

# Precancerous Lesions in Gastrointestinal Tract

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## ABSTRACT

Gastrointestinal cancer is one of the health problems which is frequently found in many people in the world until now. Studies in gastrointestinal cancer showed early detection can reduce morbidity and improve the survival of patients. The precancerous lesions of the gastrointestinal tract are highly potential turn into cancer. Precancerous lesions can be defined as a change or non-cancerous lesions that can become cancerous over time. Precancerous lesions can be found on the entire upper and lower gastrointestinal tract. Precancerous lesions of the upper digestive tract that can be found are Barrett's esophagus, chronic gastritis with or without *Helicobacter pylori* infection, atrophic gastritis, intestinal metaplasia of the gastric mucosa, epithelial dysplasia, and adenoma polyp. While precancerous lesions in the lower gastrointestinal tract are adenoma, inflammatory bowel disease, chronic infection and hereditary non-polyposis colon lesions. Precancerous lesions of the stomach in the form of chronic atrophic gastritis, intestinal metaplasia and dysplasia can be treated with anti-inflammatory and anti-free radical drugs such as rebamipide and superoxide dismutase. Precancerous lesions in the colon in the form of chronic enterocolitis, dysplasia can be treated with anti-oxidants, anti-inflammatory and anti-free radical such as anti-oxidants, rebamipide, superoxide dismutase, anti-inflammatory drugs.

**Keywords:** precancerous lesions, gastrointestinal tract, intestinal metaplasia, dysplasia.

## ABSTRAK

Kanker gastrointestinal merupakan salah satu masalah kesehatan yang sering ditemukan di dunia sampai sekarang. Studi pada kanker gastrointestinal menunjukkan bahwa deteksi dini dapat mengurangi morbiditas dan meningkatkan kelangsungan hidup pasien. Lesi prakanker pada saluran gastrointestinal sangat berpotensi berubah menjadi kanker. Lesi prakanker dapat didefinisikan sebagai lesi non-kanker yang bisa berubah menjadi kanker seiring dengan berjalannya waktu. Lesi prakanker dapat ditemukan pada semua saluran gastrointestinal bagian atas dan bawah. Lesi prakanker saluran pencernaan bagian atas yang dapat ditemukan adalah Esofagus Barrett, gastritis kronis dengan atau tanpa infeksi *Helicobacter pylori*, gastritis atrofi, "intestinal metaplasia" mukosa lambung, displasia epitel, dan polip adenoma. Sementara lesi prakanker di saluran cerna bagian bawah adalah adenoma, penyakit radang usus besar, infeksi kronis dan lesi usus besar non-poliposis bawaan. Lesi prakanker pada lambung berupa gastritis atrofik kronis, metaplasia usus dan displasia dapat diobati dengan obat anti radikal bebas/ anti-inflamasi seperti rebamipide dan superoxide dismutase. Lesi prakanker di usus besar dalam bentuk enterokolitis kronis, displasia dapat diobati dengan anti-oksidan, anti-inflamasi dan anti-radikal bebas seperti anti oksidan, rebamipide, superoxide dismutase, obat anti-inflamasi.

**Kata kunci:** lesi prakanker, saluran gastrointestinal, metaplasia intestinal, displasia

## INTRODUCTION

Gastrointestinal cancer is one of the health problems which are frequently found in many people in the world until now. Gastrointestinal cancer mortality rate is still high enough, despite there are already advance medical technologies and good medications for gastrointestinal disease.<sup>1</sup> From the studies in gastrointestinal cancer, early detection can reduce morbidity and improve the survival of patients.<sup>1</sup>

Gastrointestinal cancers arise through a cascade of precursor that is already known about inflammatory – ranging from metaplasia-dysplasia-carcinoma sequence, so it is always via the stages of precancerous lesions.<sup>2</sup> The precancerous lesions of the gastrointestinal tract are highly potential turn into cancer. The task is to find precancerous lesions of the gastrointestinal tract as early as possible, so that we can prevent the occurrence of cancer of the gastrointestinal tract.<sup>3</sup>

## DEFINITION OF PRECANCEROUS LESIONS

Precancerous lesions can be defined as a change or a non-cancerous lesions that can become cancerous over time.<sup>4</sup> Precancerous lesion is a common condition associated with increased risk to turn into cancer. If left untreated the condition will turn into cancer.

## TYPES AND CLASSIFICATION OF PRECANCEROUS LESIONS

Precancerous lesions can be found on the entire upper and lower gastrointestinal tract. Precancerous lesions of the upper digestive tract that can be found are Barrett's esophagus, chronic gastritis with or without *Helicobacter pylori* infection, atrophic gastritis, intestinal metaplasia of the gastric mucosa, epithelial dysplasia, and adenoma polyp.<sup>2,3,5,6</sup>

While gastrointestinal precancerous lesions that can be found in the lower gastrointestinal tract are adenoma (tubular, tubulovillous and villous), inflammatory bowel disease (including Crohn's disease and ulcerative colitis), chronic infection and hereditary non-polyposis colon lesions.<sup>3,6</sup>

*Chronic atrophic gastritis* should be diagnosed and graded on the basis of the presence of chronic inflammatory cells, including lymphocytes and plasma cells that expand the lamina propria, and the disappearance of the normal glands.<sup>7-9</sup> In the gastric body/fundus this is associated with a loss of specialized cells and thus a reduction of gastric secretory functions. The severity of gland loss (atrophy) should be graded

although inter- and intraobserver agreement are both poor.

## EPIDEMIOLOGY

Studies in the world revealed that the annual incidence of gastric cancer from atrophic gastritis, intestinal metaplasia and dysplasia, ranging from 0-2%, 0-10% and 0-73%.<sup>10</sup> A study from the Netherland found that the annual incidence of gastric cancer is 0.1% for patients with atrophic gastritis, 0.25% for intestinal metaplasia, 0.6% for mild-to-moderate dysplasia and 6% for severe dysplasia within 5 years after diagnosis.<sup>1</sup> Risk factors for gastric cancer increased the severity of gastric premalignant lesions at the time of initial diagnosis, for example, severe dysplasia (HR = 40.14, 95%), Increased age (75-84 years, HR = 3.75, 95%), and male gender (HR = 1.50). The authors concluded from this study that patients with premalignant gastric lesions are at increased risk of gastric cancer.<sup>1</sup>

A population study in Shandong province of China with gastroscopy examination found that the prevalence of chronic atrophic gastritis 98%, gastric intestinal metaplasia obtained 33%, 20% gastric dysplasia. Found no sex differences in the prevalence of chronic atrophic gastritis. The prevalence of intestinal metaplasia and dysplasia lesions increased significantly corresponding increase in age.<sup>11</sup>

Colorectal adenomatous polyp has chance to develop into carcinoma about 0.25% per year; the transformation rate is proportional with the size of adenoma. Adenomas with size less than 1 cm had much lower chance to transform into carcinoma compared with adenomas sized > 2 cm (1% vs. 50%). The tubulovillous and villous adenoma polyp had 50% chance for developing colorectal cancer. The colorectal adenoma can be found as incidental findings during colonoscopy screening in 40% of people older than 60 years old.<sup>12</sup> Study from Korea showed that patients with ulcerative colitis had cumulative risk of developing colorectal cancer for 0.7% at 10 years, 7.9% at 20 years, and 33.2% at 30 years.<sup>13</sup> Meta-analysis showed that the cumulative risk of developing colorectal cancer following diagnosis of Chron's disease is 2.9%.<sup>14</sup>

## PATHOGENESIS

The changes from normal lesions become precancerous lesions and then into gastrointestinal cancers triggered by many factors such as. genetics, infection (e.g. *Helicobacter pylori* infection in gaster,

intestinal tuberculosis infection, etc.), inflammation (e.g. Crohn's disease, ulcerative colitis), diet, stress (anxiety, depression), and oxidative stress or free radicals.<sup>15-17</sup>

Chronic inflammation cells will produce microenvironment that may promote the cancer development and progression.<sup>18</sup> Prolonged and overproduction of cytokines e.g. Tumor Necrosis Factor (TNF- $\alpha$ ), interleukin-6 (IL-6) may induce the production of free radical agents such as reactive oxygen and nitrogen species (ROS and NOS). ROS and NOS will induce DNA damage, genomic instability and alter the transcription factors (nuclear factor-kB), signaling proteins, carcinogenesis factors (p53, DNA Mismatch Repair proteins).<sup>12,18-20</sup> Proinflammatory cytokines may act as tumor growth factor, therefore may induce proliferation of tumor cells. Chronic inflammation also can induce epithelial mesenchymal transition, angiogenesis, and metastasis.<sup>18</sup>

## SUPPORTING EXAMINATION

Supporting examinations used for diagnosis or screening and follow-up of precancerous lesions of the gastrointestinal tract are endoscopy, histopathology examination, examination miRNA.<sup>3,9,21</sup> Gastrointestinal endoscopy must be done regularly and consists of esophagogastroduodenoscopy, colonoscopy and enteroscopy with Chromo-endoscopy staining (blue methylen, indigocarmine, Lugol) or Narrow band imaging technique (NBI) or endo-microscopy examinations. Histopathology examination is an important examination that should be performed to diagnose the presence of precancerous lesions. Histopathology examination of mucosal biopsies obtained through the digestive tract. Histopathology examination was performed with specific staining such as Haematoxylin-eosin (to detect intestinal metaplasia, dysplasia), PAS and HID Alcian blue Alcian blue (to detect subtypes of intestinal metaplasia) or other staining.<sup>9</sup> Examination of endo-microscopy performed using confocal laser endomicroscope Pentax or with Cellvizio probe-based optical mini microscope.<sup>22-25</sup> MiRNA expression can differentiate normal to pathological lesions, and among precancerous lesions, it may be able to classify different subtypes.<sup>3</sup>

## MANAGEMENT

The diagnosis of precancerous lesions of the GI tract is done by history taking of the patients complaints & clinical manifestations, family history of GI tract cancer,

physical examination and supporting examinations.<sup>26</sup> Supporting examinations which is necessary include blood hemoglobin level, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), stool examination i.e. Fecal occult blood (stool occult blood test), fecal calprotectin and fecal M2 Pyruvate Kinase (M2PK).<sup>26-28</sup> Examination with high sensitivity and specificity close to 100% to diagnose precancerous lesion/cancer are esophagogastroduodenoscopy examination, colonoscopy, enteroscopy, Chromo-endoscopy and confocal laser endomicroscopy with biopsy examination and histopathology examination.<sup>21,29</sup> These supporting examinations must be performed periodically to monitor the progress of precancerous lesions.

European Society of Gastroenterology (ESGE), EHSO, ESP and SPED proposed the management of precancerous conditions and lesions in the stomach.<sup>2</sup> Conventional white light endoscopy can not accurately differentiate between and diagnose pre-neoplastic gastric conditions/lesions. Magnification chromoendoscopy or narrow-band imaging (NBI) endoscopy with or without magnification may be offered in these cases as it improves diagnosis of such lesions. At least four biopsies of the proximal and distal stomach, on the lesser and greater curvature, are needed for adequate assessment of premalignant gastric conditions.<sup>2</sup> Systems for histopathological staging (e.g. operative link for gastritis assessment and operative link for gastric intestinal metaplasia assessment) may be useful for identifying subgroups of patients with different risks of progression to gastric cancer, namely those with extensive lesions (i.e., atrophy and/or intestinal metaplasia in both antrum and corpus). Low serum pepsinogen levels can also predict this phenotype and, in such patients, *Helicobacter pylori* serology may be useful for further detection of high risk individuals. Family history of gastric cancer, neither age, gender, *H. pylori* virulence factors, or host genetic variations change these clinical recommendations.<sup>2</sup> Patients with extensive atrophy and/or extensive intestinal metaplasia should be offered endoscopic surveillance every 3 years. Patients with mild to moderate atrophy/intestinal metaplasia only in antrum do not need follow-up. If *Helicobacter pylori* infection is present, eradication should be offered to prevent high grade dysplasia or carcinoma. Currently, the use of cyclooxygenase-2 (COX-2) inhibitors or the use of dietary supplementation with antioxidants (ascorbic acid and beta-carotene) are not endorsed as approaches to decrease the risk of progression of gastric precancerous lesions. Patients with dysplasia

without a visible endoscopic lesion should be closely followed up, either immediately and 6 to 12 months thereafter, or within 12 months, for those with high grade or low grade dysplasia. Those with dysplasia or cancer within an endoscopically visible lesion should undergo staging and resection.<sup>2</sup>

Precancerous lesions of the stomach in the form of chronic atrophic gastritis, intestinal metaplasia and dysplasia can be treated with anti-inflammatory and anti-free radical drugs such as rebamipide and superoxide dismutase (SOD).<sup>30-32</sup> Chronic gastritis caused by *Helicobacter pylori* infection must get an eradication therapy for *H. pylori*.<sup>33</sup> The principle of eradication therapy for *Helicobacter pylori* divided into triple and quadruple therapy. Triple therapy consisted of proton pump inhibitor and 2 antibiotics. Quadruple therapy consisted of bismuth agent (bismuth subcitrate etc), proton pump inhibitor and 2 antibiotics. The proton pump inhibitors which can be used are omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, tenatoprazole. Antibiotics that can eradicate *Helicobacter pylori* infection are amoxicillin, clarithromycin, metronidazole, azithromycin, tetracycline, and levofloxacin.<sup>33,34</sup>

Precancerous lesions in the colon in the form of chronic enterocolitis, dysplasia can be treated with anti-oxidants, anti-inflammatory and anti-free radical anti-oxidants (vitamin A, vitamin C, vitamin E, polyphenols and astaxanthin), rebamipide, superoxide dismutase (SOD), anti-inflammatory drugs (sulfasalazine, mesalamine/5-ASA, corticosteroid), aspirin).<sup>30-32,35-42</sup> Chronic infections in the intestine must be treated with antibiotics according to the cause of infection. If the cause is tuberculosis infection, the patient must be treated with anti tuberculosis drugs for 9-12 months. The anti tuberculosis drugs are isoniazid, rifampicine, ethambutol, pirazinamide, etc.<sup>43,44</sup> Adenoma polyp in the gaster, small intestine and colon must be removed by endoscopic polypectomy as soon as possible.<sup>45,46</sup>

**ALGORITHM OF MANAGEMENT OF PRECANCEROUS LESIONS OF THE GI TRACT**

European Society of Gastroenterology (ESGE), EHSG, ESP and SPED proposed an algorithm (flowchart) for the management of precancerous lesions of the gaster.<sup>2</sup>

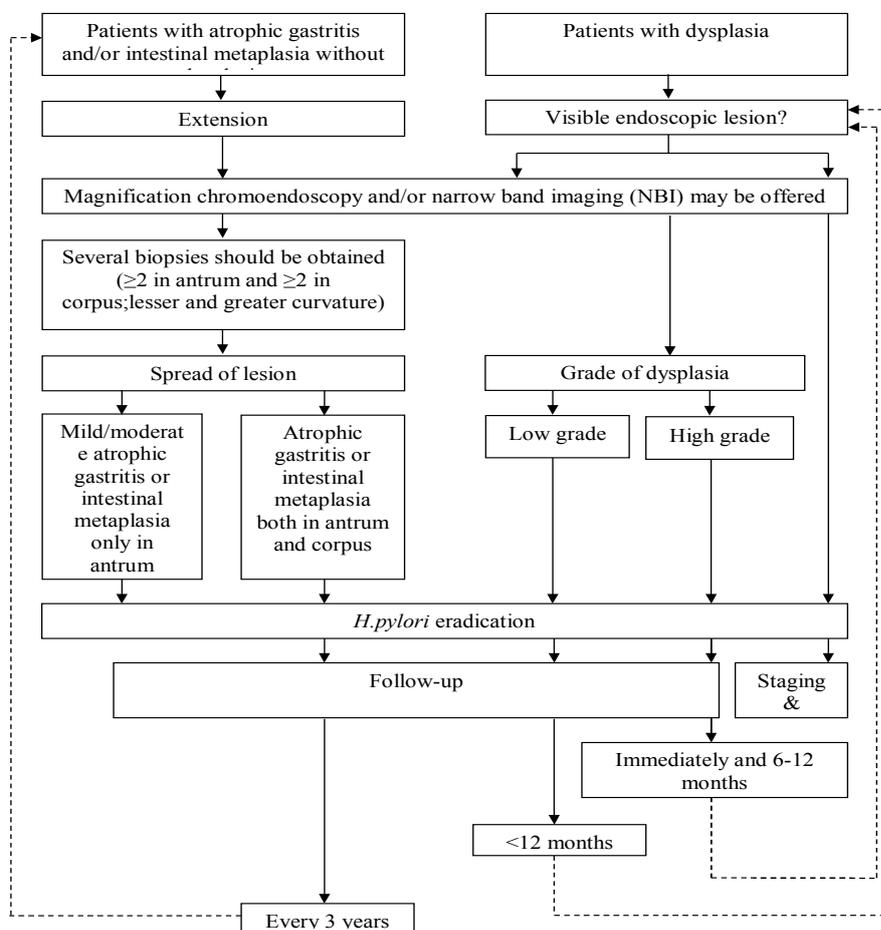


Figure 1. Algorithm (flowchart) for the management of precancerous lesions of the gaster [cited from 2]

World Gastroenterology Organization recommends guidelines for colon cancer and precancerous colon lesions, namely: (1) screening test with a stool test, the fecal occult blood test and fecal DNA; (2) screening test with endoscopy/colonoscopy and CT colonography.<sup>47</sup>

## CONCLUSION

Precancerous lesions of the gastrointestinal tract are lesions that can turn into cancer. Detection, diagnosis, and treatment of precancerous lesions have to be done as early as possible so that we can prevent the occurrence of gastric cancer.

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