ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

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Missing the Mark: Optimizing Endoscopy for Intestinal Metaplasia and Gastric Cancer Detection in the United States



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G&H What is the risk of gastric cancer relative to that of colorectal cancer worldwide and in the United States?

JHH Colorectal cancer, broadly speaking, affects almost everybody uniformly. There is a high rate of colorectal cancer in the United States (35 per 100,000 persons). Globally, gastric cancer incidence is similar, although not quite as high as that of colorectal cancer; there are regions in the world that have much higher incidence than others. Overall, the United States has a relatively low incidence of gastric cancer, with rates of about 7 per 100,000 persons. However, there are populations in the United States at very high risk, with incidences of gastric cancer similar to that of colorectal cancer, and these are the Japanese and Korean immigrant populations. Looking at the heat map for gastric cancer around the world, gastric cancer has the highest incidence in East Asia, Eastern Europe, and the Western Coast of South America. The regions with the highest incidence are in Korea, Japan, China, Vietnam, and Southeast Asia, which translates to the populations most affected in the United States. It is important to note that as part of colorectal cancer screening with colonoscopy, which is an invasive test that requires a bowel prep and sedation and can take the entire day for a patient, an upper endoscopy can be easily added on, with minimal additional effort, to examine the stomach of patients who are at high risk. Technically, upper endoscopy is an easier procedure because it does not require any preparation beyond an overnight fast and is a much faster examination.

G&H Within the United States, are certain subgroups at high risk for this type of cancer?

JHH People often say that there is a lack of data on the incidence and risk of gastric cancer in the United States. However, there is quite a bit of epidemiologic data in the United States, most of which is from California because this state disaggregates Asian ethnicities. One of the problems in the United States is the aggregation of ethnicity data. Asians represent 60% of the world's population, but they are often aggregated into one ethnicity in the United States. Certain states, such as California and New York, have started to disaggregate their data and have identified Asian subethnicities, including Korean, Vietnamese, Chinese, Japanese, and so on. When the data are disaggregated, it becomes apparent that the risk is much higher in certain Asian ethnicities, ie, Korean, Japanese, Chinese, Vietnamese, and other Southeast Asians. What offsets the risk is the South Asian (Indian) population, which has a relatively low risk but represents a fairly large portion of the Asian population within the United States. Significant data from Shah and colleagues published in 2020 can help guide clinicians in identifying which populations are particularly high risk and need gastric cancer screening with endoscopy similar to what is done for colorectal cancer screening.

G&H Is endoscopic screening for gastric cancer indicated in the United States and, if so, in what subgroups of patients?

JHH This is an area of some controversy, although I do not think it should be that controversial. One argument against endoscopic screening has been that there are not enough prospective randomized controlled data to support it. However, data can be extrapolated from Asia, where endoscopic screening is performed in the entire population, which is high risk, and this practice has been clearly demonstrated to decrease gastric cancer mortality. The problem is that there are no large randomized controlled studies examining this in the United States, and I doubt that there will ever be. I also do not think that they are necessary because of the available global data. Another argument is that the environmental factors are different in the United States. The bottom line is that several Asian populations in the United States, especially first-generation immigrants from high-risk areas, remain at high risk for gastric cancer as demonstrated by the recent study from Shah and colleagues. Certainly, in those populations, gastric cancer screening with endoscopy should be considered.

Recently, the American Gastroenterological Association published a clinical practice update with Best Practice Advice Statements on screening and surveillance in individuals at increased risk for gastric cancer in the United States. The update cites evidence that there are highrisk populations in the United States and supports efforts to decrease the risk of gastric cancer in these populations, and studies are included that show these efforts are likely to be cost-effective.

G&H What is the significance of intestinal metaplasia as a risk factor for gastric cancer?

JHH Intestinal metaplasia is a change in the lining of the stomach that replaces normal gastric mucosa. Intestinal metaplasia is not a cancerous or precancerous lesion; however, it is tissue that does not belong there. It typically grows in the stomach after the stomach has been damaged from chronic inflammation. The most common cause of intestinal metaplasia in the stomach is chronic Helicobacter pylori infection, which damages the lining of the stomach over decades of infection and then intestinal metaplasia takes over. Intestinal metaplasia is thought to be the first precursor lesion to the development of gastric cancer. After intestinal metaplasia develops, the risk of gastric cancer increases sixfold over the baseline population. With ongoing inflammatory insult, intestinal metaplasia can progress to dysplasia and then to gastric cancer, known as the Correa cascade.

G&H What makes for a high-quality endoscopic screening examination (eg, the Sydney Protocol for biopsies)?

JHH The American College of Gastroenterology (ACG) and American Society for Gastrointestinal Endoscopy (ASGE) recently published their quality indicators for upper gastrointestinal (GI) endoscopy. For the first time, quality indicators have been described for performing a high-quality examination in patients who are at high risk for gastric cancer or are known to have a gastric premalignant condition such as intestinal metaplasia or prior gastric cancer. The quality indicators address the frequency of performing biopsies, use of the updated Sydney protocol

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for gastric biopsy sampling, and the frequency of performing high-definition white-light endoscopy and virtual chromoendoscopy, which is basically narrow-band imaging or blue-light imaging, in patients with known gastric intestinal metaplasia and in patients who are at high risk for gastric cancer. This is the first time that quality indicators have been identified for gastric cancer screening in the United States, specifically for patients who are at higher risk of gastric cancer, and for surveillance of patients with intestinal metaplasia. The new quality indicators for upper GI endoscopy represent a major advance for the field and need to be applied to practice moving forward.

G&H Do scientific data and guidelines support surveillance of certain patients; if so, how often?

JHH Again, it depends on how one reviews the data. Looking at global data, absolutely, they support surveillance. One of the challenges is that in East Asia, especially in Korea and Japan, biopsies are not frequently performed. Instead, the gastroenterologists there perform a very careful and thorough visual inspection of the gastric mucosa and only perform biopsies when they have concern for dysplasia or cancer. Therefore, in the literature from East Asia, the term intestinal metaplasia is often omitted. Screening is performed purely for gastric cancer, not precursor lesions. We know that all these patients have intestinal metaplasia because the amount of gastritis or atrophic gastritis has been documented. If the data from East Asia are extrapolated and applied to the right population in the United States, then I think that there would be ample data to justify gastric cancer screening.

For comparison, the difference between screening with colonoscopy and upper endoscopy is that the precursor lesion in gastric cancer is intestinal metaplasia, which is diffuse and cannot be removed, similar to Barrett esophagus. Intestinal metaplasia of the esophagus is Barrett esophagus. Intestinal metaplasia of the esophagus develops because of chronic acid reflux, which is a chronic inflammatory insult, whereas intestinal metaplasia of the stomach typically develops as a result of chronic *H pylori* infection, which is the cause of the chronic inflammation. There are parallels between Barrett esophagus and GI metaplasia. Surveillance for Barrett esophagus depending on various risk factors is recommended. Screening guidelines for Barrett esophagus should also be applied to gastric intestinal metaplasia because the risk of progression for both Barrett esophagus and intestinal metaplasia of the stomach is fairly similar.

G&H What is the role of endoscopy in the management of early gastric cancer?

JHH This is the reason why we need to screen for gastric cancer and why there has been increased interest in gastric cancer screening. The intervention for early gastric cancer is endoscopic submucosal dissection, which is one of the procedures that many endoscopists are interested in learning and performing. This revolutionary procedure

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was developed for the treatment of early gastric cancer in Japan, where it has been highly successful. In Japan, gastroenterologists have become so good at identifying and managing early gastric cancer that there are few gastric cancers for the surgeons to operate on anymore. This is fantastic for the patient; the only person who loses is the gastric cancer surgeon. When gastric cancer is identified at an early enough stage, where it has not developed deep submucosal invasion, it can be cured using endoscopic submucosal dissection. This is life-altering because patients who undergo a curative resection with endoscopic submucosal dissection: (1) are often cured of their gastric cancer, and (2) they do not have to undergo a major operation that removes part or all of their stomach. The only way to improve outcomes for patients is to detect gastric cancer at an early stage and be able to intervene.

G&H What knowledge gaps need to be filled in order to improve precancerous lesion detection in the stomach?

JHH Similar to Barrett esophagus, not all gastric intestinal metaplasia progresses. Many patients in the world have gastric intestinal metaplasia, of which only a small percentage progresses to cancer. Screening everyone is expensive and is not beneficial to health care systems. To perform more targeted surveillance, gastroenterologists need to further risk-stratify and better identify patients with intestinal metaplasia who are at high risk for progressing. Two unanswered questions are: Who is going to progress to dysplasia and/or cancer, and what is the optimal interval for surveillance endoscopies in patients who are at high risk? The reality is there will be some low-risk people who either do not require any surveillance or require surveillance at a much longer interval, and there will be high-risk patients with a higher likelihood of progression in the next few years who need closer surveillance.

Currently, there are a few risk stratification tools. The best one, the operative link on gastric intestinal metaplasia (OLGIM), is a pathologic staging system that helps stage the severity of intestinal metaplasia based on the distribution: how much of the stomach is affected, and how severe is the intestinal metaplasia. It ranges from stage 0 to IV, with the higher the stage, the higher the risk of progressing. Data have shown that OLGIM helps predict which patients may progress, and the grading system is starting to be applied clinically, although it has not yet become accepted practice with many pathologists in the United States. However, better risk stratification tools are needed. Ideally, having a noninvasive way to further risk-stratify patients would help reduce the frequency of screenings with endoscopy and decrease the number of people who need to be subjected to a surveillance program.

Another knowledge gap is, for a quality examination, how much time is needed for examining the stomach? Unlike with colonoscopy, which has a certain withdrawal time to increase the likelihood of polyp detection, there are no guidelines in terms of how long one should spend examining the stomach. Similar to the bowel prep score in colonoscopy, upper GI endoscopy should also have some type of cleanliness score to ensure that the gastric mucosa has been thoroughly evaluated. There are proponents of spending 1 minute per centimeter of Barrett esophagus to ensure adequate examination of the area. The duration of upper GI endoscopy will probably become a recommendation in the ACG/ASGE quality indicators in the future.

G&H Could you describe the novel technologies for detection on the horizon?

JHH At Stanford, we are participating in a research study with AI Medical Service, which is collecting data from our direct pathology assessments and using artificial intelligence (AI) to help better identify intestinal metaplasia, dysplasia, and cancer. The results will be beneficial in the United States, where intestinal metaplasia and gastric cancer are rarely seen. There is a saying "the mind cannot see what the mind does not know" based on a quote from D. H. Lawrence. This AI program helps democratize endoscopic findings because it contains data from many examinations. These lesions can be very subtle, so examiners have to know what to look for in order to accurately identify them.

Disclosures

Dr Hwang is a consultant for Olympus, Boston Scientific, Medtronic, Fujifilm, MicroTech, and Erbe.

Suggested Reading

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