

Early diagnosis of early gastric cancer

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The prognosis of gastric cancer is closely related to the stage of disease at diagnosis. Early gastric cancer, whereby disease is limited to mucosa and submucosa, confers a survival rate of greater than 90% in 5 years in many centres. Gastric cancer is still a major cause of cancer mortality worldwide. In high incidence areas such as Japan, screening of asymptomatic population has been advocated. However, in Western countries, mass screening is not cost-effective. Hence, strategy has been directed to screen symptomatic individuals who are at higher risk of gastric cancer. Most patients with early gastric cancer present with symptoms indistinguishable from benign peptic ulcer disease. Screening for this group of patients improves detection rate of early gastric cancer and therefore its prognosis. Endoscopy for surveillance of premalignant lesions has been explored with this objective in mind. Serology testing for biomarkers such as pepsinogen, anti-*Helicobacter pylori* antibody and gastrin has been studied as an alternative to endoscopy. There is compelling evidence for the role of *H. pylori* in the initiation

of Correa's cascade (stepwise progression from chronic active gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and finally adenocarcinoma). Regression of premalignant lesions has been demonstrated with *H. pylori* eradication. However, it is not known whether this might effectively prevent gastric cancer in either low or high-risk population. *Eur J Gastroenterol Hepatol* 18:821–829

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Introduction

The detection of gastric cancer in the early stage is vitally important in ensuring an excellent prognosis. Every effort needs to be made to facilitate the diagnosis. The Japanese Society of Gastroenterological Endoscopy in 1962 coined the definition of early gastric cancer (EGC) as a malignant tumour limited to the mucosa or submucosa irrespective of the presence of lymph node metastases [1]. Many Japanese series have consistently reported 5-year survival rates of over 90% for EGC [2–5]. In the west, 5-year survival rates are more variable, ranging from 68 to 92% [6–11]. More encouragingly, a 10-year survival rate of greater than 90% has also been reported by a few series from Japan [2,3,5].

Gastric cancer remains one of the most common malignancies and is the second commonest cause of cancer deaths worldwide [12]. In 2002, on a global scale, it accounted for more than 900 000 new cancer cases diagnosed and 700 000 deaths. There is a wide geographical variation in its incidence. High incidence countries are those in eastern Asia, with Korea taking the lead (age-standardized rate in men of 69.7 per 100 000). This is followed by Japan (62 per 100 000) and China (41.4 per 100 000), whereas most of Europe, north America and Africa are low-risk areas [13].

Screening in high-incidence areas: asymptomatic groups

Historically, gastric cancer was one of the most serious public health problems facing Japan. In 1960 alone, gastric

cancer accounted for 51.6% of deaths in men and 38.4% in women [14]. This led to a pressing need to detect gastric cancer at an early stage, with the aim to reduce mortality. A mass screening programme was subsequently started in 1960 for persons over the age of 40 years. Double contrast X-ray examination was the initial test of choice, with suspicious lesions further investigated by endoscopy [15]. Despite the lack of randomized controlled trials to confirm effectiveness, mass screening for gastric cancer had taken off, and has since become widely available throughout Japan. This has led to a significant increase in the proportion of EGC from 8% during the period 1960–1964 to 50% in 1975–1979. The 5-year survival rate has also improved proportionately for all resections from 27 to 64% for the two periods, respectively. This survival improvement is likely to be partly caused by the early detection of gastric cancer despite lead-time and length biases [16]. Although the incidence and mortality of gastric cancer have been declining steadily since the 1950s worldwide, the mortality has declined more sharply in Japan. Again, the latter may be explained by the fact that gastric cancers are being detected early, with a subsequent favourable survival outcome [17]. Oshima and co-workers [18] carried out a case-control study on a series of 93 patients diagnosed with EGC, and demonstrated that unscreened patients are twice as likely to die, when compared with the screened group.

In Japan, up to 60% of gastric cancers are diagnosed as early cancers [14]. In Western countries, however, early disease is much less frequently detected, only accounting

for between 10 and 20% of all gastric cancers [9]. The high pick-up rate in Japan can partly be explained by their mass screening programme. There is, however, controversy with respect to the different diagnostic criteria for the histological diagnosis of EGC between Japanese and Western pathologists. Schlemper *et al.* [19] carried out a study involving eight pathologists from Japan, north America and Europe examining microscope slides of 17 Japanese patients with lesions ranging from EGC to adenoma, dysplasia, and reactive atypia. The study concluded that Japanese pathologists gave more emphasis to the nuclear features and glandular structures, whereas Western pathologists would only diagnose gastric cancer when there was evidence of invasion. The discrepancy in diagnostic criteria may result in the diagnosis of non-invasive neoplasia in the West, but classified as invasive gastric carcinoma by Japanese pathologists. This may explain the better treatment results of gastric cancer in Japan. Furthermore, a multicentre collaborative study carried out by the British Society of Gastroenterology [20] evaluated a series of 319 patients from 41 hospitals with histological findings of EGC, dysplasia and worrying mucosal appearances. All the histological materials were then re-examined by a panel of pathologists. There is a 6.5% disagreement between referral pathologists and panel pathologists with respect to dysplasia versus EGC, and a 23.8% disagreement when early and advanced gastric cancers were concerned. This has again demonstrated the need to have widely agreed histopathological criteria for the diagnosis of EGC and dysplasia so that a meaningful comparison of data between different centres can be achieved.

Screening in low-incidence areas: symptomatic groups

In countries where the incidence of gastric cancer is low, such as the United Kingdom and the United States, with age-standardized mortality rates in the order of 10 per 1 000 000 and five per 1 000 000 [13], mass screening will not be cost effective. In these areas, targeted screening programmes for patients who are deemed to be at high risk of gastric cancer will be more appropriate.

Dyspepsia and open access gastroscopy

Dyspeptic symptoms are common in patients with EGC. It has been suggested that 60–90% of patients with EGC have dyspeptic symptoms [21], as defined by the presence of heartburn or abdominal pain or discomfort centred in the upper abdomen. These symptoms are generally indistinguishable from benign gastric disease. It is therefore crucial to consider the diagnosis of gastric cancer in at-risk patients when symptoms are benign. The screening of this group of patients can potentially improve the detection rate of EGC [6]. Open access gastroscopy (OAG) is seen as an approach to influence the stage of cancer at diagnosis. It is defined as 'the provision of a diagnostic endoscopic procedure by direct request of a

general practitioner without previous hospital consultation, but including the provision of screening the appropriateness of any referral' [22]. The screening of symptomatic patients through OAG has been reported to achieve a higher incidence of EGC. In Birmingham, a policy of screening dyspeptic patients over the age of 40 years in the 1990s had seen an improvement of detecting EGC from 1 to 26%. Curative resections had also increased in parallel from 20 to 63% [23]. Similar results have been confirmed in Leeds, with a 4% incidence of EGC in 1970 increasing to 26% in 1980 [9]. The benefit of screening patients with benign symptoms via OAG is, however, not consistent throughout the United Kingdom. Suvakovic and colleagues [21] carried out a 5-year prospective survey on the OAG service provided in Middlesbrough. They showed a higher EGC rate in the OAG patients when compared with patients referred to a specialist via the conventional UK pathway. The difference was not significant. They concluded that the advantages of OAG might be substantially compromised by diagnostic failure, including a lack of awareness of EGC on the part of endoscopists.

Acid suppression therapy

The symptoms of EGC are often indistinguishable from those of benign disease. This group of patients may be started on treatment with acid suppression drugs, including proton pump inhibitors and H₂ blockers before referral to a specialist or before gastroscopy. The diagnosis of EGC can potentially be delayed as a result of an improvement in dyspeptic symptoms. EGC may also 'heal' by acid suppression, and make endoscopic identification of the EGC impossible, even by experienced endoscopists. 'Healing' of a malignant ulcer has been observed within 4 weeks with proton pump inhibitors [24–27]. By the same token, healing of 'gastric ulcer' after a course of acid suppression therapy does not exclude malignancy, and follow-up endoscopy with multiple biopsies is essential to prevent missed cancer.

Bramble and colleagues [28] in a retrospective primary care based survey revealed that 55% of patients who attended OAG were treated with acid suppression drugs before the index gastroscopy. The diagnosis of gastric cancer was made in all patients not taking previous acid suppression therapy at index gastroscopy. However, 37% of patients with gastric cancer, who were previously taking acid suppression therapy, were missed at index gastroscopy. This led to a mean delay in diagnosis of 26 weeks from the commencement of medication.

Primary care physicians should therefore refrain from prescribing acid suppression drugs in patients over the age of 45 years with dyspepsia before endoscopy in order to minimize the risk of missing EGC. The possibility of gastric malignancy should also be borne in mind if patients require the repeated prescription of acid suppression drug to control dyspeptic symptoms.

Helicobacter pylori infection

Gastric cancer is generally accepted as a multistep progression disease from chronic gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia and subsequently to cancer. Infection with *Helicobacter pylori* has been linked to gastric carcinogenesis [29]. It is the main pathogenic factor in the development of chronic atrophic gastritis and intestinal metaplasia [30]. The lifetime incidence of gastric cancer in *H. pylori*-infected patients has been estimated to be approximately 1–2% [31]. In 1994, epidemiological evidence led the World Health Organization and the International Agency for Research on Cancer consensus group to classify *H. pylori* as a definite class I carcinogen [32].

The EUROGAST study group, in a multicentre investigation, showed a sixfold increased risk of gastric cancer in populations with 100% *H. pylori* infection compared with populations that have no infection [33]. Three meta-analyses [34–36] evaluating the epidemiological evidence have suggested a two to threefold increased risk of gastric cancer in those individuals infected with *H. pylori*. Furthermore, in a recent large prospective follow-up study in a high-risk population, Uemura *et al.* [37] revealed that gastric cancer was only found in patients infected with *H. pylori*. Among patients with *H. pylori* infection, those with severe gastric atrophy, corpus predominant gastritis, and intestinal metaplasia were at a significantly greater risk of gastric cancer. Individuals with non-ulcer dyspepsia, gastric ulcers or gastric hyperplastic polyps except duodenal ulcers are also at risk. Several epidemiological studies have also indicated that populations with *H. pylori* infection are at increased risk of developing gastric cancer of both Lauren's [38] intestinal and diffuse types, but more frequently with the former [33,35,39]. In a meta-analysis [36], *H. pylori* infection has also been revealed to be strongly associated with non-cardiac cancer but not cardiac cancer. A nested case-control study demonstrated a sixfold increase in non-cardiac cancer with *H. pylori* infection [40].

It is, however, not known why some individuals with *H. pylori* infection develop gastric cancer whereas others do not. The virulence factors of *H. pylori* have been investigated. There is increasing evidence to suggest that certain *H. pylori*, containing a gene called CagA, associated with cytotoxin expression, are more strongly associated with gastric cancer [41]. CagA-positive *H. pylori* is likely to induce greater degrees of acute and chronic inflammation than the CagA-negative phenotype [42,43]. Several studies have suggested that CagA-positive *H. pylori* is more common in patients who develop gastric cancer. In a recent meta-analysis, Huang *et al.* [44] estimated a twofold increased risk of non-cardiac cancer in CagA-positive *H. pylori* individuals over CagA-negative *H. pylori* individuals. The vacA, iceA and babA genes have also been implicated in increased gastric cancer risk [45].

The European *Helicobacter pylori* Study Group strongly recommended *H. pylori* eradication for patients with atrophic gastritis, after gastric cancer resection, and first-degree relatives of patients with gastric cancer [46]. Parsonnet and colleagues [47] calculated that preemptive *H. pylori* eradication might be cost-effective in high-risk populations, based on a cancer risk of 3.6-fold.

There are emerging data that intestinal metaplasia [48] and atrophic gastritis [49–52] regress after *H. pylori* eradication. Three recent randomized controlled trials on *H. pylori* eradication in Columbia, China and Mexico with short-term follow-up, have shown some evidence of regression or inhibition of the progression of premalignant lesions in treatment groups [53]. This may subsequently intercept the development of gastric cancer. It may be argued that *H. pylori* screening and treatment is an effective strategy in cancer prevention [54–56].

In a recent randomized placebo-controlled, population-based primary prevention study of 1630 healthy carriers of *H. pylori* in a high-risk population in China [57], the study found no difference in the incidence of gastric cancer over a 7.5-year follow-up between placebo and the *H. pylori*-eradicated group. However, in the subgroup of patients without premalignant lesions, the incidence of gastric cancer was significantly higher in the placebo group. The concept of 'point of no return' has been speculated for the group with premalignant lesions.

Premalignant lesions/conditions**Chronic gastritis and chronic atrophic gastritis**

Chronic gastritis is closely associated with *H. pylori* infection. It has been demonstrated that *H. pylori*-related chronic gastritis progresses to chronic atrophic gastritis with time by progressive damage of the gastric glands [58,59]. *H. pylori*-related atrophic gastritis is a multifocal disease. It is more prevalent in populations with a high gastric cancer risk. Atrophic lesions are localized mostly around the incisura angularis. They will progress gradually to the antrum, corpus and finally the fundus over the course of time [60]. *H. pylori*-related atrophic gastritis has been associated with a sixfold increased risk of developing intestinal-type gastric cancer [61]. Kato and co-workers [62] estimated that the gastric cancer risk in individuals with atrophic gastritis was 25-fold for intestinal-type cancer and 3.5-fold for diffuse-type cancer. Sipponen *et al.* [63] calculated the relative risk of gastric cancer in severe antral atrophic gastritis to be approximately 18-fold and approximately 4.5-fold in severe body atrophic gastritis.

Autoimmune atrophic gastritis is less common. It is associated with antiparietal cells and intrinsic factor antibodies and the subsequent development of pernicious anaemia. The lesion diffusely involves the corpus

and the fundus where the parietal cells are found. It is also associated with an increased risk of gastric cancer but to a lesser extent than *H. pylori*-related atrophic gastritis [64,65]. In a Swedish study involving 4517 patients with pernicious anaemia followed for a mean 5.9 years, an approximately threefold increase in gastric cancer risk was observed [66].

Intestinal metaplasia

Intestinal metaplasia occurs when the stomach mucosa has been replaced by mucosa resembling that of the intestine. It represents an advanced stage of chronic atrophic gastritis. Three subtypes of intestinal metaplasia have been described: (I) complete; (II) incomplete with mild glandular distortion; and (III) incomplete with severe glandular distortion [67]. Individuals with intestinal metaplasia are estimated to have more than a 10-fold increased risk of developing gastric cancer [68]. Intestinal metaplasia has also been identified to be more closely correlated with the intestinal type [odds ratio (OR) 12.83] than the diffuse type of cancers (OR 3.14) [69]. Type III intestinal metaplasia has been shown to have a higher malignant potential. In a large prospective study in Slovenia, Filipe and colleagues [68] observed a 3.8-fold increased risk of gastric cancer in the presence of type III intestinal metaplasia compared with type I intestinal metaplasia. In addition, types II and III intestinal metaplasia are found to be four times more likely to progress to dysplasia, when compared with chronic atrophic gastritis without metaplasia or type I intestinal metaplasia [70]. An endoscopic follow-up study on patients with type III intestinal metaplasia showed that 42% developed EGC within 5 years of follow-up, reflecting the high malignant potential of this subtype of intestinal metaplasia. Screening for this group of patients will be particularly valuable [71].

Non-invasive neoplasia

Non-invasive neoplasia (formerly dysplasia) is generally divided into three grades: mild, moderate and severe. The Padova classification has divided non-invasive neoplasia into two grades: low-grade and high-grade [72]. Atrophic gastritis represents the main background of dysplastic lesions (87 of 93, 93%), and the highest grade of gastric atrophy was detected in association with the most severe dysplasia [63]. The majority (50–80%) of patients progress to invasive carcinoma [73]. High-grade non-invasive neoplasia is particularly predictive of subsequent cancer. It is also considered to be a warning marker of co-existing carcinoma [74]. In a prospective endoscopic follow-up study by Rugge and colleagues [75] on 118 patients with non-invasive neoplasia over a mean period of 52 months, EGC accounted for 86.6% of the 20 gastric cancer cases detected. They also demonstrated that the evolution of gastric cancer increases proportionately with increasing grades of non-invasive neoplasia. Furthermore, regression to normal mucosa has also been

observed, although it is least likely in severe non-invasive neoplasia. The importance of endoscopic surveillance for non-invasive neoplasia has also been supported by other studies [76,77].

Gastric polyps

Hyperplastic polyps are the most common epithelial polyps of the stomach and are found throughout the stomach, ranging in size from a few millimetres to centimetres. They are mostly found in the gastric antrum (60%) [78,79]. They occur in less than 1% of the general population. They are characterized by hyperplastic foveolae with variable amounts of inflamed stroma. They have a malignant potential of 1.5–3% [80,81]. Hyperplastic polyps (85%) have been reported in association with various types of chronic gastritis, particularly autoimmune gastritis, *H. pylori* gastritis, and reactive/chemical gastropathy [78]. There is evidence that hyperplastic polyps in association with *H. pylori* infection may regress after *H. pylori* eradication [82].

Adenomatous polyps are at high risk of malignant transformation. Their frequency increases with age, from 0.1% in the third decade to 3.7% in the ninth decade. An endoscopic follow-up study revealed malignant transformation in 11% of gastric adenomas [83]. Cristallini and colleagues [84] have also confirmed the apparent risk of adenomas undergoing malignant transformation. Based on the available evidence, endoscopic surveillance should be advocated with the intention to detect early cancer.

Postgastrectomy

A previous history of gastric surgery for benign diseases is a risk factor for the subsequent development of gastric cancer, with over a twofold increase in risk. The risk only increases significantly after a latency of 15–20 years post-surgery [85]. The risk is greater in gastric (4.5-fold) than in duodenal (3.7-fold) ulcer after 20 years [86]. Furthermore, patients who were treated with the Billroth II operation are three to four times more at risk than those treated with the Billroth I procedure [87]. Given the increased risk of cancer associated with partial gastrectomy for benign diseases, endoscopy surveillance has been suggested [88]. However, an endoscopic screening programme has not been proved to be useful [89]. Since the introduction of H₂ blockers and proton pump inhibitors as well as the identification of *H. pylori* in its role of gastritis/peptic ulcer induction, gastric surgery for benign conditions has reduced significantly. The importance of postgastrectomy cancer risk is diminishing progressively.

Family history

A family history of gastric cancer in first-degree relatives increases the risk of cancer by approximately threefold [90]. Zanghieri *et al.* [91], in a population-based gastric cancer registry study, observed a 10–15% cancer risk in patients with a family history, suggesting the possibility of

a genetic susceptibility to gastric cancer. Family history remains an independent risk factor, even after controlling for *H. pylori* status. Observation of families with a clustering of diffuse gastric cancer has led to the identification of germline mutations in the E-cadherin (CDH-1) gene. Data indicate that up to 75% of patients with CDH-1 germline mutations will develop diffuse gastric cancer [92].

Certain familial cancer syndromes also increase cancer risk. Familial adenomatous polyposis (FAP) is commonly associated with fundic gland polyposis and gastric/duodenal adenoma. Gastric/duodenal adenomas are found in between 35% and 51% of cases [93–95]. In view of its inherent risk of gastric cancer, surveillance endoscopy was recommended every 3–5 years [94]. Fundic gland polyps are identified in between 26 and 52% of patients with FAP [93–95]. They have been observed frequently to carry the somatic adenomatous polyposis coli gene, which is pathogenetically distinct from sporadic familial gastric polyps [96]. On the basis of molecular evidence, FAP-associated fundic gland polyps may be considered neoplastic polyps. Furthermore, neoplastic progression of FAP-associated fundic gland polyps has also been reported [97]. Close endoscopic surveillance of patients with fundic gland polyps in the setting of FAP may be warranted.

Patients with hereditary non-polyposis colorectal cancer have an approximately 11% chance of developing gastric cancer of the intestinal type [98]. Surveillance gastroscopy in this group of individuals has, however, not been shown to be beneficial [99].

Endoscopic identification of early gastric cancer

Age and symptoms

The European *Helicobacter pylori* Study Group and American Gastroenterological Association recommend endoscopy for patients with dyspepsia and alarm symptoms or those over 45 years of age. This cut-off was taken as gastric cancer below the age of 45 years is rare. Younger patients who have uncomplicated symptoms can therefore be treated empirically unless symptoms persist despite treatment [46,100]. Using age limit and the presence of alarm symptoms as clinical predictors for significant pathology and indications for endoscopy has been controversial. A study by Gillen and McColl [101] in Scotland suggested that the age limit can safely be raised to 55 years as gastric cancer is rare in patients with uncomplicated dyspepsia below that age. They found that 169 patients with upper gastrointestinal tract cancers were less than 55 years and 164 out of 169 of them had alarm symptoms. Similarly, Christie and co-workers [102] in England, who retrospectively reviewed a cohort of 319 patients diagnosed with gastric cancer, found 25 patients to be less than 55 years of age and again 24 out of 25 had

alarm symptoms. On the other hand, Schmidt *et al.* [103] showed that up to 8.6% of gastric cancer can be missed by increasing the age limit for endoscopy from 45 to 55 years. In areas of high prevalence of *H. pylori*, where gastric cancer is high, the age cut-off for endoscopy may need to be reduced to minimize the risk of missing EGC. Dzuba *et al.* [104] proposed endoscopic screening for those over 30 years of age in Russia, where *H. pylori* infection is prevalent. In contrast, a recent multicentre database study involving 3815 patients, Wallace and colleagues [105] found that age and alarm symptoms were poor clinical predictors for significant upper gastrointestinal pathology.

Gastric biopsy protocol

A standardized protocol for gastric biopsy is critical in detecting EGC like the one recommended by the Sydney System [106]. Furthermore, any gastric mucosal abnormalities should be subject to additional targeted biopsy sampling. It has been demonstrated that the recommendation of the sites and numbers of gastric biopsies by the Sydney System is sufficient in identifying significant gastric pathology in high-risk populations [107].

Surveillance of premalignant lesions

The identification of premalignant lesions will provide the prospect of intercepting Correa's cascade in the progression to invasive carcinoma. Endoscopic surveillance of premalignant lesions will offer an opportunity to identify more gastric cancer in the early stage. Whiting *et al.* [108] have recently shown that endoscopic surveillance of patients with premalignant lesions allows the detection of more new gastric cancers at an early stage than those detected at open access. The 5-year survival was improved from 10 to 50%. Again, close endoscopic surveillance of type III intestinal metaplasia has been shown to detect EGC at increasing frequency [71]. However, the interval of endoscopic surveillance has been controversial. Furthermore, the cost implications to the healthcare system and the level of acceptance by patients should be considered.

Missed diagnosis

The missed diagnosis of gastric cancer on endoscopy is a common occurrence. Studies have been published on cancers missed or possibly missed at previous endoscopy.

False-negative rates have been reported to be between 10 and 19% [109]. Suvakovic and colleagues [21], in a retrospective study on the presentation of gastric cancer, showed that for those diagnosed with gastric cancer endoscopically, one out of six had had endoscopy within 3 years before the diagnosis. Based on the gastric cancer doubling time of approximately 2–3 years [110], those cancers would be considered missed on initial diagnosis.

Yalamarthy *et al.* [111] conducted a retrospective study on 305 consecutive patients diagnosed with oesophageal and gastric cancers. Thirty patients (9.8%) were identified to have had at least one endoscopy within the previous 3 years. Twenty-two patients were definitely missed, whereas the remaining eight patients were possibly missed. The majority of missed diagnoses were secondary to endoscopist error, including sampling errors. The remainder were attributed to histological misinterpretation.

It is crucial that endoscopists are properly trained and equipped with the ability to recognize the different appearances and characteristics of EGC. A high index of suspicion and low threshold for biopsy as well as adherence to appropriate sampling protocol will ensure a minimal false-negative rate. Furthermore, primary care physicians should be educated on the fact that the majority of patients with EGC have dyspeptic symptoms. Emphasis should be placed on referral when symptoms are still benign in order to improve early detection [6]. Advances in endoscopic techniques such as chromoendoscopy and magnifying endoscopy are promising in improving detection rates.

Endoscopic appearance of early gastric cancer

The experience of the endoscopist is crucial in identifying gastric lesions and making appropriate tissue sampling. EGC can easily be overlooked by untrained eyes. The macroscopic features of EGC are better understood now owing to the experience of mass screening in Japan. The Japanese Endoscopic Society has classified the macroscopic appearances of EGC into protruding (type I), superficial (type II) and excavating (type III). Type II is further subdivided into elevated (IIa), flat (IIb) and depressed (IIc) [1]. Combined types of EGC also frequently occur in a single cancer. For example type I + IIa. Type IIb is understandably the most difficult type to diagnose endoscopically. Type IIc is the most common EGC found in Japan (34%) [112] and Korea (66.1%) [113]. Everett and Axon [114] tabulated data from western and Japanese series and found that the majority of EGC are of type IIc or III or both in more than 60% of cases, equally across all series. Craanen and colleagues [115] in a clinicopathological study revealed that types I and IIa lesions are likely to represent the intestinal type, whereas diffuse-type EGC are likely to be of types IIc or III lesions.

Advances in endoscopic techniques

Recent advances in endoscopic technology have improved the sensitivity of detecting EGC. Chromoendoscopy using non-absorbable dye such as indigo carmine is one example. This involves spraying the dye over the gastric mucosa to enhance tissue irregularities and therefore facilitate the identification and biopsy of abnormal areas [116]. Magnifying endoscopy (capable of magnifying approximately 80 ×) is useful in assessing gastric lesions

at the level of microvascular architecture and thus providing the possibility of predicting the histological nature of the cancer. It is, however, not suitable for surveying the entire gastric mucosa [117]. Light-induced fluorescence endoscopy is promising as a useful adjunct to conventional white-light endoscopy. In a small sample of cases, Kobayashi and co-workers [118] have reported a sensitivity and specificity of 94 and 86%, respectively, for this spectroscopic technique in detecting EGC. The infrared video endoscope is another new technique whereby infrared light gives deeper tissue penetration and therefore the possibility of obtaining information about the submucosal aspect of EGC [119].

Biomarkers for gastric cancer

Gastroscopy is expensive and unpleasant for the patient. It also carries a small risk of complications. The cost implications of screening for gastric cancer to the healthcare system can be considerable. Screening methods that are inexpensive, non-invasive and suitable for a large general population have been sought. Several serology tests have been investigated to establish their suitability as screening tools to identify patients with premalignant lesions or gastric cancer for close surveillance.

Pepsinogen

Pepsinogen is the precursor of pepsin. It exists as two main types, pepsinogen group I (PGI) and pepsinogen group II (PGII). PGI is secreted only by the chief cells of the corpus and PGII is produced in the antrum, corpus chief cells, and in Brunner's glands of the duodenum. The PGI level is low in corpus-predominant atrophic gastritis and when the mucosa is replaced by intestinal mucosa [120,121]. The continued production of PGII in the antrum, duodenum and residual corpus results in a relative increase in the PGII level so that the PGI and PGII ratio is reduced. It has been demonstrated that serum pepsinogen levels are useful for the screening of atrophic gastritis and a low PGI/PGII ratio is predictive of an increased risk of gastric cancer [122,123]. Kitahara and colleagues [124] demonstrated that pepsinogen screening using a combination of PGI and PGI/PGII ratio with an appropriate cutoff point is effective in identifying gastric cancer in patients with a background of severe atrophic gastritis. It was, however, not a suitable test to detect gastric cancer in patients with mild atrophic gastritis. The Eurohepgast Study Group found that the PGI/PGII ratio is an acceptable biomarker for atrophic chronic gastritis and *H. pylori*-related corpus-predominant or multifocal atrophy [125].

Helicobacter pylori antibody

H. pylori antibody is a marker of infection. A prospective study in Leeds has shown that *H. pylori* serology is a useful screening tool for dyspeptic patients under the age

of 45 years with a sensitivity of 97% and specificity of 87%. No peptic ulcer or gastric cancer was missed in the patients studied [126]. Individuals with a negative test can safely be excluded from having endoscopy. In contrast, a retrospective study from Birmingham has reported *H. pylori* serology screening to be a poor screening tool for gastric cancer in patients older than 40 years of age with dyspeptic symptoms. Over 30% of gastric cancer cases may be missed [127]. However, in a recent prospective follow-up study involving a large cohort of 9293 healthy and asymptomatic Japanese individuals, the combination of *H. pylori* antibody and pepsinogen was demonstrated to be a valid screening biomarker in predicting the likelihood of gastric cancer development, and who should be subjected to a close endoscopic follow-up [128].

Gastrin-17

Gastrin is synthesized in G cells found in the antrum. Over 90% of the gastrin secreted is of type G-17. In cases of atrophic gastritis, the loss of antral G cells will result in low gastrin levels despite an achlorhydric stomach. G-17 is consequently an indicator of the status of antral mucosa [129]. In an observational case-control study, Sipponen and colleagues [130] demonstrated that using a combination of pepsinogen and gastrin levels in connection with *H. pylori* antibody status can effectively identify and distinguish different types of atrophic gastritis with a sensitivity and specificity of 89% and 93%, respectively. This observation has also been substantiated by recent studies [131,132].

Conflict of interest

None declared.

Authors' contributions

Both authors contributed to the writing and editing of the manuscript.

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