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REVIEW

Gastric cancer: Prevention, screening and early diagnosis

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Abstract

Gastric cancer continues to be an important healthcare problem from a global perspective. Most of the cases in the Western world are diagnosed at late stages when the treatment is largely ineffective. *Helicobacter pylori* (*H. pylori*) infection is a well-established carcinogen for gastric cancer. While lifestyle factors are important, the efficacy of interventions in their modification, as in the use of antioxidant supplements, is unconvincing. No organized screening programs can be found outside Asia (Japan and South Korea). Although several screening approaches have been proposed, including indirect atrophy detection by measuring pepsinogen in the circulation, none of them have so far been implemented, and more study data is required to justify any implementation. Mass eradication of *H. pylori* in high-risk areas tends to be cost-effective, but its adverse effects and resistance remain a concern. Searches for new screening biomarkers, including microRNA and cancer-autoantibody panels, as well as detection of volatile organic compounds in the breath, are in progress. Endoscopy with a proper biopsy follow-up remains the standard for early detection of cancer and related premalignant lesions. At the same time, new advanced high-resolution endoscopic technologies are showing promising results with respect to diagnosing mucosal lesions visually and targeting each biopsy. New histological risk stratifications (classifications), including OLGA and OLGIM, have recently been developed. This review addresses the current means for gastric cancer primary and secondary prevention, the available and emerging methods for screening, and new developments in endoscopic detection of early lesions of the stomach.

Key words: Gastric cancer; *Helicobacter pylori*

Core tip: Gastric cancer remains an important healthcare problem from a global perspective during the upcoming decades. Most of the cases in the Western world are diagnosed at late stages when the treatment is substantially less effective. *Helicobacter pylori* infection is a well-established carcinogen for gastric cancer.

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INTRODUCTION

Altogether 989000 new gastric cancer (GC) cases are estimated to arise annually worldwide[1], but with substantial regional differences in incidence. The highest is in East Asia, Eastern Europe, and parts of central and Southern America, with the lowest in Southern Asia, North and East Africa, Australia and North America[1-3]. More than 70% of gastric cancers occur in developing countries due to poor standards of hygiene and higher

Helicobacter pylori (*H. pylori*) prevalence rates[2].

The majority of gastric cancer cases are related to *H. pylori* infection, with a conservative estimate of 74.7% of all the non-cardia GCs (*i.e.*, 650000 cases annually) being related to this infection[4], but realistically the proportion of these infection-related cancers could be higher. The Eurogast-EPIC study in Europe found 93.2% of gastric cancer cases positive for *H. pylori*[5], whereas in Japan only 0.66% of the cancer patients showed no signs of infection[6].

The World Health Organization (WHO) had classified *H. pylori* as a class I carcinogen as early as 1994[7], and this has been reinforced more recently by the International Agency for Research on Cancer (IARC)[8]. The cascade of premalignant (pre-cancerous) lesions preceding the development of GC and including atrophy, intestinal metaplasia (IM) and dysplasia of the stomach mucosa is well-recognized[9]. Dysplasia is further subdivided into low-grade and high-grade dysplasia, both being considered advanced premalignant lesions, but with the latter bearing a higher GC development risk[10]. The term premalignant or precancerous is reserved for clinical conditions associated with a significantly increased risk of cancer, but not is obligatorily characterized by a specific histological abnormality; gastric ulcer and mucosal hyperplasia would also be attributable to this group[10,11].

The disease incidence shows a falling trend over several decades, starting in subjects born after the beginning of 19th century[12]. In addition to the decline in prevalence of *H. pylori* infection *per se*, this has most likely been the result of a significant reduction in a number of risk factors, including changes in food preservation, improved hygiene, fall in smoking, and increase in the use of antibiotics[13]. At the same time, rising gastric cancer incidences in some indigenous groups have emerged from a recent systematic review by Arnold *et al*[14].

Although the incidence and mortality of the disease are declining globally when estimated in age-standardized figures, the absolute number of GC cases remains stable or may even increase due to the predicted growth of the world population and increasing longevity[15].

The 5-year survival rate continues to be poor, with the exception of Japan. In Western countries, including Europe and the United States, 5-year survival does not exceed 25%[16], whereas 52% survival has been reported in Japan[17], and where early diagnosis of diagnosed cancer confined to the inner lining of the stomach wall has been confirmed, a 5-year survival rate of 95% can be reached[18]. The problem of late diagnostics is due to a substantial proportion of patients with early stage disease being asymptomatic, or else unspecified[19].

Therefore, it is critical to diagnose the disease at an early stage for radical cure to be possible. Ideally, the disease should be prevented before premalignant lesions have developed, either by the reduction (elimination) of the risk factors or surveillance and management of the premalignant (precancerous) conditions. Thereafter, we have tried to review both the available and the potential strategies that could help reach this goal by addressing their benefits and drawbacks.

PREVENTION

Primary and secondary prevention

The ideal and ultimate aim of GC prevention is to minimize cancer incidence and mortality rates. GC prophylaxis includes both primary and secondary prevention strategies. Primary prevention involves avoidance of known carcinogens, enhancement of host defense mechanisms, changes in lifestyle, and chemoprevention[20]. In infection-related cancers, eradication of the responsible pathogen has to be considered as a measure of primary prevention[21]. Secondary prophylaxis includes screening and treating premalignant lesions or early stage cancers[22]. The latter might be considered also tertiary prevention, *i.e.*, follow-up of patients in whom the disease has been confirmed.

The primary cancer prevention strategy has an epidemiological and a medical approach. The purpose of the epidemiological method is to decrease cancer rate and mortality by improving lifestyle through exclusion of causal factors and supplementation with preventive factors known to be anti-carcinogenic. The purpose of the medical method is to eradicate the causative microorganism and to inhibit development of the cancer by prescribing medicines with direct anti-carcinogenic actions. Eradication of *H. pylori* by antimicrobial treatment, with additional administration of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, has been assessed for chemoprevention of GC[20].

Impact of lifestyle and antioxidants

The impact of lifestyle has been addressed in either epidemiological retrospective studies or experimental investigations, as well as interventional studies. The possibility of interfering with lifestyle changes or agents bearing low adverse event risk, such as antioxidants, would be of considerable interest; however, the results of interventional studies have to be clearly separated from epidemiological evidence due to the different durations that individuals are exposed to these above mentioned factors.

A study using an animal model (Mongolian gerbils infected with *H. pylori*) demonstrated dose-dependent augmentation of stomach carcinogenesis by salt, along with alterations in the mucous microenvironment[23]. The augmenting action of salt was absent in *H. pylori*-negative Mongolian gerbils. Consumption of fresh fruit and vegetables significantly reduces gastric cancer risk, as demonstrated in numerous prospective studies. A cohort study by the Japan Public Health Center revealed, after 10 years of follow-up, that consumption of vegetables and fruit on one or more days per week was related to a lower GC risk than consumption less than once per week[24]. Cohort studies published before 2004 indicated the opposite association between fruit and vegetable

intake and GC incidence, stronger for follow-up periods of > 10 years[25].

The protective effect of vegetables and fruit against GC might be explained by the content of ascorbic acid, carotenoid and beta-carotene. Ascorbic acid is an anti-oxidant that significantly reduces mitotic activity in tumor cells without disturbing the growth of normal cells[26]. Carotenoid is another important anti-oxidant that protects against free radical-induced injury[27]. Since beta-carotene, a retinol precursor, possesses anti-cancer activities, it could be used to prevent gastric carcinogenesis[28]. Green tea contains polyphenols, better known as catechins. These include epigallocatechin-3-gallate, a substance proven to suppress carcinogenesis in *in vitro* and *in vivo* studies[29,30].

Three publications about chemoprevention were aimed at assessing the antioxidant effects of vitamin supplementation on precancerous stomach lesions[31-33]. These randomized trials, designed as double-blind and placebo-controlled, were conducted on cohorts at high risk of GC. The trial results were conflicting, and the quality of the results was compromised by substantial loss to follow-up and/or withdrawal in two of the studies[31,32]. Correa *et al*[31] reported that the patients randomized to a distinct active intervention with either ascorbic acid (1 g BID), beta-carotene (30 mg/d) or anti-*H. pylori* eradication therapy were three times more likely to exhibit improved mucosal legion histology in the stomach following a 6-year period of observation. However, this antioxidant advantage vanished over a further 6-year period without continuous vitamin supplementation, as revealed by re-evaluation after 12 years of the study[34].

Conversely, a trial in Linqu County, Shandong, China, failed to report any beneficial effect on the frequency of precancerous stomach conditions and/or lesions after 7.2 years of vitamin supplement investigation (250 mg ascorbic acid with 100 IU vitamin E and with 37.5 μL selenium BID)[33]. Correspondingly, Plummer *et al*[32], in a study with randomized patients receiving either vitamins (250 mg ascorbic acid with 200 mg vitamin E and with 6 mg beta-carotene/TID) or placebo over three years, found no noteworthy link between vitamin supplementation and the progression or regression of precancerous stomach conditions and/or lesions.

The above-mentioned studies were conducted in Columbia, Venezuela, and China, in cohorts with a high incidence of GC[31-33], which makes it difficult to extrapolate the data and conclusions more widely, to cohorts with a lower incidence of GC.

Therefore, the studies do not present unequivocal evidence that antioxidant supplementations of the regular diet for medicinal purposes helps prevent GC[10]; one possible explanation is that such trials have not run long enough to assess the true situation.

Chemoprevention

In addition to antioxidant supplementation for chemoprevention discussed above, the potential use of NSAIDs has been under investigation. Overexpression of cyclo-oxygenase (COX)-2 has been detected, and the possibility that its inhibition can be chemopreventive has been investigated in a number of cancers. COX-2 overexpression arises in non-cardiac stomach cancers and also in well-differentiated stomach cancers[35]. A cohort study with a meta-analysis indicated that aspirin significantly reduced the risk of non-cardiac cancer but not of cardiac cancer[36]. A Taiwanese cohort study with multivariate analysis suggested that systematic use of NSAIDs was an autonomous defensive against GC development[37]. Long-term use of a selective COX-2 inhibitor decreased the rate of development of metachronous cancer after endoscopic resection of early cancer of the stomach, with similar effectiveness to *H. pylori* eradication[38]. Systematic administration of non-selective NSAIDs such as aspirin seems to decrease the risk for development of stomach cancer, according to the results of retrospective cohort studies[37] and meta-analyses[39].

Meta-analyses of observational studies have established that longstanding non-selective suppression of COX using NSAIDs is a powerful chemopreventive approach to gastric carcinogenesis[39,40].

The efficacy of COX-2 inhibitors in preventing the progression of precancerous gastric lesions was investigated in several medical trials including Asian populations. The overall assessment varied, irrespective of the drugs used. Apart from one placebo-controlled randomized controlled trial (RCT)[41], the protective activity of these drugs on precancerous stomach mucosal lesions was demonstrated only in low quality trials, including one small RCT[42], one pilot trial[43] and two prospective cohort studies[38,44]. The studies were performed on very diverse populations including first-degree relatives of stomach cancer patients, or dyspeptic patients suffering from rheumatological diseases, or patients with early stomach cancer, *etc*. This precludes any possibility of overview and analysis of the results.

The efficacy on precancerous gastric lesions was studied in trials of selective COX-2 inhibitors such as rofecoxib, etodolac, and celecoxib. In an RCT, rofecoxib taken by patients over two years conferred no important advantage for regression of IM after eradication of *H. pylori*[41]. Yanaoka *et al*[38] treated patients with 300 mg/d of etodolac and reported an increased incidence of metachronous cancer after a long follow-up period. The authors observed no important variation in the range of precancerous conditions and/or lesions, either with or without administration of etodolac.

A series of studies investigated the ability of a selective COX-2 inhibitor, celecoxib, to decrease the degree of precancerous stomach mucosal conditions and/or lesions after *H. pylori* eradication. In a small randomized trial, a 67% reduction in precancerous gastric lesions was revealed after 12 wk administration of celecoxib[42]. In another study, administration of celecoxib for eight weeks led to a comprehensive regression of IM in 29% of patients with established eradication of *H. pylori*[43]. Fur-

thermore, an improvement in IM severity was noticed in those patients without complete regression ($P < 0.007$)[43]. Yang *et al*[44] demonstrated that dyspeptic patients with rheumatological diseases exhibited a greater degree of regression of IM with prolonged use of celecoxib than in non-NSAID users, but only after successful *H. pylori* eradication. Currently no medical chemoprevention can be recommended for routine use in preventing the development of GC[10].

H. pylori eradication

It is generally recognized and accepted that most GCs, including both intestinal and diffuse types, develop in stomach mucosa infected by *H. pylori*, and that GC very rarely appears in gastric mucosa in the absence of inflammation. *H. pylori* is therefore significant in the development of GC[45]. Certain *H. pylori* virulence factors and certain host genetic polymorphisms are known to affect the risk of any specific individual developing *H. pylori*-associated disease, particularly peptic ulcer and GC[46]. *H. pylori cagA*-positive strains have been confirmed as significantly associated with GC[47].

In experimental models of gastric cancer conducted on Mongolian gerbils, *H. pylori* eradication lowered the rate of GC[48]. This experiment implied that early *H. pylori* eradication was as successful at suppressing stomach carcinogenesis as in the medium or late stages[49].

The regression of atrophic gastritis after *H. pylori* eradication has been shown in several controlled[33,50,51] and uncontrolled studies[52]. Atrophic gastritis of the gastric body is of particular interest as it may pose a higher risk of cancer, and fortunately evidence of its regression, with eradication, seems to be assured[53]. However, a meta-analysis of this subject indicated that gastric atrophic changes could be reversible in cases located in the corpus but not the antrum[54]. The possibility of regression of gastric mucosal atrophy seems to depend on the size and topographical distribution of atrophy[54]; yet it is uncertain whether the results of *H. pylori* eradication differ with the site and the size of atrophy.

A randomized trial and a meta-analysis revealed that *H. pylori* eradication significantly restores gastric histology to normal[55,56] in chronic gastritis and atrophic gastritis without IM. In a systematic review it was established that atrophic gastritis can undergo regression within one or two years after successful eradication of *H. pylori*[57].

The presence of IM in *H. pylori*-associated chronic gastritis suggests a less reversible stage than atrophic gastritis alone. The evidence suggests that eradication at the IM stage is less effective and more likely to progress[54]. The idea of reversibility of IM after *H. pylori* eradication has been completely refuted[58,59]. Lower *H. pylori* colonization of areas with IM could indicate that the advantage of eradication is limited. The results of two meta-analyses on this topic also established that there is no substantial regression of IM following *H. pylori* eradication[54,56]. Nevertheless, Correa *et al*[31] in a randomized 6-year follow-up trial, indicated that successful anti-*H. pylori* treatment in patients with preneoplastic mucosal changes, along with dietary antioxidant micronutrient supplementation, can inhibit the precancerous process, most probably by accelerating the regression of precancerous stomach mucosal conditions and/or lesions as well as IM. This reversion of atrophy and IM was confirmed after twelve years of follow-up[34]. However, there is need to prove whether eradication at the stages of atrophy and/or IM decreases the risk of GC.

One randomized trial from China was unsuccessful in proving that *H. pylori* eradication considerably reduced the rate of GC[60]. However, taking into account only the group of patients deprived of preneoplasic conditions and/or lesions at the outset, the incidence of GC over 7.5 years decreased after *H. pylori* eradication. A further meta-analysis, containing four randomized intervention trials with observation over 5-12 years matching *H. pylori* eradication therapy against placebo therapy for preventing GC, demonstrated a minor trend in favor of *H. pylori* eradication therapy. Further examination with insertion of non-randomized trials with observation from 3 to 8.5 years revealed a substantial decrease in cancer rate after eradication[61]. The meta-analysis updated by the authors revealed that the comparative risk for GC after *H. pylori* eradication was 0.65[62]. The authors proposed that the reduction of gastric cancer incidence could be relevant for a subgroup of patients, possibly those in the initial stages of non-atrophic gastritis[61,62]. De Vries *et al*[57] in a systematic review, established satisfactory clinical proof that *H. pylori* eradication can help to prevent GC in patients with both chronic non-atrophic and atrophic gastritis. A prospective trial also indicated that *H. pylori* eradication preceding the appearance of IM is possibly more successful in decreasing the rate of gastric cancer[63].

In four prospective trials assessing the effect of *H. pylori* eradication on the development of premalignant conditions and/or lesions up to GC, the authors were unable to detect a substantial decrease in cancer risk[33,34,50,60].

Studies of patients with previous endoscopic resection of GC who had widespread IM demonstrated that the risk of cancer was considerably decreased after successful *H. pylori* eradication[64,65]. In any case, *H. pylori* eradication decreases the development of IM in the stomach mucosa[50,66,67]. Yet GC still arises in the setting of IM[63,68] even following successful *H. pylori* eradication. Therefore, evidence concerning the ability of *H. pylori* eradication to reduce the risk of cancer in cases of widespread IM is lacking, though it seems to reduces progression.

Kodama *et al*[69] examined their subjects each year for 10 years at 5 sites of the gastric mucosa, in accordance with the updated Sydney system following eradication of *H. pylori*. Atrophy at all 5 points and IM in the lesser curvature of the corpus showed significant improvement during the follow-up period, which suggests that improvement of gastric atrophy and IM might be associated with the reduction of GC occurrence.

Lee *et al*[70] first assessed the advantage of mass eradication of *H. pylori* infection for suppressing precancerous

gastric lesions. This mass eradication began in 2004 for Taiwanese patients of over 30 years of age in Matzu island, where *H. pylori* infection is prevalent. Patients who were positive for the ^{13}C-urea breath test underwent endoscopy and received clarithromycin-based triple therapy. If the treatment was ineffective, a 10-d triple therapy based on levofloxacin was prescribed. The main results were changes in the frequencies of *H. pylori* infection and precancerous gastric lesions. The mass eradication of *H. pylori* infection was associated with a substantial decrease in gastric mucosal atrophy but not in IM. The efficacy of the chemoprevention in decreasing the gastric cancer rate was 25%.

Park *et al*[71] concluded that appropriately designed studies are now required before deciding on population-wide prevention programs, which should also consider the potential risks of mass antibiotic treatment and its effect on gut flora[71].

H. pylori eradication has been suggested by numerous societies. For instance, there are guidelines for patients with GC after subtotal gastrectomy[72-74]. The eradication of *H. pylori* in GC patients with prior endoscopic resection reduces the incidence of new tumors and the extent of IM[65]. In a multicenter randomized controlled study[64], patients with GC were assigned for eradication or none, with analogous starting point characteristics in each group. After three years of follow-up, 24 metachronous tumors had arisen in the non-eradication group compared with nine in the eradication group. These examples demonstrate the protective effect of *H. pylori* eradication against the development of metachronous tumors after resection of the primary tumor.

The data regarding the effect of *H. pylori* eradication on the development of gastric epithelial dysplasia are contradictory[31,33,34]. Overall, the evidence to date suggests that dysplastic changes are unaffected by eradication, but a possible benefit of eradication for patients with dysplasia is a lower incidence of metachronous tumors. These considerations indicate that *H. pylori* eradication is strongly recommended for patients with a previous history of GC or dysplasia.

Choi[75] has published a summary of the Consensus reports on *H. pylori* eradication treatments published for many geographical regions[46,74,76-79]. Reliable indications in these guidelines, with high levels of evidence, are (1) peptic ulcer; and (2) low-grade gastric MALT (mucosa-associated lymphoid tissue) lymphoma. *H. pylori* eradication is recommended in the guidelines as a preventive tool for GC in definite circumstances, in accordance with existing evidence[80]. The best-supported recommendation is the use of *H. pylori* eradication after endoscopic resection of GC[46]. Other recommendations for *H. pylori* eradication aimed at preventing GC are family members of GC patients, patients with diagnosis of gastric atrophy, and persons who want eradication therapy. At present, the recommendation for *H. pylori* eradication with a high level of straight evidence for GC prevention is indicated for patients after endoscopic tumor resection in early gastric cancer (EGC)[64]. There is no direct evidence that the method reduces GC frequency in other situations. Stomach mucosal atrophy can decrease after eradication, as proved in many reports[56], but a reduction in GC rate in patients with atrophic gastritis is unproven.

H. pylori eradication in a family history of GC

A family history of stomach cancer is a well-known risk factor[81], and the phenomenon seems to be multifactorial. Investigations of first-degree relatives of GC patients reveal common factors increasing the likelihood of GC, for instance genetic aspects and ecological factors, particularly in childhood[82]. A study of *H. pylori* prevalence and gastric mucosal changes in family members revealed that first-degree relatives had a considerably greater rate of *H. pylori* infection. Moreover, they exhibited more advanced stages of mucosal atrophy and greater extent of IM than control groups[83]. An increased prevalence of *H. pylori* and a higher stage of IM in the stomach corpus mucosa were demonstrated in young relatives of patients with GC diagnosed before the age of 40[84]. In Western countries, the first-degree relatives of patients with GC were also found to have an increased prevalence of *H. pylori* infection, advanced stages of gastric mucosal atrophy, and IM even at an early age[85].

In general, the current guidelines recommend *H. pylori* eradication for patients with a family history of GC. However, there is still no direct confirmation that eradication strategies really decrease the GC rate in this cohort.

Massarrat *et al*[52] examined the change and topography of inflammation, atrophy and IM in first-degree relatives of GC patients following *H. pylori* eradication. This was associated with regression of gastric atrophy, but not IM even in its early stages. Gastric atrophy and IM in the antrum progress more rapidly in cases left untreated for *H. pylori* infection (> 4% years follow-up) compared to *H. pylori*-eradicated cases.

Prevention of metachronous cancer after endoscopic resection

Metachronous gastric cancer after endoscopic resection of the primary tumor can often be detected at another location within the stomach mucosa[22]. The results of a multi-center study of metachronous gastric cancers after endoscopic resection demonstrated that *H. pylori* eradication decreases the risk of appearance of new gastric cancers, even in patients at the highest risk[64]. They also suggested that *H. pylori* eradication was protective in patients with mucosal atrophy and IM. Conversely, some trials have demonstrated that the protective effect of *H. pylori* eradication on the incidence of gastric cancer is restricted to subgroups of patients without gastric mucosal atrophy or IM[60,86]. A retrospective trial on metachronous GC in patients with early GC after endoscopic resection demonstrated a higher tumor incidence in the group with persistent *H. pylori* than the eradicated group[87]. A study by Kato *et al*[22,45] revealed that *H. pylori* eradication

protects the stomach mucosa from the development of metachronous GC in patients after endoscopic resection, with significantly higher rates of the cancer in the control group than in patients after successful *H. pylori* eradication.

H. pylori infection is implicated in both the initiation and progression of GC[88]. The results of many studies demonstrate that *H. pylori* eradication is effective in complete suppression of tumor growth at the precancerous gastric mucosal lesion stage. *H. pylori* eradication could inhibit latent cancers (tiny cancers that are undetectable by endoscopy) not merely by slowing their growth, but also, potentially, by completely suppressing them[89].

SCREENING

General principles of cancer screening in settings of an organized program

The effectiveness of a population-based cancer screening program can be measured by reduction of mortality from a specific cancer, the results depending on the extent of organization, *i.e.*, how well different components of a screening process are associated[90]. In 1968 and on behalf of WHO, Wilson and Jungner[91] defined the criteria for screening of a disease. In addition to the epidemiology, and disease management issues, the accuracy of the test-system in parallel to cost-efficacy considerations were listed in the criteria. High sensitivity of the screening test is one key aspect in not missing cases of the disease at a curable stage. Organized cancer screening is the most effective approach for achieving the target, and IARC has defined the features with which such a program has to comply[92].

Current nationwide screening programs

Japan and South Korea are countries with ongoing nationwide organized GC screening programs. The screening program was launched in 1960 in Japan, with the only recommended screening method being photofluorography (after a barium meal)[93]. From February, 2013, *H. pylori* eradication is reimbursed in Japan, but organized screening program. Upper endoscopy is used in conjunction with photofluorography screening in South Korea[94].

Kazakhstan has also decided to introduce bi-annual screening, with upper endoscopy for esophageal and gastric cancers for the age group 50-60. Starting from the beginning of 2013, this has been implemented in 6 of the 16 regions in the country with the intention to expand it to the entire country. However, the set-up of the program is unlikely to adopt or correspond to the criteria required of an organized program, giving little expectation that the target will be reached.

Regional screening initiatives

A number of regional opportunistic screening activities that have been conducted should be considered more as pilot studies. The screening tools are mainly addressing precursors of GC, the presence of premalignant lesions (such as atrophy) or broadly the presence of *H. pylori* infection.

Leung *et al*[95] reviewed their experience with GC screening in Asia. Data on a screen-and-treat study from Matzu island where there is a high gastric cancer incidence of *H. pylori* have now been published[70]. There seems to be a substantial decrease of atrophy and peptic ulcer disease following the eradication; the incidence of GC has also decreased by 25% during the study period (however, lack of a control group prevents any confirmation of a causal relationship).

A large *H. pylori* eradication study is currently in progress in Linqu county, China[96].

Meta-analysis of pepsinogens in GC, dysplasia and atrophic gastritis screening either in Japan or outside it has been published by Dinis-Ribeiro *et al*[97]. Another meta-analysis of 27 population-based screening studies (comprising 296 553 subjects) and 15 selected group studies (with 4385 subjects) by Miki[98] indicated that the pepsinogen test had a sensitivity of 77% in detecting GC, with negative predictive values ranging from 99.1 and 99.9%. These ran between 1982 and 2002, most originating from East Asia. At the same time, studies from other parts of the world (*e.g.*, Finland and Venezuela) were also included. The author reaches the conclusion that this method is useful in identifying high-risk subjects rather than cancer itself.

Lomba-Viana *et al*[99] have also demonstrated the feasibility of pepsinogen screening in a European population. Other regional activities using a set of biomarkers - GastroPanel (pepsinogen Ⅰ, pepsinogen Ⅱ, gastrin-17, IgG group antibodies to *H. pylori*) - are under way in Northern Italy and Germany.

Currently available non-invasive tests

It is unlikely that endoscopy or photofluorography screening methods will become effective population-based gastric screening tools in countries outside Asia, either because of the epidemiology of GC or the cost implications. Therefore, the potential use of non-invasive screening approaches will be addressed in greater detail.

Pepsinogens

Pepsinogens are pro-enzymes of pepsin, and their serum or plasma levels reflect, indirectly, secretion by the stomach. Pepsinogen Ⅰ (Pg Ⅰ) is exclusively produced by the chief and mucous neck cells of the corpus, whereas pepsinogen Ⅱ (Pg Ⅱ) is also produced by cardiac, pyloric and Brunner gland cells[100]. Only a minor proportion (about 1%) of the secreted pepsinogens reaches the bloodstream, but this is sufficient to assess stomach function.

Pepsinogen levels decrease in atrophic gastritis, but are increased during inflammation. To eliminate the possibility of a false normal result when atrophy and *H. pylori* infection co-exist, the ratio between Pg Ⅰ and Pg Ⅱ (Pg Ⅰ / Ⅱ) is considered a more reliable marker than Pg

I alone[98,101,102].

The diagnostic cut-off values for Pg I and the Pg I / Ⅱ have varied in previous studies[103]. Different test-systems and methods have been traditionally used in assays conducted in Asia and Europe; most of the recent Asian studies, in particular in Japan, have used the latex agglutination method, whereas ELISA testing is mainly in use in Europe. Although there is a relatively good correlation between these results, the absolute values differ. Thus results based on absolute values cannot be translated between the different studies where non-identical test systems are used[104]. Therefore, the current guidelines emphasize the need for regionally validated test-systems[46].

Although as previously reported[98], sensitivity results on pepsinogens for GC identification might be considered acceptable in screening settings, worse performances have been reported in many of the studies. Whilst the results are better for the detection of atrophy, *i.e.*, sensitivity of 66.7%-84.6% and a specificity of 73.5%-87.1%[105-108], significantly lower sensitivity of GC detection using the same cut-off values (36.8%-62.3%) has been reported[109-111]. This might result in missing half or more of the GC cases in a population-based screening settings.

Therefore, regional validation of the tests and additional pilot studies in screening settings are required before the tests can be implemented, at least outside Asia, in any organized screening programs.

Gastrin-17

An additional marker has now been suggested to characterize atrophy in the antral part of the stomach - amidated gastrin-17 (G-17), which is secreted exclusively by the G-cells in the area[112]. In Europe, a combined set of Pg I , Pg Ⅱ , G-17 and *H. pylori* IgG antibody detection is available under the brand, *GastroPanel*[113].

Although theoretically the combination of G-17 detection to pepsinogens would be an ideal reflection of the functional status of the stomach, as well as the atrophy in the entire organ, the performance of this test in practical terms is far from meeting expectations.

G-17 levels in plasma are influenced by multiple factors, including acidity regulating pharmaceuticals, food intake, and inflammation[113]. G-17 measurement following provocation with a protein-rich meal is considered the best indicator of antral G-cells functioning[114,115]. Such a procedure is impractical and inconvenient in screening settings; therefore fasting G-17 levels are being taken in many studies[100]. However the sensitivity of the test in the fasting state or after food stimulation (15.8% at fast and 36.8% after the stimulation)[116] seems unacceptable for screening purpose.

Many reports confirm the acceptability and accuracy of the *GastroPanel* test-system, including G-17, for detecting atrophy in the gastric mucosa[113,117,118]; however this seems to reflect the performance of pepsinogen tests more than G-17.

Emerging developments

During recent years there has been an increasing interest in the potential use of molecular biology approaches in GC risk detection. This paper will not discuss hereditary GC with a clear association to CDH1 mutation; guidelines on how to deal with individuals at potential risk exist[119]. Extensive work has been conducted on the role of host-genetics to stratify the risk of GC development. However, currently no polymorphisms of proinflammatory cytokines are being routinely used for the stratification of GC risk in an individual patient due to the lack of association strength and of screening[46].

MicroRNAs

MicroRNAs are endogenous, small (about 22 nt in length), non-coding RNA molecules modulating post-transcriptionally gene expression[120]. Due to their stability in different tissue, analysis of specific microRNA signatures may become an important diagnostic and prognostic tool for different cancers, including GC[121].

Extensive work to identify microRNAs that are up-regulated and downregulated in GC as well as the related premalignant lesions has been carried out. Several reviews of this topic have recently been published[122-125]. More work is required to identify the microRNA signature that can be reliably used in the early detection of GC, as well as in analysing the reproducibility of the results from different populations.

Cancer autoantibodies

Another potential tool for early GC diagnostics is a specific cancer autoantibody panel. Autoantibodies against tumor-associated antigens have been identified in several cancer types[126,127]. Although the availability antibodies against particular tumor-associated antigens is limited, typically ranging from 1% to 15%, an approach of panel-testing is now being used to explore cancer-specific antibodies[128]. Such a panel antibody search has been conducted in GC, in which 45-autoantibody signature was found to discriminate GC from healthy controls with 59% sensitivity and 90% specificity[128].

Volatile markers

Volatile components found in the exhaled breath and identified either by gas-chromatography coupled mass-spectroscopy or nanosensor technology could also make a reliable and easy-to-use tool for detecting cancer[129]. A recent pilot study suggests the possibility of using a highly sensitive, cross-reactive, nanomaterial-based gas sensor to identify and separate volatile marker patterns between GC patients and those with benign gastric conditions with 89% sensitivity, 90% specificity and 90% accuracy[130]. However, geographical differences between the content of volatile substances do exist[131], making local adaptation of the method ("teaching of the electronic nose") might be required.

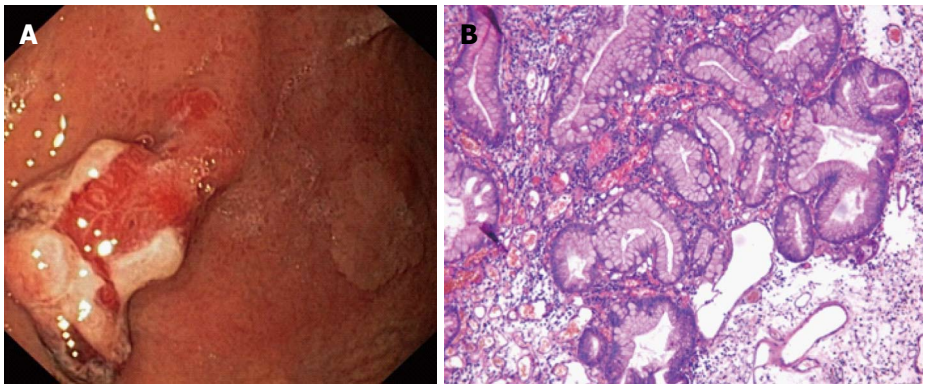

Figure 1 White light endoscopy of the stomach of a 60-year-old man. A: Hyperplastic gastric polyp 40 mm × 20 mm in size is clearly visible in the foreground. The flat lesion in the background has been missed during first outpatient esophagogastroduodenoscopy; B: Pathomorphology after initial biopsy and polypectomy confirmed the hyperplastic nature of the polyp.

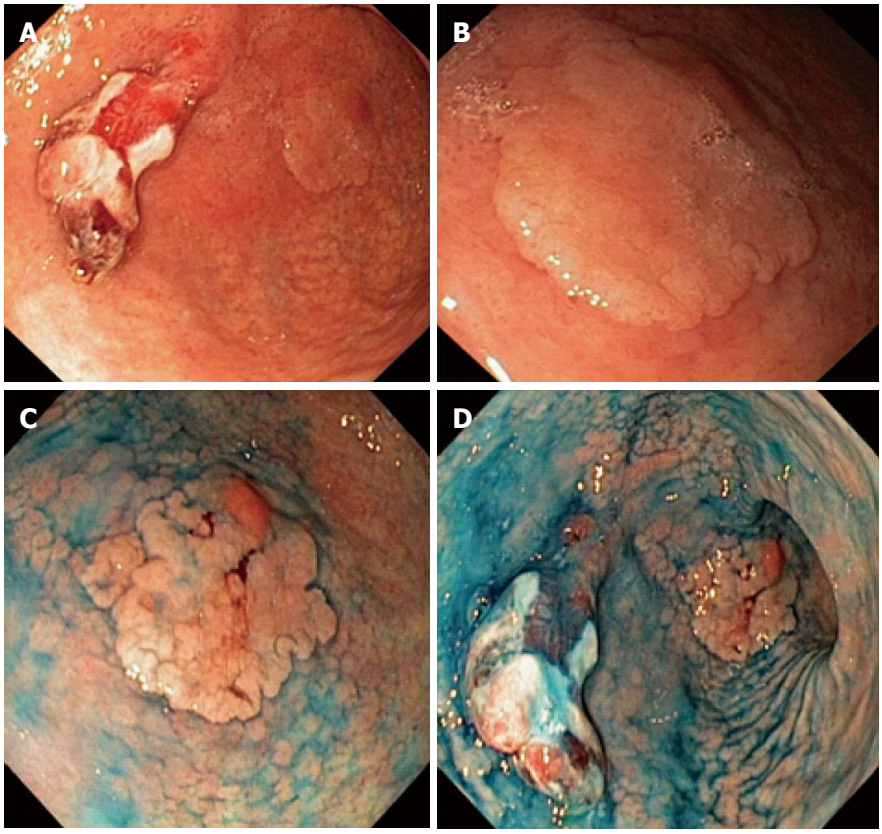

Figure 2 Esophagogastroduodenoscopy of the same patient. A: The flat lesion in the background can been viewed more easily when better lit; B: Closer view of the superficial elevated lesion; C: After chromoendoscopy with indigo carmine - a roundish lesion 25 mm in diameter can be seen, with a smooth lobulated surface and a 6-mm, reddish protrusion in the distal part; type 0-Ⅱa+Is according to Paris classification; D: Due to the marked inflammation and presence of intestinal metaplasia the precise proximal margin of the lesion is still unclear, even with the use of chromoendscopy.

Cost implications

Endoscopic screening only becomes cost-effective in moderate- to high-risk populations[132,133]. Two recent systematic analyses have confirmed the cost-effectiveness of *H. pylori* screen-and-treat strategy in preventing GC, even in areas with rather low incidences of GC[134,135]. However, the adverse effects of broad antibiotic use for *H. pylori* widespread eradication need consideration in future studies[135]. Insufficient evidence is available on the cost-effectiveness of pepsinogen or other newer potential screening modulation approached in screening settings for GC.

EARLY ENDOSCOPIC DIAGNOSIS

Endoscopic diagnosis of early gastric cancer (EGC) is quite difficult because it often shows only subtle changes; endoscopists have to be well trained and familiar with new techniques.

The first step in diagnosing EGC endoscopically is

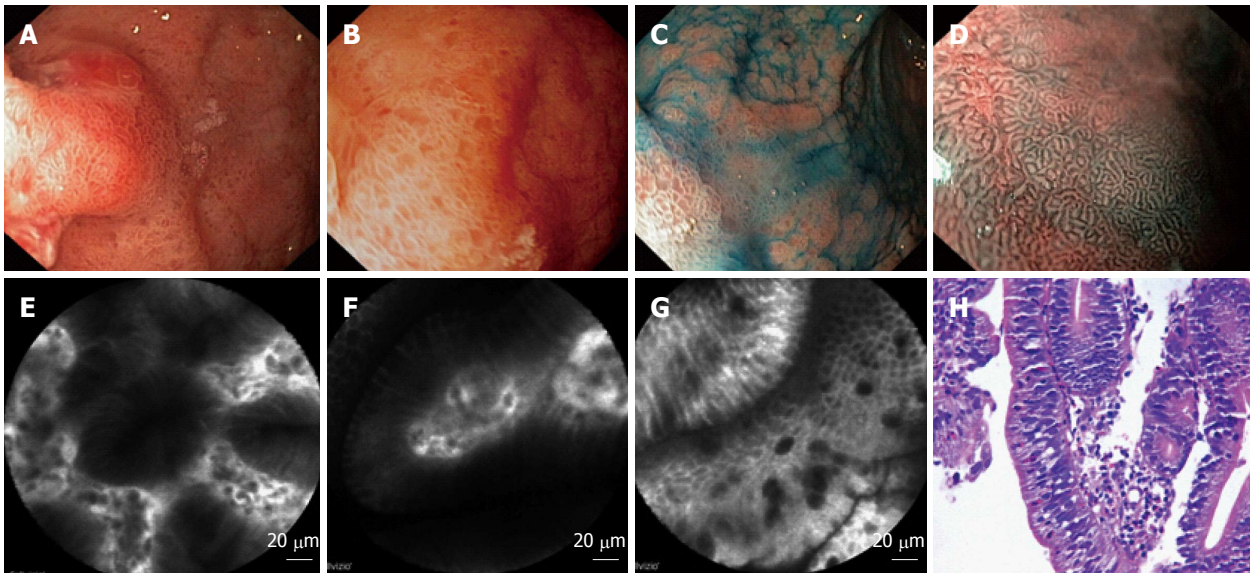

Figure 3 Characterization of the surrounding mucosa of the same patient. A-C: WLE + chromoendoscopy: pronounced focal mucosal hyperemia, edema, petechiae, multiply foci of intestinal metaplasia; D: Narrow band imaging (NBI) + magnified endoscopy (zoom). The results, according to VS-classification[138]: the surrounding mucosa is inflamed, with a regular stick-like microsurface pattern, slightly irregular wavy microvascular pattern; E: Confocal laser endomicroscopy (CLE): A cross-section of normal glands; F: CLE: A longitudinal section of normal glands; G: CLE: Marks of intestinal metaplasia - Goblet cells; H: Pathomorphology: Active chronic Hp+ gastritis with incomplete intestinal metaplasia and low grade epithelial dysplasia.

to detect any suspicious lesions, to characterize them and make an accurate diagnosis (Figures 1-7). The third step is good reporting, based on the Paris classification as the current standard[136].

Several simple, but very important aspects, have to be observed for the endoscopic diagnosis of EGC, such as the best preparation for an endoscopic examination in minimizing the time and effort taken in removing mucus (drinking a mixture of water with mucolytic and defoaming agents before the procedure), which is very popular in Eastern countries, but is not always used in Western countries, at least not in daily clinical practice.

Second,to avoid blind spots during endoscopy, it is necessary to use a standardized procedure to map the entire stomach. The European Society of Gastrointestinal Endoscopy (ESGE) recommendations for quality control in gastrointestinal endoscopy: guidelines for image documentation in upper and lower GI endoscopy[137] proposes that 8 images should be taken to illustrate the examination of the stomach in its totality (complementary images should be taken in the case of a specific lesion). A recent review[138] proposes a minimum required standard, a "systematic screening protocol for the stomach (SSS)" that comprises 22 endoscopic photos as a minimum standard. If another lesion is found, additional pictures have to be taken. The longer the examination time and the more pictures taken, the easier it is to improve the detection of lesions[139].

Detection of subtle gastric mucosal changes during examination requires advanced endoscopic techniques. Different techniques, such as magnifying endoscopy, chromoendoscopy (CE), novel high-resolution (HR) virtual chromoendoscopy techniques with narrow-band imaging (NBI) with or without magnification (NBI-ME), flexible spectral imaging color enhancement (FICE) endoscopy with or without magnification (FIME) and confocal laser endomicroscopy (CLE), have been tested for the diagnosis of EGC, with promising results. The most investigated endoscopic technique seems to be NBI, which has given promising results.

NBI ENDOSCOPY FOR EGC/DYSPLASIA DIAGNOSIS

Many studies have aimed at directly distinguishing cancerous lesions from non-cancerous lesions using NBI. The most assessed endoscopic technique for detection of EGC has been NBI-ME (Table 1), which has high sensitivity and specificity.

GC differentiation

The first NBI clinical studies published dealt with cancer differentiation. Table 2 shows the data available regarding gastric cancer differentiation using NBI-ME.

Table 3 summarizes the studies evaluating the horizontal extent (DL) of EGC on NBI-ME.

Possible data aggregation for NBI's studies

A recently published systematic review[140] using available data from several studies working groups calculated a pooled sensitivity, specificity and DOR of 0.90 (95%CI: 0.84-0.94), 0.83 (95%CI: 0.80-0.86) and 47.61 (95%CI: 4.61-491.34), respectively, for the diagnosis of dysplasia.

Cancer delineation using NBI

NBI endoscopy may also help in assessing the extent of

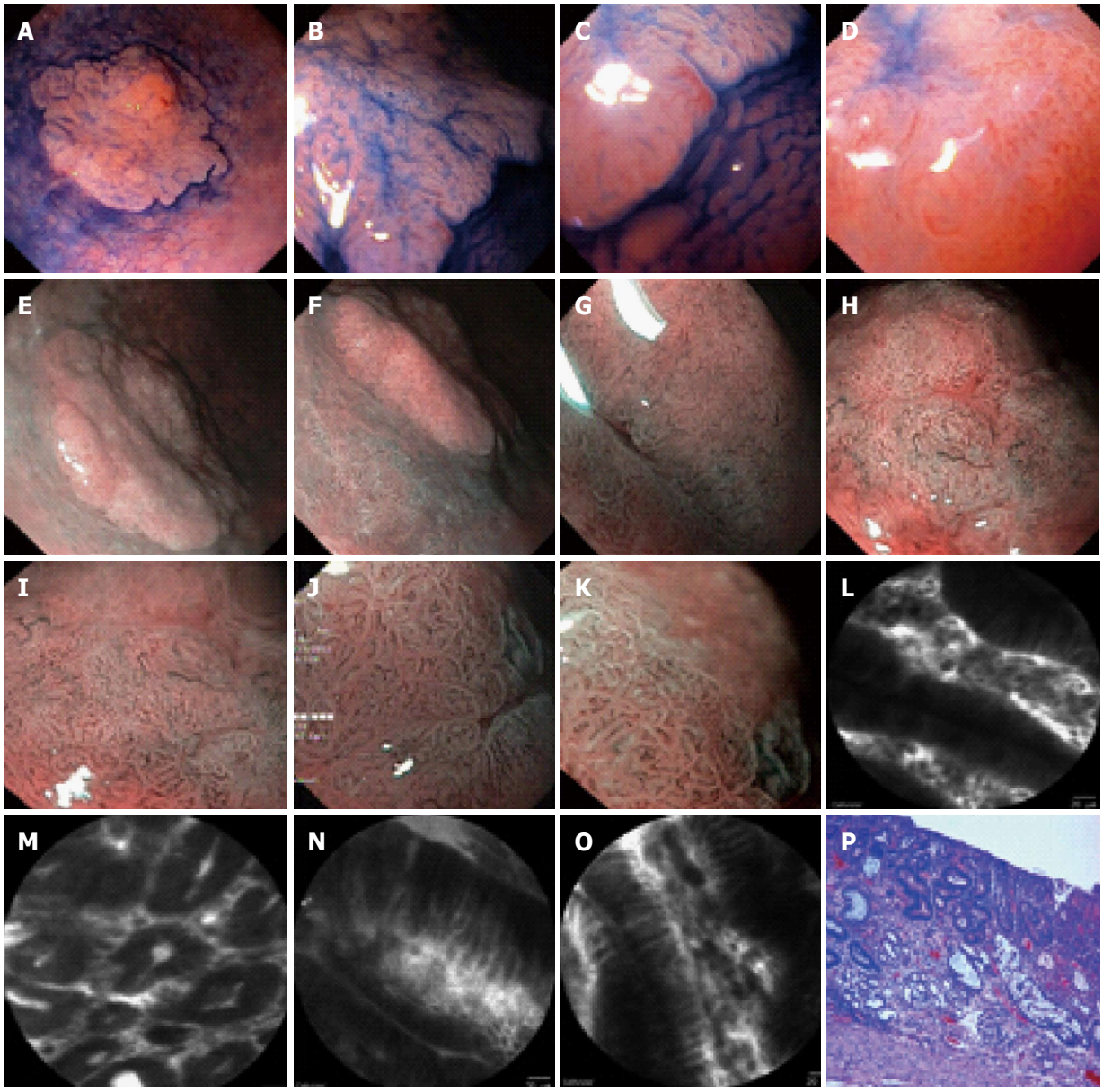

Figure 4 Some patient after 2 wk of *Helicobacter pylori* eradication therapy. The characterization of the flat (Ⅱa) part of the lesion type 0-Ⅱa+Is is neoplastic: A-D: High definition Video-EGD + chromoendoscopy + Zoom: Shows a clear demarcation line between the lesion and surrounding mucosa; E-G: NBI + zoom: A clear demarcation line between the lesion and the surrounding mucosa; H, I: NBI + zoom: An irregular microsurface pattern - elongated and different in size and shape; J, K: An irregular microvascular pattern - tortuous, different in shape and size of the capillaries, forming an irregular network; L: CLE: Marks of intestinal metaplasia - Goblet cells; M: CLE: Deformed glands; N: CLE: Dark irregular glands; pseudostratified epithelium; O: CLE: Dark irregular glands; pseudostratified epithelium; P: Pathomorphology: Incomplete intestinal metaplasia and high grade dysplasia with foci of well-differentiated adenocarcinoma.

lesions (determining the margin between cancerous and non-cancerous mucosa),and in improving safety margins and cure rates during endoscopic resection of EGC.

As described before, different studies have reported various descriptions of GC mucosal and vascular patterns, as well as the demarcation line (DL). A recent invited review[138] suggested the VS classification system for making a differential diagnosis between cancerous and noncancerous lesions for NBI-ME endoscopy.

This simple but structured system classed the microvascular (V) and microsurface (S) patterns into three categories: regular, irregular and absent.

FICE for dysplasia/cancer diagnosis and delineation

Although several studies evaluated EGC by FICE endoscopy, most looked at the DL between a GC and its surrounding area with the FICE system [with and without magnification, with ultraslim, with small-caliber endoscopy and with indigo carmine (I-FICE)]. Table 4 summarizes the evaluations of the horizontal extent (DL) of EGC on FICE.

Although FICE endoscopy seems to be a promising tool for EGC DL detection, more studies are necessary and welcome.

New HR advanced endoscopic technologies could

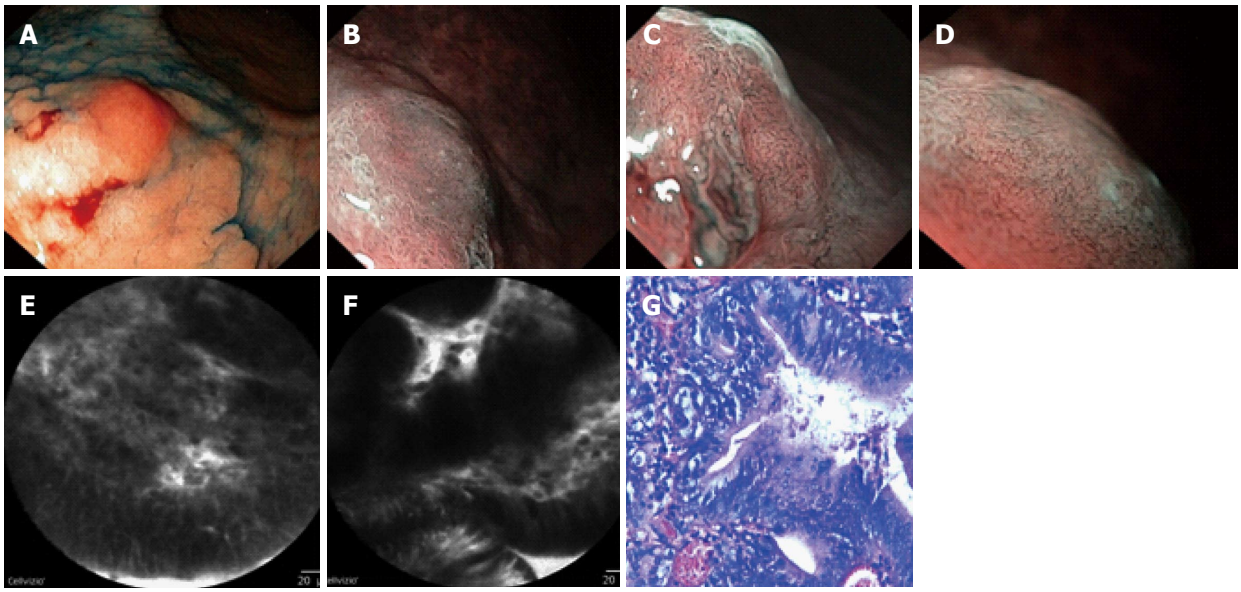

Figure 5 Some patient after 2 wk of *Helicobacter pylori* eradication therapy. The characterization of the protruded (Is) part of the lesion type 0-Ⅱa+Is is a differentiated adenocarcinoma. A: High definition Video-EGD + chromoendoscopy: A closer view of the protruded part of the lesion; B-D: Barrow-band imaging (NBI) + zoom: Unclear shredded microsurface pattern with an irregular network microvascular pattern - the capillaries differ in shape and diameter and are tortuous; E: Confocal laser endomicroscopy (CLE): Dark irregular glands; pseudostratified epithelium; irregularly shaped nuclei; F: CLE: Dark irregular glands; pseudostratified epithelium; G: Pathomorphology: A well-differentiated adenocarcinoma.

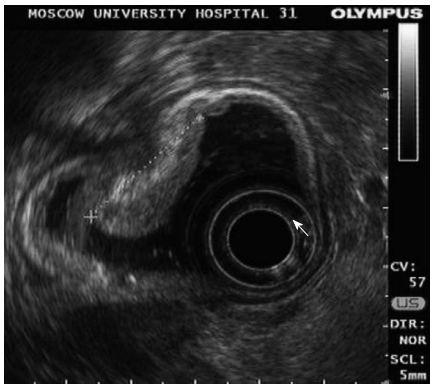

Figure 6 Same patient. Endosonography of the lesion 0-Ⅱa + Is. Area of the lesion (25 mm in size): Thickening of mucosa up to 5-7 mm; submucosal layer is clear under the tumor; lymph nodes are not visualized.

be helpful in detecting subtle mucosal features invisible by standard WLE, and might improve the identification of EGC. At present, NBI-ME is probably the most frequently examined endoscopic technique, with the largest amount of technical data available.

However endoscopic training and experience are highly essential, as well as good preparation for an endoscopic examination. The most important process is scrutinizing all gastric areas with targeted biopsies as histopathological examination remains the gold standard for the final diagnosis of EGC.

Another problem is the continuing lack of consensus and of mucosal features description system with these high-resolution technologies, even for any of the technologies examined separately.

RISK STRATIFICATION

Recent guidelines emphasize the importance of GC risk stratification for the individual patient[46,141]. Chronic atrophic gastritis, IM and dysplasia are defined as precancerous conditions for dysplasia and gastric adenocarcinoma development[141].

High grade gastric epithelial dysplasia-associated risk

Most patients who develop high-grade gastric epithelial dysplasia are at high risk for developing invasive gastric carcinoma[142]. According to the MAPS guidelines, histological diagnosis of high-grade dysplasia in the absence of endoscopic data indicates an immediate need for endoscopic re-examination with wide biopsy sampling and subsequent surveillance at six-month to one-year intervals[141].

Low grade gastric epithelial dysplasia-associated risk

The risk of development of GC in patients with low-grade gastric epithelial dysplasia is comparable to (or even significantly higher than) the risk of cancer after resection of colonic adenomas, or in Barrett's esophagus, or in chronic inflammatory bowel disease[143-145]. In contrast to patients with high-grade gastric epithelial dysplasia, low-grade dysplasia patients have a lower risk of progression to invasive gastric carcinoma. According to a nation-wide study in the Netherlands, the annual incidence of GC 5 years after diagnosis was 0.6% in patients with mild-to-moderate dysplasia, but 6% with severe dysplasia[146]. It is recommended that in cases of histologically-detected low-grade dysplasia without an endoscopically-detected lesion, the patients should be followed for a year; but if

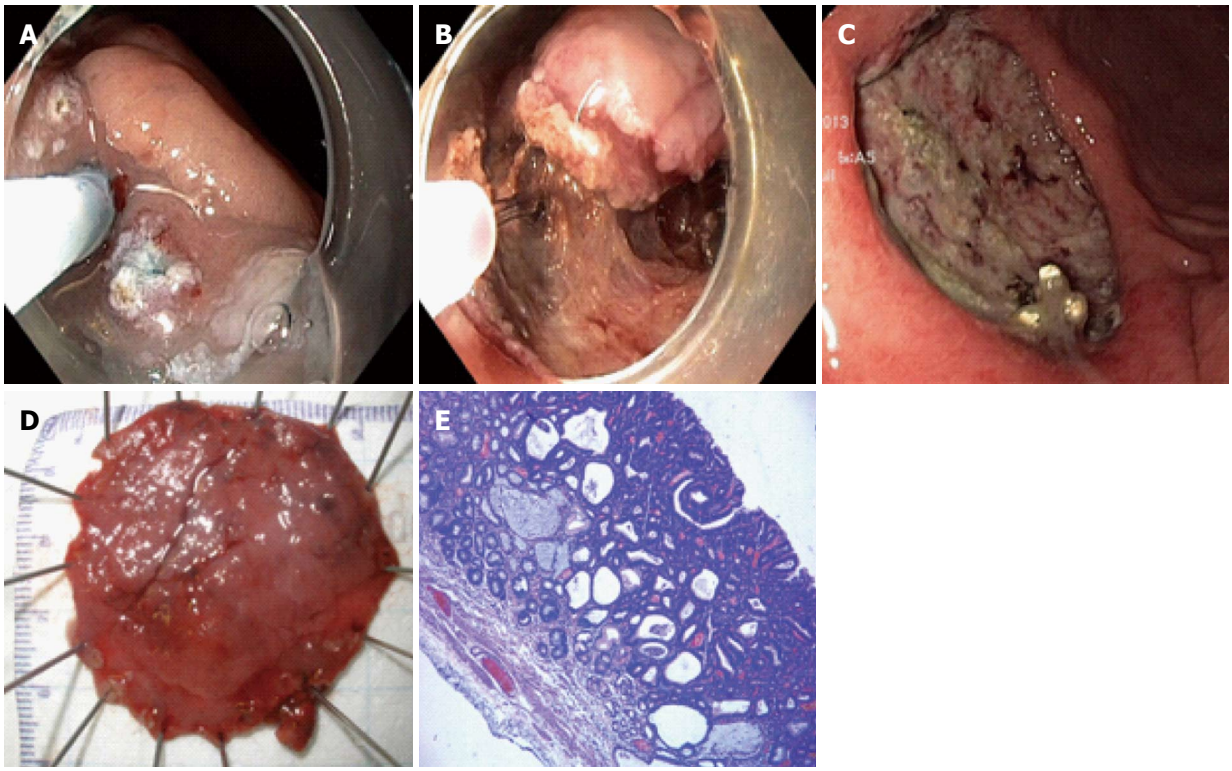

Figure 7 Same patient. A-D: The lesion was removed en-block using triangle and IT-2 knives at endoscopic submucosal dissection without any complications; E: Well-differentiated adenocarcinoma no invasion in submucosa, clear horizontal and vertical margins, absence of vascular and lymphatic invasion.

an endoscopically defined lesion is found, endoscopic resection should be considered[141].

Atrophy or IM-associated risk

As early detection of GC can improve the survival of patients, surveillance of precancerous gastric mucosal conditions and/or lesions seems significant, as demonstrated by numerous trials. The speeds of progression of gastric mucosal atrophy and IM range respectively from 0 to 1.8% and from 0 to 10% per year[141].

The Maastricht Ⅳ guidelines suggest that pre-neoplastic high-risk conditions, such as atrophy and IM, require endoscopic follow-up; that regular follow-up should be considered in patients with moderate-to-severe atrophy at 2-3 year intervals; and that there is a need, however, for prospective studies to determine the correct timing of follow-up[46].

In considering that the overall risk of developing GC is too low to validate endoscopic surveillance for every patient with chronic atrophic gastritis and IM, MAPS guidelines suggest endoscopic surveillance only for patients with extensive atrophy or IM (*i.e.*, both in the antrum or the corpus); surveillance is recommended over three-year intervals[141].

OLGA and OLGIM staging systems

It has recently been suggested that OLGA[147] and OLGIM[148] staging systems for gastric premalignant lesions can simplify the clinical approach, while using the same biopsy work-up as the Sydney system (5 biopsies). The abbreviation OLGA stands for Operative Link on Gastritis Assessment, whereas OLGIM emphasizes the importance of IM.

Atrophy is defined as loss of appropriate glands (with or without metaplasia). In each compartment (*i.e.*, mucous-secreting antral and oxyntic/corpus mucosa), atrophy is scored on a 4-tiered scale (0-3) according to the visual analogue scale of the Houston-updated Sydney system. The staging result from the combination of atrophic changes was assessed in the 2 mucosal compartments that were considered. OLGIM basically incorporates the OLGA frame, but replaces the atrophy score with an assessment only of IM.

By itself, this staging does not allow one to judge the topography of the lesion detected (in particular for the lower stages), but it may be potentially linked to the prognosis and management issues since most cancer cases are expected to progress from stages Ⅲ and Ⅳ[149]. This stage distribution is also convenient for research purposes[150].

CONCLUSION

GC has been a substantial healthcare problem in a large part of the world for decades. Even though the incidence in age-adjusted standardized figures is on the decline, more rapid decrease could be achieved by implementing preventive measures. Screening for cancer and precancerous lesions could be beneficial, but the currently available methods are not yet readily implementable in

Table 1 Narrow-band imaging endoscopy for early gastric cancer/dysplasia diagnosis

Ref.	Endoscopic technique	Mucosal and vascular pattern for GC	Accuracy
Kaise *et al*[151]	NBI-ME for superficial depressed gastric lesions *vs* WLE	The triad: Absence of fine mucosal structure with microvascular dilation and heterogeneity	NBI-ME specificity (85%, theoretically calculated if all of the triad were positive), which was significantly ($P < 0.001$) superior to WLE general diagnosis (65%)
Kato *et al*[152]	NBI-ME *vs* WLE	The triad: Absence of fine mucosal structure with microvascular dilation and heterogeneity	NBI-ME sensitivity (93%) and specificity (95%)
Ezoe *et al*[153]	NBI-ME *vs* WLE	Irregular V pattern with a mucosal DL	NBI the diagnostic accuracy was significantly higher for than for WLI (79% *vs* 44%; $P = 0.0001$), as was its sensitivity (70% *vs* 33%; $P = 0.0005$). The diagnostic specificity of NBI (89%) was higher than that of WLI (67%), but the difference was not statistically significant
Capelle *et al*[154]	NBI without ME	Complete loss of architectural and mucosal pattern	The sensitivity, specificity, PPV and NPV for detection of premalignant lesions were 71%, 58%, 65% and 65% for NBI and 51%, 67%, 62% and 55% for WLE, respectively
Maki *et al*[155]	NBI-ME *vs* WLE to differentiate between cancer and adenoma in superficial elevated lesions of the stomach	WLE: Red coloring NBI-ME: An irregular V pattern with a DL, or irregular S pattern with a DL	The sensitivity, specificity, and accuracy of WLE *vs* NBI-ME were 64% (52%-76%) *vs* 95% (90%-100%), 94% (86%-100%) *vs* 88% (77%-99 %), and 74% (66%-83%) *vs* 92% (86%-98%), respectively
Tsuji *et al*[156]	NBI-ME	VS classification: (1) irregular V pattern with a DL between the lesion and the surrounding area; and (2) irregular S pattern with a DL between the lesion and the surrounding area	Sensitivity and specificity for carcinoma were 75.0% and 84.9%, respectively. PPV was 81.4%
Omori *et al*[157]	NBI-ME	Fine network (net-like appearance consisted of irregular shaped micro vessels), core vascular (clearly visible coiled or wavy vessels in the central area of the mucosal structure), and unclear patterns (micro vascular patterns is not observed)	Sensitivity 86.2%, specificity 97.0%
Wang *et al*[158]	NBI-ME *vs* CLE	NBI: "VS" classification system	Accuracy of the CLE and the NBI-ME diagnosis was 88% (95%CI: 78%-98%) and 81% (95%CI: 69%-93%), respectively
Kaise *et al*[159]	NBI-ME *vs* WLE	The triad: Disappearance of fine mucosal structure, microvascular dilation, and heterogeneity	The sensitivity and specificity for NBI-ME diagnosis using the triad (92.9% and 94.7%, respectively) were significantly better than those for WLE (42.9% and 61.0%, respectively)
Pimentel-Nunes *et al*[160]	NBI	"Irregular vessels and mucosa" (pattern C)	Accuracy 95%; 95%CI: 90%-99%; LR+ = 44.33

EGC: Early gastric cancer; GC: Gastric cancer; NBI-ME: Narrow-band imaging with or without magnification.

Table 2 Gastric cancer differentiation using narrow-band imaging with or without magnification

Ref.	Endoscopic technique	Differentiated-type EGC (D-EGC)	Undifferentiated-type EGC (UD-EGC)
Nakayoshi *et al*[161]	NBI-ME	Relatively regular fine network pattern	Relatively irregular, twisting or corkscrew pattern, with a relatively low density of microvessels
Endo *et al*[162]	NBI-ME	Grid network pattern with hypervascularity	Short twig or branch-like pattern with hypovascularity
Tamai *et al*[163]	NBI-ME describing depressed gastric adenomas *vs* protruding adenomas	Intramucosal carcinomas were more frequently found in depressed adenomas (reddish in color, a regular ultrafine network pattern of mucosal microvasculature) (25%) than in protruding adenomas (4.5%)	
Yao *et al*[164]	NBI-ME	WOSa white substance within the neoplastic epithelium that may obscure the subepithelial microvascular pattern. More frequent in non-advanced neoplasia than in advanced carcinomas and that 100% of non- advanced lesions demonstrated a regular distribution of WOS	
Yokoyama *et al*[165]	NBI-ME	Amongst the D-EGC lesions, fine-network pattern, intra-lobular loop pattern-1, intra-lobular loop pattern-2 and corkscrew pattern were observed in 15.7%, 59.6%, 24.2% and 0.5%, respectively. D-EGCs mainly exhibited fine-network pattern or intra-lobular loop pattern	In UD-EGC intra-lobular loop pattern-2 and corkscrew pattern were observed in 41.2% and 58.8%, respectively. Therefore, UD-EGCs were all classified as intra-lobular loop pattern-2 and corkscrew pattern

NBI-ME: Narrow-band imaging with or without magnification; EGC: Early gastric cancer.

Table 3 Studies evaluating the horizontal extent (DL) of early gastric cancer on narrow-band imaging with or without magnification

Ref.	Endoscopic technique	Aim of the study	Results
Okada *et al*[166]	NBI-ME	Assessment the comparative relationship between NBI-ME images and histopathological findings in patients with UD-type EGCs prior to either ESD or surgery	NBI-ME images of UD-type EGCs proved to be very closely related to the histopathological findings
Nonaka *et al*[167]	NBI-ME	Estimating a DL on NBI-ME in comparison with biopsy findings as a gold-standard	The DL that could be recognized at 2 points on the orifice and anal sides of each lesion during ME-NBI was consistent with the pathological findings in 22 patients with 0-Ⅱc lesions, 7 with 0-IIb lesions, and 2 with 0-Ⅱb + Ⅱc lesions, showing an accuracy of 100%
Kiyotoki *et al*[168]	NBI-ME *vs* ICC	Evaluated the usefulness of NBI-ME for determining the tumor margin compared with ICC (indigocarmine-chromoendoscopy)	The rate of accurate marking of the ME-NBI group was significantly higher than that of the ICC group (97.4% *vs* 77.8%, respectively; $P = 0.009$)
Nagahama *et al*[169]	NBI-ME *vs* CE	To investigate the usefulness and limitations of NBI-ME when CE is unsuccessful for determining the horizontal extent of EGC	The proportion of cancers showing unclear margins using CE was 18.9% (66/350). Of these, 62 of 66 cancers were examined using ME with NBI, with the entire margins successfully delineated in 72.6% (45/62) of the lesions that had shown unclear margins using CE. The success rate was 0% for undifferentiated cancers, significantly lower than that for differentiated lesions ($P < 0.00001$)

UD-type EGCs: Undifferentiated-type EGCs; ESD: Endoscopic submucosal dissection; ICC: Indigo carmine chromoendoscopy; NBI-ME: Narrow-band imaging with or without magnification.

Table 4 Studies evaluatingthe horizontal extent (DL) of early gastric cancer on flexible spectral imaging color enhancement

Ref.	Endoscopic technique	Aim of the study	Results
Jung *et al*[170]	FIME *vs* WLME	Discrimination of non-neoplastic lesion, adenoma, and cancer of the stomach	The proportion of agreement and the degree of agreement between endoscopic and pathological diagnosis by WLME were 0.85 and 0.76, respectively, and those by FIME were 0.91 and 0.86, respectively
Mouri *et al*[171]	FICE *vs* WLE	78 differentiated, 22 undifferentiated EGC were analyzed before an endoscopic or surgical resection	The score of the FICE observation improved in 46 cases (46%), was unchanged in 54 cases (54%), and decreased in no cases (0%)
Tanioka *et al*[172]	FICE with ultra-slim endoscopy *vs* WLE	Endoscopy focusing on the enhanced contrast between tumor and non-tumor lesions	Visibility with FICE was superior to WLE in 54% of the observations and comparable to WLE in 46% of the observations
Osawa *et al*[173]	small-caliber FICE *vs* WLE	Evaluate median color differences between malignant lesions and the surrounding mucosa	Greater median color differences were present in FICE images compared with WLE, resulting in images with better contrast (27.2 *vs* 18.7, $P < 0.0001$)
Osawa *et al*[174]	OBI(without magnification and with 40-fold magnification) *vs* WLE	Delineating the depressed-type EGC	DL of the depressed-type EGC was easily identified by OBI without magnification in 26 of 27 cases (96%)
Yoshizawa *et al*[175]	OBI *vs* WLE	The identification of the DLs of an elevated-type EGC without Magnification and the rate of success in identifying the abnormal surface structure of GC by using low-magnified OBI images	DLs were easily identified in OBI images, even without magnification
Jung *et al*[170]	FIME *vs* WLME	The discrimination of non-neoplastic lesion, adenoma, and cancer of the stomach	The proportion of agreement and the degree of agreement between endoscopic and pathological diagnosis by WLME were 0.85 and 0.76, respectively, and those by FIME were 0.91 and 0.86, respectively
Dohi *et al*[176]	I-FICE *vs* WLE, FICE and CE	To evaluate the usefulness of I-FICE in EGC demarcation	The median ranking score for I-FICE images was significantly higher than that obtained from the other methods

FIME: Magnifying endoscopy with flexible spectral imaging color enhancement system; WLME: White light magnifying endoscopy; FICE: Flexible spectral imaging color enhancement; OBI: Optimal band imaging; DL: Demarcation line I-FICE- FICE with indigo carmine; CE: Chromoendoscopy (indigo carmine).

organized screening settings. Additional research is required to prove both the rationale and cost-efficacy of implementation. Additional attention should now be paid to early diagnosis, in particular in the Western world.

A number of non-invasive biomarkers are available for screening of GC risk; however, the accuracy might not be sufficient for organized screening programs unless further studies provide additional data; a search for

new biomarkers is in progress as an alternative.

Currently a standardized biopsy strategy is required during upper endoscopy to stratify the risk of GC; however, in the future targeted biopsies based on the visual evaluation of mucosal defects could be the way forward. However, more studies are required to prove the appropriateness of such a strategy.

New high-resolution endoscopic technologies could be helpful in detecting subtle mucosal features invisible with standard WLE, which might improve the identification of EGC. However, endoscopic training and experience are highly essential, as well as good preparation for an endoscopic examination, and the most important scrutinized visualisation of all gastric areas with targeted biopsies for histopathological examination remains the gold standard for final EGC diagnosis.

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