrease the risk of gastric cancer. There may be a future role for screening selected asymptomatic individuals for *H. pylori* (eg, individuals who are both first-generation immigrants from areas of high gastric cancer incidence and have a first-degree relative with gastric cancer) [67]. However, further studies are needed before it can be recommended in any asymptomatic population. (See "Risk factors for gastric cancer", section on 'Importance of Helicobacter pylori infection' and "Clinical features, diagnosis, and staging of gastric cancer", section on 'Issues related to helicobacter pylori infection'.)

Other indications for testing and eradication of *H. pylori* are discussed in detail, separately. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gastric cancer".)

SUMMARY AND RECOMMENDATIONS

- Gastric cancer is one of the most common cancers worldwide. However, there are significant differences in the incidence of gastric cancer by region. Screening for gastric cancer is controversial even in areas with a relatively high incidence of gastric cancer. (See 'Introduction' above.)

- The two main modalities for screening for gastric cancer are contrast radiography and upper endoscopy. Although upper endoscopy and contrast radiography have not been directly compared, studies suggest that endoscopic screening may be a more sensitive test for screening for gastric cancer. While other modalities of screening for gastric cancer or its precursors have been proposed, there are limited data to support their use. (See 'Screening modalities' above and 'Test performance' above.)

- Although screening for gastric cancer may be cost-effective in high-risk subgroups, whether screening improves clinical outcomes (ie, gastric cancer-related mortality) is unclear. While some observational studies suggest that the screening has contributed to detection of cancer in early stages and an overall decline in gastric cancer mortality, there are no data from large controlled trials. (See 'Effectiveness' above.)

- Recommendations for screening differ based on the endemic incidence of gastric cancer. Universal or population-based screening for gastric cancer has been implemented in some countries with a high incidence of gastric cancer (eg, Japan, Korea, Venezuela, and Chile). In areas of low gastric cancer incidence, screening for gastric cancer with upper endoscopy should be reserved for specific high-risk subgroups. Individuals at increased risk for gastric cancer include those with gastric adenomas, pernicious anemia, gastric intestinal metaplasia, familial adenomatous polyposis, and Lynch syndrome. There may be a future role for screening selected asymptomatic individuals for *H. pylori* (eg, individuals who are both first-generation immigrants from areas of high gastric cancer incidence and have a first-degree relative with gastric cancer). However, further studies are needed before it can be recommended in any asymptomatic population. (See 'Screening strategies' above.)

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