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REVIEW ARTICLE

Barrett's esophagus: treatment or observation of a major precursor factor of esophageal cancer?

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Summary

Barrett's esophagus (BE) is a major precursor factor of esophageal cancer (EC). The appropriate management of patients with BE depends on the presence or not of dysplasia and the type of dysplasia that occurs. Due to the small proportion of BE patients that progress to cancer, the value of surveillance programs are a matter of debate. On the contrary, in high risk group of patients surveillance programs have significant impact. Large prospective trials are needed to define the optimal management strategy. Elucidation of carcinogenesis' steps and signal transduction pathways could reveal potential biomarkers in the order of early prediction for a highly malignant neoplasm with dismal prognosis. An efficacious tailored-made manner focusing to the safety profile and associated costs should be practised for less severe disease. In this review a thorough investigation of all available methods dealing with the clinical management of BE is provided.

Key words: Barrett's esophagus clinical management, dysplasia, esophageal cancer

Introduction

EC is an aggressive neoplasm and a major cause of cancer-related deaths worldwide [1]. A total of 16,470 new cases and 14,530 deaths occurred in the USA in 2009 [2]. Despite advances in diagnosis, 50% of patients present with advanced disease [3]. Five-year relative survival rates are still low (14%) and the improvement when compared with the situation 20 years ago (10%) is not substantial [4,5]. Rapid progression to metastatic disease and an intrinsic resistance to therapy are hallmarks of EC.

Esophageal adenocarcinoma's (EAC) incidence is rising faster than that of any other cancer in western world [6]. BE is a well known premalignant condition of EAC and is characterized by the replacement of squamous stratified epithelium with a columnar metaplasia in distal esophagus [7,8]. Whether the presence of intestinal-type differentiation is a requirement for its definition is still a matter of debate. The American Gastroenterological Association Chicago workshop requires intestinal metaplasia identification [9], whereas the British Society of Gastroenterology states that this is not required for BE diagnosis [10].

In a Swedish study, BE prevalence in general population was approximately 1.6% [11]; meanwhile in a USA study this figure was 5.5% [12]. Furthermore, 5-15% of people with reflux will present with BE [13]. The risk of EAC in patients with BE is 0.5% per year [14] and the life-time risk is 30-125 fold higher than in general population [15]. BE progression is believed that is performed through metaplasia to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and EAC. LGD is until now thought to have a benign course with a high rate of regression [16], but it should be mentioned that there are also several studies that revealed contradictory results [17,18]. This unpredictability could be the result of sampling error, inter- or intra- observer variability, or instability of the dysplastic lesion. HGD's natural history is more evident and has higher malignant transformation rate with the risk for cancer progression to be almost 6.6% per year [19]. It is noteworthy to underline that diffuse HGD identification raise the risk of malignant progression [20].

Stage at presentation is a major prognostic factor,

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therefore early detection of EC is essential to improve survival rates. Nevertheless, not all the patients with BE will develop EC and identifying patients at high risk for an aggressive malignancy is a great field for research. Surveillance and examination with a minimal invasive technique as endoscopy, allow the collection of tissue samples from different stages of the disease. Therefore, BE is a model to study molecular alterations associated with cancer progression that could lead to the identification of clinical biomarkers characterizing the metaplasia-dysplasia-adenocarcinoma (M-D-A) sequence in BE.

Risk factors

BE is correlated with gastro-esophageal reflux disease (GERD) [21]. White elderly men have increased risk of BE diagnosis [22]. Hiatal hernia, central obesity rather than simple obesity [23] and the presence in reflux liquids of acid and bile are also correlated [24]. In contrast, smoking and alcohol appear to be low risk factors [25]. Contradictory results have been published regarding the damage that bile without acid could cause to the esophageal tissue [26,27].

Clinical management

The appropriate management of patients with BE depends on the presence or not of dysplasia and the type of dysplasia that occurs (Figure 1). Due to the small proportion of BE patients that progress to cancer, the value of surveillance programs are a matter of debate. On the contrary, in high risk group of patients surveillance programs have significant impact [28]. The Aspirin Esomeprazole Chemoprevention Trial (AspECT), a phase III randomized study of aspirin and esomeprazole chemoprevention in Barrett's metaplasia, could provide an evidence-based answer if it is possible to prevent BE progressing to adenocarcinoma [29].

In the situation that LGD is identified, histology should be confirmed by an experienced gastrointestinal (GI) pathologist. Esophago-gastro-duodenoscopy (EGD) should be performed after 6 months and then annually until two serial endoscopies are negative for dysplasia. In the case of HGD also histology confirmation should be verified by an experienced GI pathologist. The risk of concomitant early EAC also should be investigated. The alternative options offered to this stage (BE/HGD) are: aggressive surveillance through endoscopy and biopsies every 3 months, ablation therapy followed by surveillance or esophagectomy [28].

Esophagectomy

A high concordance that reaches 30-50% of the cases with HGD is observed between HGD and occult EC [30,31]. Due to this fact, esophagectomy is traditionally the standard treatment for BE with HGD. Esophagectomy in patients without muscularis mucosa involvement confers 5-year survival rates >80% [32]. Despite advances in surgical techniques, esophagectomy is re-

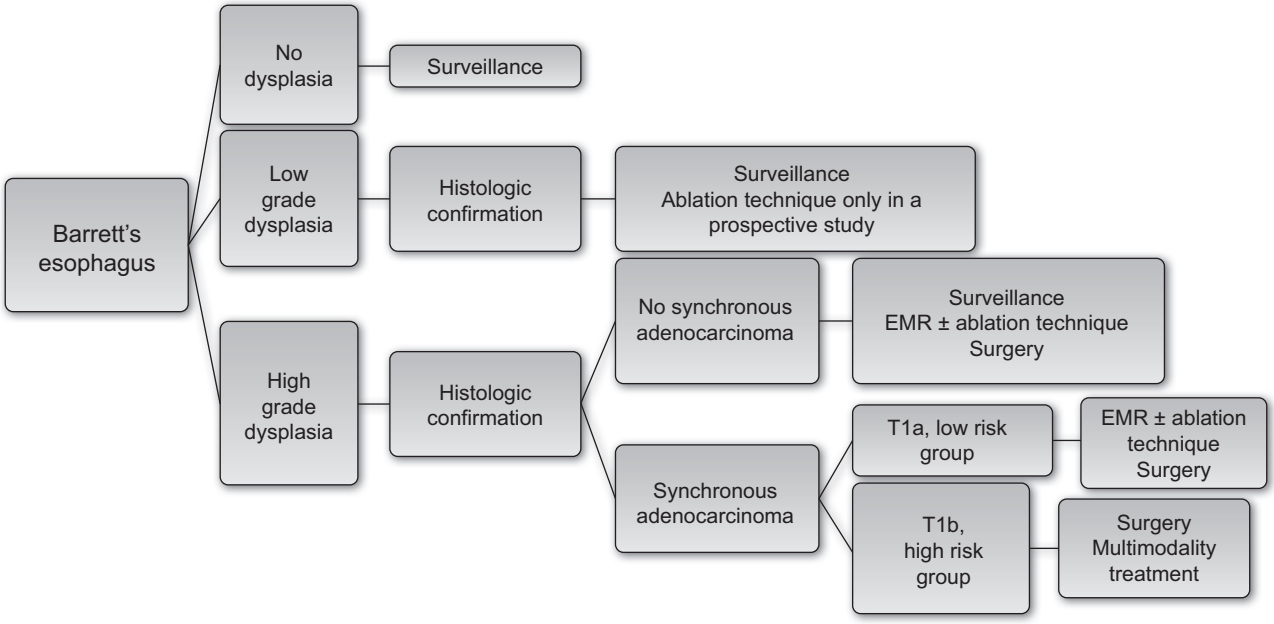

Figure 1. Barrett's esophagus algorithm for clinical management. Low risk group: grade (G): 1-2, lymph vessel infiltration (L): 0, venous infiltration (V): 0. High risk group: G: 3, L: 1, V: 1, submucosal cancer. EMR: endoscopic mucosal resection.

lated with significant mortality, ranging from 1-10% depending from the volume of the treating Centre [33]. Furthermore, morbidity rates ranging from 30-50% [34]. Although minimal invasive approaches of esophagectomy have been found to be safe with better peri-operative outcomes, randomized trials are needed to evaluate them in comparison with open procedures [35].

Ablation techniques

Mucosal adenocarcinomas have been related with a low rate of lymph node involvement (<2%) [36]. This observation provides a basis that less invasive approaches, as ablation techniques, could be performed as curative strategies in this group of patients with expectations of equivalent effectiveness but with significant decrease in mortality and morbidity rates (Figure 2).

Prior to the ablative techniques esophageal ultrasound (EUS) and computed tomography scanning (CT) should be performed to evaluate the size, the depth of the lesion, lymph node involvement and exclude distant metastasis.

Lasers

Light amplification by stimulated emission of radiation (LASER) beam is directed against the lesion and destroy it. There are various types of lasers: argon, neodymium: yttrium-aluminum-gannet (Nd:YAG), potassium titanyl phosphate (KTP), KTP: YAG, with different wavelength emissions. Gossner and colleagues studied 10 patients (LGD=4, HGD=4, early EC=2) using a (Nd: YAG) KTP laser system [37]. After a mean follow up of 10.6 months a complete response was observed to all patients. In 2 patients Barrett's submucosa was identified. Weston et al. also presented the results of 14 patients with BE and HGD/ intramucosal carcinoma (IMC) treated with Nd: YAG contact laser [38]. They reported successful elimination of their HGD and/ or cancer in all patients. Eleven of 14 achieved complete histological ablation of Barrett's tissue and no buried columnar epithelial tissue was observed. Odynophagia and early dysphagia were reported in 30.6% and 16.3% of the patients, respectively.

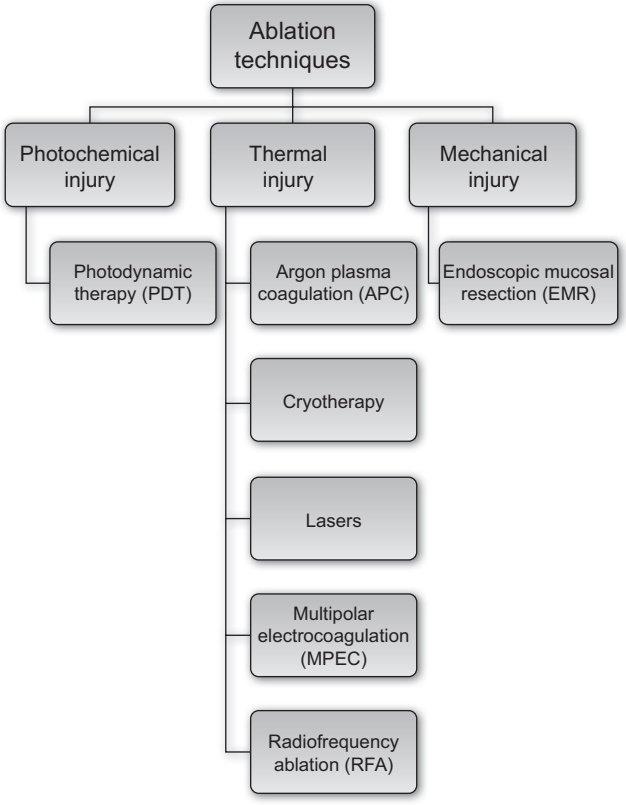

Figure 2. Ablation techniques.

Photodynamic therapy (PDT)

The basis for PDT is the administration of a photosensitizer (porfimer sodium [POR], i.v., 5-aminolevulinic acid per os) that has properties to bind the neoplastic area through an unknown mechanism. After an exposure to intense laser light, vascular thrombosis and cell necrosis is caused. Overholt and colleagues studied 100 patients (LGD=14, HGD=73, IMC=13) with a mean follow up of 19 months [39]. BE and HGD elimination was observed in 43% and 88% of the patients, respectively. Progression or failure was founded in 21 patients. Complications observed were stricture (34%) and sub-squamous Barrett's (6%). An international randomized phase III trial was also conducted by Overholt et al. [40]. They studied 208 patients to compare PDT using POR plus omeprazole (n=138) vs. omeprazole only (n=70). There was a significant difference ($p < 0.0001$) in favor of POR PDT compared with omeprazole (27/70; 39%), resulting in complete eradication of HGD at any time during the follow up period. The occurrence of EAC in the POR PDT group was 13%, significantly lower compared with the omeprazole group being 28% ($p < 0.006$).

Multipolar electrocoagulation (MPEC)

Two or more electrodes of MPEC probe allows the delivery of thermal energy to the desired area and destruct that. In a multicenter trial 58 patients were studied. After a follow up of 6 months 78% of the patients achieved complete response. Residual BE was identified in 4 out of 58 patients. One patient developed stricture and the most common side effect was chest pain (19/58) [41]. Kovacs et al. [42] studied 27 patients with BE treated with MPEC and lansoprazole with an inten-

tion to reverse histology. Twenty-two patients had successful reversal and the most common side effect was dysphagia (41%).

Argon plasma coagulation (APC)

Through the flow of ionized argon gas a high-frequency monopolar current is directed to neoplastic tissues. Attwood et al. studied 29 patients with HGD with a mean follow up of 37 months [43]. The median number of treatments were 2 and complete regression was observed in 25 out of 29 patients (86%). Recurrence was identified in 4 out of 25 patients (16%). Ackroyd and co-researchers randomized patients with BE to intervention with APC (n=20) vs. surveillance (n=20) [44]. After a 5-year follow up 14/20 patients treated with APC presented >95% BE regression vs. 5/20 in the surveillance arm. No patient in the intervention group progressed to HGD. On the contrary, 2/20 in the surveillance group progressed. Two patients treated with APC developed stricture managed endoscopically.

Radiofrequency ablation (RFA)

This technique requires the application of a balloon with circular electrodes delivering with radiofrequency the energy in circumferential way (HALO ^{360}). In addition, for focal lesions a plate device can be used (HALO ^{90}). Roorda et al. studied 13 patients (6 with BE,4 with LGD,3 with HGD) [45]. After a mean follow up of 12 months eradication of BE was observed in 6 patients (46%) and eradication of dysplasia in 5 out of 7 (71%). Fleischer at al. presented their data regarding 61 patients with intramucosal carcinoma [46]. Complete remission was observed in 98% of the patients after a median follow up of 30 months. In both studies no complications were presented. Shaheen and co-researchers presented the results of a randomized, multicenter prospective trial comparing RFA with a sham procedure in BE with dysplasia [47]. 127 patients (LGD=64, HGD=63) with a 12-month follow up were studied. Complete eradication of LGD and HGD occurred in 90.5% and 81% respectively in the ablation group ($p<0.001$). Compared with complete elimination of LGD and HGD that occurred in 22.7% and 19% in the control group ($p<0.001$), a clear superiority for RFA was observed. Furthermore, this superiority was revealed for eradication of BE with 77.4% (RFA group) as compared with 2.3% of those in the control group ($p<0.001$). Patients in the ablation group had fewer cancers (1.2 vs. 9.3%, $p = 0.045$) and less disease progression (3.6 vs. 16.3%, $p = 0.03$). Six percent of the patients treated with RFA developed stricture and one had gastrointestinal bleeding.

Endoscopic mucosal resection (EMR)

After the injection of fluid to separate the mucosal and muscle layers resection is performed. Ell et al. first reported their experience with EMR [48]. They studied 64 BE patients with HGD or IMC; 35 patients belonged to low risk group and 29 to high risk group according to histological grade, lesion size and macroscopic appearance. BE eradication was observed in 97% and 59% in low and high risk group respectively after a mean follow up of 12 months. The incidence of recurrence or metachronous lesions was 13.63% and 17.14%, respectively. Larghi et al. also reported their results with this technique in 24 BE patients with HGD or IMC after a mean follow up of 28 months [49]. Complete eradication was observed in 87.5% of the patients (21 out of 24). Complications were observed in 5 patients (2 with bleeding and 3 with stricture). Subsquamous BE was identified in 2 patients (8%).

Cryo-spray ablation (CSA)

Through the application of liquid nitrogen gas or CO_2 cold temperatures (-196° C, -70° C, respectively) are succeeded. In these temperatures ischemic necrosis is caused. Furthermore, apart from the thermal mechanism of action, cryo-ablation has a unique mechanism that induces also apoptosis and immune stimulation. A prospective trial evaluating safety and efficacy of CSA in patients with BE and HGD or IMC by Dumot and colleagues was conducted. Thirty patients were studied for a median follow up of 12 months. At the last follow up responses were persisted in 68% for HGD and 80% for IMCA [50]. Greenwald et al. presented results of parallel prospective treatment studies at 4 tertiary care medical centers [51]. Seventy-seven patients (BE=7, BE with HGD=45, BE with IMCA=13, EC=10, severe squamous dysplasia=2) were treated. Out of 23 patients completing therapy, in 17 with HGD there was a complete response in 94% of them and complete elimination of BE in 53%. In all 4 patients with IMC a complete response was noted for cancer and 75% of BE eradication. In all 3 patients with EC (inoperable or refused surgery, ineligible or refused radiation or systemic therapy) a complete response was observed for cancer and 67% of BE elimination. One major complication occurred consisting of a gastric perforation caused by gastric distention due to nitrogen gas. The most common side effect in procedures was chest pain (17.6%) and dysphagia (13.3%).

Taking into account the available date so far, it is clear that large prospective trials are needed to define the optimal management strategy. In 3 retrospective studies comparing esophagectomy vs. endoscopic therapy in BE with HGD or IMC outcomes in terms of overall survival

were similar [52-54]. Each endoscopic technique (ET) has its disadvantages and limitations; PDT: high costs, photosensitivity, highest complication rate. Lasers: high cost. MPEC, APC: tedious point by point application. RFA: difficult to use on irregular surfaces and the esophago-gastric junction (EGJ). CSA: risk of bloating or even a gastric perforation. Stricture formation is also a usual complication after ET.

It should be underlined that all but EMR ablation techniques have the major disadvantage the lack of complete histopathologic evaluation and staging of the neoplastic lesion. Furthermore, the risk of buried Barrett's and glands underneath the re-epithelization area after ablative intervention is a matter of concern and also its malignant potential is uncertain and should be determined. The multimodality ET approach –combining EMR as a diagnostic and therapeutic procedure with RFA, CSA or other ablative interventions for eradicating the remaining stem cells– seems a promising option to optimize treatment and its efficacy needs to be assessed. There is no doubt that for less severe disease it is very important to focus on safety profile and associated costs. To that direction BE clinical management could be modified based on molecular biology. New prognostic and prediction markers to stratify risk of patients and also therapeutic targets in pathways evolving during neoplastic progression are of crucial importance.

Conclusion

Although efforts in this research task are ongoing, no reliable biomarkers have been yet identified to estimate BE malignant progression. Advances in understanding of cancer biology could lead to the identification of validated biomarkers characterizing BE progression. In the era of targeted therapies, the development of "omics" technology and also single-nucleotide polymorphism (SNP) based technologies and comparative genomic hybridization arrays could allow a more thorough investigation, identification and validation of biologic markers and targets. Elucidation of carcinogenesis' steps and signal transduction pathways reveals potential biomarkers in the order of early prediction for a highly malignant neoplasm with dismal prognosis. These could be also served as targets for novel agents in order to establish an efficacious tailored-made chemoprevention treatment or therapy with minimal toxicity.

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