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REVIEW ARTICLES

Gastric intestinal metaplasia and gastric epithelial dysplasia – precursor lesions of gastric cancer

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ABSTRACT

Introduction. Despite worldwide decreasing trends in the incidence of gastric cancer, the disease remains a significant global health burden, one of the leading causes of cancer death worldwide, and its prevention is a priority for the health system. Intestinal-type gastric carcinoma originates in dysplastic epithelium, which, in turn, develops in the environment of chronic atrophic gastritis and gastric intestinal metaplasia.

Material and methods. Narrative literature review. A bibliographic search was conducted in the databases PubMed, Hinari, SpringerLink, National Center for Biotechnology Information, and Medline. Articles published between 2000-2024 were selected based on the following keywords: "gastric intestinal metaplasia" and "gastric epithelial dysplasia", used in different combinations with the terms "epidemiology", "clinical picture", "risk factors", "classification", "diagnosis", and "management" to maximize the search yield. After processing the information from the databases according to the search criteria, 215 full articles were found. The final bibliography contains 34 relevant sources, considered representative of the materials published on the subject of this summary article.

Results. Gastric intestinal metaplasia represents the replacement of the gastric epithelium with two types of intestinal-type epithelium (enteric or colonic) as an adaptive response to chronic injury, while gastric epithelial dysplasia is defined as unequivocal neoplastic change of the gastric epithelium (intraepithelial neoplasia) without evidence of stromal invasion. Gastric intestinal metaplasia and gastric epithelial dysplasia are preneoplastic lesions of gastric cancer. The estimated annual risk of gastric adenocarcinoma in patients with gastric intestinal metaplasia is 0.13-0.25%, and in patients with gastric epithelial dysplasia it is 1.36%, depending on the extent and type of the lesion.

Conclusions. Despite the lack of a specific treatment for gastric intestinal metaplasia, the management strategy, according to current clinical guidelines, includes eradication of *Helicobacter pylori* infection, screening for early detection of gastric cancer, and control of other risk factors. Appropriate management of high-grade gastric epithelial dysplasia requires endoscopic resection due to its potential for progression to carcinoma and the possibility of coexisting carcinoma. For low-grade gastric epithelial dysplasia, which has a lower risk of malignant transformation, scientists recommend annual endoscopic surveillance with biopsy and histological examination.

Keywords: gastric intestinal metaplasia, gastric epithelial dysplasia, risk factors, serological examination, endoscopic examination, morphological examination, *Helicobacter pylori*.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

An appealing approach to reducing the incidence of gastric adenocarcinoma is to identify high-risk individuals who may benefit from screening, prophylactic, and therapeutic measures to prevent the onset of gastric cancer.

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The research hypothesis
The analysis and synthesis of contemporary literature will enable a comprehensive characterization of patients with gastric intestinal metaplasia and gastric epithelial dysplasia to establish gastric cancer prevention strategies.

The novelty added by the manuscript to the already published scientific literature
The article summarizes the latest international publications on the epidemiology, clinical picture, risk factors, classification, diagnosis, and management of patients with gastric intestinal metaplasia and gastric epithelial dysplasia.

Introduction

Despite worldwide decreasing trends in the incidence of gastric cancer (GC), the disease remains a significant global health burden, one of the leading causes of cancer death worldwide, and its prevention is a priority for the health system [1].

The sequence leading to GC – the Correa cascade – can be schematically reduced to Helicobacter pylori infection (HP) – non-atrophic gastritis – chronic atrophic gastritis (CAG) – gastric intestinal metaplasia (GIM) – gastric dysplasia (GD) – neoplasia. Intestinal-type gastric carcinoma originates in dysplastic epithelium, which, in turn, develops in the environment of CAG and GIM. Prevention of HP infection and timely eradication (until the development of extensive atrophic changes) is the most effective strategy for preventing the development of precancerous gastric lesions (PGL) and the primary prophylaxis of GC. An attractive proposal to reduce the incidence of gastric adenocarcinoma is to identify high-risk individuals who may benefit from screening, prophylactic, and therapeutic measures to prevent the onset of malignancy. For this reason, the diagnosis and effective management of CAG and GIM are very important research topics for the prevention of GC [1-5].

Among PGL, GIM is a recognized precancerous lesion, defined as the replacement of gastric epithelium with intestinal-type epithelium. The reported prevalence of GIM in international databases of gastric biopsies varies widely – from 3.4% to 29.6% [6].

GIM is commonly diagnosed, but only a small proportion of these patients will eventually develop GC. Current clinical guidelines recommend screening for active HP infection in all patients with GIM. Eradication of HP infection reverses early histological changes in CAG patients and may slow the progression of GIM to GC [2].

In this context, the article aims to develop a narrative synthesis of contemporary studies to review current concepts regarding epidemiology, clinical picture, risk factors, classification, diagnosis, and management of patients with gastric intestinal metaplasia and gastric epithelial dysplasia to establish strategies for the prevention of gastric cancer.

Material and methods

To achieve the stated objective, an initial search of specialized scientific publications was conducted, identified through the Google Search engine and the databases PubMed, Hinari (Health Internet Work Access to Research Initiative), SpringerLink, National Center for Biotechnology Information, and Medline. The article selection criteria included contemporary data on the epidemiology, clinical picture, risk factors, classification, diagnosis, and management of patients with GIM and GD, using the following keywords: "gastric intestinal metaplasia" and "gastric epithelial dysplasia", combined in various ways with the terms "epidemiology", "clinical picture", "risk factors", "classification", "diagnosis", and "management" to maximize the search yield.

For the advanced selection of bibliographic sources, the following filters were applied: full text articles, articles in English, and articles published between 1990-2024. After a preliminary review of the titles, original articles, editorials, narrative synthesis articles, systematic reviews and meta-analyses were selected, containing relevant information and contemporary concepts regarding the epidemiology, clinical picture, risk factors (RF), classification, diagnosis, and management of patients with GIM and GD. Additionally, a search of the bibliographic reference lists of the identified sources was conducted to highlight additional relevant publications that were not found during the initial database search.

The information from the publications included in the bibliography was collected, classified, evaluated, and synthesized, highlighting the main aspects of the contemporary view on the epidemiology, clinical picture, RF, classification, diagnosis, and management of patients with GIM and GD.

To minimize the risk of systematic errors (bias) in the study, thorough searches were conducted in the databases to identify the maximum number of publications relevant to the study's purpose. Only studies that met the validity criteria were evaluated, and safe exclusion criteria were applied to the articles included in the study.

If necessary, additional sources of information were consulted to specify certain notions. Duplicate publications, articles that did not correspond to the purpose of the work, and those not accessible for full viewing were excluded from the list of publications generated by the search engine.

After processing the information identified by the Google Search engine and from the databases PubMed, Hinari, SpringerLink, National Center for Biotechnology Informa-

tion, and Medline according to the search criteria, 215 articles were found that address the topic of epidemiology, clinical picture, risk factors, classification, diagnosis, and management of patients with GIM and GD. After the primary analysis of the titles, 42 articles were considered possibly relevant for the given synthesis. Following repeated reviews of these sources, 34 publications relevant to the intended purpose were finally selected.

Results and discussions

The publications, the content of which did not reflect the topic addressed, although they were selected by the search program, as well as the articles that were not accessible for free viewing either through the HINARI database or in the medical scientific library of the *Nicolae Testemițanu* State University of Medicine and Pharmacy, were subsequently excluded from the list.

Gastric intestinal metaplasia

GIM is defined as the replacement of gastric epithelium with two types of intestinal-type epithelium as an adaptive response to chronic injury, such as chronic inflammation due to HP infection [4, 5, 7-11].

Studies on the incidence of GIM are rare in the asymptomatic general population, as the diagnosis of GIM requires upper digestive endoscopy with biopsy and histological examination [3].

The prevalence of GIM is heterogeneous across different regions of the world, correlating with the endemicity of HP infection among other environmental factors and with the global incidence of GC. It increases significantly with age in both men and women [3, 8].

In previous studies, the prevalence of GIM generally ranged from 3.4% to 23.9% in patients undergoing upper digestive endoscopy with gastric biopsies and from 12% to 50% in high-risk patient groups [6, 10, 12-14]. The prevalence of GIM in large international databases of gastric biopsies also varied widely – from 3.4% to 29.6% [6]. According to the analysis of other studies, the prevalence of GIM varies from 7.1% to 42.5%, depending on the country and diagnostic methods [3].

More recent studies found GIM to be present in 25.3% of patients endoscopically evaluated for dyspepsia [15], in 2.5% of patients undergoing any upper digestive endoscopy, and in 4.8% of patients with gastric biopsies regardless of indication [6, 16-18]. The prevalence of GIM in HP-infected patients was 33.9% compared to 15.2% among HP-negative patients [15].

According to the results of a recent study published in 2020, among 223 patients with GIM, 194 (87%) had complete-type GIM, and 29 (13%) had incomplete-type GIM [5].

Risk factors. Male sex, age >50 years, and current HP infection are significant predictors of the presence of GIM [5, 8, 10].

Gene expression patterns found in different studies have provided new comparative information on CAG and GIM, which may play an important role in the development of GC [8]. An increased risk of GIM was found in subjects with the IL-8-251AT genotype (OR = 2.27; 95% CI: 1.25-4.14), in carriers of IL-8-251A alleles (OR = 2.07; 95% CI: 1.16-3.69) [19], and in subjects with the MIF-173GC genotype [20].

Several RFs have been associated with the development of GIM and GC, including HP infection and associated genomics, host genetic factors, environmental factors, rheumatological disorders, diet, and gut microbiota [3, 12]. However, for CAG, the most important RF is the virulence factor HP, while for GIM, environmental and host factors play a more significant role [3].

Intestinal metaplasia – pre-neoplastic step. GIM is a pre-malignant condition of the gastric mucosa, a precursor of GD, and an essential predisposing factor in the development of GC, associated with a more than 10-fold increase in the risk of GC [2, 5, 8, 16, 21-23].

The initial risk of GC among patients with GIM may be significantly higher depending on the anatomical extent, stage, severity, and histological subtype of metaplasia, as well as the presence of CAG and HP infection [10, 23]. The incomplete subtype of GIM is often detected around regions of GD or early gastric carcinoma and has an 8-fold higher risk of developing GC compared to the complete subtype [14, 22].

According to the results of a recent study, GIM was a significant RF for early GC (RR = 5.36; 95% CI: 1.51-19.0; p<0.01). Patients with OLGIM (Operative Link on Gastric Intestinal Metaplasia Assessment) in stages III-IV had the highest risk (RR = 20.7; 95% CI: 5.04-85.6; p<0.01) [23].

The cumulative rate of progression of GIM to GD at 3 and 5 years was 15% [16, 17, 18]. The estimated annual risk of GC in patients with GIM is 0.13–0.25% and depends on the extent and type of metaplasia [2, 4, 15, 24, 25]. The cumulative incidence rates of GC at 3, 5, and 10 years among patients with GIM were estimated to be 0.4%, 1.1%, and 1.6%, respectively [16-18, 26]. Incomplete GIM is an important FR for GC development [27]. Patients with incomplete GIM had a 3.33-fold higher risk of GC incidence compared to those with complete GIM [11].

According to the results of Japanese studies, the 5-year total cumulative incidence of GC is 1.9-10% in CAG patients and 5.3-9.8% in GIM patients [28].

GIM is considered an important stage along the continuum to GC and has an average latency period of approximately 6 years before progression to cancer, providing a window of opportunity for intervention. However, only a small proportion (0.25–2.5%) of patients with GIM ultimately progress to cancer [9].

In the process of carcinogenesis, GIM is considered an "irreversible point" that significantly increases the risk of GC. Therefore, elucidating the underlying mechanisms of GIM is of significant importance for the prevention and treatment of gastric mucosal carcinogenesis associated with HP infection [29]. Even in established GIM, HP eradication slows progression along the Correa cascade to GC [1, 9, 30].

Information on the RFs for the neoplastic progression of GIM is limited. Little is known about the molecular and genetic events that trigger GIM progression to adenocarcino-

ma. Smoking and a positive family history of GC in first-degree and/or second-degree relatives were associated with an increased but not statistically significant risk of GIM progression [31]. In addition to HP status, the two clinical factors that increase the risk of GIM progression to malignancy are age >50 years (RR = 8.8; 95% CI: 1.2-68.5) and a family history of gastric cancer in a first-degree relative (RR = 4.5; 95% CI: 1.3-15.5) [9].

The risk of GC is 4-11 times higher in patients with incomplete GIM compared to those with complete GIM [12]. Recent studies found no difference in progression to GC between extensive and limited GIM [13].

OLGIM is a validated GC risk assessment system that incorporates both the severity and topographical distribution of GIM. Patients with stage III or IV OLGIM have a significantly higher risk (20.8 times) of early gastric neoplasia compared to patients without GIM [10].

Classification. GIM is a highly heterogeneous lesion with multiple classification systems. One of the most commonly used classifications recognizes two types: complete (or enteric) GIM and incomplete (or colonic) GIM. Another classification (Jass and Filipe, 1981) currently in use recognizes 3 types of GIM: the complete "low risk" subtype (type I or small intestinal – characterized by the presence of mucin-producing goblet cells, Paneth cells, and columnar cells) and the incomplete "high-risk'' subtypes: type II (enterocolic, with mucin-producing goblet cells but lacking columnar and/or Paneth cells) and type III (colonic, with goblet cells containing irregular mucin vacuoles, and the absence of columnar and/or Paneth cells). However, the associations between the histological subtypes of GIM and the risk of GC are not universally accepted [2, 4, 11, 14, 15, 30].

Limited GIM was defined as involvement of only the distal stomach (antrum, pre-pylorus, or pylorus), while extensive GIM was defined as involvement of both the proximal and distal stomach or only the proximal stomach (body or fundus) [13].

In the specialized literature, a model of GIM known as SPEM (Spasmolytic polypeptide-expressing metaplasia) or pseudo-pyloric metaplasia, has been described. It represents the metaplastic replacement of oxyntic glands by mucin and is considered an alternative pathway to gastric neoplasia. This type of GIM represents a physiological healing response to acute injuries, but in cases of persistent injury and chronic inflammation, these reparative metaplastic lineages can evolve into pre-neoplastic (proliferative and self-renewing metaplastic and dysplastic) lesions, predisposing to GC development. Unlike intestinal metaplasia, SPEM develops in the gastric body and fornix and is strongly associated with HP infection and early GC [21, 24, 29, 30].

Diagnosis Three methods can be used to establish the diagnosis and extent of GIM: endoscopic evaluation, histological evaluation of biopsy specimens, and serological testing [30].

GIM can be diagnosed incidentally in patients with non-ulcer dyspepsia undergoing upper digestive endoscopy with random biopsies of normal-appearing gastric mucosa or targeted biopsies of subtle gastric mucosal abnormalities [6, 14].

Gross endoscopic features of GIM include dark-gray spots surrounded by pale or normal-colored gastric mucosa or irregular erythematous spots. Other endoscopic markers of GIM on narrow-band magnification endoscopy include the light blue crest (LBC), defined as a fine, light blue line on the crests of the villous and elongated epithelial *foveolae*, and opaque white matter (WOS - White Opaque Substance, lipid droplets). The latter has a distinctive appearance, which contributes to the endoscopic diagnosis of GIM with high specificity (100%) but limited sensitivity (50%) [4, 15, 25].

Several studies have suggested that endoscopy with magnification and chromoendoscopy identify GIM and GD lesions with high accuracy. The sensitivity and specificity of the endoscopic diagnosis of GIM, based on histological examination, were 24.0% and 91.9% for the antrum and 24.2% and 88.0% for the corpus [3].

Serum PGs have been used for the screening of CAG, GIM, and gastric adenocarcinoma for the past 3 decades due to their non-invasiveness and cost-effectiveness. In a prospective cohort study of 5,113 individuals in Japan, screening for GC with PG-I cutoff values <70 ng/mL and PGR < 3 showed a sensitivity of 84.6% and a specificity of 73.5% [3].

Management. To date, there are no unified clinical guidelines for the prevention of GC regarding the classification of high-risk groups that progress to GC. However, the prevention and treatment of CAG and GIM, considered precancerous lesions, could reduce the prevalence of GC [3].

Although GIM has no specific treatment, the management strategy includes the eradication of HP infection, screening for early detection of GC, and control of other RFs. Current clinical guidelines recommend that all patients with GIM be screened for active HP infection, as eradication of this infection reverses early histological changes in CAG patients and may slow the progression of GIM to GC [1, 2, 15, 16, 26, 30].

Despite the increased risk of GC among patients with GIM, there are no randomized controlled trials evaluating the benefits or harms of surveillance endoscopy in these patients. This has led to consensus-based recommendations for surveillance endoscopy in limited subgroups of patients at increased risk of developing GC [6]. Endoscopic surveillance every 3 years is recommended for patients with OLGA/OLGIM (Operative Link on Gastritis Assessment/Operative Link on Gastric Intestinal Metaplasia Assessment) stages III/IV [1, 4, 15, 16, 18, 30]. The purpose of GPL surveillance at defined intervals is to diagnose GC at an early stage and facilitate endoscopic or surgical resection with curative intent [4, 17, 22].

The results of studies suggest that GIM has a low probability of regression after HP eradication. GIM may be the "point of no return" if irreversible genetic damage occurs to gastric stem cells [24, 26], and these patients remain at risk of neoplastic progression regardless of HP infection status [17, 26]. Although substantial evidence supports the "point

of no return" concept, there is also evidence of regression with histological improvement in a subset of patients. These results indicate that GIM regression may be a long-term process, lasting many years after HP eradication [1, 17, 26, 30]. GIM does not always represent a "point of no return," as it can regress in some cases over an extended period (on average, 90 months), thus providing a mechanism for preventing intestinal-type GC through HP eradication [1, 30].

According to the results of a recent study published in 2020, among 50 patients with GIM who successfully eradicated HP, GIM disappeared in 62% of cases and persisted in 38% after a mean follow-up of 21 months [5].

According to the results of other long-term prospective studies, GIM is virtually irreversible at a more advanced stage, unless the lesion is minimal (e.g., focal and complete). These findings support the concept that the earlier HP is eliminated, the greater the benefits [27].

It is important to recognize the role of HP infection duration, among other factors, in the subsequent risk of GC [17]. No significant changes in GD were found, but there was a tendency toward greater regression and less progression among consistently HP-negative patients. A longer surveillance duration with an adequate sample size may help clarify the effect of HP eradication on GD [32].

Eradication of HP, compared with placebo, among individuals with or without GIM in the absence of gastric neoplasia was associated with a 32% reduction in the relative risk of GC incidence. Similarly, eradication of HP, compared to placebo, was associated with a 33% reduction in the relative risk of GC mortality [16]. Overall, HP testing and treatment in patients with confirmed HP infection (with or without GIM) demonstrated a protective effect against GC incidence and was associated with improved GC mortality compared to patients receiving placebo or non-antibiotic therapy [4, 17].

Dysplasia of the gastric epithelium

Definition. GD is defined as unequivocal neoplastic change of the gastric epithelium (intraepithelial neoplasia) without evidence of stromal (lamina propria) invasion [7, 21, 24]. GD is an advanced and direct precancerous lesion characterized by a combination of three basic morphologic abnormalities: (1) epithelial atypia (variation in size, shape, and orientation of epithelial cells) without deep invasion, (2) loss of native epithelial commitment, (3) disorganized glandular architecture, and (4) increased mitotic activity [7, 21].

Epidemiology. The endoscopic prevalence of GD ranges from 0.5% to 3.75% in Western countries and from 9% to 20% in areas with a high incidence of gastric adenocarcinoma [7, 15, 25, 33]. The prevalence of GD in patients with CAG, ulcers, or after gastrectomy ranges from 4% to 30%, and in patients with pernicious anemia, it can be as high as 40% [33].

GD – pre-neoplastic state. GD represents the penultimate stage of gastric carcinogenesis. Its clinical importance is determined by its close association with the risk of developing GC. Moderate to severe GD was associated with 40–100% of early GC and was detected in 5–80% of advanced adenocarcinomas, suggesting a direct role in cancer formation [33].

The results of several prospective longitudinal studies suggest that severe GD is a precursor of intestinal-type GC. In these studies, more than 30% of patients with moderate dysplasia and more than 70% of patients with severe dysplasia developed early or invasive carcinoma within a short or very short period of time [14].

The estimated risk of GC in patients with GD is 1.36% annually and 6% at 5 years [4, 25]. Both LGD (low-grade dysplasia) and HGD (high-grade dysplasia) have the potential to progress to carcinoma. The risk of progression to GC increases substantially and proportionally with the histological grade, ranging from LGD (4-18%) to HGD (up to 69%). It has been reported that approximately 15–30% of LGD progresses to HGD or adenocarcinoma [24].

A recent prospective study of a population of 9,740 subjects undergoing digestive endoscopic screening and followed dynamically for a median of 10 years identified cumulative incidence rates in patients with HGD, LGD, and CAG/GIM as 25%, 3.05%, and 1.58%, respectively. The rate of progression and risk of GC increased monotonically with each step in the Correa cascade [34].

Classification. There are several classifications of GD. According to the Vienna classification, dysplasia is currently divided into LGD and HGD [7, 21, 24, 30, 33]. LGD is characterized by minimal architectural disorder, mild to moderate cytological atypia, and mitotic activity, whereas HGD is marked by significant cytological atypia, strong mitotic activity, and complex glandular architecture [24].

The international Padua classification identifies five main categories for dysplastic lesions: 1) negative for GD, 2) indefinite for GD, 3) non-invasive neoplasia (divided into low-grade GD and high-grade GD), 4) suspicion for invasive carcinoma, and 5) invasive adenocarcinoma [7, 30, 33].

The term "dysplasia" is used synonymously with "intraepithelial neoplasia/dysplasia, non-invasive neoplasia/dysplasia" [4, 30].

Diagnostic. Detection of GD and early GC is difficult due to the lack of well-defined endoscopic criteria. Commonly described, but not exhaustive, features include color differences (more commonly red or pale), loss of vascularity, mild over- or under-elevation, nodularity, thickening, and abnormal convergence or flattening of the folds [15, 25].

Endoscopically, GD can present as a flat, depressed, or polypoid lesion, with the latter categorized as gastric (intestinal) and foveolar (adenomas) [21].

In a meta-analysis published in 2004, Dinis-Ribeiro and coauthors combined 42 studies, including 27 population studies (296,553 patients) and 15 studies of selected populations (4,385 patients), to assess the best cutoff for the diagnosis of dysplasia. A combination of PG-I ≤50 ng/mL and a PG-I/PG-II ratio ≤3.0 yilded the best results, with a sensitivity of 65%, a specificity of 74–85%, and a negative predictive value of >95% [1, 30].

Management. In general, there is no controversy regarding the appropriate management of defined HGD. Such le-

sions require endoscopic resection due to the potential for progression to carcinoma and the coexistence of carcinoma. If HGD is endoscopically indistinct, guidelines recommend immediate endoscopic reevaluation with extensive biopsy and surveillance at 6- to 12-month intervals. Given the lower risk of malignant transformation, some scholars recommend annual endoscopic surveillance with biopsy for LGD [1, 30]. Endoscopic surveillance is recommended every 6 months for high-grade GD and every 12 months for low-grade GD [1, 15, 30].

Conclusions

Gastric intestinal metaplasia represents the replacement of the gastric epithelium with two types of intestinal-type epithelium (enteric or colonic) as an adaptive response to chronic injury, while gastric epithelial dysplasia is defined as unequivocal neoplastic change of the gastric epithelium (intraepithelial neoplasia) without evidence of stromal invasion. Gastric intestinal metaplasia and gastric epithelial dysplasia are preneoplastic lesions of gastric cancer. The estimated annual risk of gastric adenocarcinoma in patients with gastric intestinal metaplasia is 0.13-0.25%, and in patients with dysplasia of the gastric epithelium, it is 1.36%, depending on the extent and type of the lesion. Advancing endoscopic technologies with high definition gastroscopes and improved imaging, medical training in endoscopy, risk stratification, and histological evaluation are essential for the diagnosis and management of precancerous gastric lesions. Despite the lack of specific treatment for gastric intestinal metaplasia, the management strategy according to current clinical guidelines includes eradication of Helicobacter pylori infection, screening for early detection of gastric cancer, and control of other risk factors. Adequate management of high-grade gastric epithelial dysplasia requires endoscopic resection because of the potential for progression to carcinoma and the coexistence of carcinoma. For low-grade gastric epithelial dysplasia, which has a lower risk of malignant transformation, scientists recommend annual endoscopic surveillance with biopsy and histological examination.

Competing interests

None declared.

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