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11087 editorial

Low risk, high cost: challenging the role of gastric cancer screening in low-prevalence countries

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Gastric cancer (GC) is the second commonest GI neoplasm and remains associated with a high mortality rate. It represented over 968,000 new cases and around 660,000 deaths in 2022 (1), with a global prevalence that varies substantially among regions under the influence of factors such as diet, genetics and *Helicobacter pylori* (HP) prevalence. According to their ASR (age-standardized incidence rate per 100,000

population/year), countries are categorized as high-risk (ASR ≥ 20), intermediate-risk (ASR ≥ 10 to < 20) or low-risk (ASR < 10).

PREVENTION METHODS

Prevention methods are aimed at reducing GC-associated mortality, and may be primary (HP eradication) or secondary, including early detection through endoscopy or measurement of serum markers such as pepsinogen (an atrophy marker, its positive result requiring then an endoscopy); no trustworthy, non-invasive markers are currently available for GC screening. In high-risk countries such as Japan (ASR = 27.6, year 2022) and South Korea (ASR = 27, year 2022), early detection via endoscopic screening has the potential to reduce mortality relative risk. According to a meta-analysis including 342,013 Asian individuals, this reduction was by 40 %, although no significant reduction in mortality was seen when compared to the expected mortality in the general population (2).

SCREENING FOR GASTRIC CANCER IN A LOW-RISK COUNTRY

In low-incidence countries such as Spain (ASR = 6 in 2022 [1]) population-wide screening is not recommended given its high cost, low diagnostic yield, and the potential for risks (anxiety, overtreatment) being greater than benefits (3).

GC screening may be inappropriate for older individuals or people with comorbidities significantly reducing life expectancy, this being the reason why the European Society for Endoscopy, as well as national societies, suggest stopping screening at 75-80 years of age or when life expectancy is shorter than 10 years (3,4).

A selective approach is suggested for high-risk groups, including those with a first-degree family history of GC (OR, 2.92; 95 % CI, 2.402-3.552 [5]) or hereditary cancer (3,6), as well as opportunistic screening during gastroscopies for other clinical indications (7).

While most cases are sporadic, 10 % display familial aggregation and 1-5 % are associated with hereditary syndromes, as is the case with hereditary diffuse GC or Lynch syndrome, which regardless of country represent a priority group for monitoring efforts with specific recommendations (6). In Spain a multicenter study showed that

endoscopic surveillance in cases of familial intestinal GC had a yield of 5 % for GC and of 44 % for preneoplastic lesions after a mean follow-up of 9 years (8).

Foreign individuals from high-incidence areas must also be considered. A meta-analysis including populations of western European and other origins showed that first-generation immigrants from high-incidence areas are at greater risk of developing GC and of dying from this cause (9).

Regarding screening methods, a recent analysis compared South Korean programs (primarily endoscopic screening) with those of Japan (primarily radiographic screening), and observed a greater reduction of mortality with the South Korean method (RR = 0.83 vs 0.97 for Japan), which underscores the efficacy and relevance of gastroscopy (10), which must be high-quality.

HIGH-QUALITY ENDOSCOPY

High-quality gastroscopy is advisable for endoscopic gastric lesion screening or monitoring (7,11,12) to maximize the ability to detect early GC and GC precursor lesions; to this end, the following factors should be considered:

1. High-quality endoscope with virtual chromoendoscopy: chromoendoscopy using NBI or BLI (blue light) offers high accuracy in the identification of intestinal metaplasia (particularly the tubular-villous pattern) and of dysplasia (13), and in the characterization of early GC by assessing the capillary and superficial pattern when magnification is available (14). Furthermore, a Japanese controlled clinical trial observed that virtual chromoendoscopy using BLI was associated with a higher identification rate of early GC when compared with white light (93.1 % vs 50.0 %; p = 0.001) (15).

2. Mucosal visibility: adequate cleanliness during gastroscopy has been independently associated with greater lesion identification in symptomatic patients (OR, 1.78; 95 % CI, 1.06-3.01, p = 0.03) (16). Studies recently highlight the use of oral simeticone at 20-60 minutes before gastroscopy to improve visibility (17). In a Spanish single-center study the administration of oral pre-medication (200 mg of simeticone and 50 mg of N-acetylcysteine diluted in 100 cc of water) over 15 minutes before gastroscopy with propofol showed a positive effect on gastric visibility (74.3 % vs 45.2 %, $p < 0.001$)

compared to a control cohort (18). While waiting for more evidence to support its routine use in gastroscopies under propofol, intraprocedural washes with water and simeticone through the endoscope's channel could be alternatively tried. It is advisable that the use of validated cleanliness scales be recorded in reports, including the Barcelona Scale (19), GRACE (Gastroscopy Rate of Cleanliness Evaluation) (20) or PEACE (Polprep: Effective Assessment of Cleanliness in Esophagogastroduodenoscopy) (16).

3. Systematic inspection: a fine technique is advisable to ensure the whole of the stomach is inspected. For instance, the exam may begin with assessing the pylorus, then keeping insufflation while frontally withdrawing the endoscope, so that upon subsequent retroversion gastric folds are already flatenned and blind spots between them may be avoided. Systematic photodocumentation is a quality indicator recommended by the European Society of Endoscopy (21), and may be an indirect marker of thorough inspection, as put forward by Yao in his "Systematic Screening protocol for the Stomach" (SSS) (22).

4. Inspection time: in a Korean retrospective analysis of 1257 interval GCs diagnosed within 6 to 36 months after an uneventful gastroscopy, inspection time (identified from time stamps in photos) < 3 minutes was associated with a greater risk for interval cancer (OR, 2.27, 95 % CI, 1.2-4.3) (23). A retrospective study showed that "slow" endoscopists (≥ 7 minutes per standard endoscopy) are twice as likely to detect high-risk gastric lesions and thrice as likely to identify dysplasia or cancer (OR, 3.42, 95 % CI, 1.25-10.38) when compared to "fast" endoscopists (< 7 minutes). Because of this, the European Society of Endoscopy recommends gastroscopy with a duration above 7 minutes (21).

5. Risk stratification: biopsy sample collection (2 from the de antrum +/- incisura angularis, and 2 from the corpus, in separate jars, Sydney protocol) is recommended to assess HP status and stage risk using the Operative Link on Gastric Intestinal Metaplasia (OLGIM) classification (3,7,11,12), plus targeted biopsies from suspect, potentially dysplastic lesions. Endoscopy may identify signs of atrophy (loss of gastric folds, increased visibility of blood vessels on a pale mucosa) and of intestinal metaplasia (grayish patches, white opaque substance or tubular-villous pattern, or the

light blue crest sign using virtual chromoendoscopy), and it is recommended that the Kimura Takemoto and EGGIM validated classifications be used to assess the extent of atrophy and of intestinal metaplasia, respectively, as they may help predict GC risk in a manner similar to histological classifications (24), and may even replace them when used by experts.

MANAGEMENT

HP eradication is recommended, as is resection of the visible lesions identified (previously biopsied (3,7) (Table 1).

MONITORING

Endoscopic surveillance is advisable for patients with high-risk precursor lesions such as extensive atrophy or intestinal metaplasia (EGGIM 5+, OLGIM III/IV), particularly when associated with incomplete metaplasia or a family history with GC. While international recommendations display some heterogeneity, shorter monitoring intervals (3 years vs 5 years) might be beneficial for these patients regardless of their country of origin, but further evidence is required to establish definitive guidelines (3,7,11). Furthermore, after R0 endoscopic resection of an early gastric malignancy at low or very low (even nil) risk for nodal metastatic disease ("curative" resection), a quality gastroscopy is advisable at 3-6 months and then annually, although risk stratification has been suggested to define monitoring intervals more cost-effectively using the FAMISH classification (Family history, Advanced age, Male sex, Intestinal metaplasia in the corpus, Synchronous gastric lesions, and persistent *Helicobacter pylori* infection) (25).

CONCLUSIONS

In countries with a low prevalence of GC population screening is not cost-effective. However, selective, opportunistic screening combined with high-quality gastroscopy and well-defined monitoring strategies allows for more effective management. Further research is key, hence many European initiatives are underway to assess the advisability of screening and which approach would be optimal (Towards Gastric

Cancer Screening Implementation in the European Union, TOGAS EU4H-2022-PJ-01).

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Table 1. Indications of endoscopic resection for gastric lesions

Indications of endoscopic resection	Comments
Absolute (classic) indications	
Dysplastic lesions of any size	Based on optical diagnosis with prior consistent biopsies. Lesions confined to the epithelium without risk of lymphatic involvement
Differentiated adenocarcinomas (WHO: papillary, differentiated tubular; Laurén: intestinal) with no evidence of deep submucosal invasion, any size if no ulceration present, ≤ 3 cm if ulceration present	Based on optical diagnosis with prior consistent biopsies, with no evidence of deep invasion: deep ulcer, raised margin, fold convergence, nodularity, non-extension sign or submucosal tumor-like elevation
"Expanded" indications	

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Undifferentiated adenocarcinomas (WHO: poorly differentiated, poorly cohesive including signet ring-cell; Laurén: diffuse) with no evidence of submucosal invasion, < 2 cm, with no ulceration	Based on optical diagnosis with prior consistent biopsies, with no evidence of deep invasion: deep ulcer, raised margin, fold convergence, nodularity, non-extension sign or submucosal tumor-like elevation

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