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Endoscopic Screening of Gastro-Esophageal Neoplasia: Who, When and How?

Nuna Filipe Torres Carneiro

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NOME

Nuno Filipe Torres Carneiro

NÚMERO DE ESTUDANTE	E-MAIL
201807434	nunoftc95@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Ciências Médicas e da Saúde

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ORIENTADOR

Rui Jorge Guedes Dias

COORIENTADOR (se aplicável)

Pedro Filipe Vieira Pimentel Nunes

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RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT
GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Nuno Filipe Torres Carneiro, abaixo assinado, nº mecanográfico 201807434, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

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Review Article
Endoscopic Screening of Gastro-Esophageal Neoplasia: Who, When and How?
/
Rastreio Endoscópico da Neoplasia Gastro-Esofágica: Como, Quando e a Quem?

Nuna Torres[b], Miguel Martins[a,b], Pedro Pimentel-Nunes[c,d], Rui Morais[a,b]

[a] Gastroenterology Department, Centro Hospitalar Universitário de São João, Porto, Portugal

[b] Faculty of Medicine of University of Porto, Portugal

[c] Gastroenterology and Clinical Research Medical Director, Unilabs Portugal

[d] Department of Surgery and Physiology, Faculty of Medicine, University of Porto, Portugal

Short Title: Endoscopic Screening of Gastro-Esophageal Neoplasia: Who, When and How?

Corresponding author:
Rui Morais
ruimorais20@gmail.com

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Abstract/Resumo

Background: Esophageal and gastric cancers continue to represent a significant global health challenge. Early detection through effective screening programs, along with primary prevention initiatives has the potential to substantially reduce mortality rates. Nevertheless, the widespread implementation of screening programs is impeded by both logistical and economic constraints. A thorough understanding of the epidemiology, pathogenesis, and risk factors is essential for developing more personalized and effective screening strategies.

Summary: This narrative review provides an overview of the current status of endoscopic screening for gastroesophageal neoplasia, outlining the epidemiology, risk factors and primary and secondary prevention strategies. Although high-definition endoscopy, chromoendoscopy, and advanced imaging techniques have improved diagnostic accuracy, significant barriers remain in accessibility and cost-effectiveness. Consequently, the implementation of structured screening protocols and risk stratification is essential to optimize endoscopic utilization, ensuring the prioritization of high-risk populations and improving screening cost-efficiency. Concurrently, new technologies, such as artificial intelligence (AI) applications and non-endoscopic screening modalities, are being developed to improve and offer alternatives for the diagnosis of these malignancies. However, further research remains necessary to optimize these screening protocols and determine their clinical impact.

Key Messages:

Esophageal cancer (EC) and Gastric cancer (GC) remain a significant public health challenge due to their high mortality rates, associated with their late diagnosis.

Endoscopic screening plays an essential role for early detection of esophageal and gastric cancer, improving survival outcomes.

Despite technological progress, cost-effectiveness and accessibility remain major barriers to widespread implementation.

Future strategies should focus on optimizing screening protocols, expanding training programs, and exploring cost-efficient approaches to ensure broader access to early detection methods.

Contexto: Os cancros do esófago e do estômago continuam a representar um desafio significativo para a saúde global. A deteção precoce através de programas de rastreio eficazes, juntamente com iniciativas de prevenção primária, tem o potencial de reduzir substancialmente as taxas de mortalidade. No entanto, a implementação generalizada de programas de rastreio é dificultada por constrangimentos logísticos e económicos. Uma compreensão profunda da epidemiologia, patogénese e fatores de risco é essencial para o desenvolvimento de estratégias de rastreio mais personalizadas e eficazes.

Sumário: Esta revisão narrativa apresenta uma visão geral do estado atual do rastreio endoscópico das neoplasias gastroesofágicas, abordando a epidemiologia, os fatores de risco e as estratégias de prevenção primária e secundária. Embora a endoscopia de alta definição, a cromoendoscopia e as

técnicas avançadas de imagem tenham melhorado a precisão diagnóstica, continuam a existir barreiras significativas em termos de acessibilidade e custo-efetividade. Assim, a implementação de protocolos estruturados de rastreio e a estratificação de risco são fundamentais para otimizar a utilização da endoscopia, assegurando a priorização das populações de alto risco e tornando o rastreio mais eficiente em termos de custos. Paralelamente, novas tecnologias, como a inteligência artificial e métodos de rastreio não endoscópicos, estão a ser desenvolvidos para melhorar e oferecer alternativas no diagnóstico destas neoplasias. No entanto, são necessárias mais investigações para otimizar estes protocolos e avaliar o seu real impacto clínico.

Mensagens-chave:

O cancro do esófago e o cancro gástrico continuam a representar um desafio significativo para a saúde pública devido às elevadas taxas de mortalidade associadas ao seu diagnóstico tardio.

O rastreio endoscópico desempenha um papel essencial na deteção precoce do cancro esofágico e gástrico, melhorando os resultados de sobrevivência.

Apesar dos avanços tecnológicos, a custo-efetividade e a acessibilidade permanecem como barreiras significativas para a implementação generalizada do rastreio.

As estratégias futuras devem centrar-se na otimização dos protocolos de rastreio, na expansão da formação especializada e na exploração de abordagens custo-eficazes, de forma a garantir um acesso mais amplo à deteção precoce destas doenças.

Introduction

The prevalence of gastrointestinal (GI) cancers presents a significant contemporary health challenge. Epidemiological analyses have revealed that approximately 1 in 12 individuals will be diagnosed with GI cancer, with 1 in 16 dying from the disease. [1] Globally, in 2021, GI cancers were responsible for an estimated 5.26 million new cases and 3.70 million deaths.[1] In Europe alone, these malignancies account for a quarter of all cancer diagnoses with projections indicating that these figures will rise more than 24% by the year 2035.[2] Therefore, the identification and management of risk factors, together with the detection of precursor lesions, are critical strategies for early diagnosis and potential reduction of GI cancer burden.[1]

The upper GI tract is affected by several cancers, including EC and GC, which will be the focus of this article. The EC is predominantly divided into two histologic subtypes: Esophageal Squamous Cell Carcinoma (ESCC), which usually affects the stratified squamous epithelium on the upper two-thirds of the esophagus and Esophageal Adenocarcinoma (EAC) which occurs in the lower third of the esophagus.[3] Over half of this malignancies are linked to modifiable factors like alcohol and tobacco.[4] However, these malignancies are still diagnosed late, which leads to a poor prognosis and a substantial health burden.[5] Given this information, there is increasing interest in improving primary and secondary prevention measures to control these malignancies.[4]

This article reviews the epidemiology, risk factors, and prevention strategies of these malignancies, focusing on current endoscopic techniques to find the best screening protocol. This was conducted by a comprehensive search of literature published in PubMed, Scopus, and Web of Science from 2010 to 2024, including meta-analyses, randomized controlled trials, observational studies and clinical guidelines. The search terms used was “endoscopic screening”, “gastro-esophageal neoplasia”, “gastric cancer”, “Esophageal adenocarcinoma”, “Esophageal squamous cell carcinoma“ “early detection”, “Barrett’s esophagus”, “High-definition endoscopy”, “Narrow-band imaging”, “chromoendoscopy”, “artificial intelligence”, “risk stratification”, “prevention”, “risk factors”, “epidemiology”.

Global burden and Epidemiology of Gastro-Esophageal Neoplasia

EC and GC cancers are two of the most commonly diagnosed cancers globally and a major cause of global mortality, resulting in close to 1.3million deaths in the same year. [5] Despite sharing some risk factors given their anatomic proximity, their epidemiological profiles differ.[5] So, understanding the worldwide prevalence of these cancers by specific subtypes and locations supplies essential information for healthcare professionals and governments to create and implement targeted cancer control measures, aiming to reduce future cancer impact. [5] The global epidemiology of these two malignancies compared to Portugal is summarised in table 1.

Esophageal Neoplasia

EC presents a substantial global public health issue, marked by significant regional inequalities in its incidence, associated mortality, and the availability of healthcare services.[6] Each year, around 18,440 new cases of EC are diagnosed, with approximately 70% of those affected being male. [7] This incidence also increases with age with EAC typically developing in individuals aged 50 to 60, while ESCC tends to manifest roughly a decade later.[8] In the last 30 years, the total number of EC cases increased, but the age-adjusted rates have decreased, suggesting the impact of enhanced healthcare strategies.[9] However, with current trends, new cases and deaths are expected to increase by over 80% by 2050 [10] which emphasises the importance of taking action as early as possible to try to avoid this scenario.

Gastric Cancer

Global GC incidence exhibits significant geographical variation with elevated rates, exceeding 15 per 100,000 annually.[9] Notably, according to several observational studies, in nations with lower overall GC rates, this cancer disproportionately burdens vulnerable populations, such as immigrants and, within the US context, racial and ethnic minorities.[11, 12] Despite Japan and South Korea ranking second and third in GC incidence, experience significantly lower mortality rates (8 and 6 per 100,000, respectively) largely due to their established, nationwide GC screening programs. [11, 13, 14]

In Portugal, this malignancy is a major health issue, ranking fourth in incidence in 2020 (14,3/100 000 person-year) along with high prevalence of Helicobater pylori (HP) infection.[15, 16] Although mortality and incidence have decreased recently, Portugal still has the highest rate in Western Europe, with a particularly high concentration of cases in the Northern region, according to Northern Regional Oncology Registry, based at IPO-Porto. [15, 17]

Current Preventive Strategies to Reduce Burden

Risk Factors and Primary Prevention

The risk factors and preventive strategies for EC subtypes and GC are described in Table 2.

Esophageal Squamous Cell Carcinoma

ESCC is a complex, multifactorial disease that can be caused by several factors. The development of this malignancy can be linked to factors that cause chronic irritation and inflammation of the esophagus potentially which may result in DNA damage and subsequent mutations.[3] These factors are multiple and include environmental, genetic and cultural components. With this in mind, primary prevention, through the avoidance of modifiable risk factors and targeted screening of individuals with precursor lesions, stands as a critical intervention to curtail the incidence and mortality of this malignancy.[18]

Esophageal Adenocarcinoma:

EAC development results from a combination of genetic, environmental and lifestyle factors. [9]
The well-established risk factors to this malignancy are GERD, caused by chronic acid reflux, and the subsequent development of Barrett's Esophagus (BE), which is a known precursor of EAC.[3, 19] Regarding this, prevention of EAC primarily focuses on effective management of GERD and mitigating associated risk factors.

Gastric Cancer and Helicobacter Pylori eradication:

GC prevention focuses on three key areas: eradicating HP infection, dietary interventions and reducing other risk factors. HP infection is recognized as the most important risk factor, classified as a definite carcinogen by the WHO. It is estimated to be responsible for a significant proportion of all GC cases (over 70%)[20], particularly non-cardia GCs. [11, 21] HP eradication is a critical strategy, demonstrating significant efficacy, especially when implemented prior to the development of precancerous gastric lesions. In fact, several studies demonstrated that HP eradication decreases both GC incidence and mortality as well as metachronous GC risk (46%). [20] The HP test-and-treat strategy involves both detection and eradication when it's positive and is used not only for symptomatic patients but also as a screening method for asymptomatic individuals.[22] This group englobes those with certain ethnic or geographic backgrounds associated with a high risk of GC. [20]
Regarding this, it's important to know the precancerous lesions that can potentially lead to carcinoma and these include non-atrophic gastritis, atrophic gastritis (AG), intestinal metaplasia (IM), gastric stump after partial gastrectomy, gastric polyps and dysplasia.[23-25] This is explained by the Correa cascade, described by Pelayo Correa in 1988, that explains the mechanism for the development of intestinal type cancer.[26] Apart from this, there are other established non-genetic risk factors which are important to avoid. (Table 2)

Secondary Prevention and Screening

Secondary prevention is essential to reduce the burden of gastro-esophageal cancers. These malignancies often develop silently, with symptoms appearing at advanced stages when curative treatment is less effective. Implementing effective secondary prevention strategies, such as endoscopic screening and risk-based surveillance, is crucial in identifying precancerous conditions and early-stage tumors, ultimately reducing cancer-related morbidity and mortality.

Role of Endoscopy

Esophagogastroduodenoscopy (EGD) is the gold-standard diagnostic tool for detecting and monitoring precancerous lesions and early cancers in the GI tract, enabling targeted endoscopic interventions.[27] EGD enables risk stratification and targeted surveillance of high-risk individuals.[28, 29] However, its effectiveness depends on cancer prevalence in specific geographic areas, the susceptibility of different population groups, and the efficacy of established screening protocols.[27, 28, 30]

Esophageal Cancer

The complexity surrounding the causes of EC underscores the critical need for early detection through screening.[9] Given the geographical differences, screening strategies should be tailored to geographical variations in EC subtypes.[31, 32]

Esophageal Squamous Cell Carcinoma

ESCC often develops without noticeable symptoms, leading to late-stage diagnoses or its detection through screenings in high-risk populations.[33] In some cases, symptoms like heartburn, dyspepsia, cough, or GI bleeding may provide an opportunity for early detection, however, these symptoms are nonspecific.[33-35] As ESCC advances, individuals may experience dysphagia, that progresses from solid to liquids but this is a strong indicator of locally advanced disease with a 5-year survival of less than 15%.[34, 36]

Endoscopic Screening

Universal ESCC screening is infeasible due to widespread exposure to risk factors. Prioritizing high-risk individuals for endoscopy is essential, making accurate biomarkers for cancer risk crucial for secondary prevention.[37] Currently, the gold standard for ESCC diagnosis is a histological confirmation of malignancy, usually from a sample obtained during EGD.[34] It is important to note that, to date, the only known precursor lesion of ESCC is dysplasia.[34, 39]

Various endoscopic techniques have been developed to enhance detection and guide appropriate therapeutic interventions:

White-light Endoscopy (WLE)

This technique remains the cornerstone of EC screening [40] but its sensitivity in detecting early ESCC is limited due to the subtle appearance of early lesions.[31, 35, 41] Besides, several systematic reviews have reported that more than 40% of these cancers are not detected by this technique.[42]

Lugol's chromoendoscopy

This technique involves the application of Lugol's iodine, which highlights glycogen-rich normal epithelium while leaving dysplastic areas unstained.This results in a dark brown normal squamous epithelium with lighter areas indicating dysplasia. [32, 34, 35] This technique increases sensitivity providing an opportunity to target biopsies or endoscopic resection but it requires expertise to interpret findings accurately.[27, 34, 35] Also, this technique is also time consuming and labor intensive, increasing the load on clinicians, and with the possibility of allergic reactions. [43] However, a clinical trial showed that endoscopic screening with Lugol's iodine staining reduced ESCC mortality from 5.05% to 3.35% ($P < .001$) and incidence from 5.92% to 4.17% ($P < .001$) in high-risk communities over a 10-year follow-up.[38] Regarding this, this technique coupled with biopsies, is considered the most practical approach for detecting squamous dysplasia or cancer, yielding a sensitivity of up to 98% and 87% for severe dysplasia.[3, 38]

Narrow-band imaging (NBI)

Other advanced imaging techniques, such as NBI, improve lesion visualization without the need for dyes.[35, 36] NBI, through the use of specific light wavelengths, enhances the contrast between normal and abnormal mucosa by highlighting microvascular structures [35, 41] aiding in differentiating between neoplastic from non-neoplastic tissue.[6, 34] Studies have shown that NBI provides comparable sensitivity to Lugol's chromoendoscopy.[41] However, a randomized controlled trial revealed a specificity of roughly 50%.[44] This underscores the necessity for further enhancements to improve its diagnostic accuracy.

Current Strategies for Screening

Currently, a targeted screening program is implemented in a high-risk region of China, utilizing the Lugol's chromoendoscopy in a mobile endoscopy units to reach rural populations. This program has been successful in decreasing both the incidence and mortality of ESCC. [35, 45] Furthermore, NBI is widely used is Japan for early ESCC diagnosis.[34]

Conversely, European Society of Gastrointestinal Endoscopy (ESGE) recommends a more focused screening strategy, targeting high-risk individuals, such as those with over 40 years and alarming symptoms, previous or concomitant diagnosis of head and neck SCC, achalasia, prior radiation therapy for breast cancer, previous esophageal biopsies with dysplasia, history of caustic esophageal injury or tylosis.[6, 18, 27, 46, 47] For this group, is recommended a screening approach with chromoendoscopy coupled with biopsy of suspicious regions.[6] Regarding this, determining the ideal timing for screening initiation remains a subject of debate, with current practices ranging from immediate post-diagnosis to several years later. [37, 45]

Surveillance in High-Risk Populations

ESCC is relatively uncommon in Western countries, but certain populations, including those who have undergone head and neck cancer treatment, ESCC resection, experienced caustic injury, or have tylosis or achalasia, face a significantly elevated risk.[18, 48] While these high-risk groups could benefit greatly from ESCC surveillance, there is a lack of strong evidence regarding the effectiveness, cost-efficiency, and optimal frequency of such screening.[49] Since standard WLE is known to be inadequate for detecting early ESCC or its precursors, advanced imaging techniques, such as Lugol or virtual chromoendoscopy, are strongly recommended when surveillance is deemed necessary [50].

Limitations and Cost-Effectiveness

According to ESGE, the information about cost-effectiveness of SCC screening is limited.[27] In China, where SCC is more prevalent, analyses suggest that various endoscopic screening strategies, despite differing in initiation age, frequency, and follow-up intervals, can extend life expectancy.[27, 37] However, in Europe, due to lower SCC incidence and the structure of public healthcare systems, endoscopic screening for SCC is not generally considered necessary or cost-effective [27, 29].

Future Perspectives

Recent advances in AI have focused on developing deep learning models (especially convolutional neural networks) that analyze endoscopic images to detect early ESCC.[42] These AI systems combine data from different imaging modalities, such as WLE and NBI, to accurately identify subtle neoplastic changes, delineate lesion margins, and even predict invasion depth in real time.[51, 52] While these innovations show promise for reducing missed diagnoses and supporting less experienced endoscopists, they still require extensive multicenter validation to overcome training biases and ensure widespread clinical applicability.[42, 52]

Esophageal Adenocarcinoma and Barrett's Esophagus

The rising incidence in Western populations, particularly among individuals with BE, and the 5-year survival rate ranging between 15% and 25% makes EAC as a significant clinical challenge.[28, 31] Due to its asymptomatic nature in early stages, this malignancy often leads to late diagnoses and consequently, high mortality rates.[7]

Screening

EAC screening aims to detect and treat precursor lesions before its malignant transformation. [53] BE is the primary precursor lesion to EAC with a low risk of progression to high grade dysplasia or EAC (annual risk of 0.3-0.6%).[54, 55] However, given the poor prognosis and high mortality of EAC, its detection is important in order to take measures such as surveillance or treatment to prevent this scenario.[55] The adopted strategy will depend on whether the BE is associated with dysplasia or not. Patients with BE without dysplasia might benefit from endoscopic surveillance, whereas confirmed dysplasia or early EAC necessitates an eradication therapy.[53, 55]

Diagnosis and Management of BE

The ESGE provides clear guidelines on the screening and surveillance of BE, focusing on risk stratification and surveillance intervals.[56] Firstly, it's important to select the group of people at high risk in order to know the target population for screening. This society suggests that patients with ≥50 years of age with a history of chronic GERD symptoms and at least one of the following risk factors (white ethnicity, male sex, obesity, smoking, having a first-degree relative with BE or EAC) should be part of this group.[56] As far as surveillance intervals are concerned, these depend on the presence or not of dysplasia associated with BE. Table 3 explains an overview of the surveillance guidelines for BE screening, differentiating between the American and European recommendations. Regarding this, the high resolution endoscopy with virtual or acetic acid chromoendoscopy made by an expert is the favoured technique for this screening.[56]

Endoscopic Screening Techniques

White-Light Endoscopy

WLE with targeted biopsies is the gold standard method for EC screening.[3] However, it faces challenges in detecting early-stage cancers and ensuring adherence to the BE biopsy protocol, which mandates four-quadrant biopsies at 1-2 cm intervals, along with biopsies of any visually suspicious areas.[3, 36]

Narrow-Band Imaging and Chromoendoscopy

Advanced imaging techniques like NBI and chromoendoscopy have been demonstrated increasing sensitivity in detecting premalignant and malignant lesions at early stages.[41] Several randomized controlled trials and systematic reviews have examined the utility of acetic acid chromoendoscopy and had demonstrated that this technique is highly accurate in detecting HGD or early BE-related EAC.[57] However, although it is very sensitive for identifying suspicious IM, its low specificity necessitates histological confirmation of positive findings.[57]

Ultrathin Nasal Endoscopy

This technique is a less invasive alternative and demonstrates comparable accuracy and cost-effectiveness to WLE. [6, 27] However, its limited availability in clinical practice is a barrier.

Limitations and Cost-Effectiveness

The cost-effectiveness of EAC screening depends on incidence rates and the efficiency of screening methodologies.[55] In fact, EAC screening in the general population is not recommended due to the relatively low risk (estimated prevalence of 1%-2%) and lack of cost-effectiveness.[55] Regarding this, various randomized controlled trials indicate that endoscopic screening is financially viable in high-risk populations but not for the general public.[27, 31] A comparative cost-effectiveness analysis concluded that targeting individuals with GERD and additional risk factors offers the best balance between cost and early detection benefits.[27] However, several challenges persist such as low patient adherence due to invasive procedures and variability in endoscopic expertise.[19, 57, 58]

Future Perspectives

AI is proving instrumental in enhancing the detection and diagnosis of early cancerous changes associated with BE.[59] Detection systems, known as CADe, leverage AI to scrutinize endoscopic images and videos, enabling the identification of subtle lesions that might elude the human eye during standard examinations, thus improving overall detection rates.[59, 60] Beyond mere detection, diagnostic systems, or CADx, assist clinicians in characterizing suspicious areas, effectively differentiating between cancerous and non-cancerous tissue through the analysis of advanced imaging techniques NBI.[59, 61] However, despite these promising advancements, continued efforts are needed to bridge the gap between research and widespread clinical application.[60]

Additionally, non-endoscopic techniques have been developed, such as cytosponge which is a new technique for esophageal pathologies.[62] The patient ingests a gelatine capsule connected to a

thread that, once in the stomach, breaks down, releasing an expanding sponge.[63] The sponge collects cells from the esophageal lining as it is pulled back out, and these cells are then evaluated with immunohistochemistry. In fact, according to various randomized clinical trials, this technique shows a high specificity, greater than 92%, and a sensitivity of 80% when used to BE diagnosis.[62, 63]

Gastric Cancer Screening and Surveillance

Current Screening Strategies

Currently, GC screening is restricted to high-risk nations (with an age-standardized incidence rate of 20 or more per 100,000) such as Japan and Korea. [17]

In Japan, where GC once accounted for a substantial proportion of deaths, screening programs were established.[11] Initially, these programs utilized radiographic examinations for individuals aged 40 and older. However, guidelines were updated to those currently in use, indicating either radiographic or endoscopic screening every 2 years, beginning at age 50. [11]

Similarly, South Korea, recognizing GC as a significant public health issue, initiated national screening in 2002. [11] Biennial screening was recommended for asymptomatic adults aged 40 to 75, offering the choice between radiography and endoscopy.[64] Over time, the preference for and utilization of endoscopic screening have increased significantly, with its adoption rising to 31% overtime.[64] Conversely, in high risk areas of China, EGD is the only screening method used to detect GC. [14, 65] However, in Europe, only properly structured, population-based screening programs with quality assurance are recommended.[25]

Endoscopic Screening

Endoscopic screening plays a crucial role in the early detection of GC, particularly in high-risk populations. The Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) classification system is widely used for risk stratification, categorizing patients into different stages based on the extent and severity of IM which is a precursor lesion of this malignancy.[46] Patients classified as OLGIM III or IV and those with a family history of GC, are considered at high risk and are recommended for surveillance endoscopy at regular intervals.[46] Alternatively, there is another classification to assess the risk of GC. The Endoscopic Grading of Gastric Intestinal Metaplasia (EGGIM) analises the extent of IM using NBI and offers a reliable alternative to traditional biopsy-dependent methods like OLGIM.[66] Some observational studies suggest that EGGIM can streamline patient management by reducing the need for random biopsies while maintaining high diagnostic accuracy.[66] In terms of GC surveillance guidelines, they vary significantly between Europe, the United States and Asia, and these differences are described in Table 4.

High-Definition White-Light Endoscopy

This technique significantly enhances image clarity, achieving a 74.6% sensitivity, 94% specificity, and 88% accuracy in identifying GC and precancerous conditions.[67] While effective for visualizing substantial mucosal changes like nodules or depressions, it struggles with subtle, early-stage microscopic lesions, leading to a reported 9.4% miss rate.[68]

Chromoendoscopy

ESGE suggests that this technique coupled with High-Definition WLE is better than WLE alone for the diagnosis of gastric precancerous conditions and early neoplastic lesions.[66] It enhances the delineation of tumor borders, achieving an 84.1% identification rate, with notably higher success (89.9%).[57] However, this technique has drawbacks such as, inconsistent dye application, inadequate bowel preparation, and increased examination duration that can compromise its efficacy.[68]

Narrow-Banding Imaging

NBI, enhance the detection of precancerous lesions compared to conventional WLE.[41] NBI has demonstrated superiority in identifying IM and dysplasia with sensitivity and specificity of 60% and 89%, respectively.[69] It also aids in the preoperative demarcation of cancer to minimize positive surgical margins.[41] So far, it has been advocated to be a complementary tool to WLE.[41, 69]

Regarding this, to date, the most recommended technique is high resolution endoscopy with virtual chromoendoscopy. [46]

Limitations and Cost Effectiveness

In countries with low to moderate risk of GC, general population screening may not be cost-effective, making it crucial to identify high-risk individuals and provide effective screening and surveillance programs.[14, 27] Both American and European guidelines emphasize that while endoscopic screening provides a favorable cost-benefit ratio in high-incidence areas, standalone endoscopy is less cost-effective in regions with low or moderate risk.[27]

Besides, a cost-utility analysis and the MAPS II Guideline suggest that performing EGD in conjunction with screening colonoscopy is cost-effective in nations with a GC risk of 10/100,000 or higher.[70] This means that, in European countries with established colorectal cancer screening, more precisely in Portugal, the addition of EGD to colonoscopy screenings could be advantageous due to its intermediate GC incidence (ASR 13.1/100,000 inhabitants).[17]

Future Perspectives

AI has shown significant potential in improving the detection, classification, and prediction of GC during endoscopy. AI systems, particularly those based on deep learning models, have demonstrated high sensitivity (94.2% for AI compared to 94.5% for expert endoscopists)[71] in detecting gastric lesions and assisting in their classification as neoplastic or non-neoplastic. Besides, advanced imaging techniques, such as magnifying NBI, have shown high accuracy (85.3%)[72] in distinguishing EGC from gastritis, even in challenging cases with AG.[72] Additionally, AI has demonstrated promising results in predicting tumor invasion depth, which is crucial for determining appropriate treatment strategies.[72] Despite these advancements, challenges remain, including false positives, data diversity, and regulatory integration.[73] Regarding this, future research should focus on refining AI models, validating their clinical application, and ensuring their seamless incorporation into routine endoscopic screening to improve early detection and patient outcomes.[71]

Conclusion

The upper GI cancers continue to pose a major health challenge worldwide. Early detection through effective screening programs, coupled with primary prevention efforts, can significantly reduce mortality. However, widespread endoscopic screening faces logistical and economic challenges, especially in resource-limited areas. Regarding this, emerging non-endoscopic methods, such as biomarkers and cytosponge, and AI offer promising, less invasive alternatives to improve accessibility and early detection. Additionally, tailored screening strategies based on individual risk and regional epidemiology will maximize its impact. Nevertheless, further research is needed to fully understand the applicability and effectiveness of these techniques in diverse clinical and demographic settings.

Statements:

All papers must contain the following statements after the main body of the text and before the reference list. More detailed information can be found at Publication Ethics and Editorial Policies | Karger Publishers.

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Annexes:

Table 1. Global Burden and Epidemiology. Comparison with Portuguese Epidemiology.

Aspect	Esophageal Cancer	Gastric Cancer
Global Incidence **(according to Global Cancer Observatory, 2022) [16]**	**11th** most commonly diagnosed cancer.	**5th** most commonly diagnosed cancer.
Global Mortality **(according to Global Cancer Observatory, 2022) [16]**	**7th** leading cause of cancer-related deaths. (74.0% of deaths occur in Asia)	**3rd** leading cause of cancer-related deaths. (70.1% of deaths occur in Asia)
Global Prevalence [16]	**74.9%** of global cases occur in **Asia**	**71.4%** of global cases occur in **Asia**
Subtypes (EC) [9]	ESCC: 85% of cases. EA: 14% of cases	Not applicable for this review
Epidemiological Trends [3, 11-13]	**in EAC in Western countries** due to lifestyle factors such as GERD, BE, obesity, and high-fat diets. _____ **in ESCC** linked to decreased smoking and alcohol consumption.	**Increasing**: - **Asia**: Despite some reductions in countries like Japan and South Korea, the absolute number of cases continues to rise due to population aging. - **South America**: Especially in countries with lower socioeconomic development. _____ Decreasing: [74] - **North America** **- Western Europe**:
High-Risk Regions [3, 11]	ESCC: Eastern Asia (China), Central and South Asia and Southern Africa _____ EAC: Northern Europe and North America	**Highest Incidence** in Eastern Asia, Eastern Europe, and South America. _____ **Lowest Incidence:** North America and many parts of Africa
Epidemiology in Portugal (current trend) [9, 15]	EC ranks outside the top 15 most prevalent cancers in Portugal. But, the trend is similar to other Western countries: **ESCC** **EAC**	4th most common cancer (14.3/100,000) Highest incidence in **Northern regions** of Portugal. Mortality rates declining but still the **highest rate in Western Europe**

5-year Survival [8, 25]	~ 20% for all stages	~25% across Europe Higher in countries with screening programs, such as Japan and South Korea.

ESCC, Esophageal Squamous Cell Carcinoma; EAC, Esophageal Adenocarcinoma; GERD, Gastroesophageal Reflux Disease; BE, Barrett's esophagus

Table 2. Risk Factors and Preventive Strategies for EC subtypes and GC.

Cancer Type / Preventive Measures	Lifestyle Risk Factors	Genetic Risk Factors	Diet-Related Risk Factors	Medical Conditions
ESCC	**- Smoking** **- Heavy alcohol consumption [18, 47]** - Poor oral health [47] - Low esophageal microbial diversity [48]	- Genetic predisposition [19, 55] - Male sex [7]	- Hot beverages - High-temperature foods - Low fruit intake - High pickled vegetable intake - Mate tea consumption [18, 33, 47]	- Esophageal conditions (Achalasia, Tylosis, Esophageal Lichen Planus) - Head and neck cancer history [48] - Cirrhosis [45] - HPV (inconsistent findings) - Dysplastic precursor lesions (inconsistent findings) [3, 33, 34]
Preventive Measures (ESCC)	- Smoking cessation [75] - Alcohol reduction or cessation [76] - Improve oral health care [47] - Increase esophageal microbial diversity (e.g., probiotics) [34, 37]	- Genetic counseling for high-risk individuals	- Reduce consumption of hot beverages and high-temperature foods [3] - Increase fruit and vegetable intake - Adopt a Mediterranean diet (rich in fruits, vegetables, and antioxidants) [5] - Avoid pickled vegetables and mate tea [3, 11, 12, 58]	- Regular surveillance for high-risk individuals - HPV vaccination (if evidence supports its role) [18, 33]
EAC	- Smoking [19] - Obesity [3] - Sedentary behavior [3]	- Genetic predisposition [19, 55] - Male sex [3] - Age [3] - Family history of EAC [3] - Inherited germline mutations [19, 55]	- High-fat diet [3] - Low fruit and vegetable intake [3] - Nitrosamines (inconsistent findings) [3, 35]	- GERD (chronic acid reflux) [3, 19] - Barrett's esophagus (BE) [3, 19] - HPV (inconsistent findings) [3, 35]

Preventive Measures (EAC)	- Smoking cessation [6, 19] - Weight management (e.g., diet and exercise) [6, 19] - Physical activity [3]	- Genetic counseling for high-risk individuals [6]	- Adopt a low-fat diet [6, 19] - Increase fruit and vegetable intake [6, 19]	- Early detection and surveillance of Barrett's esophagus (BE) [55] - GERD control (e.g. lifestyle changes, anti-reflux therapies such as proton pump inhibitors (PPIs)) [55]
GC	- Smoking [21] - Heavy alcohol consumption - Obesity (primarily for cardia GC) [11, 14]	- Genetic predisposition [11, 14] - Family history [14] - Hereditary syndromes such as: [14] Hereditary Diffuse Gastric Cancer Lynch syndrome Li-Fraumeni syndrome Familial Adenomatous Polyposis Peutz-Jeghers syndrome	- High-salt diet - Salt-preserved foods - Red and processed meats [11, 12]	- Helicobacter pylori infection [22] - Precursor lesions (non-AG, AG, intestinal metaplasia, gastric polyps, dysplasia) - Gastric stump after partial gastrectomy [23-25]
Preventive Measures (GC)	- Smoking cessation [11, 14] - Alcohol reduction or cessation [11, 14] - Weight management (e.g., diet and exercise) [11, 14]	- Genetic counseling for high-risk individuals (e.g., those with hereditary syndromes) [17] - Prophylactic gastrectomy in high-risk cases (e.g., Hereditary Diffuse Gastric Cancer) [24]	- Reduce salt and salt-preserved food intake [22] - Limit red and processed meat consumption [22] - Adopt a Mediterranean diet (rich in fruits, vegetables, and antioxidants) [14]	- Helicobacter pylori eradication (test-and-treat strategy) [20] - Surveillance for precursor lesions (e.g., AG, IM) [20] - Regular endoscopic screening for high-risk individuals [20]

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; GC, gastric cancer; AG, atrophic gastritis; IM, intestinal metaplasia; GERD, gastroesophageal reflux disease; BE, Barrett's esophagus

Table 3. Overview of Surveillance Guidelines for BE and EAC Screening. Differences between American and European recommendations.

	Recommended Approach	
Criteria	**European Society of Gastrointestinal Endoscopy [55, 56]**	**American Gastroenterological Association [53, 77]**
Target Population	Patients with GERD for >5 years and multiple risk factors including age >50, male sex, obesity, smoking, and family history of BE or EAC.	Patients with ≥3 established risk factors for BE and EAC, such as male sex, non-Hispanic white, age >50, obesity, smoking history, chronic GERD and a first-degree family history of BE or EAC.
Short-segment BE (1–3 cm) without dysplasia	Endoscopy every 5 years	Surveillance every 3–5 years
Long-segment BE (3–10 cm) without dysplasia	Endoscopy every 3 years	Surveillance every 3 years
BE >10 cm	Referral to a specialized center for closer surveillance	Referral to an expert center for closer surveillance
Irregular Z-line or columnar-lined esophagus <1 cm	No routine biopsies or surveillance needed	No routine biopsies or surveillance needed
Low-grade dysplasia	Confirmed by expert pathologist → Surveillance every 6 months. If confirmed in multiple biopsies, endoscopic ablation recommended	Confirmed by expert pathologist → Surveillance every 6–12 months or endoscopic ablation as preferred option
High-grade dysplasia	Endoscopic eradication therapy recommended. Post-treatment surveillance at 1, 2, 3, 4, 5, 7, and 10 years	Endoscopic eradication therapy is strongly recommended. Post-treatment surveillance at 3, 6, and 12 months, then annually
Patients treated for dysplasia	Structured surveillance post-treatment, depending on initial diagnosis	Structured surveillance post-treatment, based on initial diagnosis
Patients ≥75 years or with limited life expectancy	Consider stopping surveillance if life expectancy <5 years	Case-by-case evaluation, balancing risks and benefits
GERD as a risk factor	The latest AGA Clinical Practice Update does not consider GERD an essential risk factor.	

GERD, Gastroesophageal reflux disease; AGA, American Gastroenterological Association; BE, Barrett's Esophagus; EAC, Esophageal Adenocarcinoma

Table 4. Gastric Cancer Surveillance Guidelines: European vs. American vs. Asian Approaches

	Asian Guidelines (Japan, South Korea)	**American Guidelines (AGA, ACG, USA)**	**European Guidelines (ESGE, MAPS II)**	**Preferred Endoscopic Technique**
OLGIM III/IV (moderate-severe metaplasia)	Every 2–3 years	Up to 5 years	Every 3 years	**Asia:** Chromoendoscopy/NBI **USA:** HD-WLE **Europe:** NBI/Chromoendoscopy
Corpus-extended intestinal metaplasia	Every 2–3 years	No clear consensus	Every 3 years	**Asia:** Chromoendoscopy/NBI **USA:** HD-WLE **Europe:** NBI/Chromoendoscopy
First-degree Family History of gastric cancer	Annual or every 2 years	Only if additional risk factors	Every 3–5 years	**Asia:** Chromoendoscopy/NBI **USA:** HD-WLE **Europe:** NBI/Chromoendoscopy
Incomplete-type intestinal metaplasia	Every 1–2 years	Every 3–5 years	Every 1–3 years	**Asia:** Magnification Endoscopy + NBI **USA:** HD-WLE **Europe:** Magnification Endoscopy
Autoimmune gastritis	Not specifically addressed	Every 1–2 years	Every 1–2 years	**Asia:** Not specified **USA:** HD-WLE + Biopsy **Europe:** HD-WLE + Biopsy
Persistent Helicobacter pylori infection	Routine screening and eradication	Test and treat, but no routine endoscopic follow-up	Treat and stratify by risk	**Asia:** NBI/Chromoendoscopy if needed **USA:** HD-WLE if indicated **Europe:** NBI/HD-WLE if risk persists

OLGIM, Operative Link on Gastric Intestinal Metaplasia Assessment; NBI, Narrow-Banding Imaging; HD-WLE, high-definition white light endoscopy; AGA: American Gastroenterology Association; ACG, American College of Gastroenterology; MAPS, Management of epithelial precancerous conditions and lesions in the stomach.

Scale for the Assessment of Narrative Review Articles – SANRA

Please rate the quality of the narrative review article in question, using categories 0–2 on the following scale. For each aspect of quality, please choose the option which best fits your evaluation, using categories 0 and 2 freely to imply general low and high quality. These are not intended to imply the worst or best imaginable quality.

1) Justification of the article's importance for the readership

The importance is not justified. — 0
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The importance is explicitly justified. — 2

2

2) Statement of concrete aims or formulation of questions

No aims or questions are formulated. — 0
Aims are formulated generally but not concretely or in terms of clear questions. — 1
One or more concrete aims or questions are formulated. — 2

2

3) Description of the literature search

The search strategy is not presented. — 0
The literature search is described briefly. — 1
The literature search is described in detail, including search terms and inclusion criteria. — 2

2

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Key statements are not supported by references. — 0
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2

5) Scientific reasoning

(e.g., incorporation of appropriate evidence, such as RCTs in clinical medicine)

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2

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(e.g., absolute vs relative risk; effect sizes without confidence intervals)

Data are presented inadequately. — 0
Data are often not presented in the most appropriate way. — 1
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2

Sumscore 10

Fig. 1 SANRA - Scale

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Justification of importance for the readership must be seen in the context of each journal's readership.
Consider how well the manuscript outlines the clinical problem and highlights unanswered questions or evidence gaps – thoroughly (2), superficially (1), or not at all (0).

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A good paper will propose one or more specific aims or questions which will be dealt with or topics which will be reviewed.
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Item 3 – Description of the literature search

A convincing narrative review will be transparent about the sources of information on which the text is based. Please rate the degree to which you think this has been achieved. To achieve a rating of 2, it is not necessary to describe the literature search in as much detail as for a systematic review (searching multiple databases, including exact descriptions of search history, flowcharts, etc.), but it is necessary to specify search terms, and the types of literature included. A manuscript which only refers briefly to its literature search would score 1, while one not mentioning its methods would score 0.

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No manuscript references all statements. However, those that are essential for the arguments of the manuscript – "key statements" – should be backed by references in all or almost all cases. Exceptions could reasonably be made for rating purposes where a key statement has uncontroversial face-validity, such as "Diabetes is among the commonest causes of chronic morbidity worldwide."
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The item describes the quality of the scientific point made. A convincing narrative review presents evidence for key arguments. It should mention study design (randomized controlled trial, qualitative study, etc), and where available, levels of evidence.
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Item 6 – Appropriate presentation of data:

This item describes the correct presentation of data central to the article's argument. Which data are considered relevant varies from field to field. In some areas relevant data would be absolute rather than relative risks or clinical versus surrogate or intermediate endpoints. These outcomes must be presented correctly. For example, it is appropriate that effect sizes are accompanied by confidence intervals. Please rate how far the paper achieves this – thoroughgoingly (2), partially (1), or hardly at all (0). Unlike item 5, which relates to the use of evidence and of types of evidence in the manuscript's arguments, this item is concerned with the selection and presentation of concrete outcome data.

Fig. 2 SANRA—explanations and instructions document

REGRAS DE FORMATAÇÃO DA REVISTA ESCOLHIDA:

About the Journal

Aims and Scope

The *GE – Portuguese Journal of Gastroenterology* (formerly Jornal Português de Gastrenterologia), founded in 1994, is the official publication of the Sociedade Portuguesa de Gastrenterologia (Portuguese Society of Gastroenterology), Sociedade Portuguesa de Endoscopia Digestiva (Portuguese Society of Digestive Endoscopy), and Associação Portuguesa para o Estudo do Fígado (Portuguese Association for the Study of the Liver). The journal publishes clinical and basic research articles on gastroenterology, digestive endoscopy, hepatology, and related topics. Review articles, clinical case studies, images, letters to the editor, and other articles such as recommendations or papers on gastroenterology clinical practice are also considered. Only articles written in English are accepted.

Journal Sections

Images in Gastroenterology and Hepatology
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Endoscopic Snapshots
This section is intended for the publication of rare or educational cases or novel techniques in digestive endoscopy. Submissions to this section should be submitted under the article type "Case Reports" and should have no more than 6 authors.

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Clinical Case Studies are Case Reports which present a case study, case report, or other description of a case. Case Reports present significant new insights or cases with an unusual and noteworthy course. Submissions can be based on a case or a number of similar cases. The most important aspect of the presentation is that it should provide a new perspective on a recognized clinical scenario or may represent an entirely new clinical condition. The novelty of the case(s) may lie in the phenotype, the presentation, the investigation, and/or the management. Submissions to this section should be submitted under the article type "Case Reports" and should have no more than 6 authors.

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Endoscopic Snapshots: Intended for the publication of rare or educational cases or novel techniques in digestive endoscopy. The text should not exceed 500 words and up to 5 references. Up to 3 figures with brief captions may be included. An abstract is not required, but the manuscript should have a title and keywords in Portuguese. The text should have no more than 6 authors.

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