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Management of Intestinal Metaplasia and Gastric Cancer

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EPIDEMIOLOGY OF GASTRIC CANCER

Gastric cancer is the fifth most common and fourth most deadly cancers worldwide.[1] The World Health Organization estimates that in 2018, gastric cancer accounted for 783,000 deaths globally.[2] Gastric cancer incidence and mortality varies geographically.

Gastric cancers can be divided based on anatomic location into cardia and non-cardia gastric cancers. The non-cardia gastric cancers, arising from the antrum, incisura, body, and/or fundus are associated with Helicobacter *pylori* (H.*pylori*) infection.

Adenocarcinoma is the most common type (90-95%) of gastric cancer followed by some other types including gastrointestinal stromal tumors (GIST), neuroendocrine tumors like carcinoids, lymphoma, leiomyosarcoma and lipomas. Adenocarcinoma are further divided into intestinal and diffuse type.

Asian countries like Japan, Mongolia and Korea have high incidence whereas lower incidence is observed in United States and Northern Europe. In men of South-Central Asian countries, including Iran, Afghanistan, Turkmenistan, and Kyrgyzstan it is the most commonly diagnosed cancer and

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leading cause of death. According to Global cancer statistics 2020 (GLOBACON), one million new cases were added in 2020.[1] Incidence in males is twice as compared to females. Its incidence is decreasing worldwide but it is still associated with high mortality making it a significant public health concern.

In the United States, gastric cancer ranks 15th in incidence among the major types of cancer.[3] The majority of gastric cancers in the United States are non-cardia gastric cancers. In the United States only 10% to 20% of all cases diagnosed are early-stage diagnosis. The remaining patients present with metastatic disease. The median age of diagnosis is 68 years. Over the past 50 years the incidence of gastric cancer has decreased from 33 to 10 cases in males and 30 to 5 cases in female per 100,000. In the United States, 1 in 103 men and women will be diagnosed with gastric cancer in their lifetime.

Overall, 5-year survival rate of gastric cancer is estimated to be 32% (including all stages of cancer). For localized disease this survival rate is 70% whereas for distant metastatic disease the rate is 6%.[3] In early limited cancer the 5-year survival rate is more than 95% in Japan. In Japan, endoscopic resection techniques have been refined and is probably related to reduced mortality despite overall high incidence.

RISK FACTORS FOR GASTRIC CANCER

The incidence and mortality of gastric cancer are highly variable geographically. Certain risk factors have been identified which contribute to increase in the incidence of gastric cancer. These are summarized in table.[1]

Diet is a modifiable risk factor for gastric cancer. Multiple studies including case-control and cohort studies have suggested high risk associated with salt rich diet including pickle, decreased intake of high fiber diet, particularly fruits.[4] Low Vitamin C consumption might play a role in prevalence of gastric cancer. Consumption of processed meat, dairy foods and N-nitroso compounds are associated with higher rates of gastric cancer. Ingestion of green tea is associated with lower risk. Due to modernization and availability of refrigeration the cooked food is safer for longer duration thereby reducing the risk.

Obesity and lack of physical activity has been recognized as a risk factor in gastric cancer. Cigarette smoking is also related to increase incidence. Moderate amount of physical activity is protective.

The risk of gastric cancer in immigrants is similar to the population of their original country. The birth-place is a stronger risk predictor than the current residential location. Thus, showing the importance of childhood exposure in the etiology of gastric cancer. Migrants do not lose their risk in the first-generation migrants or their young children. Generally, after two generations the risk in immigrant population becomes similar to adopted country. Positive family is a strong predictor of gastric cancer.

Approximately one to three percent of gastric cancer is hereditary in nature. Hereditary diffuse gastric cancer is less than one percent of total gastric cancer cases. It is associated with increased incidence of gastric and breast cancer. Other familial syndromes associated are familial adenomatous polyposis (FAP) and Peutz–Jeghers syndrome (PJS).[5] In both the above-mentioned disease polyp and dysplasia lead to development of cancer.

Atrophic gastritis and intestinal metaplasia are precancerous lesions for gastric cancer. Certain studies have linked Helicobacter *pylori* infection with the above. Eradication of Helicbacter *pylori* leads to reduce incidence of gastric cancer.[6] Pernicious anemia due to vitamin B12 deficiency secondary to autoimmune gastritis, affects 2%–5% of the elderly population. Studies have shown that patients with pernicious anemia could have an increased risk of cancer. Vitamin B12 will improve the anemia but have no effect on autoimmune gastritis.

H.*pylori* infection has been linked to non cardia gastric cancer which is the most prevalent gastric cancer in the United States. Multiple studies have shown that testing and eradication of H. *pylori* worldwide has resulted in reduced incidence of gastric cancer.

Its prevalence is higher in older males. As the prevalence also increases with safe drinking water

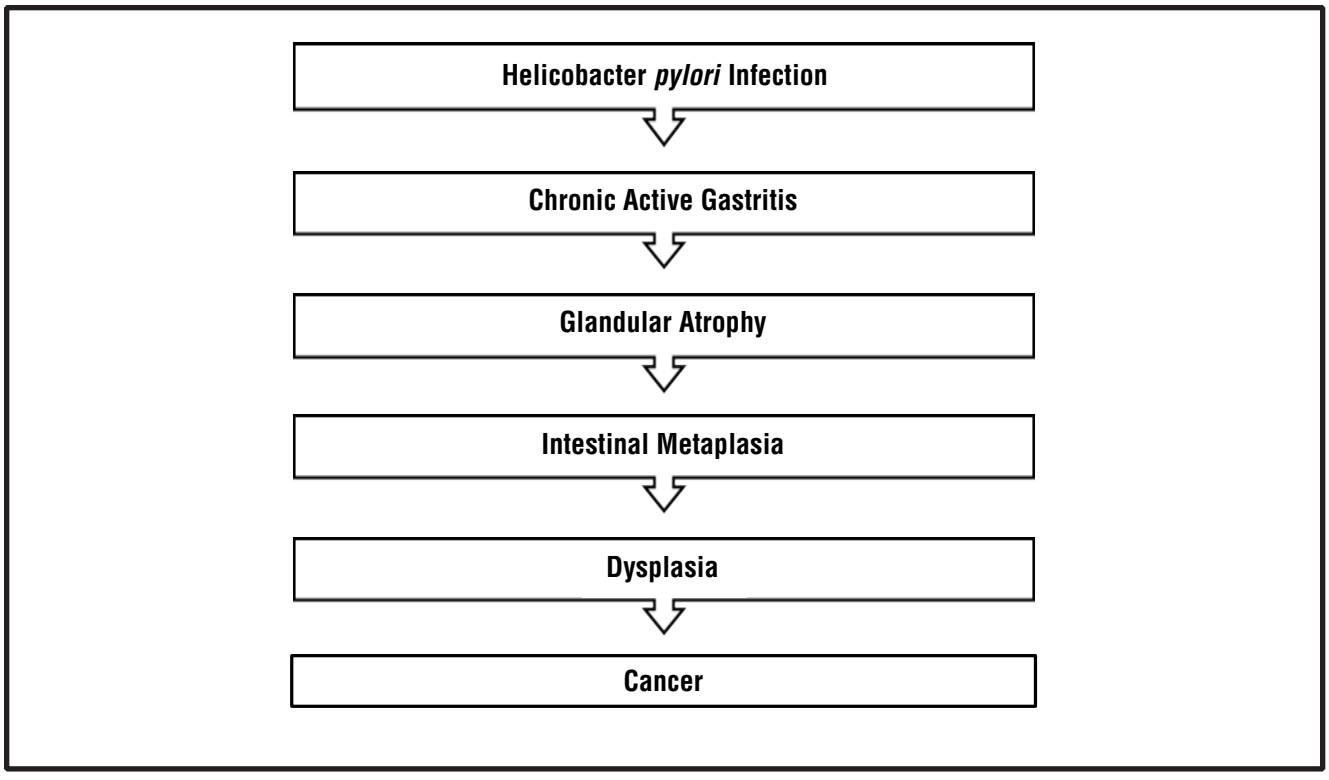

Figure 1. Gastric Cancer Progression Model

and food, logically it is more rampant in lower socio-economic groups. Foundry workers are at risk for developing gastric cancer with dust iron being an important cause. It has also noted to be present in Hiroshima and Nagasaki survivors.

H. *PYLORI*: DISCOVERY TO CARCINOGEN STATUS

H. *pylori* was discovered first in 1982 by Australian physicians Drs. Barry Marshall and Robin Warren. It is a gram negative, spiral shaped bacterium living in the stomach. It is transmitted through the feco-oral routes. Studies have shown that this accounts for 50-70 % of gastric ulcers. It is also associated with gastric adenocarcinoma. In 1975 Correa et al. outlined a cascade leading to development of gastric adenocarcinoma.[7] They suggested the following sequence of events normal gastric mucosa / nonatrophic gastritis / multifocal atrophic gastritis without intestinal metaplasia / intestinal metaplasia of the complete (small intestine) type / intestinal metaplasia of the incomplete (colonic) type / low-grade dysplasia / high-grade dysplasia / invasive adenocarcinoma. H. *pylori* infection causes gastritis and then in some patients follows the above cascade to eventually gastric adenocarcinoma. (Figure 1)

Patients with peptic ulcer disease (PUD), a past history of PUD (with no documented treatment), low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or a history of endoscopic resection of early gastric cancer (EGC) should be tested for H. *pylori* infection. Strong consideration is made for people younger than 60 years with dyspepsia with no alarming can be tested and if positive treated to postpone the EGD. In patients undergoing EGD for dyspepsia biopsies should be taken and tested for H. *pylori*. Antimicrobial treatment of chronically infected people might trigger antimicrobial resistance as almost half of the world population is infected with H. *pylori* infection.[8] Vaccination against has been shown effective in experimental animal models, but so far, such efficacy has not been studied in humans. Studies have shown that among patients with H. *pylori* infection with or without intestinal metaplasia, H. *pylori* treatment was associated with a lower risk of incident gastric cancer compared to placebo.

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Proton pump inhibitor (PPI) use is associated with worsening of gastric atrophy, particularly in H. *pylori*–infected individuals. One study analyzed 63,397 patients who had been treated for H. *pylori* and who had appeared to be cleared of the infection.[9] The results suggested that people who used PPI after treatment of H. *pylori* were twice at risk of gastric cancer as compared to people who did not use PPI.

First-line treatment of H. *pylori* is bismuth quadruple therapy or concomitant therapy consisting of a PPI, clarithromycin, amoxicillin, and metronidazole. Certain factors like previous antibiotic exposure and previous treatments should be put in perspective. If first line therapy fails, a salvage regimen avoids antibiotics previously used and can use other drugs like levofloxacin.

INTESTINAL METAPLASIA AND PROPOSED PROGRESSION TO GASTRIC CANCER

Gastric intestinal metaplasia (GIM), defined as the replacement of normal healthy gastric mucosa by epithelium resembling intestinal cells. It is associated with an increased risk for intestinal-type gastric adenocarcinoma. There is increased discussion about further endoscopic testing or surveillance for the same reason. In 1975, Correa et al. described the cascade of steps leading to the development of intestinal-type gastric adenocarcinoma. Less than 0.25% of patients with GIM every year progress to gastric cancer. It has been recognized as a pre malignant condition, when exposed to environmental stimuli like H. *pylori*, smoking and high salt intake may result to advancement of gastric cancer.

Certain indicators like location, extent and severity of GIM will influence the transformation of GIM to gastric cancer. Lesions found in gastric body are more likely to advance into gastric cancer. One-fourth of the patients diagnosed with high grade dysplasia (HGD) will advance to adenocarcinoma. Once H.*pylori* infection is diagnosed it should be treated in these patients.

There is no common guideline for surveillance of GIM. In high-grade dysplasia with no endoscopically defined lesions, surveillance at six months or one year is recommended. In low-grade dysplasia with no endoscopically defined lesion, patients should receive follow up within a year after diagnosis.[10] In the presence of an endoscopically

Table 1. Risk Factors for Gastric Cancer

1.	**Dietary factors:** salt rich diet, smoked food, fermented food, low intake of fruits and vegetables, low intake of vitamin C
2.	**Lifestyle:** lack of exercise and physical activity, alcohol consumption, cigarette smoking, obesity
3.	**Hereditary syndromes:** hereditary diffuse gastric cancer (HDGC), familial adenomatous polyposis (FAP) and Peutz–Jeghers syndrome (PJS)
4.	**Family history:** positive family history of gastric cancer
5.	**Precursor condition:** chronic atrophic gastritis, reflux, history of gastrectomy and gastric surgery, intestinal metaplasia, pernicious anemia, blood type A
6.	**Infections:** Helicobacter pylori, Human Papilloma Virus
7.	**Demographics:** old age, male, race, lower socio-economic condition, level of education
8.	**Occupational exposure:** cement, mineral dust, chrome
9.	**Ionizing radiation:** noted in survivors of Hiroshima and Nagasaki

defined lesion, resection should be considered to obtain a more accurate diagnosis.

A standard surveillance protocol is needed which should focus on the patients at greatest risk. In countries with lower incidence, high risk individuals should be identified. Multiple factors such as genetic risk, epidemiological factors and status of H. *pylori* infection should be considered. After the initial screening, high-risk patients with intestinal metaplasia should enter surveillance protocols for uniformity of care and future trends.

RECOMMENDATIONS FOR SCREENING FOR GASTRIC CANCER

As evident from the discussion above, there is a high-risk population which is known for gastric cancer. Guidelines to identify precursor lesions and then appropriate screening and surveillance will help in early detection and prevention of gastric cancer. In countries like Japan which are considered high-risk, high false positive results have been identified as a consequence of screening. In the United States, screening high risk populations like older males with pernicious anemia, atrophic gastritis and familial syndromes like FAP, could be a clinically justified method of screening.

ASGE guidelines suggests that patients with GIM at high-risk of gastric cancer due to ethnic background or family history should undergo surveillance endoscopy. Future surveillance endoscopies can be discontinued if two consecutive endoscopies have been negative for dysplasia and eradication of H. *pylori* has been achieved.

AGA guideline by Gupta S et al. and Gawron AJ et al. are recommended reading for recommendations for surveillance endoscopy in patients with GIM and high-risk individuals.[10,12]

FUTURE RESEARCH AREAS

Despite decreasing incidence of gastric cancer, its mortality is still very high and diagnosis is made at a later stage of the disease. Screening methods available for even high-risk populations do not yield good positive predictive value. Multiple studies aim to identify non-invasive biomarkers from other bodily fluid like urine, saliva, gastric juice or blood.

On routine endoscopy we can miss almost ten percent of the lesions. High-definition endoscopy with virtual chromoendoscopy is superior to white light endoscopy alone. The endoscopist can identify high-risk lesions better with these enhanced imaging modalities. Biopsy of these targeted lesions increases the positive predictive value. ■

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