ENDOSCOPIC TREATMENT OF BARRETT'S ESOPHAGUS

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Abstract : *Barrett's esophagus, characterized by proximal migration of Z – line with intestinal metaplasia is seen in 6%- 12%of patients with gastro-esophageal reflux disease. Barrett's esophagus is a premalignant condition associated with increased risk of esophageal adenocarcinoma. The risk is increased by 60 to 125 times with annulised risk of 0.5%. The risk is highest in patients with high grade dysplasia. Though the standard treatment for high grade dysplasia and early esophageal cancer has been surgical, it is associated with high morbidity and significant mortality. Endoscopic therapy, in the form of endoscopic mucosal resection(EMR) combined with ablative techniques appears reasonably safe and effective procedures especially in the high risk patients.*

Key words*: GERD, Barrett's esophagus, Endoscopic Mucosal Resection, Photodynamic Therapy, Argon Plasma Coagulation & Multipolar Electrocoagulation, early esophageal adenocarcinoma*

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic disease, occurring due to abnormal reflux of gastric contents into the esophagus, and causing heartburn and regurgitation. GERD is very common in adults with 7% of adults having heartburn daily and 20% weekly[1]. The disease is equally common in both the sexes. Endoscopically, majority (50 to 70%) of the patients have normal mucosa (NERD-Negative Endoscopy Reflux Disease) and only 50% of patients with typical symptoms have erosive esophagitis in tertiary referral centres[2]. As GERD is a chronic disease, it is associated with *long term complications* like peptic stricture, **Barrett's esophagus (BE)** and esophageal adenocarcinoma.

CLASSIFICATION & EPIDEMIOLOGY

It is a combined endoscopic and histological diagnosis. It is characterised by proximal migration of squamocolumnar junction (Z line) from anatomical esophagogastric junction and histological changes of intestinal metaplasia in the endoscopic biopsies taken from the involved area. This condition was first described by Norman Barrett, a British surgeon in 1950. It is found in 6 to 12% of patients undergoing endoscopy for symptoms of GERD and in 1-2% in unselected patients undergoing endoscopy3. The length of involved area may be long (≥3cm) or short (< 3cm).Generally patients with short segment BE have less time with esophageal pH less than 4, better preserved anti reflux barrier and better esophageal clearance. Although length of BE is probably related to cancer risk, the biological significance of this is unclear. Recently, Sharma et al[4], proposed a new endoscopic classification for BE called Prague C & M criteria. It assesses both the circumferential and maximum proximal extent of BE. Histologically, the BE is classified on the basis of dysplasia. It is reported as negative, indefinite, low grade or high grade dysplasia. This histological assessment should preferably be done by GI pathologist. There is good inter observer and intra observer agreement in cases negative for dysplasia and HGD but considerable variability for indefinite and low grade dysplasia. Epidemiologically, BE is more common in elderly with mean age at diagnosis of 63 years. The prevalence of BE increases with age but the length of columnar lined mucosa remains remarkably stable. It is more common in males (ratio 2:1). Its' prevalence varies in various ethnic groups. In contrast to GERD, which it is equally common in various races, BE was detected in 7.8% in whites, 4.8% in Hispanics, 1.3% in Asians and 1.1% in Blacks. Most of patients with BE have classic reflux symptoms, but 25% discovered at endoscopy have on reflux symptoms[5]. Clinically, it may be difficult to distinguish BE patients from GERD patients. However, greater severity and longer duration of symptoms, nocturnal reflux symptoms, complications of GERD like ulcerations, stricture and bleeding may suggest BE. A subset of patients may have a family history of reflux esophagitis, BE or esophageal adenocarcinoma.

The significance of BE lies in its being *precancerous*. The risk of developing esophageal adenocarcinoma is increased by 30 to 125 times in patients with BE. In fact, esophageal adenocarcinoma is the most common esophageal cancer in USA and Europe with incidence trebling in last 30 years. The annualised risk of cancer is estimated at 0.5%[6]. The mean interval from developing BE to evolution to adenocarcinoma may be 20 to 30 years[7].

DIAGNOSIS - SURVEILLANCE STRATEGIES

The diagnosis of BE involves endoscopic evaluation, taking note of esophagogastric junction, squamocolumnar junction or Z line, presence of hiatus hernia, presence and grading of esophagitis, presence of ulcer, stricture, nodularity or mass lesion. Efforts should be made to first aggressively treat reflux esophagitis before evaluating for BE. NBI, chromoendoscopy or magnification endoscopy can be used for better assessment. Four quadrant biopsies every 1 to 2cm should be taken and evaluated by the expert GI pathologist. This can be combined with brush cytology and flow cytometry to increase the pick up rate of malignancy. Various markers used for diagnosing dysplasia are p53, 17p, cyclin D1 & DNA content abnormalities. Immunostaining with p53 and AMACR have shown promise as marker for dysplasia. In cases

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with evidence of dysplasia, evaluation by another pathologist and a repeat endoscopic biopsy should be done. The *surveillance guidelines* given by American College of Gastroenterology (2008)8 are as follows

Table: *Dysplasia Grade and Surveillance interval*

Dysplasia	Documentation	Following
None	Two EGDS with biopsies within 1 year	Endoscopy every 3 yrs
Low Grade	* High grade on repeat EGD with biopsies within 6 months * Expert pathologist confirmation	1year interval No dysplasia x 2
High Grade	* Mucosal irregularity * Repeat EGD with biopsies to rule out EAC within 3 months * Expert pathologist confirmation	ER continued 3 months surveillance or interventions based on results and patient

*EGD – Esophagogastrodudenoscopy; ER – endoscopic resection; EAC – esophageal adenocarcinoma

TREATMENT OF BARRETT'S ESOPHAGUS

As discussed earlier, Barrett's esophagus is a premalignant condition leading to development of esophageal adenocarcinoma. In order to prevent or reduce the risk of development of EAC, it is important to remove this metaplastic mucosa. Since the risk of progression to EAC is highest with high grade dysplasia, maximum efforts have been directed against eradication of HGD. As per AGA guidelines, patients of BE negative, indefinite or having low grade dysplasia should be kept under regular endoscopic surveillance with biopsies. Patients with high grade dysplasia and those with visible mucosal abnormalities like nodules, ulcer or stricture should be offered definitive therapy. Earlier, surgery in the form of esophagectomy was the mainstay of therapy. Reason for this surgical approach has been the presence of cancer in approximately 40% of resected specimens in patients with HGD. But esophagectomy even in well equiped centres carries high morbidity (20 to 50%) and mortality (2 to 5%)[9]. With the advancement in both diagnostic and therapeutic endoscopic techniques, more and more centres are managing these patients, endoscopically especially who are poor surgical risk. The newer diagnostic techniques include NBI, high resolution endoscopy, chromoendoscopy and autofluorescence imaging. The **therapeutic endoscopic techniques**[10] include – **resection** (endoscopic mucosal resection) and ***ablation*** **-** photodynamic therapy (PDT), *argon plasma coagulation, laser* and recently reported *radiofrequency ablation and cryotherapy.*

Endoscopic Mucosal Resection (EMR)

EMR or mucosectomy removes lesions by resecting through the middle or deep layers of submucosa[11]. This technique does not destroy the tissue thereby helping the pathologist to correctly stage the lesion by examining the lateral and deep margins. Technique of EMR involves correct assessment of the lesion to be resected, marking the margins for inclusion during resection (usually 5 to 10mm away from the lesion) by using needle knife or snare, submucosal injection under the lesion to lift it (non lifting preludes resection) and reduce the risk of perforation by injecting normal saline or sodium hyaluronate and then resecting the tissue using polypectomy snare.

Techniques of EMR : **1. The strip biopsy technique**-it requires double channel endoscope and two assistants. It involves holding of lesion by forceps in the centre and resection by the polypectomy snare using electrocautery. **2. EMR- C:** In this technique, transparent caps of different shapes or sizes are fitted at the tip of a diagnostic or therapeutic endoscope and are preloaded with snare. After marking of the lesion and submucosal injection of saline, the lesion is sucked in the cap and resected with snare using cautery. **3. EMR- L:** This techniques uses standard variceal ligator device fitted at the tip. After marking the lesion, lesion is sucked in the hood, rubber band applied as in variceal banding and then the ligated mucosa is resected using polypectomy snare. **4. EMR using needle knife:** With this technique, larger and circumferential lesions can also be treated. It involves marking of the resection margins, submucosal injection just outside the margin, small incision using conventional needle knife followed by completion of incision of margins with insulated tip needle knife followed by submucosal injection of saline or sodium hyaluronate in the lesion and removal using polypectomy snare. EMR is a safe technique usually done on outpatient basis. Patients are routinely started on proton pump inhibitors before EMR and for several weeks thereafter. The most common immediate post procedure complication is bleeding which can be managed using epinephrine injection, electrocoagulation or APC. Perforation is rare and if small can be closed with clipping.

EMR USE in Barrett's Esophagus

This involves excision of the affected mucosa having high grade dysplasia or early neoplasia using snare. The resected samples provide correct histopathological assessment of the lesion by identifying involvement of the lateral and basal margins. As compared to endoscopic ultrasound which may under or overstage the lesion, EMR provides more accurate assessment of the lesion in terms of depth of invasion. In a study by Nijhawan and Wang[12] on role of diagnostic EMR in patients of BE with endoscopic appearance of HGD or EAC, EMR diagnosed superficial EAC in 52% and HGD in 16%. There was upgrading of lesions in 8 cases and downstaging in 3 cases. Similarly,Lightdale et al[13] reported upstaging of disease in 58.5% of patients. These results highlight the importance of correct staging of lesions. Endotherapy in a patient with missed submucosal invasion will give poor outcome. EMR as treatment modality is recommended for patients with HGD or mucosal adenocarcinoma. The resected lateral and basal margins should be free of disease. In cases with positive margins, further EMR or additional ablative therapy or surgery should be considered. In a study by Ell et al[14], 100 patients with low risk EAC were evaluated for the efficacy of EMR as therapeutic modality. Complete remission was achieved in 99% of patients after 1.9 months (range, 1-18months) and maximum of three sessions. During follow up period of 36.7 months , 11% patients developed recurrent or metachronous cancer, all of whom were successfully treated with endoscopic resection. The calculated 5-year survival rate was 98%. In a study by Peters et al[15], role of stepwise radical excision of Barrett's esophagus with HGD and early neoplasia was studied. In 37 patients, EMR was done using cap technique every six weeks. Complete eradication of neoplasia was achieved in all cases and complete removal of BE was achieved in 89% of patients in a median number of 3 sessions.

Symptomatic stenosis occurred in 26% of patients requiring dilatation. This circumferential EMR may provide complete removal of BE with more sustained response and less risk of recurrence of cancer.

EMR is relatively safe procedure with bleeding and perforation being two significant complications which can be managed nonsurgically. The main drawbacks of this technique are relatively small lesions which can be removed en block. Larger lesions require piecemeal resection. There is up to 20% risk of recurrent cancer during follow-up[16].

Photodynamic Therapy

Photodynamic Therapy (PDT) is an ablative treatment for rapidly proliferating tissues, including dysplastic and malignant lesions. It employs administration of a photosensitizing agent followed by application of specific wavelength of light, leading to intracellular photo excitation and injury[17]. Cellular localisation and depth of injury are dependent upon the sensitizing agent, the interval between dosing and light stimulation, and the light dosimetry and wavelength. The two most commonly used photosensitizing agents for PDT are-porfimer sodium and 5-aminolevulinic acid (5-ALA). Porfimer sodium is the only drug approved for systemic use in USA. It is given in a dose of 2 mg/kg as infusion over 3 to 5 minutes. It is *contraindicated* in patients taking other photosensitizing agents, including fluoroquinolones, griseofulvin, sulfonylurea, tetracyclines and thiazides. The light application by laser at wavelength of 630 is given after 48 hours of administration. The depth of penetration is usually between 4 and 6 mm. 5-ALA is a prodrug. It is given orally in a dose of 40mg/kg mixed with fruit juice. It has shorter half life and levels peak in 4 to 6 hours. The PDT is performed after 4 to 5 hours. *Side effects* include transient raised liver enzymes in 50% of patients. The depth of penetration is 2 mm. The light is delivered using wire guided PDT balloon under endoscopic guidance.

Results in BE: PDT has been the most extensively studied ablative technique in BE. As compared to EMR, this can be used to treat larger areas. In a recently published study, Overholt et al18, report five year follow up on the efficacy and safety of Photofrin PDT in Barrett's high grade dysplasia. A total of 208 patients were included. Of these, 138 were given PDT along with omeprazole and 70 patients were given only omeprazole. At 5 years, PDT was significantly more effective than omeprazole in eliminating HGD (77% vs, 39%). Also, likelihood of progression to cancer was less in PDT group (15% vs 29%). In another prospective study by Peters et al[16], role of combined EMR and PDT was assessed in 33 patients with Barrett's esophagus and early neoplastic lesions less than 2cm, endoscopic treatment was successful in 93% of the cases. Five patients had recurrence of HGD which was successfully treated with EMR. The most important complication of PDT is esophageal strictures, developing in 20 to 36% of treated patients.

Argon Plasma Coagulation (APC)

This technique causes non contact thermal coagulation of tissues using a high frequency monopolar current, which is conducted to tissues via an ionized argon gas. The depth of penetration is less than that of laser or PDT. In a study by Pereira- Lima JC[19], 33 patients with Barrett's esophagus (14 cases with low grade dysplasia and one case of HGD) were treated with APC. All had restoration of squamous mucosa. In another study by Attwood et al, ablation with APC in 29 patients with HGD showed complete response in 86%20.

Multipolar Electrocoagulation (HPEC)

Here the thermocoagulation of tissues is achieved using electrocoagulation probes. This technique is cheap, widely available and easy to use. It is safe with significant complications in less than 5%. Small case series have shown nearly complete ablation in the majority of treated patients. In a prospective randomized trial comparing APC with MPEC combined with pantaprazole, MPEC achieved 88% endoscopic ablation vs. 82% for APC group[21]. Histologically neosquamous epithelisation was observed in 81% in MPEC group and 65% in APC group. The drawback of these techniques is presence of specialised intestinal metaplasia beneath neosquamous epithelium.

Laser therapy

Laser therapy has been used in many small series for patients with BE. The commonly used laser types are- Argon, Nd: YAG and KTP. The depth of penetration and tissue ablation depends on the laser characteristics and as well as optical properties of the tissue. Complications are similar to APC but stricture formation is higher. Sharma et al[22] reported good results in 6 patients with mucosal EAC treated with laser and MPEC.

Radiofrequency Energy Ablation (RFA)

A recent study by Sharma et al[23], evaluated the role of RFA in the ablation of Barrett's esophagus. Seventy patients were enrolled. At 12 months, 70% of patients showed complete response and there were no strictures or buried metaplastic epithelium.

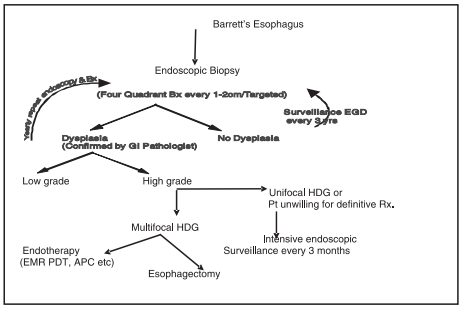
Cryotherapy

Greewald et al24 reported their preliminary results on safety and efficacy of endoscopic cryotherapy ablation in patients of BE with HGD and early EGC. Out of 21 patients, only 7 completed the treatment. But the results were encouraging.

Residual BE has been described with all the ablative techniques. It is less common with RFA and PDT. The malignant potential of this buried or residual BE is not known but probably is low.

Of all the endoscopic techniques for management of BE, EMR with or without additional ablative procedure like PDT appear to be the best studied and most effective procedures.

MANAGEMENT PROTOCOL FOR BE (FIG.)



Management protocol for BE

The decision to treat or not to treat BE and the best treatment option depends on following factors

1. **Patient factors**- age, presence of comorbid conditions, length of BE, degree of dysplasia (low grade, high grade, unifocal or multifocal, early mucosal cancer), presence of hiatus hernia and patient's preference
2. **Treating team**- experienced endoscopists (specialist in advance diagnostic and therapeutic endoscopy), GI pathologists, surgical experts
3. **Equipment** – high quality endoscopes for imaging and treating the lesions, instruments and accessories for resection and ablative procedures

All patients with BE should have *enhanced endoscopic imaging* with emphasis on accurate assessment of length and circumferential involvement, presence of mucosal lesions followed by four quadrant biopsies every 1 to 2cm. The biopsies should be reported by expert GI pathologist.

a) LGD – should be kept under surveillance as per AGA guidelines. Those wishing for intervention can be included for trials on ablative techniques or chemoprevention.
b) HGD or early cancer- should undergo EMR. If histology shows no or low grade dysplasia, patient to be kept under endoscopic surveillance. In case of HGD or early cancer but negative lateral and basal margins, continue close surveillance. In case of larger lesions or positive lateral but negative basal margins, continue EMR or add ablative procedure.
c) EMR shows invasive cancer- surgery is the treatment of choice.

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ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory *clinical trails* on new drugs, a number of *diagnostic procedures, therapeutic interventions and prevention measures* including the use of vaccines, are being introduced which involve human subjects. Further the advent of *new medical devices* and *radio-active materials* and therapeutic benefits of *recombinant DNA products* have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in mind the following **principles** of : i) **essentiallity**, (ii) **voluntariness, informed consent**, (iii) **non exploitation**, (iv) **privacy** and **confidentially**, (v) **precaution** and **risk minimisation**, (vi) **professional competence**, (vii) **accountability & transparency**, (viii) **maximisation of public interest** and **distributive justice** (ix) **institutional arrangements** (x) **public domain** (xi) totality of **responsibility** and (xii) **compliance**.

Recent advances in the field of **Assisted Reproductive technologies, organ transplantation, Human genome analysis**,and **gene therapy** promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)

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