Title	Helicobacter pylori associated gastric intestinal metaplasia: Treatment and surveillance
Author(s)	Liu, KSH; Wong, IOL; Leung, WK
Citation	World Journal of Gastroenterology, 2016, v. 22 n. 3, p. 1311-1320
Issued Date	2016
URL	http://hdl.handle.net/10722/223361
Rights	This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i3.1311

World J Gastroenterol 2016 January 21; 22(3): 1311-1320
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Helicobacter pylori associated gastric intestinal metaplasia: Treatment and surveillance

Kevin Sze-Hang Liu, Irene Oi-Ling Wong, Wai K Leung

Kevin Sze-Hang Liu, Wai K Leung, Department of Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

Irene Oi-Ling Wong, School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

Author contributions: Liu KSH, Wong IOL and Leung WK prepared literature review and wrote the paper.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Correspondence to: Wai K Leung, MD, Department of Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China. waikleung@hku.hk
Telephone: +852-22553348
Fax: +852-28162863

Received: May 12, 2015
Peer-review started: May 14, 2015
First decision: July 14, 2015
Revised: August 4, 2015
Accepted: November 30, 2015
Article in press: November 30, 2015
Published online: January 21, 2016

Abstract

Gastric cancer (GC) is one of the leading causes of cancer related death in the world, particularly in East Asia. According to the Correa's cancer cascade, non-cardia GC is usually developed through a series of mucosal changes from non-atrophic gastritis to atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia and adenocarcinoma. Atrophic gastritis and IM are therefore generally considered to be pre-neoplastic gastric lesions. *Helicobacter pylori* (*H. pylori*) infection is an important initiating and promoting step of this gastric carcinogenesis cascade. Emerging long-term data showed that eradication of *H. pylori* reduced the risk of subsequent cancer development. It however remains confusing whether eradication of the bacterium in individuals with pre-neoplastic gastric lesions could regress these changes as well as in preventing cancer. Whilst *H. pylori* eradication could likely regress AG, the presence of IM may be a point of no return in this cascade. Hence, surveillance by endoscopy may be indicated in those with extensive IM or those with incomplete IM, particularly in populations with high GC risk. The optimal interval and the best tool of surveillance endoscopy remains to be determined in future studies.

Key words: *Helicobacter pylori*; Gastric cancer; Intestinal metaplasia; Treatment; Surveillance

Core tip: Gastric intestinal metaplasia (IM) is generally considered to be a pre-neoplastic gastric lesion, which is usually triggered by chronic *Helicobacter pylori* (*H. pylori*) infection. However, the role of *H. pylori* eradication in treating gastric IM remains controversial. It remains uncertain whether the presence of gastric IM signifies an irreversible step of histological progression. Despite the definite increase in risk of gastric cancer development, the role of endoscopic surveillance remains dubious. This review will summarize the latest literature on treatment and surveillance of gastric IM.

Liu KSH, Wong IOL, Leung WK. *Helicobacter pylori* associated gastric intestinal metaplasia: Treatment and surveillance. *World J Gastroenterol* 2016; 22(3): 1311-1320 Available from: URL:

http://www.wjgnet.com/1007-9327/full/v22/i3/1311.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i3.1311

INTRODUCTION

Gastric cancer (GC) is one of the most common cancers in the world and is the third leading cause of cancer mortality[1]. Although the incidence of GC is declining worldwide, the number of new cases is still rising due to population growth and the aging population[2]. In particular, the burden of the disease remains high in East Asian countries. In 2012, almost one million new gastric cancers were diagnosed in the world and half of them occurred in East Asia[3]. Since early cancers are usually asymptomatic, two-thirds of the patients presented at an advanced stage when curative resection was not possible. Despite the advances in treatment, the prognosis of patients with advanced gastric cancer remained dismal with a median survival of less than 1 year[4].

The development of GC is generally believed to be a multistep process involving sequential changes of the gastric mucosa from non-atrophic gastritis to atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia and finally carcinoma[5]. The process is thought to be initiated and promoted by *Helicobacter pylori* (*H. pylori*) and as a result, this bacterium has been classified by the International Agency for Research on Cancer of the World Health Organization as a class Ⅰ carcinogen[6]. In a recent meta-analysis, the relative risk (RR) of developing non-cardia GC in *H. pylori* infected patients was 2.8[7].

Intuitively, eradication of *H. pylori* may halt the progression of the gastric carcinogenesis cascade and therefore reduce the risk of developing GC. Indirect evidence from populations with very low prevalence of *H. pylori*, such as Malays in the northeastern region of Malaysia, also support a decreased risk in developing pre-neoplastic lesions and GC in those populations[8]. However, previous studies that examined the role of *H. pylori* eradication in preventing GC yielded conflicting results, which may be accounted by the heterogeneity in sample size, ethnicity of study population and follow up duration. It remains even more controversial whether the presence of gastric IM is the point of no return in this gastric carcinogenesis cascade. This review examines the latest evidences on the prevention and treatment of *H. pylori* gastric pre-neoplastic conditions, as well as the role of surveillance of these lesions.

H. PYLORI ERADICATION IN PREVENTION OF GASTRIC CANCER IN INDIVIDUALS WITH BASELINE PRE-NEOPLASTIC LESIONS

Due to the long lag time between *H. pylori* infection and cancer development, clinical trials design to investigate the effects of *H. pylori* eradication in preventing GC development are complicated. These trials will require not only prolonged follow-up duration but also large sample size to be conducted in high-risk populations. Several randomized trials have been conducted in the past and the results are summarized in a recent meta-analysis, which showed that eradication of *H. pylori* resulted in 34% reduction in the incidence of GC[9]. However, the benefits may be more prominent in Asian patients where GC is more prevalent, particularly in Chinese men whom the number needed to treat was as low as 15.

Despite the potential benefits of *H. pylori* eradication in preventing GC, it remains more controversial whether the presence of pre-neoplastic lesions will preclude the benefits of eradication in cancer prevention. In the subgroup analysis of a randomized trial of *H. pylori* eradication in preventing gastric cancer in China[10], Wong *et al*[10] showed that the potential benefits of *H. pylori* eradication in preventing GC was limited to patients without precancerous lesions at baseline. In a recent meta-analysis, Chen *et al*[11] looked at the baseline histological changes and the risk of GC after *H. pylori* eradication. They found that although the risk of GC was lowered in the anti-*H. pylori* treatment group (RR = 0.64, 95%CI: 0.48-0.85), subgroup analysis in patients with existing IM and dysplasia could not confirm the potential benefits (RR = 0.88, 95%CI: 0.59-1.31). *H. pylori* eradication also had no effect on regression of these lesions (RR = 0.81, 95%CI: 0.64-1.03). Hence, the presence of IM was believed to be a "point of no return" in the cancer cascade of GC where treatment of *H. pylori* appears to be of no benefit. Nonetheless, in a more recent subgroup analysis of the 15-year effects of *H. pylori* treatment on gastric cancer incidence and mortality, Li *et al*[12] demonstrated that treatment was still associated with a significant reduction in gastric cancer incidence even in patients with baseline IM and dysplasia.

Based on the latest evidence, *H. pylori* treatment should still be recommended to individuals with existing pre-neoplastic lesions with the hope of reducing the risk of GC. The recent revised guidelines from Eastern countries (China, Japan and Korea) and Europe (Maastricht Ⅳ Consensus report) all support *H. pylori* eradication to reduce the risk of gastric cancer[13-16]. Recommended *H. pylori* eradication regimen differed slightly in each region because of the difference in local antibiotic resistance profile. Table 1 summarized the recommended first and second line *H. pylori* eradication regimen from each region. Unfortunately, due to the rising clarithromycin resistance[17], the eradication rate of clarithromycin containing triple therapy is declining globally, sometimes to an unacceptable eradication rate of less than 80%[18]. Several new *H. pylori* eradication regimens, including sequential therapy and concomitant therapy of three antibiotics given over a period of 10-14 d, have been

Table 1 Recommended first and second line *Helicobacter pylori* eradication regimen

	1st line regimen	2nd line regimen
Japan[15]	PPI, amoxicillin 750 mg, clarithromycin 200 mg to 400 mg twice daily Duration: 7 d	PPI, amoxicillin 750 mg, metronidazole 250 mg twice daily Duration: 7 d
Korea[14]	PPI, amoxicillin 1 g, clarithromycin 500 mg twice daily Duration: 7-14 d	PPI, bismuth 120 mg four times daily, tetracycline 500 mg four times daily, metronidazole 500 mg three times daily Duration: 7-14 d
Europe[16]	PPI-clarithromycin containing triple therapy OR Bismuth or non-bismuth containing quadruple[1] Duration: 7-14 d	Bismuth-containing quadruple therapy OR levofloxacin-containing triple Duration: 10 d
China[13]	No preferential choice. Options include: (1)PPI, amoxicillin 1 g, clarithromycin 500 mg twice daily (2) PPI, amoxicillin 1 g, levofloxacin 200 mg twice daily (or levofloxacin 500 mg daily) (3) PPI, amoxicillin 1 g, furazolidone 100 mg twice daily (4) PPI, tetracycline 750 mg, metronidazole 400 mg twice daily (or metronidazole 400 mg three times per day) (5) PPI, bismuth 220 mg plus any of the two antibiotics above twice daily Duration: 7-14 d	

[1]Bismuth quadruple or non-bismuth quadruple (sequential or concomitant) as the preferred choice in regions with high clarithromycin resistance profile (> 20%). Choice of PPI includes lansoprazole 30 mg, omeprazole 20 mg, rabeprazole 20 mg, esomeprazole 20 mg, or pantoprazole 40 mg. PPI: Proton pump inhibitor.

developed to overcome the problem of antimicrobial resistance.

GASTRIC PRE-NEOPLASTIC LESIONS AND RISK OF GC

Whilst gastritis is seen in virtually all *H. pylori* infected subjects, only around 10% of the infected individuals with chronic active gastritis progressed to severe AG[19]. Since this progression is related to chronic inflammation of the gastric mucosa, there is a strong age-associated increase in the prevalence of IM as well[20]. Male gender and those with first-degree family history of GC have been shown to have an increase in risk of developing IM[21]. We have also shown that presence of certain *H. pylori* genotype (*vac*A m1) and polymorphisms of the host inflammatory cytokines (interleukin-1β) were associated with the presence of gastric IM in Chinese population[22]. In the meta-analysis by Marques-Silva *et al*[23], it was also shown that there were wide geographic variations of AG and IM. The prevalence of AG in the worldwide population in general was 33.4% and increased to 42% in countries with high incidence of GC. The prevalence of IM in the worldwide population was 25% whereas extensive IM was found in 13%. In low-prevalence western cohort, the annual incidence of progression to GC is 0.1% for AG, 0.25% for IM and 0.6% for mild to moderate dysplasia[24]. The rate of progression however appears to be higher in Asian population. In a Japanese study, Uemura *et al*[25] showed that the RR of progression to cancer was 1.7, 4.9 and 6.4 in patients with moderate atrophy, severe atrophy and IM, respectively.

Histologically, IM can be further classified into complete or incomplete as originally proposed by Matsukura *et al*[26], which depends on the presence of small intestinal digestive enzymes. It is currently separated into complete or incomplete by the resemblance of small intestinal or colonic epithelium, respectively[27]. Another classification was developed by Jass and Flipe[28], which further classified incomplete IM into type Ⅱ or Ⅲ by the mucin expressions. Type Ⅰ, or complete IM, expresses only sialomucins and type Ⅲ expresses sulfomucins. Type Ⅱ is a hybrid form which expresses a mixture of gastric and intestinal mucins. These subtyping would require the use of combined high-iron diamine and alcian blue staining which is not widely available in routine service laboratory. It also remains undetermined whether there are sequential changes from type Ⅰ to type Ⅲ, and simultaneous expression of different types of mucins are not infrequent[27]. In a recent review by González *et al*[29], the prevalence of type Ⅲ IM were significantly higher in GC in 13 of 14 cross-sectional studies and there was a significant association of type Ⅲ or incomplete IM with GC in 6 of 10 follow-up studies.

Apart from the IM subtypes, the extent of IM is also crucial in determining the subsequent risk of GC. In general, lesions along the lesser curve from the cardia to pylorus [odds ratio (OR) of 5.7] and with diffuse pattern involving essentially the entire gastric mucosa (OR of 12.2) are at higher risk of GC[30]. To this end, the operative link assessment of gastritis assessment (OLGA) staging system was proposed to stage the severity and extent of AG into stages 0 to Ⅳ (Table 2)[31]. This staging system was shown to be very useful in predicting the risk of GC development, particularly in patients with stage Ⅲ-Ⅳ AG. While the unequivocal diagnosis of AG is sometimes difficult and IM is more easily recognizable histologically, a modification to the OLGA to the new staging system of operative link for gastric intestinal metaplasia assessment (OLGIM) by replacing AG with IM system was proposed[32].

Table 2 Operative Link for Gastritis Assessment[31]

	Corpus			
	No atrophy (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
Antrum (including incisura angularis)				
No atrophy (score 0)	Stage 0	Stage Ⅰ	Stage Ⅱ	Stage Ⅱ
Mild atrophy (score 1)	Stage Ⅰ	Stage Ⅰ	Stage Ⅱ	Stage Ⅲ
Moderate atrophy (score 2)	Stage Ⅱ	Stage Ⅱ	Stage Ⅲ	Stage Ⅳ
Severe atrophy (score 3)	Stage Ⅲ	Stage Ⅲ	Stage Ⅳ	Stage Ⅳ

Although the OLGIM was found to provide a better inter-observer agreement than OLGA, a significant proportion of patients with stage Ⅲ-Ⅳ OLGA were missed if only the OLGIM was applied[33]. In high GC risk population such as Korea, it was found that old age, smoking and *H. pylori* infection were associated with high risk OLGA and OLGIM stages[33]. High-risk OLGIM stages were infrequent before the age of 40 (2.8%) but increased to 30.1% for those in the 60s.

H. PYLORI ERADICATION AND CHANGES OF GASTRIC PRE-NEOPLASTIC LESIONS

While eradication of *H. pylori* could restore the gastric mucosa to normal in individuals with *H. pylori* associated chronic gastritis alone[34,35], the role of *H. pylori* treatment in reversing gastric pre-neoplastic changes remain less certain[36]. The presence of IM in the stomach is usually associated with a lower level of *H. pylori* colonization due to the change in gastric mucus and acidity. Hence, the potential therapeutic effect of *H. pylori* eradication may be minimal. In our previous randomized controlled trial in Chinese population, we found that progression of IM was more often in those with persistent *H. pylori* infection, male subjects and those aged more than 45 years[37]. However, eradication of *H. pylori* alone did not prevent progression in all patients, particularly in those with more extensive and severe IM at baseline. In a meta-analysis that included 16 studies[38], the investigators found that there was significant improvement of AG in the gastric antrum and the gastric corpus after treatment for *H. pylori*. As for IM, significant improvements were only seen in the antrum but not in the corpus. Yet, two previous meta-analyses did not find any improvement in IM regardless of the location of the lesions[39,40].

Further long-term follow up studies are therefore necessary to determine whether *H. pylori* eradication could regress gastric IM, particularly those in the corpus. Studies are also needed to address whether there are any changes in gastric IM subtypes after treatment against *H. pylori*.

OTHER TREATMENTS FOR GASTRIC PRE-NEOPLASTIC LESIONS

Apart from treatment against *H. pylori*, other agents have been used for treatment of gastric pre-neoplastic lesions including anti-oxidants and cyclooxygenase-2 (COX-2) inhibitor. COX-2 is an enzyme responsible for the conversion of arachidonic acid to prostaglandins. It has been shown to be overexpressed and involved in gastric IM and cancer[41]. Whilst COX-2 selective inhibitors have been shown to reduce the risk of various cancers including colon and breast cancer, the role of COX-2 inhibitors have been tested in two randomized controlled trial in Chinese patients[42,43]. In our previous randomized controlled study, patients with gastric IM after eradication of *H. pylori* were allocated to receive rofecoxib or placebo for 24 mo. There was no significant difference in the percentage of patients with regression or complete resolution of IM after rofecoxib treatment. In another randomized trial by Wong *et al*[43] patients with *H. pylori* infection and advanced gastric lesions including severe chronic AG, IM and dysplasia were assigned to receive different treatment options including eradication of *H. pylori*, a 2-year course of celecoxib, combination of both or placebo[44]. They found that when compared to placebo, the proportions of patients with regression of gastric lesions were significantly increased in the celecoxib group and the *H. pylori* treatment group. There was however no significant effect in the group who received both anti-*Helicobacter* therapy and celecoxib. More importantly, 9 patients developed early gastric cancer in this study and all except one have indefinite dysplasia or dysplasia at baseline. The remaining patient had baseline deep IM. Together, these data do not suggest an additional benefit of COX-2 inhibitor over treatment of *H. pylori* alone in preventing the progression of gastric IM (Table 3).

Vitamins and other anti-oxidants have also been tested in the treatment of gastric precancerous lesions in a randomized trial in China[44]. Subjects were randomly assigned in a factorial design to receive anti-*Helicobacter* therapy; vitamin C, vitamin E, and selenium (vitamin supplement); or an aged garlic extract and steam-distilled garlic oil (garlic supplement). Although *H. pylori* eradication significantly reduced the combined prevalence of chronic AG, IM, dysplasia or cancer, vitamin or garlic supplement had no effect on gastric precancerous lesions. Hence, there is so far no compelling evidence to support the routine use of vitamins or anti-oxidants.

Smoking and high salt diet have also been linked to the development of gastric pre-neoplastic lesions[45,46].

Table 3 Pharmacological treatment of gastric intestinal metaplasia

Ref.	Intervention	Study design	Countries	Number of patients	Results
Kong *et al*[38], 2014	*H. pylori* eradication	Meta-analysis of 16 trials (including 1 RCT and 15 observational studies)	China, Japan, Italy and Columbia	3432	Antral IM: pooled WMD with 95%CI: 0.23 (0.18-0.29) Corpus IM: pooled WMD with 95%CI: -0.01 (-0.04-0.02)
Leung *et al*[42], 2006	Rofecoxib for 24 mo	RCT (*vs* placebo)	China	213 after *H. pylori* eradication	Antrum IM regression: 24.5% *vs* 26.9% in placebo Corpus IM regression 4.3% *vs* 2.2% in placebo
Wong *et al*[43], 2012	Celecoxib for 24 mo	RCT (*H. pylori* eradication, celecoxib or both)	China	1024 *H. pylori* positive	OR for regression of gastric lesions 1.72 (95%CI: 1.07-2.76)
You *et al*[44], 2006	Vitamins or Anti-oxidants	RCT (*H. pylori* eradication, vitamins or garlic supplements)	China	3365	Both vitamins and garlic supplements have no effect on gastric precancerous lesion

H. pylori: *Helicobacter pylori*; RCT: Randomized controlled trial; WMD: Weighted mean difference.

As yet, there is no clinical trial to look into the role of smoking cessation or diet manipulation on changes of gastric pre-neoplastic lesions.

Whilst gastric dysplasia can also be treated by endoscopic resection like endoscopic mucosal resection or endoscopic submucosal dissection, the role of endoscopic treatment for gastric IM is not defined. With the high success of eradicating IM in the esophagus in patients with Barrett's esophagus[47], we have recently examined the role of endoscopic radiofrequency ablation (RFA) for gastric IM and dysplasia[48]. Although endoscopic RFA could ablate gastric low-grade dysplasia, gastric RFA failed to completely ablate gastric IM. Hence, endoscopic treatment may not be indicated in these patients with gastric IM only.

SURVEILLANCE OF PRE-NEOPLASTIC CONDITIONS

Despite the risk of progression of gastric pre-neoplastic lesions, there is so far no definitive evidence to support the routine surveillance of gastric IM. In a recent Cochrane systemic review of surveillance of gastric IM in the prevention of GC[49], no studies met the inclusion criteria including randomization and a proper comparative group. Hence, there is a genuine need for properly conducted clinical trials to address this issue.

On the other hand, there are several western guidelines published on the recommendation for surveillance of gastric IM. Due to the low risk of gastric cancer in the United States, the American Society for Gastrointestinal Endoscopy does not uniformly recommend surveillance for gastric IM[50]. However, endoscopic surveillance with topographic mapping of the entire stomach in subjects at increased risk of gastric cancer on the basis of ethnic background, immigration from a geographic location with high gastric cancer risk, or family history is recommended. There is also no recommendation on surveillance interval. In 2012, the European Society for Gastrointestinal Endoscopy (ESGE) recommended that patients with IM or GA at both antrum and corpus should be offered surveillance every 3 years[51]. For patients with isolated IM in the antrum, regular surveillance is not recommended. Figure 1 summarizes the management approach recommended by ESGE. It remains to be proven whether this approach is also applicable to Asia where GC is prevalent. In fact, screening of GC is widely practiced in Japan and Korea[52] but there is no national guideline on surveillance of gastric IM. In a recent survey from Korea, it was shown that 95% of specialists perform annual endoscopic surveillance for IM[53].

Since AG and IM are not uniformly distributed in the stomach, proper mapping of the stomach with biopsies taken from both antrum (including incisura) and corpus are necessary for comprehensive assessment of the extent of the lesions. It remains to be determined whether further classification of IM into different subtypes would have more clinical implications on surveillance strategy. It is however prudent to treat extensive IM and incomplete IM cautiously since the risk of progression to GC appears to be higher than patients with focal IM in the antrum only. Further studies are needed to determine the optimal surveillance strategy for patients with different severities of gastric pre-neoplastic lesions, in a manner similar to what we are practicing for surveillance of different colonic adenoma[54].

Although endoscopic surveillance is recommended by the ESGE, the way how it is performed remains uncertain. Unlike colonoscopy performed for colorectal adenoma detection, there is no reliable quality indicator for gastroscopic examination. Routine white light endoscopy with multiple biopsies taken from the antrum and corpus to map the extent of the disease appears to be the standard approach. A recent study from Singapore showed that endoscopic examination times of longer than 7 min identified a greater number of high-risk gastric lesions including cancer, dysplasia, IM and AG than examinations shorter than 7 min[55]. There was a 2-fold difference in the detection rate of high-risk lesions among slow endoscopists regardless of their seniority. Despite the wide use of chromoendoscopy in Japan for gastric cancer screening, this is not widely practiced in other countries

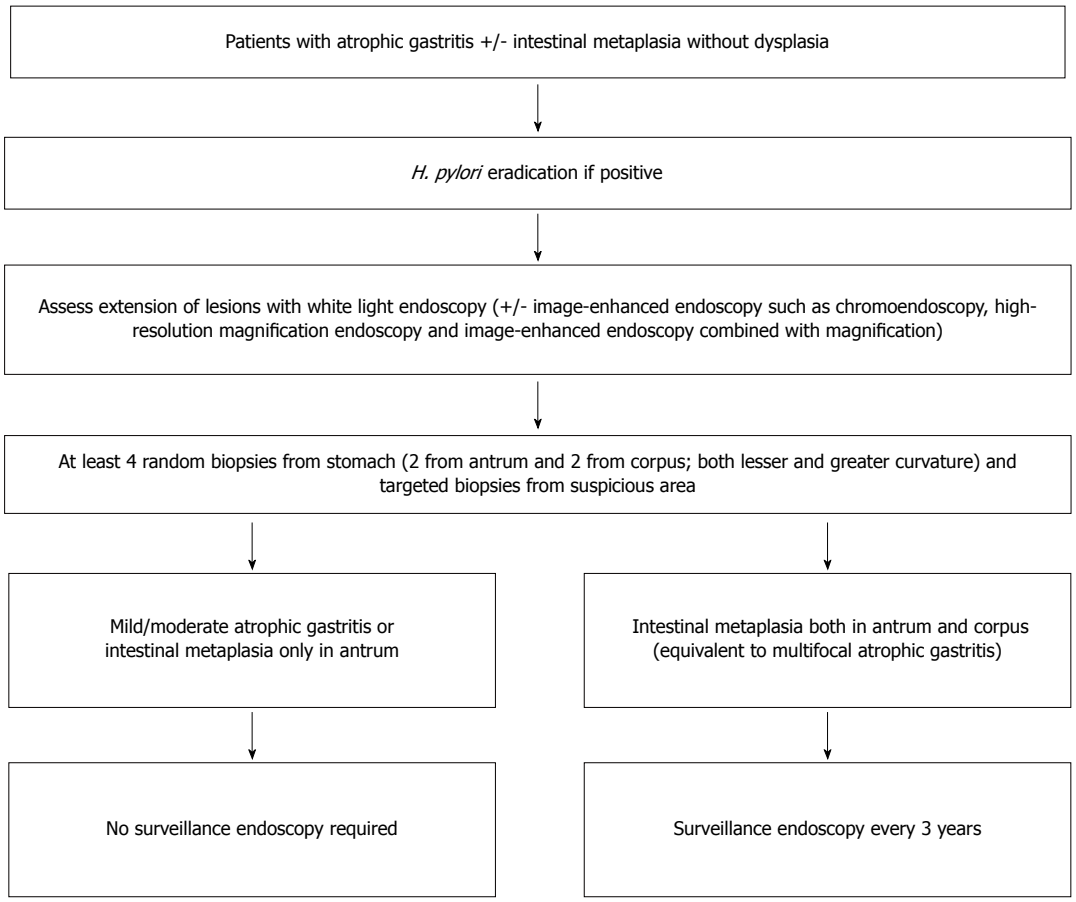

Figure 1 Flow chart for the management of patients with pre-neoplastic conditions. Modified from Dinis-Ribeiro *et al*[51].

due to various issues including examination time and cost. A recent meta-analysis comparing the diagnostic efficacy of white light endoscopy or magnifying endoscopy with narrow band imaging showed that the latter had a higher diagnostic sensitivity than conventional white light endoscopy[56]. Further support of the use of image-enhanced endoscopy was published from the recent Kyoto Global Consensus Conference[57]. In the consensus report, experts recognized the shortfall of random biopsies using conventional endoscopy and suggested that image-enhanced endoscopy including chromoendoscopy, high-resolution magnification endoscopy and image-enhanced endoscopy combined with magnification to increase the yield from biopsies. Nonetheless, there is a need to define in future studies or guidelines the appropriate endoscopic modality for surveillance of these gastric pre-neoplastic lesions.

Over the last decade, there are increasing research on the relationship between genetic alterations and GC development. A number of genes whose functional effects range from inflammation to signal transduction and cell cycle regulation had been identified[58]. For the studies that examined *H. pylori* and pre-neoplastic changes, they generally showed positive association with the frequency of the specific genetic polymorphism with increased severity of changes in gastric mucosa. One particular genome wide association study by Maran *et al*[59] showed specific single nucleotide polymorphisms (SNPs), namely *UFM1*, *THBS4*, *CYP2C19* and *MGST1* genes, were associated with AG, complete IM, incomplete IM and dysplasia, respectively. This may provide an indirect method on surveillance of pre-neoplastic changes and avoid the sampling error from random gastric biopsies. Unfortunately, the genetic polymorphisms association may only be applicable to certain ethnic group. Therefore, the findings of these SNPs changes with different degree of pre-neoplastic changes need to be validated in a different cohort of patients before it can be applied globally.

Another less invasive and simple strategy for surveillance of gastric pre-neoplastic lesions is the use of serum pepsinogen (PG) levels. PGI is secreted by chief and mucous neck cells in the corpus and fundic glands, whereas PGⅡ is secreted by these cells as well as cells in the pyloric glands and Brunner's glands. Hence, any reduction in PGI levels is strongly associated with corpus atrophy. Unlike endoscopic examination that is invasive and skill dependent, measurement of serum PG levels is non-invasive and mass population screening is also possible. In Japanese series, a low serum PGI or a PGI/Ⅱ ratio is a reliable marker for predicting risk of GC[60]. The

use of serum PG screening was also found to be more effective than endoscopic screening in a recent cost-effective analysis[61].

Further non-invasive testing of pre-neoplastic gastric lesions and GC *via* exhaled breath is being investigated. Amal *et al*[62] demonstrated that by applying nanoarray analysis on the exhaled volatile organic compounds could accurately differentiate normal gastric mucosa, pre-neoplastic gastric lesions (based on OLGIM staging system) and GC. The results were encouraging and could be used as a future screening and surveillance tool for gastric pre-neoplastic lesions.

COST EFFECTIVENESS ANALYSIS OF *H. PYLORI* ERADICATION AND SURVEILLANCE OF PRE-NEOPLASTIC CONDITIONS FOR GC PREVENTION

Cost-effectiveness analysis with the use of mathematical model is the mainstream method for economic evaluation in health technology assessment in recent decades[63]. This method is particularly useful to policy makers for making decisions related to healthcare intervention assessment and resource allocations in view of increased healthcare costs and limited budget. Such model is able to simulate disease evolution (*i.e*., provide insights into those uncertain aspects of the natural history of the disease concerned), present a comprehensive epidemiologic model by means of model-based estimates and to improve the basis for projecting the future course of the disease burden. Under such mathematical framework, multiple and diverse data sources on costs, clinical effects, and health-related issues concerning the effects of alternative strategies on one's quality of life are synthesized to estimate intermediate and long-term clinical outcomes. This serves as one of the valuable tools to extend the time horizon of existing clinical trials to assess public health policies than in a single trial, and to evaluate incremental costs and effectiveness of alternative strategies to reduce disease burden[64]. Although primary preventive strategies such as eradicating *H. pylori* infection have been shown in both Caucasian and Asian populations[65-70] to be cost-effective by using the mathematical modeling approach with a population screening scenario, special attention must be paid for the secondary prevention which focuses on surveillance of precancerous lesions in preventing GC. With the huge variations in the GC incidence, prevalence of *H. pylori* infection and pre-neoplastic lesions as well as the cost of screening, the results may not be applicable to all countries. A recent systematic review summarized that there was no consistent evidence on cost-effectiveness of endoscopic surveillance for premalignant gastric conditions[51,71]. Hassan *et al*[72] study concluded that yearly endoscopy surveillance was not cost-effective compared to non-surveillance policy in American patients with IM [incremental cost-effectiveness ratio (ICER) of US$72519 per life-year gained]. Similarly, Yeh *et al*[73] work demonstrated that endoscopic surveillance of less advanced lesions (for IM) did not appear to be cost-effective (ICER of US$544500 per quality-adjusted life-year (QALY) for endoscopic mucosal resection with surveillance every 10 years) for a cohort of US men with a recent incidental diagnosis of gastric precancerous lesions (AG, IM or dysplasia), except possibly for immigrants from high risk countries. Conversely, Areia *et al*[74] study suggested that endoscopic surveillance every 3 years of patients with premalignant conditions was cost-effective compared to no surveillance in a Portuguese population (ICER of Euro$18336 per QALY). The inconsistent results might be likely due to different parameter estimates on progression rates (*e.g*., rates from IM to dysplasia, from dysplasia to gastric cancer) and costing data (*e.g*., endoscopy) being used[51]. There is also no cost-effectiveness analysis study conducted in high-risk population such as Chinese. More research on cost-effectiveness of endoscopic surveillance in IM patients and high-risk groups are warranted.

CONCLUSION

H. pylori is one of the most important causes of GC as well as pre-neoplastic gastric lesions. Eradication of *H. pylori* appears to be the best approach in preventing the development and subsequent progression of gastric pre-neoplastic lesions. Treatment of *H. pylori* should ideally be given at an early stage prior to the development of gastric pre-neoplastic lesions to have the best long-term outcome, but encouraging results are still seen in more recent data of subgroup analysis of older patients with advanced gastric lesions. On the other hand, the role of endoscopic surveillance of these advanced gastric lesions remain uncertain. Universal surveillance is unlikely to be helpful, particularly in low risk population. A selected group of patients at high risk of GC development as identified by proper mapping and staging of gastric histology by OLGA or OLGIM would be the likely sustainable surveillance strategy. More clinical data is desperately needed to characterize the best screening tool as well as the optimal surveillance interval for patients with gastric pre-neoplastic lesions.

REFERENCES

1 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

2 **Yeh JM**, Goldie SJ, Kuntz KM, Ezzati M. Effects of Helicobacter pylori infection and smoking on gastric cancer incidence in China: a population-level analysis of trends and projections. *Cancer*

Causes Control 2009; **20**: 2021-2029 [PMID: 19642005 DOI: 10.1007/s10552-009-9397-9]
3 **Ferlay J**, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 V1.0, Cancer Incidence and Mortality Worldwide. Minnesota: IARC CancerBase No.11, 2013
4 **Cervantes A**, Roda D, Tarazona N, Roselló S, Pérez-Fidalgo JA. Current questions for the treatment of advanced gastric cancer. *Cancer Treat Rev* 2013; **39**: 60-67 [PMID: 23102520 DOI: 10.1016/j.ctrv.2012.09.007]
5 **Correa P**, Piazuelo MB, Camargo MC. The future of gastric cancer prevention. *Gastric Cancer* 2004; **7**: 9-16 [PMID: 15052434 DOI: 10.1007/s10120-003-0265-0]
6 Infection with Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum* 1994; **61**: 177-240 [PMID: 7715070]
7 **Cavaleiro-Pinto M**, Peleteiro B, Lunet N, Barros H. Helicobacter pylori infection and gastric cardia cancer: systematic review and meta-analysis. *Cancer Causes Control* 2011; **22**: 375-387 [PMID: 21184266 DOI: 10.1007/s10552-010-9707-2]
8 **Lee YY**, Mahendra Raj S, Graham DY. Helicobacter pylori infection--a boon or a bane: lessons from studies in a low-prevalence population. *Helicobacter* 2013; **18**: 338-346 [PMID: 23607896 DOI: 10.1111/hel.12058]
9 **Ford AC**, Forman D, Hunt RH, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2014; **348**: g3174 [PMID: 24846275 DOI: 10.1136/bmj.g3174]
10 **Wong BC**, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004; **291**: 187-194 [PMID: 14722144 DOI: 10.1001/jama.291.2.187]
11 **Chen HN**, Wang Z, Li X, Zhou ZG. Helicobacter pylori eradication cannot reduce the risk of gastric cancer in patients with intestinal metaplasia and dysplasia: evidence from a meta-analysis. *Gastric Cancer* 2016; **19**: 166-175 [PMID: 25609452 DOI: 10.1007/s10120-015-0462-7]
12 **Li WQ**, Ma JL, Zhang L, Brown LM, Li JY, Shen L, Pan KF, Liu WD, Hu Y, Han ZX, Crystal-Mansour S, Pee D, Blot WJ, Fraumeni JF, You WC, Gail MH. Effects of Helicobacter pylori treatment on gastric cancer incidence and mortality in subgroups. *J Natl Cancer Inst* 2014; **106**: [PMID: 24925350 DOI: 10.1093/jnci/dju116]
13 **Liu WZ**, Xie Y, Cheng H, Lu NH, Hu FL, Zhang WD, Zhou LY, Chen Y, Zeng ZR, Wang CW, Xiao SD, Pan GZ, Hu PJ. Fourth Chinese National Consensus Report on the management of Helicobacter pylori infection. *J Dig Dis* 2013; **14**: 211-221 [PMID: 23302262 DOI: 10.1111/1751-2980.12034]
14 **Kim SG**, Jung HK, Lee HL, Jang JY, Lee H, Kim CG, Shin WG, Shin ES, Lee YC. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. *J Gastroenterol Hepatol* 2014; **29**: 1371-1386 [PMID: 24758240 DOI: 10.1111/jgh.12607]
15 **Asaka M**, Kato M, Takahashi S, Fukuda Y, Sugiyama T, Ota H, Uemura N, Murakami K, Satoh K, Sugano K. Guidelines for the management of Helicobacter pylori infection in Japan: 2009 revised edition. *Helicobacter* 2010; **15**: 1-20 [PMID: 20302585 DOI: 10.1111/j.1523-5378.2009.00738.x]
16 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]
17 **Mégraud F**, Lamouliatte H. Review article: the treatment of refractory Helicobacter pylori infection. *Aliment Pharmacol Ther* 2003; **17**: 1333-1343 [PMID: 12786627]
18 **Graham DY**, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**: 1143-1153 [PMID: 20525969 DOI: 10.1136/gut.2009.192757]
19 **Venerito M**, Malfertheiner P. Preneoplastic conditions in the stomach: always a point of no return? *Dig Dis* 2015; **33**: 5-10 [PMID: 25531491 DOI: 10.1159/000369185]
20 **Sonnenberg A**, Lash RH, Genta RM. A national study of Helicobactor pylori infection in gastric biopsy specimens. *Gastroenterology* 2010; **139**: 1894-1901.e2; quiz e12 [PMID: 20727889 DOI: 10.1053/j.gastro.2010.08.018]
21 **Leung WK**, Ng EK, Chan WY, Auyeung AC, Chan KF, Lam CC, Chan FK, Lau JY, Sung JJ. Risk factors associated with the development of intestinal metaplasia in first-degree relatives of gastric cancer patients. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 2982-2986 [PMID: 16365021 DOI: 10.1158/1055-9965.EPI-05-0181]
22 **Leung WK**, Chan MC, To KF, Man EP, Ng EK, Chu ES, Lau JY, Lin SR, Sung JJ. H. pylori genotypes and cytokine gene polymorphisms influence the development of gastric intestinal metaplasia in a Chinese population. *Am J Gastroenterol* 2006; **101**: 714-720 [PMID: 16635219 DOI: 10.1111/j.1572-0241.2006.00560.x]
23 **Marques-Silva L**, Areia M, Elvas L, Dinis-Ribeiro M. Prevalence of gastric precancerous conditions: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2014; **26**: 378-387 [PMID: 24569821 DOI: 10.1097/MEG.0000000000000065]
24 **de Vries AC**, van Grieken NC, Looman CW, Casparie MK, de Vries E, Meijer GA, Kuipers EJ. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology* 2008; **134**: 945-952 [PMID: 18395075 DOI: 10.1053/j.gastro.2008.01.071]
25 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297 DOI: 10.1056/NEJMoa001999]
26 **Matsukura N**, Suzuki K, Kawachi T, Aoyagi M, Sugimura T, Kitaoka H, Numajiri H, Shirota A, Itabashi M, Hirota T. Distribution of marker enzymes and mucin in intestinal metaplasia in human stomach and relation to complete and incomplete types of intestinal metaplasia to minute gastric carcinomas. *J Natl Cancer Inst* 1980; **65**: 231-240 [PMID: 6931245]
27 **Correa P**, Piazuelo MB, Wilson KT. Pathology of gastric intestinal metaplasia: clinical implications. *Am J Gastroenterol* 2010; **105**: 493-498 [PMID: 20203636 DOI: 10.1038/ajg.2009.728]
28 **Jass JR**, Filipe MI. The mucin profiles of normal gastric mucosa, intestinal metaplasia and its variants and gastric carcinoma. *Histochem J* 1981; **13**: 931-939 [PMID: 7338482]
29 **González CA**, Sanz-Anquela JM, Gisbert JP, Correa P. Utility of subtyping intestinal metaplasia as marker of gastric cancer risk. A review of the evidence. *Int J Cancer* 2013; **133**: 1023-1032 [PMID: 23280711 DOI: 10.1002/ijc.28003]
30 **Cassaro M**, Rugge M, Gutierrez O, Leandro G, Graham DY, Genta RM. Topographic patterns of intestinal metaplasia and gastric cancer. *Am J Gastroenterol* 2000; **95**: 1431-1438 [PMID: 10894575 DOI: 10.1111/j.1572-0241.2000.02074.x]
31 **Rugge M**, Meggio A, Pennelli G, Piscioli F, Giacomelli L, De Pretis G, Graham DY. Gastritis staging in clinical practice: the OLGA staging system. *Gut* 2007; **56**: 631-636 [PMID: 17142647 DOI: 10.1136/gut.2006.106666]
32 **Capelle LG**, de Vries AC, Haringsma J, Ter Borg F, de Vries RA, Bruno MJ, van Dekken H, Meijer J, van Grieken NC, Kuipers EJ. The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. *Gastrointest Endosc* 2010; **71**: 1150-1158 [PMID: 20381801 DOI: 10.1016/j.gie.2009.12.029]
33 **Isajevs S**, Liepniece-Karele I, Janciauskas D, Moisejevs G, Putnins V, Funka K, Kikuste I, Vanags A, Tolmanis I, Leja M. Gastritis staging: interobserver agreement by applying OLGA and OLGIM systems. *Virchows Arch* 2014; **464**: 403-407 [PMID: 24477629 DOI: 10.1007/s00428-014-1544-3]
34 **Valle J**, Seppälä K, Sipponen P, Kosunen T. Disappearance of gastritis after eradication of Helicobacter pylori. A morphometric

study. *Scand J Gastroenterol* 1991; **26**: 1057-1065 [PMID: 1947772]

35 **Genta RM**, Lew GM, Graham DY. Changes in the gastric mucosa following eradication of Helicobacter pylori. *Mod Pathol* 1993; **6**: 281-289 [PMID: 8346176]

36 **Hojo M**, Miwa H, Ohkusa T, Ohkura R, Kurosawa A, Sato N. Alteration of histological gastritis after cure of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2002; **16**: 1923-1932 [PMID: 12390101]

37 **Leung WK**, Lin SR, Ching JY, To KF, Ng EK, Chan FK, Lau JY, Sung JJ. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on Helicobacter pylori eradication. *Gut* 2004; **53**: 1244-1249 [PMID: 15306578 DOI: 10.1136/gut.2003.034629]

38 **Kong YJ**, Yi HG, Dai JC, Wei MX. Histological changes of gastric mucosa after Helicobacter pylori eradication: a systematic review and meta-analysis. *World J Gastroenterol* 2014; **20**: 5903-5911 [PMID: 24914352 DOI: 10.3748/wjg.v20.i19.5903]

39 **Wang J**, Xu L, Shi R, Huang X, Li SW, Huang Z, Zhang G. Gastric atrophy and intestinal metaplasia before and after Helicobacter pylori eradication: a meta-analysis. *Digestion* 2011; **83**: 253-260 [PMID: 21282951 DOI: 10.1159/000280318]

40 **Rokkas T**, Pistiolas D, Sechopoulos P, Robotis I, Margantinis G. The long-term impact of Helicobacter pylori eradication on gastric histology: a systematic review and meta-analysis. *Helicobacter* 2007; **12** Suppl 2: 32-38 [PMID: 17991174 DOI: 10.1111/j.1523-5378.2007.00563.x]

41 **Sung JJ**, Leung WK, Go MY, To KF, Cheng AS, Ng EK, Chan FK. Cyclooxygenase-2 expression in Helicobacter pylori-associated premalignant and malignant gastric lesions. *Am J Pathol* 2000; **157**: 729-735 [PMID: 10980112 DOI: 10.1016/S0002-9440(10)64586-5]

42 **Leung WK**, Ng EK, Chan FK, Chan WY, Chan KF, Auyeung AC, Lam CC, Lau JY, Sung JJ. Effects of long-term rofecoxib on gastric intestinal metaplasia: results of a randomized controlled trial. *Clin Cancer Res* 2006; **12**: 4766-4772 [PMID: 16899628 DOI: 10.1158/1078-0432.CCR-06-0693]

43 **Wong BC**, Zhang L, Ma JL, Pan KF, Li JY, Shen L, Liu WD, Feng GS, Zhang XD, Li J, Lu AP, Xia HH, Lam S, You WC. Effects of selective COX-2 inhibitor and Helicobacter pylori eradication on precancerous gastric lesions. *Gut* 2012; **61**: 812-818 [PMID: 21917649 DOI: 10.1136/gutjnl-2011-300154]

44 **You WC**, Brown LM, Zhang L, Li JY, Jin ML, Chang YS, Ma JL, Pan KF, Liu WD, Hu Y, Crystal-Mansour S, Pee D, Blot WJ, Fraumeni JF, Xu GW, Gail MH. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. *J Natl Cancer Inst* 2006; **98**: 974-983 [PMID: 16849680 DOI: 10.1093/jnci/djj264]

45 **Kim N**, Park YS, Cho SI, Lee HS, Choe G, Kim IW, Won YD, Park JH, Kim JS, Jung HC, Song IS. Prevalence and risk factors of atrophic gastritis and intestinal metaplasia in a Korean population without significant gastroduodenal disease. *Helicobacter* 2008; **13**: 245-255 [PMID: 18665932 DOI: 10.1111/j.1523-5378.2008.00604.x]

46 **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740 [PMID: 1458460]

47 **Shaheen NJ**, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, Galanko JA, Bronner MP, Goldblum JR, Bennett AE, Jobe BA, Eisen GM, Fennerty MB, Hunter JG, Fleischer DE, Sharma VK, Hawes RH, Hoffman BJ, Rothstein RI, Gordon SR, Mashimo H, Chang KJ, Muthusamy VR, Edmundowicz SA, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Falk GW, Kimmey MB, Madanick RD, Chak A, Lightdale CJ. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009; **360**: 2277-2288 [PMID: 19474425 DOI: 10.1056/NEJMoa0808145]

48 **Leung WK**, Tong DK, Leung SY, Chan FS, Ho RS, Chu KM, Law SY. Treatment of gastric metaplasia or dysplasia by endoscopic radiofrequency ablation: A pilot study. *Hepatogastroenterology* 2015; **62**: 748-751 [DOI: 10.5754/hge14816]

49 **O'Connor A**, McNamara D, O'Moráin CA. Surveillance of gastric intestinal metaplasia for the prevention of gastric cancer. *Cochrane Database Syst Rev* 2013; **9**: CD009322 [PMID: 24062262 DOI: 10.1002/14651858.CD009322.pub2]

50 **Hirota WK**, Zuckerman MJ, Adler DG, Davila RE, Egan J, Leighton JA, Qureshi WA, Rajan E, Fanelli R, Wheeler-Harbaugh J, Baron TH, Faigel DO. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006; **63**: 570-580 [PMID: 16564854 DOI: 10.1016/j.gie.2006.02.004]

51 **Dinis-Ribeiro M**, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, Pereira C, Pimentel-Nunes P, Correia R, Ensari A, Dumonceau JM, Machado JC, Macedo G, Malfertheiner P, Matysiak-Budnik T, Megraud F, Miki K, O'Morain C, Peek RM, Ponchon T, Ristimaki A, Rembacken B, Carneiro F, Kuipers EJ. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). *Endoscopy* 2012; **44**: 74-94 [PMID: 22198778 DOI: 10.1055/s-0031-1291491]

52 **Leung WK**, Wu MS, Kakugawa Y, Kim JJ, Yeoh KG, Goh KL, Wu KC, Wu DC, Sollano J, Kachintorn U, Gotoda T, Lin JT, You WC, Ng EK, Sung JJ. Screening for gastric cancer in Asia: current evidence and practice. *Lancet Oncol* 2008; **9**: 279-287 [PMID: 18308253 DOI: 10.1016/S1470-2045(08)70072-X]

53 **Shin WG**, Kim HU, Song HJ, Hong SJ, Shim KN, Sung IK, Kim JG. Surveillance strategy of atrophic gastritis and intestinal metaplasia in a country with a high prevalence of gastric cancer. *Dig Dis Sci* 2012; **57**: 746-752 [PMID: 21984437 DOI: 10.1007/s10620-011-1919-0]

54 **Levin B**, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, Dash C, Giardiello FM, Glick S, Johnson D, Johnson CD, Levin TR, Pickhardt PJ, Rex DK, Smith RA, Thorson A, Winawer SJ. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008; **134**: 1570-1595 [PMID: 18384785 DOI: 10.1053/j.gastro.2008.02.002]

55 **Teh JL**, Tan JR, Lau LJ, Saxena N, Salim A, Tay A, Shabbir A, Chung S, Hartman M, So JB. Longer examination time improves detection of gastric cancer during diagnostic upper gastrointestinal endoscopy. *Clin Gastroenterol Hepatol* 2015; **13**: 480-487.e2 [PMID: 25117772 DOI: 10.1016/j.cgh.2014.07.059]

56 **Zhang Q**, Wang F, Chen ZY, Wang Z, Zhi FC, Liu S, Bai Y. Comparison of the diagnostic efficacy of white light endoscopy and magnifying endoscopy with narrow band imaging for early gastric cancer: a meta-analysis. *Gastric Cancer* 2015; Epub ahead of print [PMID: 25920526 DOI: 10.1007/s10120-015-0500-5]

57 **Sugano K**, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, Haruma K, Asaka M, Uemura N, Malfertheiner P. Kyoto global consensus report on Helicobacter pylori gastritis. *Gut* 2015; **64**: 1353-1367 [PMID: 26187502 DOI: 10.1136/gutjnl-2015-309252]

58 **Mocellin S**, Verdi D, Pooley KA, Nitti D. Genetic variation and gastric cancer risk: a field synopsis and meta-analysis. *Gut* 2015; **64**: 1209-1219 [PMID: 25731870 DOI: 10.1136/gutjnl-2015-309168]

59 **Maran S**, Lee YY, Xu S, Rajab NS, Hasan N, Syed Abdul Aziz SH, Majid NA, Zilfalil BA. Gastric precancerous lesions are associated with gene variants in Helicobacter pylori-susceptible ethnic Malays. *World J Gastroenterol* 2013; **19**: 3615-3622 [PMID: 23801863 DOI: 10.3748/wjg.v19.i23.3615]

60 **Watabe H**, Mitsushima T, Yamaji Y, Okamoto M, Wada R, Kokubo T, Doi H, Yoshida H, Kawabe T, Omata M. Predicting the development of gastric cancer from combining Helicobacter pylori antibodies and serum pepsinogen status: a prospective endoscopic cohort study. *Gut* 2005; **54**: 764-768 [PMID: 15888780 DOI:

10.1136/gut.2004.055400]
61 **Yeh JM**, Hur C, Ward Z, Schrag D, Goldie SJ. Gastric adenocarcinoma screening and prevention in the era of new biomarker and endoscopic technologies: a cost-effectiveness analysis. *Gut* 2015; Epub ahead of print [PMID: 25779597 DOI: 10.1136/gutjnl-2014-308588]
62 **Amal H**, Leja M, Funka K, Skapars R, Sivins A, Ancans G, Liepniece-Karele I, Kikuste I, Lasina I, Haick H. Detection of precancerous gastric lesions and gastric cancer through exhaled breath. *Gut* 2015; Epub ahead of print [PMID: 25869737 DOI: 10.1136/gutjnl-2014-308536]
63 **Hunink MGM**. Decision making in health and medicine: integrating evidence and values. New York: Cambridge University Press, 2001
64 **Goldie SJ**. Chapter 15: Public health policy and cost-effectiveness analysis. *J Natl Cancer Inst Monogr* 2003; (**31**): 102-110 [PMID: 12807953]
65 **Parsonnet J**, Harris RA, Hack HM, Owens DK. Modelling cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer: a mandate for clinical trials. *Lancet* 1996; **348**: 150-154 [PMID: 8684154]
66 **Fendrick AM**, Chernew ME, Hirth RA, Bloom BS, Bandekar RR, Scheiman JM. Clinical and economic effects of population-based Helicobacter pylori screening to prevent gastric cancer. *Arch Intern Med* 1999; **159**: 142-148 [PMID: 9927096]
67 **Xie F**, Luo N, Lee HP. Cost effectiveness analysis of population-based serology screening and (13)C-Urea breath test for Helicobacter pylori to prevent gastric cancer: a markov model. *World J Gastroenterol* 2008; **14**: 3021-3027 [PMID: 18494053 DOI: 10.3748/wjg.14.3021]
68 **Xie F**, Luo N, Blackhouse G, Goeree R, Lee HP. Cost-effectiveness analysis of Helicobacter pylori screening in prevention of gastric cancer in Chinese. *Int J Technol Assess Health Care* 2008; **24**: 87-95 [PMID: 18218173 DOI: 10.1017/S0266462307080117]
69 **Yeh JM**, Kuntz KM, Ezzati M, Goldie SJ. Exploring the cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer in China in anticipation of clinical trial results. *Int J Cancer* 2009; **124**: 157-166 [PMID: 18823009 DOI: 10.1002/ijc.23864]
70 **Wong IO**, Schooling CM, Cowling BJ. Cost-effectiveness of Helicobacter pylori screening and treatment for gastric cancer in Hong Kong: a decision analytic approach. *Hong Kong Med J* 2014; **20** Suppl 7: 13-15 [PMID: 25647818]
71 **Areia M**, Carvalho R, Cadime AT, Rocha Gonçalves F, Dinis-Ribeiro M. Screening for gastric cancer and surveillance of premalignant lesions: a systematic review of cost-effectiveness studies. *Helicobacter* 2013; **18**: 325-337 [PMID: 23566268 DOI: 10.1111/hel.12050]
72 **Hassan C**, Zullo A, Di Giulio E, Annibale B, Lahner E, De Francesco V, Ierardi E. Cost-effectiveness of endoscopic surveillance for gastric intestinal metaplasia. *Helicobacter* 2010; **15**: 221-226 [PMID: 20557364 DOI: 10.1111/j.1523-5378.2010.00752.x]
73 **Yeh JM**, Hur C, Kuntz KM, Ezzati M, Goldie SJ. Cost-effectiveness of treatment and endoscopic surveillance of precancerous lesions to prevent gastric cancer. *Cancer* 2010; **116**: 2941-2953 [PMID: 20564399 DOI: 10.1002/cncr.25030]
74 **Areia M**, Dinis-Ribeiro M, Rocha Gonçalves F. Cost-utility analysis of endoscopic surveillance of patients with gastric premalignant conditions. *Helicobacter* 2014; **19**: 425-436 [PMID: 25164596 DOI: 10.1111/hel.12150]

P- Reviewer: Gucin Z, Kim GH, Lee YY, Ruiz-Bustos E
S- Editor: Yu J **L- Editor**: A **E- Editor**: Zhang DN

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327