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Endoscopic approach in the treatment of Barrett esophagus: resective and ablative tecniques

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Barrett esophagus (BE) is a condition whereby the normal squamous epithelium is replaced by specialised or intestinalised columnar epithelium. The prevalence in the general population is 0.9 to 4.5% and there is a progression of 0.5% per year from BE to adenocarcinoma. Proton pomp inhibitors are widespread as first line therapy for symptom controls for BE patients. Non dysplasia (ND) and Low Grade Dysplasia BE are usually treated with periodical surveillance. The use of radiofrequencies ablation has been taken into account as conservative approach in non dysplastic or Low Grade Dysplastic (LGD) Barrett disease. Endoscopy, surgery and strict periodical surveillance has recommended for High Grade Dysplasia (HGD) BE in order to avoid lead time bias and obtain early diagnosis of adenocarcinoma. Endoscopic treatment includes endoscopic mucosal resection (EMR) and ablation. More aggressive endoscopic interventions consisting of removing larger slices of esophageal mucosa or submucosal dissection have been described, but with long-term data uncertain, they remain somewhat controversial. EMR allows a 1.5-2 cm diameter piece of oesophageal mucosa to be removed. This provides better pathology for diagnosis and staging, and if the lesion is confined to the mucosa and fully excised, EMR can be curative. The combination of EMR and radiofrequency ablation has been used for multifocal lesions, but long-term outcomes are unknown. The new endoscopic interventions for BE and early esophageal cancer have the potential to improve clinical outcomes, although evidence that confirms superiority over esophagectomy is limited. Latest recommendation from worldwide literature have been examined and reviewed about diagnosis and treatment of Barrett's esophagus.

Key words: Barrett esophagus - Endoscopy - Gastroesophageal reflux - Proton pump inhibitors.

Barrett esophagus (BE) is a condition whereby the normal squamous epithelium is replaced by specialised or intestinalised columnar epithelium. The presence of mucus-secreting goblet cells characterize this metaplasia. Chronic gastroesophageal reflux disease (GERD) tend to compromise esophageal mucosal. The etiopathogenesis of Barrett's disease has to be referred to the chronic injury squamous cells are exposed to and the consequent conversion into columnar epithelium during the healing process.[1] This specific cells turnover is known as intestinal metaplasia. In the earliest stage the disease can be characterized by low grade dysplasia that can potentially turn into high grade dysplasia up to oesophageal adenocarcinoma. The mean age of BE onset is 50 years and the overall pooled male/female sex ratio is 1.96/1.[2] In the last decades Barrett disease prevalence has increased from 0.9% to 4.5%.[3] The aim of this review is focused on discussion about the latest innovation in diagnosis, management and treatment of BE underlining present and future perspectives.

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Diagnosis

Endoscopic and histological criteria has to be satisfied for a correct diagnosis. BE arises between the squamocolumnar junction and the gastroesophageal junction at the proximal margin of the gastric folds. The diagnosis of BE requires an accurate recognition of the columnar-lined esophagus at endoscopy. However, a universally accepted standardized endoscopic grading system of BE was lacking prior to the development of the Prague 'circumferential and maximal' criteria. In this system, the landmark for the esophagogastric junction (EGJ) is the proximal end of the gastric folds, not the distal end of the palisade vessels, which are used to endoscopically identify the EGJ in Japan. Although the circumferential and maximal criteria are clinically relevant, an important shortcoming of this system may be failure to identify short-segment BE, a lesion that is found frequently in the Japanese. Even if it remains controversial which landmark is better for the endoscopic diagnosis of BE, it is important to systematically educate and train endoscopists in order to improve diagnostic consistency in patients with BE. The normal stratified squamous epithelium of the distal esophagus is pearly, whereas the intestinalised columnar epithelium is salmon pink like. The line at which the columnar epithelium transitions to the

squamous epithelium (i.e., the squamocolumnar junction) is known as the Z-line. Normally, the Z-line corresponds to the gastroesophageal junction. In patients with BE, the columnar epithelium extends proximally up the esophagus. At pathological examination intestinal metaplasia can be detected by the presence of mucus-secreting goblet cells at esophageal mucosal biopsy. Three different columnar epithelia have been assessed from BE biopsies: intestinal metaplasia, fundic mucosa and cardiac gastric mucosa. The risk of fundic mucosa cancerization is not actually known[4]. When intestinal metaplasia is not detected in salmon-pink like esophageal mucosa specimen, the biopsy can be defined as suspicious for BE.

Management of non dysplastic Barrett's esophagus

Conservative management is recommended for patients with BE without any histological evidence of dysplasia or cancer. Symptoms controls and periodic endoscopic surveillance can be helpful to avoid overall disease progression. Lifestyle modifications in weight, smoking, alcohol, caffeine, citrus, chocolate, spicy food and late-evening meal assumption represent first-line measures for patients with GERD in order to improve pH profiles. Head of bed elevation, weight loss and early-evening meals can improve symptom relief for GERD. Citrus, sparkling drinks, tomatoes, onions and spicy food could be acid and corrosive. Although there is physiologic evidence that exposure to tobacco, alcohol, chocolate, and high-fat meals decreases lower esophageal sphincter pressure and predispose to gastroesophageal reflux disease, there were no published data of the efficacy of dietary measures.[5] Antiacid drugs can be considered the gold standard therapy in GERD. Medical treatment of BE is aimed at decreasing reflux of acid into the esophagus. The use of proton pump inhibitors (PPIs) or H2-receptor antagonists (H2RAs) is widespread in reducing acid secretion in the stomach. The result is a better intragastric pH control upper to 4 reducing erosive gastritis effects. PPIs seem to be more effective than H2RAs in heartburn symptom relief[6]. After medical treatment radiofrequencies ablation can be taken into account for BE therapy. Radiofrequency ablation (RFA) is a safe and effective option for the treatment of BE that attains lasting response. Progression of disease, which can precede cancer, was rare in patients who underwent RFA treatment, and there was no procedure or cancer-related mortality. To assess the dose-response, safety, and efficacy of circumferential endoscopic ablation of BE by using an endoscopic balloon–based ablation device, Sharma P. *et al.*[7] designed a study conducted in 2 serial phases (dosimetry phase and effectiveness phase) to evaluate a balloon-based ablation device that delivers a pre-set amount of energy density (J/cm^2) to BE tissue. They used 10 J/cm^2 (delivered twice [×2]) for all patients, followed by EGD with biopsies at 1, 3, 6, and 12 months. A second ablation procedure was performed if BE was present at 1 or 3 months. Patients received esomeprazole 40 mg twice a day for 1 month after ablation, and 40 mg every day thereafter. A complete response was defined as all biopsy specimens negative for BE at 12 months. A complete response for BE was achieved in 70% of patients. Very low rate of complications are possible after RFA such as strictures or buried glandular mucosa. To conclude guidelines recommendation on management of non dysplastic BE suggest that patients with two consecutive negative surveillance endoscopies showing no dysplasia may undergo subsequent surveillance every three years[8].

Management of low grade dysplasia Barrett esophagus

Patients presenting LGD BE have usually conservative therapy. After LGD diagnosis is performed, endoscopic surveillance should be done after six months in order to confirm LGD. American College of Gastroenterology (ACG) recommends a one-year endoscopic follow up until two consecutive negative surveillance endoscopies show no more dysplasia. Moreover American Gastroenterological Association recommends a one-year endoscopic follow-up for LGD, in cases of doubt about the complete remission in two consecutive surveillance, re-examination is mandatory in the following two years. In the meantime GERD symptoms must be managed with lifestyle measures and antiacid drugs.

Management of high grade dysplasia Barrett esophagus

Significant rate of histological variability can be found for HGD BE. Diagnosis has to be confirmed by expert pathologist. Several options can be selected for HGD patients such as endoscopic therapy, surgical therapy, or intensive endoscopic surveillance till when an adenocarcinoma in detected after biopsy. Seattle biopsy protocol is a biopsy protocol consisting of 4 quadrant jumbo biopsies (every 1 cm) with biopsies of mucosal abnormalities. It is considered to be the optimal method for detecting early cancers in patients with high-grade dysplasia, although it has never been validated.

Management of intramucosal oesophageal carcinoma on Barrett esophagus

Intramucosal carcinoma is characterized by tumour cells penetrating through the basement membrane and infiltrating into the lamina propria as single cells or in clusters. Sometimes it can be extremely difficult to distinguish between high grade dysplasia and intramucosal carcinoma. According to TNM from AJCC classification, T1 is a tumour invading lamina propria or muscularis mucosae (T1a) or the submucosa (T1b). Intramucosal carcinoma BE is classified as T1a. The esophageal mucosal cancers can also be subclassified into M1 (intraepithelial cancer), M2 (lamina propria mucosae corresponding to T1a according to TNM) and M3 (muscularis mucosae) in clinical view points. Lesions infiltrating the submucosal can be further split in SM1, SM2, SM3. M1 and M2 esophageal cancers which had no lymph node metastasis could be treated completely by EMR.[9] On the other hand, the patients with M3 cancer which showed lymph node metastasis in 10% of the cases can be treated by esophagectomy with lymph node dissection.[10, 11] Endoscopic Ultrasound (EUS) and Computed Tomography (CT) are useful imaging tools in intramucosal oesophageal carcinoma staging. EUS shows great accuracy in locoregional staging whereas CT is used for distant metastases detection. EMR can also find applica-

tion for oesophageal cancer staging. Endoscopic treatment options can be chosen as follows: endoscopic or EMR ablation with photodynamic therapy (PDT), (RFA) or cryoablation. Isolated HGD or intramucosal carcinoma (IMCA) foci local excision with EMR leaving even non dysplastic Barrett epithelium may expose patients to high rate of metachronous cancer (more than 35%). Ablation of residuary Barrett mucosa dramatically reduces the risk of local recurrence or metachronous cancers. No statistically relevant outcomes are published on rate of recurrence for patients treated with RFA. Nearly certain combination of EMR followed by ablation can be considered as means for attentive and safe management of high risk BE patients.

Conclusions

BE is an insidious disease. Once developed can progress of 0.5% per year for patient. At present time medical treatment can manage with reflux symptoms, but are unable to reduce the evolution of dysplasia. Endoscopic therapy can allow to reduce dysplastic lesions. Wider mucosal excision in now question of ongoing trials. Most recent outcomes show that a multiple step approach is required for a complete BE management. Surveillance, ablation, mucosal resection and esophagectomy set a multidisciplinary approach up that represents the best therapeutic strategy for these critical patients.

Riassunto

Titolo riassunto

L'esofago di Barrett è una condizione in cui l'epitelio squamoso normale è sostituito da un epitelio colonnare specializzato o intestinali. La prevalenza nella popolazione generale è dell' 0,9-4,5%, e non vi è un aumento dello 0,5% l'anno, di adenocarcinoma, da esofago di Barrett. Gli inibitori della pompa protonica sono utilizzati nella terapia di prima scelta, per il controllo dei sintomi. La non displasia (ND) e il Barrett dell'esofago con displasia di basso grado sono di solito trattati con sorveglianza periodica. L'uso dell'ablazione con radiofrequenze è stata presa in considerazione come approccio conservativo, nelle forme non displasiche o nella displasia di basso grado (LGD). L'endoscopia, la chirurgia e la rigorosa sorveglianza periodica è raccomandata per la displasia di alto grado (HGD), al fine di evitare trasformazioni e ottenere una diagnosi precoce di adenocarcinoma. Il trattamento endoscopico comprende resezione endoscopica della mucosa (EMR) e ablazione. Interventi di endoscopia più aggressivi costituiti dalla rimozione di pezzi di mucosa esofagea più grandi o la dissezione sottomucosa sono stati descritti, ma presentano a lungo termine dei dati incerti, e quindi rimangono in qualche modo discutibili. La resezione endoscopica della mucosa (EMR) consente la rimozione di un pezzo di 1,5-2 cm di diametro della mucosa esofagea. Questo fornisce una migliore possibilità per la diagnosi e la stadiazione, e se la lesione è limitata alla mucosa, e completamente asportata, l'EMR può essere curativa. La combinazione di ablazione EMR e radiofrequenza è stata utilizzata per lesioni multifocali, ma i risultati a lungo termine sono sconosciuti. I nuovi interventi endoscopici per l'esofago di Barrett e del cancro esofageo in fase iniziale, hanno il potenziale di migliorare i risultati clinici, anche se le prove che confermano la superiorità sull'esofagectomia sono limitate.

PAROLE CHIAVE: Esofago di Barrett - Endoscopa - Reflusso gastroesofageo - Inibitori della pompa protonica.

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