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Review Article

Gastric cancer screening in Western countries: A call to action

Fabio Farinati[a,b,*], Filippo Pelizzaro[a,b]

[a] Department of Surgery, Oncology and Gastroenterology, University of Padova, Via Giustiniani 2, Padova 35128, Italy
[b] Gastroenterology Unit, Azienda Ospedale-Università di Padova, Via Giustiniani 2, Padova 35128, Italy

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ABSTRACT

Gastric cancer is a major cause of cancer-related death worldwide, despite the reduction in its incidence. The disease is still burdened with a poor prognosis, particularly in Western countries. The main risk factor is the infection by *Helicobacter pylori,* classified as a class I carcinogen by the IARC, and It is well-known that primary prevention of gastric cancer can be achieved with the eradication of the infection. Moreover, non-invasive measurement of pepsinogens (PGI and PGI/PGII ratio) allows the identification of patients that should undergo upper gastrointestinal (GI) endoscopy. Gastric non-cardia adenocarcinoma is indeed preceded by a well-defined precancerous process that involves consecutive stages, described for the first time by Correa et al. more than 40 years ago, and patients with advance stages of gastric atrophy/intestinal metaplasia and with dysplastic changes should be followed-up periodically with upper GI endoscopies. Despite these effective screening and surveillance methods, national-level screening campaigns have been adopted only in few countries in eastern Asia (Japan and South Korea). In this review, we describe primary and secondary preventive measures for gastric cancer, discussing the need to introduce screening also in Western countries. Moreover, we propose a simple algorithm for screening that could be easily applied in clinical practice.

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1. Introduction

Gastric cancer (GC) is one of the most common malignancies and a leading cause of mortality worldwide [1]. GC includes two main anatomical subtypes, cardia GC and non-cardia GC with different epidemiology and risk-factors, and two histological subtypes, intestinal type (with a glandular growth pattern) and diffuse type (with poorly cohesive cells with no glandular growth pattern, including signet ring cell carcinomas and linitis plastica) [2]. Diffuse type GC is mostly caused by mutations in genes that affect pathways related to cell-to-extracellular matrix interactions. By contrast, intestinal type GC, that represent the large majority of GCs worldwide, typically originates from chronic atrophic gastritis, which is caused mainly by *Helicobacter pylori* (HP) [3,4]. It is preceded by a well-defined precancerous process involving consecutive stages (known as the Correa cascade) [5,6]: HP infection causes chronic gastritis that, after decades, may transform into atrophic gastritis; this atrophy subsequently predisposes to intestinal metaplasia (IM), dysplasia and, finally, adenocarcinoma. These different stages in gastric carcinogenesis and the risk factors that initiate this process (e.g., HP infection) are well known, treatable and potentially surveyable. Therefore, we would able to apply in these situations both primary and secondary preventive measures. Considered that the worldwide mortality rate for GC remains high and this cancer continues to be a major contributor to the burden of global disability-adjusted life-years [7], we must ask ourselves whether the time has come to foster a population screening with the aim of improving patients' survival. In this review, we describe opportunities and challenges associated with GC screening, discussing whether the time has come to introduce GC screening also in Western countries. We also propose a practical approach to screening for GC that could be easily applied at a population level.

2. The burden of gastric cancer

Based on the last available data, GC ranks as the fifth most common cancer and the fourth leading cause of cancer-related death globally (with 1089,000 new cases and 769,000 deaths in 2020, respectively) [1]. Despite an overall decline in incidence rates globally, the trends in incidence and mortality rates for GC vary between countries [8–10]. In 2020, the highest incidence rates of GC were recorded in eastern Asia (22.4 per 100,000), that accounted for almost two-thirds of global GC diagnoses (n = 696,112), fol-

* Corresponding author at: Department of Surgery, Oncology and Gastroenterology, Gastroenterology Unit, University of Padova, Via Giustiniani 2, Padova 35128, Italy.
E-mail address: fabio.farinati@unipd.it (F. Farinati).

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lowed by central and eastern Europe (11.3 per 100,000) and South America (8.7 per 100,000), whereas North America (4.2 per 100,000) and Africa (3–4 per 100,000) had the lowest incidence rates globally [1]. The incidence rates reach 32.5 per 100,000 and 13.2 per 100,000 in eastern Asian males and females respectively, with a male-to-female ratio of 3:1 [1]. Consistent with global incidence rates, eastern Asia (14.6 per 100,000) and central and eastern Europe (8.3 per 100,000) have the highest GC mortality rates, whereas North America (1.8 per 100,000) had the lowest [1].

According to the most recent epidemiologic data, an estimated 15,000 new cases of GC are expected in Italy in 2023 (9000 in males and 6000 in females, with a male-to-female ratio of 1.5) [11]. In the same year, 9900 patients are estimated to die from the disease with a mortality-to-incidence ratio of 0.66 (similar to that reported in eastern Asia, where it is approximately 0.55 [12]). Despite the progress in patient care, the actual 5-years survival rate of 30 % in males and 35 % in females is identical to that observed 15 years ago, demonstrating the lack of a clear prognostic improvement [11]. A total of 82,400 patients are currently living in Italy after having received a diagnosis of GC [11]. Differently from Eastern countries, where the incidence curve of GC starts to increase around the age of 45, in Italy this happens about 10 years later (at an age of 55), probably due to dietary and, less frequently, genetic co-factors [13,14].

In Italy, the epidemiology of GC varies deeply among different regions: in males, incidence is high (≥30 per 100,000) in Emilia-Romagna, Umbria, Marche, Toscana, Friuli Venezia-Giulia and Basilicata, intermediate (20–30 per 100,000) in Liguria, Lombardia, Piemonte, Valle d'Aosta, Veneto, Lazio, Abruzzo, Calabria and Molise, while it drops down to < 20 per 100,000 in Trentino Alto-Adige, Campania, Puglia, Sicilia and Sardinia [15]. In females, although lower, the geographical distribution of the incidence is comparable to that of males. Sharp differences are also observed for 5-years survival rates that is highest in North and Center Italy, whereas lower survival is observed in Southern Italy and islands [16].

3. Screening for gastric cancer in a situation of heterogeneous risk

The endpoint of cancer screening is to reduce the mortality for that specific disease. National-level GC screening programs have been adopted in only few countries. In Japan, that has long been engaged in a battle against this disease, a double-contrast radiographic screening was empowered locally in the sixties, with a nationwide campaign in 1983 [17]. In 2013, the Japanese government implemented a national GC prevention program that involves HP screening and treatment (primary prevention) as well as post-HP eradication endoscopic surveillance (secondary prevention in subjects with atrophic gastritis) [18–20]. Overall, these approaches led to a progressive drop in GC mortality of about 10 % [21]. According to the South Korean guidelines, both men and women ≥40 years of age should undergo GC screening with upper gastrointestinal (GI) endoscopy or radiography every 2 years to identify high-risk patients, harboring precancerous lesions (e.g., IM or dysplasia) for early diagnosis [22]. One prospective and several observational studies demonstrated the ability of endoscopic screening to reduce cancer-specific mortality [23–25].

Considered these results, it can be deduced that GC screening works. However, in planning a screening campaign, a number of variables that could impact on its success must be considered, starting from the incidence of the disease in the screened population. A recently published commentary [26] stated that, given the significant difference in GC risk among different countries, no unique screening policy is worldwide conceivable. While in high-risk countries screening programs have yielded substantial results and are strongly recommended, in low-risk areas the strategy should be identifying individuals harboring precancerous lesions, with a surveillance based on their weighted risk [26].

But should we accept this approach as it stands? There are several reasons for not sticking to these indications. First, the mortality for GC in Italy is as high as 15 years ago. Second, despite the decline in GC incidence [27], in Western countries and particularly in Italy, the age distribution of the population is deeply changing and a large share of subjects will be over 60 years of age by 2050. Since the risk of cancer increases with age, these demographic changes will have a deep impact on all types of cancers incidence, including GC, thus balancing the present reduction in its incidence.

Third, in Italy, migratory flows from Central and Eastern Europe, where GC incidence is at least 1.5-times higher than in Southern Europe, are modifying GC epidemiology [1]. This aspect also will counterbalance the present reduction in GC incidence. Fourth, despite all the advances in endoscopic equipment and the widespread use of upper GI endoscopy, no clear-cut progress in the diagnosis of early gastric cancer has been observed in Western countries. Indeed, the share of GCs diagnosed in early-stage in these regions does not exceeds 20 %, as compared to the 50 % or more registered in South Korea and Japan [28]. Fifth, there are regions in Italy (Marche, Toscana, Umbria, Emilia-Romagna and Friuli Venezia-Giulia) that cannot be considered as low-risk areas, with a GC incidence overlapping to that registered in east Asia [15]. Endoscopic screening could be extremely useful in these regions, considering that, in Europe, screening proved to be cost-effective for an incidence of GC ≥10 per 100,000 per year [29].

4. Eradication of helicobacter pylori in gastric cancer primary prevention

In addition to a number of indications regarding diet, alcohol consumption, vitamin intake and smoking habit [30–33], primary prevention of GC can be achieved by eradicating HP. Studies evaluating the global prevalence of HP infection reported a substantial overlapping between high prevalence of HP and high incidence of GC [34]. The link between the infection and GC is so close that in 1994 the International Agency for Research on Cancer (IARC) classified HP as a carcinogen (i.e., a group 1 agent) for non-cardia GC on the basis of epidemiologic data [35].

A metanalysis of international randomized controlled trials compared the risk of GC in HP-positive adults that received eradication therapy, placebo or no therapy [36]. Compared to the other groups, patients receiving eradication therapy had a lower risk of developing GC (RR 0.54, 95 % CI 0.40–0.72) and a reduction in GC-related mortality (RR 0.61, 95 % CI 0.40–0.92) [36]. Since the evidence in favor of the benefit of eradication therapy risk is quite large [37–42], the WHO endorses population screening for HP to prevent GC [43]. The same suggestion came from the Taipei and, more recently, from the Maastricht VI consensus [44]. Despite these recommendations and several prospective studies demonstrating the effectiveness of the "test and eradicate" approach [37,45,46], only a few organized efforts exist.

The first question to ask before implementing a "test and eradicate" campaign is whether this strategy is affordable from a population-based perspective. Population-based serology screening and eradication of HP infection demonstrated to be cost-effective when performed in subjects >50 years of age in areas with a high GC burden [43,47]. Moreover, under favorable assumptions this strategy becomes cost-effective even in populations with GC rates as low as 4.2 per 100,000 [47]. Targeted screening in high-risk populations living in countries with overall low incidence of GC could be cost-effective, but it has not been so far proven. Compared to endoscopic screening, the "test and eradicate" approach is cost-

effective with, according to a Japanese study, prevention of 4.5 million GC cases in Japan and a concomitant reduction of expenses of about 28 billion dollars [48]. Data from China further confirm the affordability of this approach, that turned out to be the most sustainable strategy in terms of quality-adjusted life-years saved [49]. Unfortunately, no similar data on that point coming from Western Countries are currently available.

It could be argued that the "test and eradicate" approach may suffer from several factors among which compliance to screening and treatment, antibiotic resistance and/or adverse events. Nevertheless, a community-based interventional Chinese trial demonstrated that 73 % of affected patients can be eradicated without relevant adverse events [50] and, in Europe, empirical treatment with sequential, concomitant or bismuth-based quadruple therapy is effective in >90 % of cases [51]. Moreover, some critical issues of a population-based HP screening and eradication campaign have to be considered:

- A potential increase in the incidence of gastro-esophageal reflux disease (GERD) [52]. However, several data clearly demonstrate that eradication of HP in infected patients neither increases the risk of new onset GERD [53,54] nor the relapse of the disease [55,56].
- Potentially dangerous changes in gastric microbiota. While HP infection is significantly associated to a gastric dysbiosis [57,58], the diversity of gastric microbiota after eradication is restored to that found in uninfected individuals [59,60].
- High HP infection recurrence rate. In a metanalysis, the global annual HP recurrence and reinfection rates were estimated to be 4.3 % (95 % CI, 4–5) and 3.1 % (95 % CI, 2–5), respectively [61]. More recently, however, an annual reinfection rate of about 1.5 % per person-year was demonstrated in a prospective study [62], with early reinfection (< 24 months), probably representing an unsuccessful eradication, slightly more frequent [63].
- Emergence or worsening of antibiotic resistance, one of the major concerns in mass HP screening and eradication. First, it seems not acceptable to preclude the treatment of HP infection for GC prevention because of the emergence of antibiotic resistance is multifactorial [57,64]. Moreover, even though the antibiotic resistance rate of surrogate intestinal bacteria is increased shortly after HP eradication [65–71], it is restored to basal state at long term [69].
- The risk of a low response-rate to HP eradication. This is an important point to consider, since it could dramatically reduce the efficiency of a "test and eradicate" campaign. In Italy, the most frequently used protocols for HP eradication in first line, the sequential therapy and the quadruple therapy with bismuth, or in second-line, the triple therapy with levofloxacine or rifabutine, or the quadruple therapy with bismuth, offer eradication rates >90 % in the first line and 85–92 % in the second line [51], even in case of antibiotic resistance [72].

All these issues have therefore a low impact in a "test and eradicate" campaign approach, while waiting for an effective vaccine against HP infection [73].

In addition, HP eradication cannot be considered exclusively as a primary prevention, since screening for HP also helps in individuating the patients in whom the Correa's cascade [5] has already begun, thus allowing us to eradicate HP and include the patients in an adequate follow-up protocol. Screening and eradication of HP are indeed part of a continuum that involves both primary and secondary GC prevention.

4.1. The role of serology in gastric cancer prevention

The simultaneous determination of pepsinogen type I and II (PGI and PGII), PGI/PGII ratio, gastrin-17 (G17) and anti-HP IgG antibodies (a test commonly known as GastroPanel®) may have a role in the setting of GC prevention. GastroPanel® is conceived to diagnose diffuse atrophic gastritis, a well-known precancerous step for GC [5]. Already more than 30 years ago, a number of studies demonstrated that PGI or PGI/PGII ratio values below the cut-off could pinpoint patients at high-risk for GC [74–76]. Our research group, since a long time involved in the management of gastric precancerous conditions and lesions, also evaluated the sensitivity, specificity and overall accuracy of the GastroPanel® test in a prospectively recruited cohort of patients with gastric ulcer, chronic atrophic gastritis, gastric epithelial dysplasia and GC [77]. PGI and PGI/PGII ratio were significantly reduced in GC patients, with sensitivity, specificity and overall accuracy of PGI being around 60 %, 95 % and 52 %, respectively [77]. In the attempt to better stratify the risk of GC and identifying those deserving upper GI endoscopy, three categories of patients were identified based on GastroPanel® results (ABC method) [78]: patients with no HP infection and normal PGI (at null risk, A); patients with HP infection but normal PGI levels (at low risk, B); and patients with HP infection and PGI below the cut-off (at high risk, C). A comprehensive metanalysis including 49 studies, demonstrated for GastroPanel® a pooled sensitivity of 70 % and a pooled specificity of 93 % in diagnosing extensive gastric atrophy of the corpus, with an area under the curve of 90 % [79]. A study is currently recruiting patients from high-risk areas of Latvia (GISTAR study), randomizing them in a group undergoing HP testing and PGI/PGII ratio determination and in a control group [80]. Those positive for HP infection are eradicated, while an upper GI endoscopy is performed in patients showing PGI level below the cut-off. A preliminary report of this study (based on $n = 1045$ patients), confirmed the high specificity of PGI assay but a low sensitivity (40.5 % for atrophy/metaplasia of the corpus was detected) [81].

4.2. The utility of "liquid biopsy" in gastric cancer prevention

Liquid biopsy is conventionally defined as the molecular analysis of circulating cancer by-products, such as cell-free DNA, cell-free non-coding RNA, extracellular vesicles and circulating tumor cells. Conceptually, liquid biopsy could be applied in the diagnosis of early-stage disease and also to identify patients with precancerous lesions who deserve further diagnostic examinations.

After first reports on the utility of liquid biopsy in GC patients [82], countless papers on the topic have been published so far. In particular, different panels of circulating microRNAs (miRNAs) were investigated in diagnosing early-stage GC. A recent study demonstrated that a signature of three miRNAs (miR-18a, miR-181b, and miR-335) exhibited high diagnostic accuracy in diagnosing all stage GC patients (AUC 0.86, 95 % CI 0.83–0.90) as well as early stage I GC (AUC 0.85, 95 % CI 0.79–0.91) [83], outperforming endoscopic screening in a cost-effectiveness analysis [83]. Similar results were obtained in another large multicenter study, in which a 12-miRNA panel reached an AUC of 0.85 (95 % CI 0.81–0.88), significantly higher than HP serology and PGI/PGII ratio [84].

As a non-invasive detection method, liquid biopsy remains a promising tool for GC screening. Nevertheless, several issues have to be considered, among them the lack of standardized commercial tests, the absence of standard operating procedures and data analysis methods, the undefined thresholds and the high costs. As a consequence, no liquid biopsy method has yet entered the clinical routine. Probably in the near future, once technological standardization and cost affordability have been achieved, liquid biopsy will emerge as a very useful tool.

4.3. Secondary prevention: the role of upper gastrointestinal endoscopy and histology

Gastric adenocarcinoma is preceded by a chronic atrophic gastritis with IM, with a risk that increases proportionally with severity of atrophic/metaplastic changes [85,86]. The 5-year GC development rate in a milestone study was 0.6 % in atrophic gastritis, 1.2 % in IM, 3.1 % in mild-to-moderate dysplasia and 29.5 % in high grade dysplasia [87]. Due to the low risk of cancer in patients with atrophic gastritis overall, staging systems of gastritis able to identify the threshold of atrophic changes beyond which endoscopic surveillance is cost/effective have been developed. The Operative Link on Gastritis Assessment (OLGA) staging system was initially proposed [88,89] and then validated in prospective cohort studies [90,91]. Since only patients with multifocal diffuse atrophic changes, (i.e., OLGA stages III and IV) are at risk for GC, only these cases should be enrolled in surveillance for secondary prevention (i.e., early diagnosis). In absolute agreement with this statement, the main Italian Gastroenterology and Internal Medicine scientific societies in a recently published position paper recommended surveillance only in advanced stages of chronic atrophic gastritis [92]. Similarly, another staging system evaluating the extent of IM in the gastric antrum and in the corpus-fundic area (Operative Link on Gastric Intestinal Metaplasia assessment, OLGIM) was proposed [86], with comparable reliability in identifying patients at risk who should undergo endoscopic surveillance [93]. Therefore, the use of one of these two staging systems is mandatory in the pathology report.

IM is not a homogeneous entity and different subtypes inherently carry different GC risk. Indeed, IM could be stratified in complete (type I, with sialomucins in goblet cells) and incomplete (type II, with sialomucins also in columnar cells, or type III, with sialomucins and solfomucins in Goblet cells). Available data show that incomplete IM is associated with a higher GC risk [94–96]. This concept was confirmed in a recent metanalysis showing that, compared to complete IM, patients with incomplete IM were at a higher risk of GC and non-invasive neoplasia (RR 3.7, 95 % CI 1.4–9.7) [97]. Consequently, the use of IM subtypes should be integrated in stratification of patients for GC surveillance.

Different considerations are necessary for autoimmune gastritis (AIG), which is a chronic inflammatory immune-mediated disorder affecting the oxyntic (acid-secreting gastric compartment) mucosa, leading to progressive mucosal atrophy [98]. In this type of atrophic gastritis, the inflammation is restricted to the corpus and fundus of the stomach [98]. Despite the real prevalence of AIG is uncertain (because of high rate of asymptomatic or pauci-symptomatic patient), its prevalence has been estimated to be ~0.5 - 4.5 % globally [99]. AIG is more commonly diagnosed in females and is often associated with other autoimmune diseases, in particular with Hashimoto's thyroiditis [100–103]. According to some authors, HP infection plays a triggering role in the development of AIG in genetically predisposed subjects [104–106]. Given a frequent overlap with HP infection-related chronic atrophic gastritis, the real GC risk in AIG is difficult to ascertain. In early studies, AIG patients carried a 3–7-fold increased GC risk, with an incidence of 0.9–9 % [107–109]. A population-based case-control study demonstrated that individuals with pernicious anemia, associated to AIG, had a significantly increased risk of non-cardia GC (OR 2.18; 95 % CI, 1.94–2.45) [110]. Moreover, at least two metanalyses addressing this topic have been published: the first included 13 studies and demonstrated an incidence rate of 0.14 % per person-year and a relative GC risk of 11.05 (95 % CI: 6.39–19.11) [111]; the second (27 studies including 22,417 patients with pernicious anemia) found a GC incidence of 0.27 % per person-year and a GC recurrence rate of 6.8 % (95 % CI 2.6–18.1) [109].

Nevertheless, a recently published long-term prospective study by our research group aimed at elucidating the natural history and the associated cancer risk of 211 patients with AIG (all negative for HP at histology, serology and even molecular biology), after a cumulative follow-up of 10,541 person years, demonstrated only 5 cases of low-grade epithelial dysplasia, with no high-grade dysplasia or invasive GC cases [112]. Similarly, in another group of 220 AIG patients with no HP infection at histology and serology followed in our center for a mean of 7.5 years, only two cases of high-grade dysplasia/invasive GC were diagnosed in patients with known previous HP infection (unpublished data). Therefore, in our experience the risk of gastric adenocarcinoma is much lower than that reported in the literature. This difference may rely on the fact that in the majority of studies patients with concurrent or previous HP infection, in which the extent of atrophy could have been wider due to the involvement of the antral area, have not been excluded from the analysis. Indeed, for obvious reasons, patients with "pure" AIG could have a maximal OLGA stage II, because inflammation is restricted to the corpus and fundus areas of the stomach. By contrast, any OLGA stage $\geq$ III implies the actual or previous involvement of HP in the gastritis process, with concomitant antral atrophy. In any case, whatever is the exact risk of GC, in AIG the endoscopic follow-up is mandatory for the high incidence of neuroendocrine gastric lesions (NET) [113]. Indeed, with endoscopic and histologic surveillance in patients with AIG and/or pernicious anemia, type 1 gastric NETs are observed in 4–12 % of patients [107,114–116].

As postulated in the Correa's cascade [5], the immediate precursor of GC is gastric epithelial dysplasia, now more correctly renamed intra-epithelial neoplasia or non-invasive neoplasia (NiN). The risk of evolution into invasive cancer is high in both low-grade and high-grade dysplasia, with an annual incidence of GC within 5 years after diagnosis of 0.6 % in the former and 6 % in the latter case [87]. In our experience the odds of progression of low-grade intraepithelial neoplastic lesions were not negligible but still relatively low (~5 %) [117], while the risk of GC was sharply higher in patients with high-grade NiN, with about 60 % of them developing invasive GC [118]. Of the 23 GC patients that underwent surgery in that study, 20 (87 %) were staged as early GC [118]. This share dramatically exceeds the percentage of early GC usually diagnosed in Western countries and in Italy, where it is never above 20 % [119,28]. These data obviously call for an adequate follow-up protocol and endoscopic treatment in patients with gastric NiN.

The recently updated guidelines on the management of epithelial precancerous lesions in the stomach (MAPS II) [120] provided the following recommendations regarding the endoscopic management of patients with precancerous conditions and lesions (Fig. 1A):

- Patients with chronic atrophic gastritis should be surveilled when atrophy or IM involves both antrum and corpus-fundus area (i.e., OLGA/OLGIM III and IV stages), with upper GI endoscopy every 3 years; if the patient has fist-degree family history of GC the interval between endoscopies should be shortened (every 1–2 years).
- Patients with antrum or corpus restricted atrophy or IM have to be considered for surveillance only if there is family history of GC, incomplete IM, or persistent HP infection, with endoscopy every 3 years.
- Patients with AIG may benefit from endoscopic follow-up every 3–5 years; obviously, in patients with demonstration of gastric NETs, particularly when relapsing, the time interval between upper GI endoscopies needs to be shortened.
- In patients with dysplasia, endoscopic reassessment should be made at a reference center with high-definition chromoendoscopy, and patients should be sub-grouped in those with and

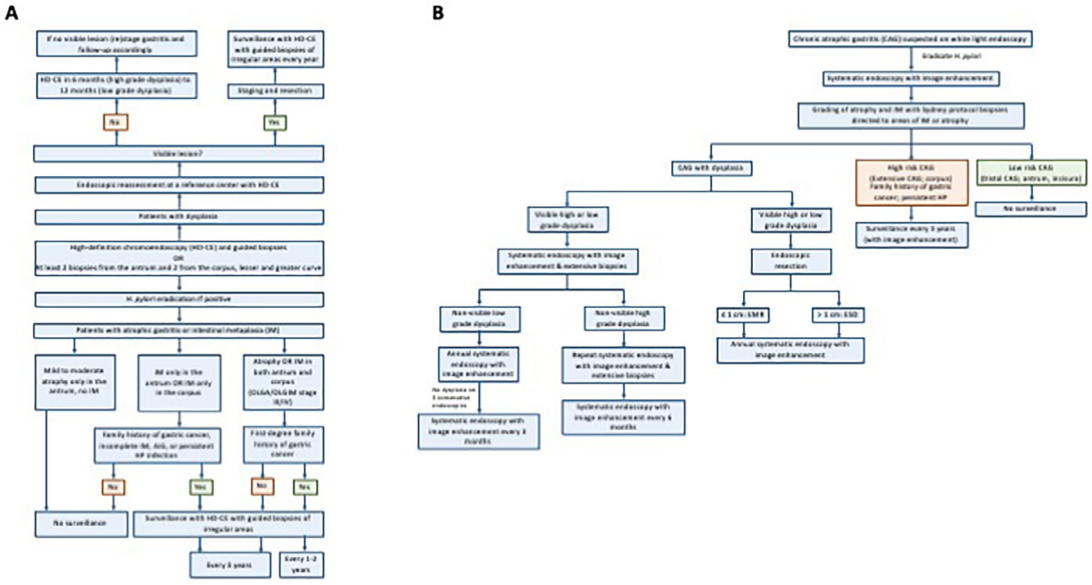

Fig. 1. Management of patients with atrophic gastritis, gastric intestinal metaplasia, or gastric epithelial dysplasia according to MAPS II guidelines (**A**) and British Society of Gastroenterology (BSG) guidelines (**B**). Modified from [120] and [121].

without visible lesions. The former should undergo endoscopic resection, while in the latter a strict endoscopic follow up, with upper GI endoscopy every 6 months for high-grade dysplasia or every 12 for low-grade dysplasia.

The British Society of Gastroenterology guidelines on the management of patients at risk for GC [121] provide slightly different recommendations (Fig. 1B):

- Similarly to MAPS II guidelines, patients with chronic atrophic gastritis should undergo endoscopy every 3 years in case of extensive atrophy or IM (antrum and corpus); surveillance is not recommended in patients with atrophy or IM limited to antrum unless there are additional risk factors, such as family history of GC or persistent HP infection.
- No specific recommendation is made regarding AIG.
- In patients with non-visible low- or high-grade dysplasia, an endoscopy with image enhancement and extensive biopsies is mandatory. Endoscopy should be repeated annually in case of confirmed non-visible low-grade dysplasia, while the interval should be shortened to 6 months in case of non-visible high-grade dysplasia.
- In case of low-grade or high-grade dysplasia on a visible lesion, endoscopic removal of the lesion should be pursued (endoscopic mucosal resection for lesions $\leq$ 1 cm, and endoscopic submucosal dissection for larger lesions).

5. The need for a high-quality endoscopy

High-quality endoscopy is of paramount importance in the setting of GC prevention, and lacking the basic conditions for a high-quality upper GI exploration is detrimental. In order to be defined of high-quality, endoscopy should be characterized by [122–124]:

- An adequate time slot and patient's sedation;
- High-definition video endoscopic systems;
- The possibility to take photographic documentation of relevant anatomic landmarks and of any visible lesion;
- The use of advanced endoscopic imaging tools (Narrow Band Imaging – NBI, Linked Color Imaging – LCI, or others) with description of glandular pattern;
- The use of Paris classification for lesion description [125].

The importance of advanced imaging tools in high-quality endoscopy is beyond doubt and, just an example, a recently published systematic review on the role of NBI in the detection of gastric IM demonstrated a sensitivity and a specificity of 80 % and 93 %, respectively [126].

Unfortunately, in our daily clinical practice, we are only asked to increase the number of endoscopies performed, cutting down the waiting lists, with no attention to appropriateness. In this situation, the quality of the endoscopies we are performing is open to debate. Endoscopy sessions specifically dedicated to patients with gastric precancerous changes are likely mandatory.

Among the new tools available for GI endoscopy, artificial intelligence (AI) has been investigated in recent years with the aim to improve the diagnostic ability of the operator. Even though there are several papers in the literature and solid data demonstrating that AI improves the performance measures in the setting of colon cancer screening [127], less defined is the situation regarding the utility of AI in upper GI endoscopy. In a large multicenter prospective study, the accuracy of an AI system (ENDOANGEL-LD) was compared with that of expert endoscopists: AI achieved a significantly higher sensitivity (100 % vs. 85.5 % $\pm$ 3.4 %; $p = 0.003$]) and negative predictive value (100 % vs. 86.4 % $\pm$ 2.8 % [$p = 0.002$], respectively) in detecting GC [128]. Moreover, the AI system (IDEA system) showed a clear-cut correlation between quality score and endoscopy accuracy [129]. Nevertheless, the use of AI in the early diagnosis of GC is "under development". Compared to AI in colonoscopy, less literature is available, most data derive from Eastern countries, and the majority of papers use AI in early GC diagnosis. Computer-assisted detection systems for GC are being actively developed [130–133], but this is a challenging task given the large number of GCs, early cancers and epithelial dysplasia images required to train the system. Most AI systems are based on data collected by expert endoscopists, indicating that the use of AI may be useful, but experienced and accurate endoscopists remain the cornerstone of endoscopic diagnosis.

6. Screening for gastric cancer in subjects at genetically-determined "high risk"

The precise identification of patients at genetically high risk of GC remains obscure to several clinicians, mostly because of the un-

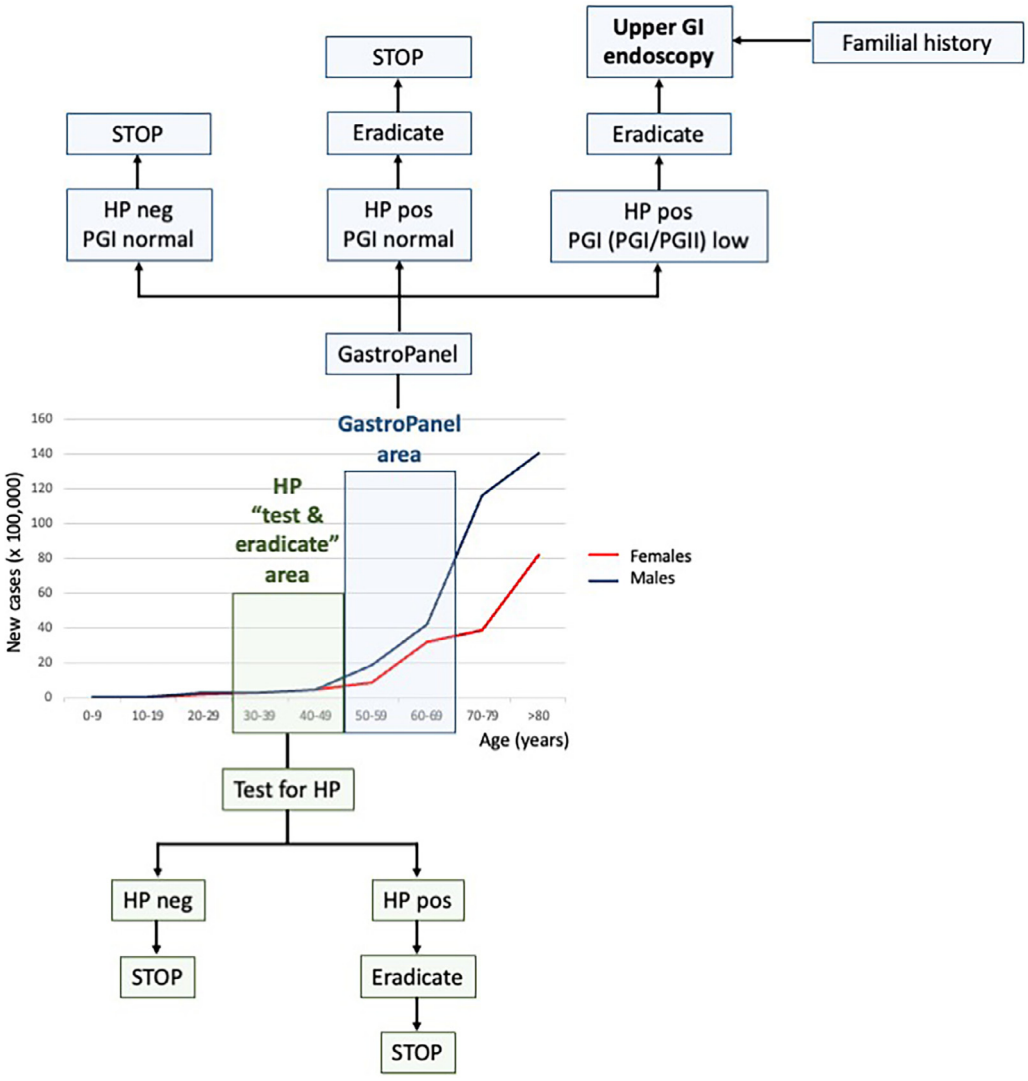

Fig. 2. A practical proposal for gastric cancer prevention and screening in Italy. In patients of 30–50 years of age, test for HP and eradication of the infection is sufficient ("test and eradicate" area). In patients of 50–70 years of age, a GastroPanel is necessary to stratify the risk: patients negative for HP and with normal PGI do not deserve further investigations; patients positive for HP and with normal PGI need to be eradicated, but do not deserve endoscopy; patients positive for HP and with a reduction of PGI need to be eradicated and should perform an upper GI endoscopy.

certainty regarding how to identify these patients from a genetic standpoint, how to determine which is the mutational profile that has to be studied and how to manage the patients and their family members.

Several clinical conditions or syndromes increase the risk of GC: familial gastric cancer, hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) syndrome, familial adenomatous polyps (FAP) and attenuated FAP syndrome, juvenile polyposis, Peutz-Jeghers syndrome, Li-Fraumeni and Lynch syndrome. In this already complex field, the frequent changes of definition, as in the case of familial gastric cancer [134], add more complexity. Moreover, indications for screening, surveillance timing and methodologies are conflicting according to different scientific societies; for instance, in Lynch syndrome the European Society of Digestive Oncology (ESDO) recommend surveillance for GC every 1–2 year, the American Gastroenterology Association (AGA) every 3–5 and the British Society of Gastroenterology (BSG) recommends no surveillance at all [135]. Some guidelines, such as those for hereditary diffuse GC or GC and GAPPS, are updated every few years [136]. Additionally, even though multi-genes panel testing and next generation sequencing (NGS) may be advantageous, single gene analysis is still routinely used [137]. In any case these genetic syndromes confer a very different life-time risk of GC, from less than 1 % in Lynch syndrome, to over 40 % in males with HDGC [138]. As a consequence, in order to reduce missed diagnoses, our suspicion should be kept elevated and few simple rules should be used to stratify the need for a more structured GC surveillance, investigating: age of the patient, number of cases in the family, presence of cancers in other sites and coexistence of colonic polyposis [139].

7. Conclusions

GC is among the few malignancies for which the prognosis has not improved in the last 15 years. In Western countries, where most GCs are diagnosed in an advanced stage, due to a late diagnosis. Indeed, based on an incorrect idea that this cancer has an incidence too low in the West to allow a cost-effective screening, GC has received very little attention by policy-makers, research funding agencies and health providers despite the significant health burden [140]. Now, we can no longer hesitate in the effort to tackle this deadly disease. The lack of a perfect bullet against HP and

GC cannot represent an "alibi", and molecularly-based susceptibility profiling for the selection of personalized eradication regimens is still far to be widely available [141]. Since any results we will be able to obtain will not be a "tomorrow morning effect" [142], we should not waste any more time, agree on a methodology and start screening at least in the high-risk area of Italy, as well as in intermediate to high-risk areas in the Western world.

Considered the age-dependent incidence curve of GC, that sharply increases after 50 years of age, a reasonable approach to primary and secondary prevention of GC in Western countries, including Italy, could be the following (Fig. 2):

- In people aged 30-to-50 years, test and treat for HP, with no additional measures.
- In individuals older than 50, screening with GastroPanel® (or with PGI and HP stool antigen test, possibly taking advantage of fecal occult blood test screening for colorectal cancer, as attempted in Taiwan [143]). Subjects positive for HP with normal PGI should be eradicated, without additional investigations; by contrast, those positive for HP and with low PGI level, eradication of the infection and upper GI endoscopy with advanced imaging techniques (e.g., NBI) and extensive biopsy sampling should be offered.

Patients with biopsy-confirmed atrophic-metaplastic gastritis should enter endoscopic surveillance programs (i.e., secondary prevention) when they have an advanced stage atrophy (OLGA stage III and IV) that puts them at risk of developing GC in a cost/effectiveness perspective. In such a secondary prevention strategy, to increase the efficiency of the endoscopic screening and surveillance, a multidisciplinary environment involving gastroenterologists, clinical pathologists and experienced pathologists is mandatory. These specialists must interact closely to tailor endoscopic surveillance to the clinical, endoscopic and histological characteristics of the individual patient. These specialists, equipped with the necessary professional competence and expertise, can carry out this task and achieve the goal, as it has been done with the colorectal cancer screening program.

In Italy, screening programs should be implemented in regions with high risk of GC. In order to succeed, these screening efforts must necessarily be accompanied with an adequate follow-up with high-quality endoscopy of patients with extensive atrophy/metaplasia, and with an expert endoscopic management of patients with high-grade dysplasia and early gastric cancer. In addition, proper identification and correct surveillance of patients at genetic increased risk is mandatory. Finally, additional efforts should be made in the search of an effective, acceptable and low-cost liquid biopsy method to further refine GC screening. The Gastroenterology and Endoscopy scientific societies, with the support of the Oncology societies and in conjunction with the Ministry of Health, should take charge of a strong initiative in the field that could finally allow us a step forward in the fight against GC.

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