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Improving Endoscopic Detection of Early Gastric Cancer and Its Precursors. A Mini Review

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Abstract

The objective of this publication is to review endoscopic techniques that allow improving the detection of gastric precancerous lesions (GPL) and early gastric cancer (EGC). These techniques can be divided into two: those used with white light endoscopy (WLE) and those that used technologies to improve endoscopic imaging. An adequate preparation to achieve optimal gastric cleaning it's necessary. In order to avoid missed lesions, a standardized procedure must be performed, with an orderly and systematic examination. And if available, use technologies that have been shown to improve the detection and characterization of early gastric cancer.

Introduction

Gastric cancer (GC) is one of the most common world´s gastrointestinal malignant tumors. In 2018, Globocan estimated more than 1 million new cases worldwide; Globally, it´s the second leading cause of cancer-related death in the world[1]. As the gastric cancer staging increases, the survival rate significantly decreases; when gastric cancer is detected in early stages, 5-year survival is greater than 90%[2]. The progression from chronic mucosal inflammation to gastric intestinal metaplasia (GIM), named Correa´s cascade, is a widely accepted model of GC pathogenesis[3]. The risk of progression to GC has been estimated at 0.1%, 0.25%, 0.6%, and 6% in those patients with chronic atrophic gastritis (CAG), GIM, mild-moderate dysplasia, and severe dysplasia, respectively[4]. In some countries with high incidence of GC, mainly on Asian continent, screening programs have been implemented. In Korea, the sensitivity of endoscopic screening compared to radiographic screening was 69.4% (vs. 38.2%) in the first round and 66.9% (vs.27.3%) in the second round[5]. Endoscopic screening has been shown to reduce the risk of gastric cancer-related mortality by 40-67%[6,7]. However, it has been published that about 10% of patients with gastric or esophageal cancers had a missed gastric cancer (false negative EGD within 3 years before diagnosis). Most of these missed cancers are related to endoscopist errors (73%): inability to detect lesions, detecting lesions but no performing biopsies, taking insufficient biopsy specimen, not performing appropriate follow-up[8]. In a meta-analysis with 3784 patients, failure to diagnose or to miss an upper gastrointestinal cancer at esophagogastroduodenoscopy (EGD) occurring in 6.4% within 1 year before diagnosis and 11.3% up to 3 years before diagnosis[9]. Another meta-analysis found a missed gastric cancer rate of 9.4%[10]. Although there's image-enhanced endoscopy (such as NBI), they aren´t available in all centers, so high quality WLE should be the gold standard as a starting point for the detection of gastric premalignant lesions and EGC[11].

Prendoscopic Preparation

All patients should fast for 6-8 hours depending on his clinical characteristics[12]. In order to improve patient tolerability and achieve adequate gastric distention, it´s recommended to perform endoscopy under intravenous desation, although this practice hasn´t been shown to improve lesion detection rate[13]. In most western cities, a cleaning protocol isn´t routinely used, however the mixture of anti-foaming (simethicone)[14,15] and mucolytic (Pronase® or N-acetylcysteine) agents have been proven to improve gastric mucosa visibility[16,17]. Monrroy et al., conducted an randomized placebo-controlled trial, to compared simethicone (S) with N-acetylcysteine 500 mg (S+NAC500) and S+N-acetylcysteine 100mg (S-NAC1000) with no intervention, water 100ml and simethicone 200mg (S); adequate gastric mucosa visibility (defined as a score <7 on Total Gastric Visibility Scale) was more frequent in the S+NAC500 and S+NAC1000 groups (65% and 67%) compared with no intervention (44%, p=0.044) and water (41%, p=0.022). Simethicone was not different from no intervention and water (p=0.56)[18]. Peristalsis can make visibility difficult, so use an antispasmodic is recommended. Extending the gastric wall by air insufflation is also important[19].

Sequential and Systematic Exploration

The complete exploration of the gastric mucosa is a quality indicator and it should be carried out in 98-100% of the studies[20]. Hosokawa et al., reviewed photos and reports of 155 patients with missed gastric cancer (false negative studies): in 6 (3.9%) explorations the lesion was clearly shown on the photograph, in 23 (15.0%) explorations the lesion was overlooked because it covered with mucus or was visualized only tangentially, in 14 (9.2%) explorations the lesions may have been missed by lack photographic documentation in the area of interest[21]. The majority of missed cancers were mainly found on body and antrum, so rigorous protocol for endoscopy must be implemented[10]. There is no globally accepted protocol. In Europe, 10 photos are recommend as minimum number to be captured in a normal endoscopic examination, but there isn't support for the diagnostic efficiency of this protocol[22]. In Japan, Yao proposed a Systematic Screening Protocol for the Stomach (SSS), a set of 22 gastric mucosa photos[19]. In the east, Emura et al., proposed. The Systematic Alphanumeric Endoscopy (SACE) based on simple, sequential, and systematic overlapping photo documentation; in the stomach SACE evaluates 5 regions and 21 areas, covering the entire gastric mucosal surface[23]. (Figure 1, Table 1) ESAC has been assessed in Latin American population: on 650 healthy Colombian volunteers between 40-70 years old, early gastric cancer were diagnosed in 0.3%[24]. In Peru, screening endoscopy was performed with this technique on 573 patients, the detection rate of gastric intraepithelial neoplasia was 2.8% (16/573), one with early gastric cancer (0.2%)[25]. More recently, in another prospective study with 50 patients between 40 and 50 years old, with average risk for gastric cancer, SACE has been proved to be more effective than conventional EGD in detecting premalignant lesions and early gastric cancer (p=0.003; OR 12)[26]. In EGD, an examination time longer than 7 min is related to high diagnostic accuracy[27]; The mean duration of SACE was 12.8 min (12.0-13.5min), so reflects a complete and adequate evaluation of gastric mucosa[26]. Endoscopic gastric cancer detection training programs have been shown to improve detection rates[28]. It hasn't been evaluated whether SACE or SSS protocols improve detection rate of benign or non-tumoral lesions.

Table 1: Endoluminal alphanumeric anatomy of the upper gastrointestinal tract

Region	Area	Alphanumeric code
Pharinx	Hypopharynx	P1
Esophagus	Upper third Middle third Lower third Esophagogastric junction	E2 E3 E4 E5
Antrum	Pyloric channel Anterior wall Lesser curvature Posterior wall Greater curvature	A6 A7 A8 A9 A10
Gastric body, lower third	Anterior wall Lesser curvature Posterior wall Greater curvature	L11 L12 L13 L14
Gastric body, middle third	Anterior wall Lesser curvature Posterior wall Greater curvature	M15 M16 M17 M18
Gastric body, upper third	Greater curvature Antero-posterior wall. Fornix. Cardia	U19 U29 U21 U22
Lesser curvature	Upper third Middle third Lower third Incisura angularis	Lc23 Lc24 Lc25 Lc26
Duodenum	Duodenal bulb Second portion	D27 D28

Image-Enhanced Endoscopy

There are different types of technologies that have been developed to improve the lesions visualization and characterization, including: **A) image enhancement endoscopy**, these are divided into conventional

Figure 1: Systematic alphanumeric-coded endoscopy. Complete and sequential exploration of the upper digestive tract.

chromoendoscopy (using dye, e.g. indigo carmine); digital as FICE (Fuji Intelligent Chromo Endoscopy), i-Scan, and optical-digital as Narrow-band imaging (NBI), Blue laser imaging (BLI), Linked color imaging (LCI), autofluorescence imaging (AFI), and i-Scan Optical Enhancement (OE). **B) Magnifying** (optical or digital). **C) Microscopic** (e.g. Confocal endomicroscopy). And **D) Tomographic endoscopy,** e.g. Optical coherence tomography (OCT)[29].

Indigo carmine dye accentuates a lesion edge and topography, improving the gastric mucosa visibility (Figure 2). A low concentration (0.05 %) is adequate for gross inspection, while a high concentration (0.2 %) is adequate to evaluate the microsurface structure under magnifying observation[30]. Zhao et al., conducted a meta-analysis, they observed that chromoendoscopy has an overall accuracy of 94%, better than WLE to detect gastric premalignant lesions (p=0.001) and EGC (p=0.005)[31]. Indigo carmine with acetic acid improves lesion characterization (demarcation line identification), but hasn´t been evaluated to improve the lesion detection rate[32,33]. Conventional chromoendoscopy has the advantage over optical-digital-enhancement that is available in all centers with low cost, however it´s

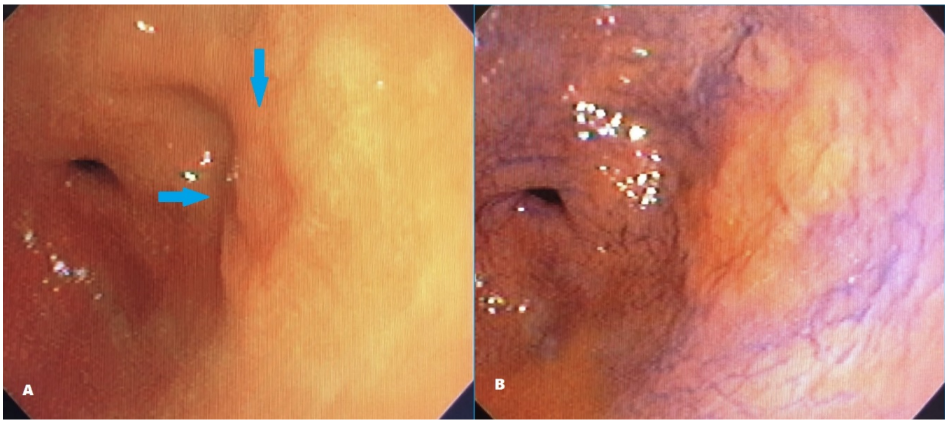

Figure 2: Type 0-IIa lesion on gastric antrum (A9 area, posterior wall). Tubular adenoma with high grade dysplasia and well differentiated intramucosal adenocarcinoma. A: White light image. Lesion's edge it's difficult to see. B: Indigo carmine chromoendoscopy help in lesion's delineation.

cumbersome and takes longer exploration times; optical-digital enhancement is available by pressing a button.

Optical-digital Image enhancement has an important role in lesions characterization, however the usefulness for early gastric cancer detection is under discussion. In a multicenter study with 238 patients, narrow band imaging (NBI) increased the detection of GIM and gastric dysplasia compared to WLE (94%vs.83%; p=<0.001)[34]. In an Asian Pacific multicenter study comparing NBI with High Definition WLE (HD-WLE); NBI increase the lesions detection rate (40.6%vs.29%, p=0.003) and GIM detection rate (17.7%vs.7.7% p=<0.001) compared with HD-WLE; there were no differences in gastric cancer detection rate (2.4%vs.1%, p=0.189)[35]. In another randomized controlled study, compared to WLE, NBI showed increase gastric atrophy detection with or without GIM (15.5%vs.8.5%, p=0.001)[36]. A meta-analysis with 1724 patients and 2153 lesions showed that Magnification Endoscopy with NBI has better diagnostic accuracy for EGC detection than WLE-M (AUC= 0.96 vs. 0.62)[37]. Although FICE and i-Scan increase diagnostic accuracy, the information is limited in the screening of preneoplastic and neoplastic gastric lesion, so, in this moment it isn´t routinely recommended[38,39]. Due to first generations of NBI, BLI and FICE does not yield a sufficiently bright image to observe EGC via distant views, new technologies such as BLI-bright have been developed; a randomized study of patients with gastric atrophy/metaplasia or under endoscopic surveillance after gastric cancer endoscopic resection, BLI-bright showed higher gastric cancer detection rate than WLE (93.1%vs.50%, p=0.001)[40]. LCI is another novel image enhancement technology, improves lesions visualization and characterization increasing luminosity in distant view[41]. Recently, a randomized study was carried out in China with 2383 patients at high risk of cancer, the EGC detection rate was better with LCI+WLE than only WLE (4.31%vs.8.01%, p=<0.001)[42]. In another retrospective study, LCI was more effective in detecting differentiated type EGC than NBI and indigo carmine[43]. The data about the role of AFI on the detection of the gastric lesions is contradictory. One trial proved combined Autofluorescence Imaging (AFI) followed NBI detected more patients with GMI than high-resolution WLE[44]. In another study, AFI has low sensitivity (64.1%vs.74.4%, p=0.79) and specificity (40.1%vs.82.7%, p=0.0003) compared with WLE to detect neoplastic lesions, due to the large number of false positives caused by regenerative hyperplasia and intestinal metaplasia[45]. In expert endoscopists, confocal laser endomicroscopy (CLE) has a sensitivity of 88% and specificity of 98% for GCA, 93% sensitivity and 98% specificity for GIM[46].

Artificial Intelligence (AI)

Recently, AI has made notable improvements in human life, and image-based medical diagnosis such as endoscopy is expected to be the first in medical fields involved in AI. Convolutional neural network (CNN) contains multilayer perceptrons (artificial neurons), simulating human neurons activity and structure on a computer; CNN undergoes "deep learning" based on training images that are introduced to the neural network. CNN leverages the multiple network layers to extract the main characteristics of all introduced training images to provide a diagnosis in a new image[47]. In gastric cancer detection, CNN has shown sensitivity of 92% but Positive Predictive value (PPV) of 30%[48]. For the detection of upper gastrointestinal cancer, the sensitivity of AI is similar to expert endoscopist (94% p=0.69), improve the performance of non-expert (85% p=<0.0001) and trainee endoscopist (72%, p=< 0.0001)[49]. Zhu et al., used AI to establish depth of gastric cancer invasion, 203 images were evaluated, the diagnostic accuracy was 89%[50]. It can also be a tool to avoid blind spots during endoscopic examination[51]. In the future it´s expected that AI could function as second observer during real-time endoscopies, helping endoscopist to detect more malignancies[52]

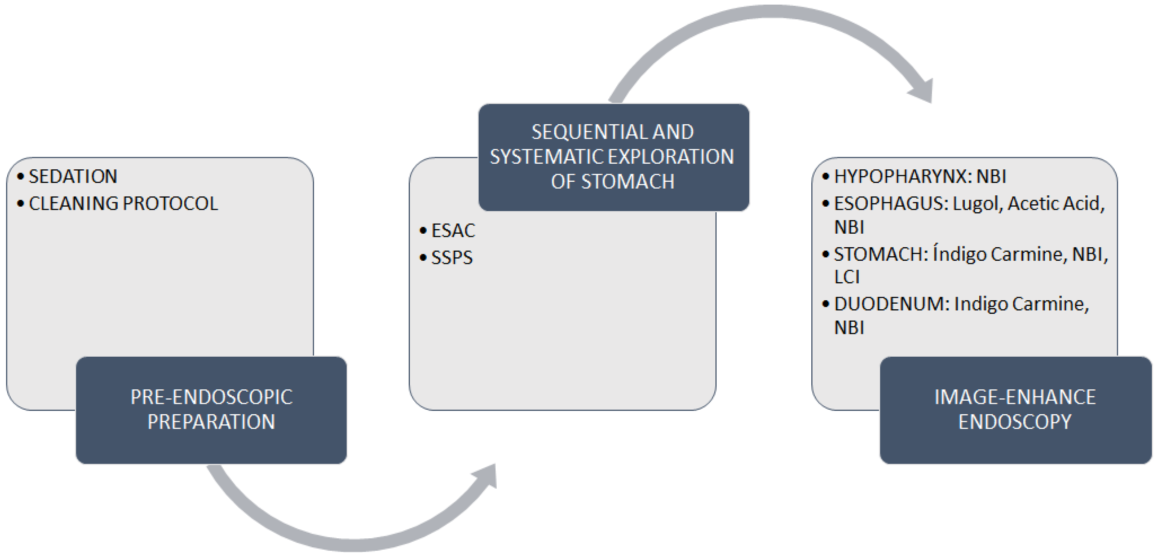

Figure 3: Upper endoscopy protocol to improve detection rate of gastric premalignant lesions and EAC.

Conclusion

- The detection of preneoplastic lesions and early gastric cancer is difficult, represents a challenge for the endoscopist.
- There´s no universally accepted screening protocol.
- It´s recommended to implement in all endoscopy units a training program and systematic protocol for detection of early gastric cancer (figure 3).
- In order to avoid blind spots, it´s necessary to carry out orderly and systematic gastric exploration, besides suitable mucosa cleaning.
- Image enhancement endoscopy appear to increase the detection of gastric preneoplastic lesions but his utility is under discussion.
- Artificial intelligence as a technology that improves gastric cancer detection is a reality, its use will be more regular in coming years.

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