INTRODUCTION

Development of gastric cancer is a multistep process, ranging from chronic gastritis to chronic atrophic gastritis (CAG), metaplasia, dysplasia, and finally neoplasia (intestinal type gastric cancer).1 There is substantial evidence that subjects carrying *Helicobacter pylori* (*H. pylori*), in their stomach, are at high risk for developing gastric carcinoma.2,3 Thus, *H. pylori* is designated as Class I carcinogen by the International Agency for Research on Cancer on the World Health Organization.4 Though intestinal metaplasia is regarded as a precancerous lesion,5,6 but gastric cancer would not develop necessarily in all individuals with this lesion; and therefore, indicating that a variety of genetic and environmental factors may be playing an influential role. This review discusses the classification, molecular markers, prevalence, etiology, treatment, and surveillance of gastric intestinal metaplasia.

META-ANALYSIS

**Gastric Intestinal Metaplasia: An Intermediate Precancerous Lesion in the Cascade of Gastric Carcinogenesis**

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**ABSTRACT**

Gastric intestinal metaplasia, an intermediate lesion in the development of intestinal-type gastric cancer, is observed in the *milieu* of long standing non-atrophic gastritis and atrophic gastritis. Most patients with intestinal metaplasia remain asymptomatic unless cobalamin deficiency occurs secondary to loss of glands (that produce intrinsic factor and acid). Genetic events that predispose to development of gastric intestinal metaplasia remains an enigma. Mechanisms leading to the progression of atrophy to metaplasia still needs to be comprehensively explored. Many studies in the literature describe a positive effect of typing intestinal metaplasia and concluded that intestinal metaplasia type III carries the highest risk for developing gastric cancer while others refute it. It is well established that *Helicobacter pylori* infection is the most important factor for the development of chronic gastritis, gastric intestinal metaplasia as well as gastric cancer. Countries with a higher prevalence of *Helicobacter pylori* infection and gastric cancer also have a high tendency of being prevalent for intestinal metaplasia. However, it remains elusive whether eradication of *Helicobacter pylori* infection tends to regress gastric intestinal metaplasia or reduce the subsequent risk of cancer development. Putting together, more prospective cohort studies should be designed to identify factors (antioxidants; anti-inflammatory drugs; food therapy) that may contribute in the regression of intestinal metaplasia, when used simultaneously with eradication therapy. Furthermore, molecular markers for evaluation of intestinal metaplasia, and the potential point-of-no-return should be further investigated. Consensus is also required to advocate a timeframe for surveillance of patients with gastric intestinal metaplasia.

**Key Words:** Atrophic gastritis. Intestinal metaplasia. Gastric cancer. Endoscopy. *Helicobacter pylori*.

**INTRODUCTION**

We performed a literature search from 1980 to 2015 using the PubMed, MEDLINE (Ovid) and Google scholar search engine. Keywords were intestinal metaplasia (IM), gastric precancerous lesion, atrophic gastritis (AG), *H. pylori*, gastric intestinal metaplasia, endoscopy, and gastric cancer. Papers of only English language were included. Over 100 articles were initially reviewed and 75 articles were shortlisted on the basis of their applicability to formulate the present review. The selection of studies is described in a flow chart shown in Figure 1. This literature review aimed to explore the classification, molecular markers, prevalence, etiology, treatment, and surveillance of gastric intestinal metaplasia.

Most patients with intestinal metaplasia remain asymptomatic unless cobalamin deficiency occurs secondary to loss of glands (that produce intrinsic factor and acid). The endoscopic finding of IM is observed as a mucosal nodular pattern, usually occurring after the occurrence of the AG.

AG is usually diagnosed at endoscopy in East Asian countries, while histological examination of biopsy obtained during endoscopy is a necessity for AG diagnosis in the western countries.7,8 Though severe cases of AG and IM can be properly diagnosed at endoscopy,9 but to make the diagnoses of mild AG and IM is often challenging.10 Furthermore, sometimes endoscopic diagnosis is not correlated to histological
diagnosis. Therefore, biopsy sampling is recommended in suspected cases of AG and IM. Lim et al. concluded that the sensitivity and specificity of endoscopic diagnosis of IM based on histology were 24.0% and 91.9% for the antrum and were 24.2% and 88.0% for the corpus.11

The second method of diagnosis of AG is histopathology. In IM, the normal columnar epithelium is differentiated into an intestinal phenotype and is characterized by the presence of goblet cells, Paneth cells and absorptive cells.12

Though various classifications for IM have been proposed to its association with GC, but the most widely used, is the classification proposed by Jass and Filipe as it aids in differentiating among the subtypes of the incomplete phenotype.13 Mucin expression classification can recognize complete and incomplete types but fails to subdivide the incomplete type.14 Jass and Filipe classification is based on the presence or absence of certain type of cells as well as secretion of mucins and divides IM into three subtypes.13 Type I is the complete metaplasia, small intestine type; characterized by the presence of goblet cells secreting acid sialomucins and sometimes sulphomucins. Paneth cells and mature, non-mucus secreting, absorptive cells are observed. Type II is the incomplete sulphomucin-negative type IM; characterized by the presence of goblet cells secreting non-sulphated mucins. Paneth cells are usually completely absent. Type III is the incomplete sulphomucin-positive type intestinal metaplasia; the columnar mucous cells secrete predominantly sulphomucins.

Numerous studies have reported about the association between cancer risk and IM subtype. Type I has no increased risk of developing carcinoma, whereas IM subtype III is identified to have an increased risk of malignant transformation.13,15,16 In a large cohort study from Slovenia with 10-year follow up, Filipe et al. concluded 4.58 fold risk for gastric cancer in patients with type III IM compared to those with type I,13 signifying the purpose of IM subtyping in identifying individuals at risk for developing GC. On the other hand, some studies have refuted the perception that IM subtype III is related to development of gastric carcinoma.17-19 Therefore, it remains controversial if subtyping IM is an important predictor of increased cancer risk.

**Gastric IM at molecular level:** Genetic events that predispose to development of gastric intestinal metaplasia remains an enigma. Various genes have been attributed to play role in the mucosal differentiation including (but not limited to) p53, homeobox gene (Cdx2), microsatellite instability and a recently reported SCHLAFEN gene. However, mechanisms leading to these changes and metaplastic progressions still need to be comprehensively explored.

**Cdx2:** Cdx2 is highly expressed in the small intestine. Expression of Cdx2 declines proportionately along the length of the small intestine. Cdx1 is highly expressed in the colon. However, neither of them is usually observed in normal gastric mucosa. Liu et al. reported that with variation in degree of expression, Cdx2 is found in precancerous lesions as well as neoplastic lesions. Cdx2 is upregulated in the complete type IM while expression is significantly reduced in incomplete IM. Expression is further reduced in dysplasia and gastric cancer.20 It has been reported that H.pylori infection has a stimulatory effect on the expression of Cdx2 in gastric mucosa.21 However, eradicating H.pylori does not correct the Cdx2 expression prompting that other molecular pathways exist in maintaining the Cdx2 expression, such as the well-established role of bone morphogenetic protein which not only positively regulates Cdx2 expression but also tends to block SOX2 (Cdx2 inhibitor).22

**Microsatellite instability (MSI):** MSI is the variation in the length of repetitive DNA sequences. Normal genome (cells) have short, repetitive DNA sequence of uniform length, though diversity exists in the length of these sequence among individuals. MSI has been associated with gastric metaplasia, dysplasia and gastric cancer. A recent study from China, investigated MSI in gastric cancer and precancerous lesions and compared with control.23 They found that presence of MSI in IM was 20.7%, in dysplasia was 22.4%, and in gastric cancer
was 47.9%, while NO MSI was present in normal tissue sample (control group). Leung et al. reported that out of 75 IM patients, only 39% had MSI while all other individuals had low-level microsatellite instability. Chronic gastritis, peptic ulcer or gastric cancer (diffuse or intestinal type) also accompanied with IM in these patients. Interestingly, they also found high frequency of MSI in intestinal type cancer group. On the contrary, low frequency MSI were observed in diffuse type cancer. Thus, MSI has somewhat significant role in gastric cancer development, regardless of the type it belongs to.

Schlafen: Schlafen (SLFN) family is a group of protein that, under the influence of interferon-1, regulates T-cell development and maturation. In human genome, SLFN5 isoform of the Schlafen family exists. In a recent published retrospective study, Nápoles et al. concluded that greater the expression of Schlafen 5 in IM samples, the greater is the risk for progression into gastric cancer than in the same lesions that did not progress to GC. Thus, acknowledging their findings, more prospective studies would indeed aid in recognizing high risk patients at an early stage.

P53: P53 serves to control many vital functions such as DNA repair, apoptosis, and cell cycle control. Mutation in p53 (tumor suppressor gene) is usually observed in human cancer, including gastric cancer. Whether, p53 mutations are evident in IM samples is conflicting. Wu et al. used immunohistochemistry techniques to detect accumulation of p53 proteins and concluded that p53 mutations existed in intestinal metastasis, particularly in type III. On the other hand, a recent publication did not find p53 protein in any of the IM sample (n=92), though p53 mutations were observed in high grade dysplasia, persuading that p53 mutations may be playing a role at a later stage of gastric carcinogenesis. More prospective studies should be carried out to determine a threshold value of p53 that might be used as a tool to indicate the progression of IM into neoplasia.

Villin: The major protein associated with actin in the microfilament core of intestinal brushborder is Villin. A recent study from China compared biopsy samples from gastric cardia of 143 patients suffering from either IM, dysplasia or cancer and compared them with control group for the presence of Villin and Cdx2 by immunohistochemistry methods. They concluded that control group did not express Villin or Cdx2 while both factors were present in most of the IM samples (Villin in 76.0%; Cdx2 in 84.0%).

Das-1 monoclonal antibody: The Das-1 monoclonal antibody (previously described as the 7E12H12 antibody, immunoglobulin [Ig] M isotype) was developed against a colonic epithelial protein (CEP) that specifically reacts with colonic epithelium and does not react with any other parts of the gastrointestinal tract (including the stomach, small bowel, and pancreas).

In 2003, Mirza et al. explored if mAb Das-1 reactivity helps to identify the colonic phenotype of metaplasia in the stomach and its association with gastric carcinoma. They divided the participants into three groups – group A included specimens from cancer areas and histologically proved GIM areas away from the cancer segments. In group B, biopsy tissue specimens were obtained containing GIM without gastric carcinoma. In group C, biopsy samples included fragments of chronic gastritis, without evidence of GIM. Group A included patients from Japan and USA, while group B and C were all Japanese patients. Most of the samples included in group A reacted intensely with mAb Das-1. In contrast, only 35% GIM samples from patients without gastric carcinoma (group B) reacted with mAb Das-1 while none of the samples in group C reacted with the antibody. Therefore, they concluded that the colonic phenotype of GIM, as identified by mAb Das-1, is strongly associated with gastric carcinoma. Another study from Spain reported similar results but concluded that Das-1 expression was weakly associated with GIM from patients with gastric cancer. Geographical variations as well as genetic and environmental factors may be responsible for the differences between the two studies.

Etiology and prevalence of gastric IM: Gastric cancer is the fourth most common cancer worldwide while it is the third most common cancer in China. Gastric cancer is subdivided into two types: intestinal and diffuse. Development of intestinal type of gastric cancer is preceded by the precursor lesions – chronic atrophic gastritis, intestinal metaplasia (IM), and adenoma/dysplasia. It is well established that H. pylori infection is the most important factor for the development of chronic gastritis, atrophic gastritis, intestinal metaplasia as well as gastric cancer. Bile reflux is another important factor – though less documented in the literature – has also been shown to play a prominent role in the promotion of metaplastic lesions in the stomach. Furthermore, increasing age, male gender, alcohol consumption, smoking, increased salt intake and family history of gastric cancer are established factors associated with IM progression while a dietary habit encouraging vegetables and fruit intake since childhood may also prevent progression to gastric cancer.

The prevalence of IM varies around the globe. Countries with a higher prevalence of Helicobacter pylori infection and gastric cancer also have a high tendency of being prevalent for AG and IM. Peleteiro et al. undertook a
systematic review to determine the prevalence of gastric intestinal metaplasia across five continents. IM was highly prevalent in China and Turkey in Asia, Ireland and Italy in Europe, New Zealand in Oceania, Egypt in Africa, Columbia and Venezuela in America. Among these countries, only China and Columbia followed the updated Sydney system for histological evaluation of gastric biopsies while with exception of Egypt, IM was more prevalent in subjects infected with Helicobacter pylori in aforementioned countries.

A recent study from China reported that IM was present in 84.33% of patients endoscopically diagnosed with CAG. They further concluded that IM correlated significantly with the severity of CAG. Olmez et al. conducted a retrospective study of 4,050 patients undergoing EGD with biopsy in Eastern Turkey and found that the prevalence of gastric IM was 13.8% while subtype III was the most common type encountered.

**Does Helicobacter pylori eradication reverse IM?** Though there is a consensus that *Helicobacter pylori* is involved in the development of gastric intestinal metaplasia and eventually gastric cancer; but: Does eradication of *Helicobacter pylori* aid in regression of metaplasia? Does the eradication reduce the incidence of gastric cancer in patients with established IM? The answer to these questions is still vague as conflicting data in the literature has been reported, some supporting the eradication plan while others in disagreement. The difference are generally attributed to sampling errors, variation in study population and histological grading. A summary of these results of studies carried out in the last decade are listed in Table I.

Reviewing the literature online, a recent large prospective study from China reported that progression of IM of the antral mucosa was halted in patients treated with anti-*Helicobacter pylori* regimen as compared to placebo group (RR=0.850, 95% CI: 0.783-0.922). Kodama et al. reported that eradication therapy has a significant positive impact on the outcome of gastric atrophy and IM. This study protocol included the histological evaluation of gastric mucosa of 118 patients, before and 8.6 years after eradication therapy. In all these patients, *Helicobacter pylori* presence was confirmed by histopathology, culture and rapid urease tests. During endoscopic examination, biopsy was taken from two points – greater curvature of antrum and corpus while updated Sydney system was used to assess atrophy and metaplasia scores. The study concluded that atrophy scores significantly reduced at antrum and corpus while intestinal metaplasia scores significantly reduced at corpus but not at antrum.

In another long-term prospective study from Japan, Toyokawa et al. concluded that ten years after successful *Helicobacter pylori* eradication therapy, gastric atrophic scores in all parts of stomach (except antrum) improved in all age groups while gastric intestinal metaplastic scores did not improve throughout the study period. However, metaplasia did not worsen reflecting that eradication does have an impact on metaplasia, too.

Multiple other studies have given corroborating results. Lee et al. from Korea reported that eradication therapy does influence atrophy and plays a role in atrophic regression but not metaplastic lesions. It should be noted that most of the studies which are in disagreement with positive impact of eradication therapy on metaplasia have a short follow-up period as indicated in Table I. Despite controversy, curing the infection would appear a reasonable approach in all IM patients as molecular markers detected by genetic and epigenetic alterations related to carcinogenesis reverse following *Helicobacter pylori* eradication.

**Is there a need for surveillance?** Though there is a general consensus that Barrett's esophagus and colonic adenomas should be monitored subject to surveillance recommendation; however, consensus lacks for surveillance of metaplastic, dysplastic and even neoplastic lesions in the stomach. Intestinal metaplasia along with its precedent, atrophic gastritis, are well established precancerous lesions. A Korean study concluded the relative risk of IM of developing into carcinoma varied from 7.52 to 9.25 in antrum and less curvature, respectively. In yet another study from Italy, where the follow-up period was 52 months for 471 patients with IM, who underwent surveillance biennially, 45 subjects developed neoplasia.

Despite being well established precancerous lesion, surveillance for IM is not endorsed in the West. The 2006 guidelines of American Society of Gastrointestinal Endoscopy do not uniformly recommend the surveillance for metaplastic lesions without dysplasia in

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the stomach. However, follow-up endoscopy is recommended (without quoting surveillance interval) for the IM subjects that are at risk-positive family history, ethnic background or immigrant from geographic location with high gastric cancer incidence. In 2012, European Society for Gastrointestinal Endoscopy proposed a 3-year timeframe for surveillance for all patients with histopathological diagnosis of IM at antrum and corpus. According to the protocol, magnified chromoendoscopy and/or narrow band imaging should identify the lesions followed by two biopsies taken from each, corpus and antrum. No surveillance is recommended for a mere antral IM. White light endoscopy is the standard approach to take multiple biopsies to map the extent of metaplastic lesion. However, a recent published report from Kyoto Global Consensus Conference, recommended the use of image-enhanced endoscopy rather than conventional endoscopy to visualize the lesions suspected for IM in order to increase the yield from biopsies.

Measurement of serum pepsinogen (PG) levels is another less invasive and simple strategy for surveillance of gastric pre-neoplastic lesions. This method is non-invasive and does not require skills as is the case with endoscopic examination. PG-I is secreted by chief and mucous neck cells in the corpus and fundic glands, whereas PG¢Ú is secreted by these cells as well as cells in the pyloric glands and Brunner's glands. Therefore, any reduction in PG-I level strongly reflects corpus atrophy. In Japanese series, a low serum PG-I or a PG-II ratio is a reliable marker for predicting risk of GC. In yet another step to prevent gastric cancer and/or precancerous lesions, Japanese H. pylori Society has recommended test-and-treat strategy for H. pylori in teenagers throughout Japan in order to get rid of gastric cancer within the next decade (personal communication with Prof. Yamaoka, 2016).

Regardless of the variation in the distribution of gastric IM around the globe, there is a need to define in future studies or guidelines the appropriate endoscopic modality for surveillance of gastric metaplastic lesions.

CONCLUSION

Gastric IM – a well-established gastric precancerous lesion – is commonly observed in H. pylori infected patients and in regions where gastric cancer is highly prevalent. Nevertheless, all patients with gastric IM will not necessarily progress to gastric cancer. The underlying mechanism associated with the development of neoplasia in IM should be further studied and illustrated. Moreover, consensus should also be reached to determine if typing or molecular markers would reflect the malignancy risk in gastric IM. This would also aid in formulating intensive surveillance guidelines in those at high risk for development of gastric cancer. Besides endoscopy, other parameters such as serum pepsinogen levels should be practiced routinely to assess the extension of preneoplastic lesions in gastric mucosa. Eradication of H. pylori appears to be one of the most effective approach in decreasing the progression of preneoplastic lesions to neoplastic lesions and, therefore, should be considered in all age groups to prevent deterioration in gastric histology. Last but not least, long-term studies will be needed to assess if any other chemo-preventive agents may play a significant role in resolving gastric IM.

REFERENCES


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