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MINIREVIEWS

Endoscopic therapy for Barrett's esophagus and early esophageal cancer: Where do we go from here?

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Abstract

Since Barrett's esophagus is a precancerous condition, efforts have been made for its eradication by various ablative techniques. Initially, laser ablation was attempted in non-dysplastic Barrett's esophagus and subsequently, endoscopic ablation using photodynamic therapy was used in Barrett's patients with high-grade dysplasia who were poor surgical candidates. Since then, various ablative therapies have been developed with radiofrequency ablation having the best quality of evidence. Resection of dysplastic areas only without complete removal of entire Barrett's segment is associated with high risk of developing metachronous neoplasia. Hence, the current standard of management for Barrett's esophagus includes endoscopic mucosal resection of visible abnormalities followed by ablation to eradicate remaining Barrett's epithelium. Although endoscopic therapy cannot address regional lymph node metastases, such nodal involvement is present in only 1% to 2% of patients with intramucosal adenocarcinoma in Barrett esophagus and therefore is useful in intramucosal cancers. Post ablation surveillance is recommended as recurrence of intestinal metaplasia and dysplasia have been reported. This review includes a discussion of the technique, efficacy and complication rate of currently available ablation techniques such as radiofrequency ablation, cryotherapy, argon plasma coagulation and photodynamic therapy as well as endoscopic mucosal resection. A brief discussion of the emerging technique, endoscopic submucosal dissection is also included.

Key words: Endoscopic mucosal resection; Barrett's esophagus; Dysplasia; Adenocarcinoma; Endoscopic therapy; Radiofrequency ablation

Core tip: Endoscopic treatment has become the standard

of care for Barrett's esophagus with dysplasia and/or early adenocarcinoma. The treatment primarily consists of resection of any visible lesions by either endoscopic mucosal resection or rarely, endoscopic submucosal dissection followed by ablation of metaplastic epithelium by one of the many available techniques (radiofrequency ablation being the most commonly used). While periodic surveillance is still required after complete eradication of intestinal metaplasia, these treatment modalities have proven to decrease the incidence of esophageal adenocarcinoma, improve the quality of life and are cost effective.

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INTRODUCTION

Barrett's esophagus (BE), defined as an extension of salmon colored mucosa into the esophagus for a distance ⩾ 1 cm above the gastroesophageal junction with biopsies confirming intestinal metaplasia (IM)[1], increases the risk of progression to esophageal adenocarcinoma (EAC). In non-dysplastic BE (NDBE), the risk of development of EAC is 0.3% annually[2] which increases to 0.5% in BE with low grade dysplasia (LGD)[3] and 7% with high grade dysplasia (HGD)[4]. While BE with HGD or intramucosal cancer (IMC) were traditionally treated by esophagectomy, the pendulum has swung from surgical to endoscopic management over the last 2 decades owing to the lower morbidity, lower cost and similar long term survival rates with endoscopic treatment compared to esophagectomy[5-9].

Endoscopic resection of visible lesions if any, followed by ablation of the rest of the BE epithelium is the current standard of care for management of BE with confirmed dysplasia and IMC[1,10,11]. Since there is a small risk of recurrence (7.1% per patient year for IM, 1.3% for LGD and 0.8% for HGD/EAC)[12], periodic surveillance is recommended after complete eradication of BE. Amongst the ablation modalities, photodynamic therapy (PDT) was one of the first techniques used for ablation and over time, various other techniques like argon plasma coagulation (APC), cryotherapy and radiofrequency ablation (RFA) have been developed with RFA being the most widely used modality currently. (Table 1)The underlying principle behind the ablation therapies is that under conditions of maximal acid suppression, injury to BE mucosa leads to regeneration of normal squamous mucosa.

The focus of this review is to examine the evidence for efficacy of various ablation modalities and the resection techniques used for eradication of BE such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).

Literature search was conducted by an experienced librarian using Ovid Medline and PubMed from 1990 to present using the search terms "Barrett's", "esophageal adenocarcinoma", "endoscopic treatment", "ablation", "radiofrequency ablation", "cryotherapy", argon plasma coagulation", "photodynamic therapy", "multipolar electrocoagulation", "endoscopic mucosal resection", "endoscopic submucosal dissection". Only articles in English language were reviewed.

RADIOFREQUENCY ABLATION

RFA is currently the most widely used technique to treat BE with dysplasia due to its ability to deliver uniform ablation to a consistent depth of the esophageal wall.

Technique

RFA causes tissue necrosis by using direct contact current to generate thermal injury. Circumferential BE longer than 3 cm is ablated by circumferential technique and non-circumferential segments or segments < 3 cm are ablated by focal technique[13]. Currently available catheters for RFA are Barrx 360 Express catheter for circumferential ablation and Barrx 90, Barrx 90 Ultra, Barrx 60 or through-the-scope (TTS) for focal ablation.

Circumferential ablation

Barrx 360 Express catheter consists of a 4 cm long bipolar electrode situated at the end of 85 cm shaft. After washing the esophagus with water or N-acetylcysteine, a guidewire is passed through the biopsy channel and the endoscope is removed. The catheter is then passed over the guidewire. The catheter, which has external markings is placed 1 cm above the proximal extent of BE under endoscopic visualization. When the pedal is pressed, the balloon inflates and self-adjusts depending on the esophageal diameter and radiofrequency energy is delivered resulting in circumferential ablation. The catheter is then advanced distally and ablation performed in a sequential manner. After the ablation is completed, the coagulum is scrapped off using a cap attached to the tip of the endoscope and the steps are repeated. Endoscopy is repeated in 8-12 wk to ablate any residual areas (with circumferential or focal method depending on residual segment).

Focal ablation

Depending on the surface area that needs to be ablated, focal catheters are selected; for example, Barrx 60 ablates 150 mm^2, Barrx 90 ablates 260 mm^2 and 90 ultra ablates 520 mm^2. The catheter is externally attached to the tip of the endoscope in the 12 O' clock position and advanced to the target area. After the tip of the endoscope is deflected to get the catheter in contact with the mucosa, radiofrequency energy is applied twice. After scraping the coagulum off, the procedure is repeated. TTS catheter can be passed through the

Table 1 Comparing the efficacy and complication rate of various endoscopic techniques

Technique	Efficacy	Complication rate
Radiofrequency ablation	CE-D: 92%-98%[15,16]	Strictures: 5%-6%[26]
	CE-IM: 88%-91%[15,16]	Chest pain: 3.8% Bleeding: 1%
Cryotherapy	CE-D: 95%[30,33] CE-IM: 88%[30,33]	Strictures: 3%-13%[33,34] Bleeding: 2%
Argon plasma coagulation	CE-IM: 58%-78%[38,40]	Stricture: 4%[40,47]
		Bleeding: 4% Perforation: 2%
Photodynamic therapy	CE-D: 80%[50,51]	Photosensitivity: 69%[57]
	CE-IM: 43%-53%[50,51]	Stricture: 36%[58]

CE-D: Complete eradication of dysplasia; CE-IM: Complete eradication of intestinal metaplasia.

biopsy channel of the scope.

Efficacy

In a landmark study conducted by Shaheen *et al*[14], 127 patients were randomized to RFA (42 each with HGD and LGD) or sham procedure (21 with HGD and 22 with LGD). The primary outcomes measured were complete eradication of dysplasia (CE-D) and eradication of intestinal metaplasia (CE-IM). After 12 mo, among patients with LGD, CE-D was seen in 90.5% patients with RFA compared to 22.7% in the sham group ($P < 0.001$). Similarly, CE-D was noted in 81% patients with HGD after RFA compared to 19% in control group ($P < 0.001$). CE-IM was seen in 77.4% in the RFA group compared to 2.3% in sham group ($P < 0.001$). Progression of dysplasia was seen more frequently in the control group (16.3% *vs* 3.6%, $P = 0.03$). During follow up of this cohort reported separately, patients in the sham group who had persistence of IM were allowed to cross over to the RFA group. After 3 years, CE-D and CE- IM was noted in 98% and 91% patients respectively[15].

To assess the utility of ablation in patients with LGD, Phoa *et al*[16] performed a randomized clinical trial comparing RFA to endoscopic surveillance in BE with LGD patients and looked at the primary outcome of progression to HGD or EAC over a follow up period of 3 years. One hundred and forty patients were randomized in a 1:1 ratio to receive RFA or endoscopic surveillance (at 6 mo, 12 mo and then annually after randomization). In the ablation group, patients were less likely to progress to HGD/EAC compared to surveillance group (1.5% *vs* 26.5% respectively, $P < 0.001$) or to EAC (1.5% *vs* 8.8% respectively, $P = 0.03$). CE-D and CE-IM was noted in 92.6% and 88.2% patients respectively. Of these patients, CE-D and CE-IM was maintained in 98.4% and 90% of patients respectively over the follow up period. Similar results supporting the use of RFA to treat LGD have been reported by Small *et al*[17] and by Qumseya *et al*[18] in a recent meta-analysis.

Recurrence

Recurrence of IM or dysplasia can occur after CE-IM. Hence, ongoing surveillance is mandatory. In the United States RFA registry, recurrence of BE has been noted in 20% patients over a follow up of 2.4 years and dysplasia was reported among 14% of those who had BE recurrence[19]. Recurrence was higher with older age, longer length of BE segment and in non-Caucasians.

In a recent meta-analysis of patients who achieved CE-IM after RFA, IM recurrence rate was 5.8 per100 patient years. The majority of recurrences were amenable to repeat endoscopic eradication therapy (EET)[20]. Neither BE nor dysplasia recurs at a constant rate. Of 119 patients in the AIM Dysplasia trial, IM recurrence rate was 10.8 per 100 person-years and dysplasia recurrence rate was 5.2 per 100 person-years[21]. There was a greater probability of recurrence in the first year following CEIM than in the following 4 years combined.

Cost-effectiveness

Among patients with HGD, RFA is more cost effective compared to surveillance followed by esophagectomy when EAC is detected[22] or proceeding straight to esophagectomy[23]. In LGD patients, RFA might be cost effective but it comes at a cost of $40915 per prevented event of progression[24]. After RFA, patients have reported significant improvement in quality of life, less stress about esophageal cancer or esophagectomy[25].

Complications

RFA is a safe procedure due to the limited depth of ablation. The most common complication after RFA is stricture formation which occurs in 5%-6% patients[26]. The other complications include post-procedure chest pain (3.8%), bleeding (1%) and perforation (0.6%).

CRYOTHERAPY

Cryotherapy involves the principle of rapid freezing and slow thawing of the tissue in multiple cycles leading to immediate cellular injury. Delayed effects include loss of microcirculation leading to anoxia and stimulation of cytotoxic T cells[27]. The cryogens which have been utilized in BE ablation are liquid Nitrogen (TrueFreeze Cryospray, CSA Medical, Lexington, Massachussets), Nitrous oxide (Coldplay CryoBalloon Focal Ablation System, C2 Therapeutics, Redwood City, California) and liquid carbon dioxide (Polar wand, GI Supply, Camp Hill, Pa). The Polar Wand system production ceased in March 2016 and will not discussed further in this review.

CRYOSPRAY WITH LIQUID NITROGEN

Technique

Liquid nitrogen is delivered through Cryospray catheter

that is passed through the biopsy channel of the endoscope. The liquid nitrogen rapidly expands into gas and freezes tissues to -196 degree Celsius. A decompression tube passed along the endoscope allows for venting during the session. The noncontact delivery allows ablation of uneven surfaces such as nodules, masses and plaques. The site is frozen for 20 s each for a total of 2 cycles, allowing for cooling for at least 45 s between the cycles.

Efficacy

Johnston *et al*[28] first reported the use of cryotherapy to treat BE in 11 patients with dysplasia degree varying from NDBE to HGD of which 9 patients completed the treatment. Out of these 9 patients, 7 (78%) had CE-IM. In 98 patients with BE and HGD (14 had previously undergone other ablation treatments), after a follow up of 10.5 mo, remission of HGD was seen in 97%, CE-D was seen in 87% and 57% had CE-IM (only 60 patients had completed all cryotherapy treatments at the time of reporting of results)[29]. The eradication response appears to be durable for up to 5 years. Over a follow up period of 5 years in 40 patients with HGD or EAC, complete remission of HGD, CE-D and CE-IM was seen in 93%, 88% and 75% of patients respectively[30]. Incidence of recurrent HGD/EAC was 1.4% per person years. Compared to RFA, patients undergoing cryotherapy are less likely to have CE-IM but efficacy of both techniques to eradicate dysplasia is similar[31]. Cryotherapy can also be used in BE refractory to RFA. In a recently published meta-analysis comprising 148 BE patients treated with cryotherapy for persistent dysplasia or IM after RFA, CE-D was 76.0% and CE-IM was 45.9%[32].

CRYOBALLOON FOCAL ABLATION SYSTEM

Technique

The balloon catheter is passed through the working channel of therapeutic endoscope and attached to a handle that contains cartridge with liquid nitrous oxide. On pressing the trigger, the balloon is inflated and the cryogen is delivered to the ablation site for 10 s cooling the tissue to -85 degree C.

Efficacy

In 41 patients with LGD (n = 13), HGD (n = 23) or IMC (n = 5), 1-year CE-D and CE-IM rates were 95% and 88%, respectively. CE-D rate was significantly lower (67%) in those with ultra-long BE compared with those with < 8 cm (100%, P = 0.02)[33].

Complications of Cryotherapy

Minor adverse events reported with Cryospray include chest pain, esophagitis, sore throat, lip ulcer, esophageal ulcers, and dysphagia[34]. Strictures have been reported in 3% to 13% of treated patients. With cryoballoon, 9.7% patients developed strictures and 2% had minor bleeding[33].

ARGON PLASMA COAGULATION

Technique

In APC, ionized argon gas is used to ablate BE. After placing a grounding pad on the patient, the machine containing the argon gas and coagulator is turned on and ablation is performed using an APC probe set to a flow rate of 1.6 liter/minute and power setting of 40-90 W. A recent advance is hybrid APC where a submucosal cushion is created before performing APC.

Efficacy

In 1998, Van Laethem *et al*[35] described their experience with use of APC. They included 31 patients with BE (26 had NDBE and 5 had LGD). After a mean of 2.4 treatments, 19/31 patients had CE-IM. On one year follow up, 9/31 patients had no histological evidence of recurrence of BE. Among the 9 patients with BE treated by Grade *et al*[36], endoscopically, squamous re-epithelialization was seen in all 9 patients but histologically, 2 of these patients had evidence of IM. Similar results were also reported by Byrne *et al*[37] in Europe. A randomized controlled trial comparing APC to periodic surveillance in 40 patients with NDBE or BE with LGD[38] reported CE-IM in 58% with APC compared to 15% in surveillance group; (P < 0.001). Use of APC for treatment of BE with HGD was reported by Attwood *et al*[39] in 2003 in 29 patients. These patients were followed up for a mean of 37 mo. HGD was successfully treated in 25 patients and 22 of these patients had CE-IM. Of the other 3 patients, HGD resolved after multiple treatments and in 1 patient, LGD persisted. A multicenter study by Manner *et al*[40] on 60 patients with NDBE reported CE-IM in 77% with APC. Recurrence rate of 18% was reported in 3 year follow up[41]. The majority of data published on APC has been on NDBE and the utility of treating BE in the absence of dysplasia and exposing patients to side effects has been repeatedly questioned[42-44] and thus this strategy fell out of favor.

Recently, use of APC following submucosal injection (Hybrid APC) to treat residual BE after endoscopic resection of early EAC was described by Manner *et al*[45] in a series of 60 patients. CE-IM was observed in 78% patients. Injection of normal saline in the submucosa limited the depth of thermal ablation and resulted in stricture formation in only 1 patient.

Compared to RFA which requires around 30 procedures to effectively treat the lesions, the learning curve of APC is shorter.

Complications

Self-limiting odynophagia or dysphagia is commonly reported after APC[46]. In their multi-center study, Manner *et al*[40] reported bleeding in 3.9%, stenosis in

3.9% and perforation in 2% of the patients.

PHOTODYNAMIC THERAPY

Technique

PDT relies on the principle that once a photosensitizer is administered and activated by light, superoxide and hydroxyl free radicals are formed that cause apoptosis of the cells. The metaplastic and neoplastic cells[47] have more affinity for photosensitizer leading to preferential damage of the BE epithelium with preservation of normal squamous mucosa. In the United States, an intravenously administered photosensitizer, porfimer sodium (Photofrin, Wyeth-Ayerst Lederle Parenterals, Carolina, PR) and in Europe, an orally administered agent 5-aminolevulinic acid (Levulan, DUSA Pharmaceuticals, Wilmington) or intravenously administered m-tetrahydroxyphenyl chlorin (Foscan, Biolitech, Pharma Ltd, Dublin, Ireland) are used. Porfimer sodium is administered at a dose of 2 mg/kg intravenously. Approximately 48 h later, upper endoscopy is performed and red light is transmitted either by optical fiber or balloon diffusing fibers that are passed through the endoscope. Porfimer sodium is activated by red light (wavelength of 630 nm) at energy of 130-200 J/cm. Endoscopy may be repeated 2-3 d later to assess the mucosal damage and re-treat if needed.

Efficacy

After the successful use of PDT in 2 patients with early EAC was described by Overholt *et al*[48] in 1993, its use in 4 patients with BE and LGD and 1 patient with BE and HGD was reported by Laukka *et al*[49] in 1995. In a large series of 100 patients (14 with LGD, 73 with HGD and 13 with EAC) treated with PDT[50], CE-IM and CE-D was observed in 43 and 79 patients respectively. In a multicenter randomized trial of 208 patients with BE and HGD with follow up of 24 mo, 52% patients in the PDT group had CE-IM compared to 7% in the omeprazole only group ($P < 0.001$). Thirteen percent of patients in PDT group developed EAC during follow up compared to 28% in omeprazole group ($P = 0.006$). Five year follow up data[51] reported that probability of maintaining complete remission was higher in the PDT group compared to omeprazole only group (48% *vs* 4%, $P < 0.0001$) and progression to cancer continued to remain low in the PDT group (15%) when compared to omeprazole group (29%) ($P = 0.027$). In a Markov Monte Carlo Model, Hur *et al*[52] proved that PDT was more effective than just periodic surveillance of HGD and esophagectomy with an incremental cost effective ratio of $12400/quality adjusted life year (QALY) and $3,300/QALY compared to surveillance and esophagectomy respectively. Similar results were also reported later by Shaheen *et al*[53].

The length of BE segment predicts the likelihood of complete ablation of BE with PDT[54]. Patients with BE $\geqslant$ 3 cm are less likely to have CE-IM compared to those with BE < 3 cm. After eradication, smoking, older age and presence of residual non dysplastic BE are associated with higher likelihood of recurrence[55].

Complications

Photosensitivity is the commonest side effect being reported in up to 69% patients after PDT treatment using porfimer sodium[56] because of absorption of porfimer sodium by the skin from the systemic circulation which is then activated by light. The reaction is mild in majority of the cases and occurs in sun-exposed areas. After PDT, patients are advised to apply sunscreen, fully cover the exposed body parts when going in sunlight for 4-6 wk. Esophageal stricture is another side effect occurring in around 36% patients[56]. The other side effects include vomiting, dyspepsia and chest pain. Treatment with 5-aminolevulinic acid is associated with lower incidence of photosensitivity reactions and stricture formation[57] but it is not commonly used in the United States.

ENDOSCOPIC RESECTION TECHNIQUES

In patients who have nodular BE with dysplasia/EAC limited to the mucosa or visible lesions with HGD/EAC, resection of the lesions is done by EMR followed by ablation of the rest of the Barrett's mucosa by RFA because there can be 30% risk of metachronous lesions in the rest of the mucosa. Endoscopic resection is largely limited to cancers confined to the mucosa because of extremely low risk of lymph node metastasis in these lesions.

ENDOSCOPIC MUCOSAL RESECTION

EMR is performed either by Lift-suck-cut technique or by Ligate and cut technique. The ligate and cut technique is the more commonly used due to shorter procedure time and less cost while having a similar side effect profile[58].

Ligate and cut technique

Once the lesion is identified, the margins of the lesions are marked using APC. A modified variceal band ligator is then mounted on the endoscope with the handle attached to the proximal end of the working channel. The rubber cap that is attached to the tip of the endoscope has 6 bands and is connected to the handle by a tripwire. After the scope is introduced into the esophagus, the lesion is sucked into the cap and a rubber band is released using the handle after which the lesion is resected using a snare.

Lift-suck-cut technique

After a clear EMR cap is fitted on the tip of the endoscope, the endoscope is advanced to the lesion and the submucosa is lifted by injection of normal saline.

The snare is then passed and positioned in the groove on the distal end of the cap. After a pseudopolyp is created by suctioning the lesion into the cap, the snare is positioned across the base and cautery is applied to resect the lesion.

Efficacy

Ell *et al*[59] were among the first to describe the use of EMR to treat EAC/HGD in a series of 64 patients (61 with EAC and 3 with HGD). The patients were divided into low and high risk groups based on tumor size, macroscopic appearance of lesion, grade on histology, evidence of submucosal invasion. In the low risk group, 34/35 patients showed complete remission at 12 mo follow up. During that follow up period, 6 patients had developed recurrence (4 had local recurrence and 2 had metachronous lesions) that was treated endoscopically. Of note, these patients had EMR of the lesions only without any treatment of the surrounding BE.

To resect the visible lesions by EMR and then to treat the rest of the Barrett's segment to prevent metachronous cancer, Buttar *et al*[60] described the technique of combining EMR with PDT in a series of 17 patients in 2001. PDT was done 4 wk after EMR. Sixteen out of 17 patients remained in remission after a median follow up period of 13 mo and BE was successfully eradicated in 53% patients. In an effort to completely eradicate the lesions and surrounding BE, the concept of using endoscopic resection of entire BE segment over multiple sessions to remove all metaplastic tissue called as stepwise radical endoscopic resection (SRER) has evolved. Various studies reported excellent outcomes with CE-IM rates varying from 86% to 96%[61-63].

Once the use of RFA to treat dysplastic BE started becoming more popular, Gondrie *et al*[64] reported good efficacy with combined use of EMR and RFA in a small series of 12 patients. A multi-center randomized trial compared EMR followed by RFA to EMR for eradication of the entire BE segment[65]. Twenty two patients were randomized to the focal EMR plus RFA and 25 patients to SRER groups respectively. With SRER, complete remission of neoplasia was achieved in 100% of patients and CE-IM in 92% patients. In focal EMR+ RFA group, complete remission of neoplasia as well as CE-IM was achieved in 96% patients. A lower complication rate was noted with focal EMR+RFA technique making this technique the preferred one for treating BE with visible lesions. The United States multicenter consortium reported follow up results of 592 patients (71% had HGD or EAC and 55% had undergone EMR). After 24 mo, CE-IM was seen in 56% patients[66] and recurrence of neoplasia was only seen in 1 patient. In a series of 1000 patients treated by EMR for EAC and different ablative techniques for the rest of BE, Pech *et al*[67] reported that complete remission was initially achieved in 96.3% patients. While 14.5% patients had recurrence, it was endoscopically treated in 115/140 patients resulting in long-term complete remission rates of 93.8%. In 2016, Baret *et al*[68] did report successful outcomes with EMR followed by RFA in a single session in patients with short segment BE but again, this method is not widely practiced yet.

While the use of EMR to treat EAC confined to the mucosa has been extensively studied as described above, its utility in treating EAC confined to submucosa has also been studied. In 2008, Manner *et al*[69] described their experience about 21 well differentiated EAC patients who had submucosal invasion confined to upper 1/3rd of submucosa without any lymph/vessel invasion. One of these patients had surgery before EMR and one died before completion of EMR. Of the remaining 19 patients, after a mean of 2.8 sessions of EMR, complete remission after EMR was achieved in 18 patients. Over a 5 year follow up period, recurrent neoplasia was seen in 3 patients and metachronous neoplasia in 2 patients. These lesions were successfully treated by EMR (4 patients) and APC (1 patient).

Complications

Tomizawa *et al*[70] reported on the safety outcomes of 684 patients who underwent EMR for BE (majority of whom had HGD/EAC). Bleeding and strictures were reported in 1.2% and 1% patients respectively. With stepwise radical EMR, the incidence of stricture formation was much higher varying between 27%and 37%[61,71] depending on the size of lesion. Perforation has been reported to occur infrequently varying from 0.2% to 1.3%[72].

ENDOSCOPIC SUBMUCOSAL DISSECTION

ESD is a technique originally developed in Japan for removal of early gastric neoplasms and subsequently extended to resection of early neoplastic lesions in other parts of gastrointestinal system. It is generally difficult to resect lesions greater than 2 cm en-bloc using EMR technique. The advantage of ESD over EMR is the ability to resect lesions *en bloc* irrespective of size. ESD can be considered in cases wherein the lesion is larger than 15 mm, when there is poor lifting, or with endoscopic features imply possible submucosal invasion[73].

Technique

Circumferential coagulation markers are placed around the lesion. Solution is then injected into the submucosal space to lift the lesion. Using an electrosurgical knife, a circumferential incision is made around the lesion after which the submucosa is carefully dissected and the lesion is removed en-bloc.

Efficacy

The use of ESD for visible lesions combined with RFA for the rest of the BE segment was described by Neuhaus *et al*[74] in 2012 on 30 patients (EAC in 24 and HGD in 6). ESD was successful in removing the lesions in

29 patients. Of the 28 patients that were followed up, remission from neoplasia was seen and in 1 patient who had residual cancer, EMR was successful in removing the cancer. 15 patients had complete remission of intestinal metaplasia by ESD alone. Of the other 13, 10 had RFA done of which 8 had complete remission of metaplasia. In a recently published meta-analysis of ESD in early BE neoplasia , complete and curative resection rates were 74.5% and 64.9% respectively[75]. Incidence of recurrence after curative resection was 0.17% at a mean follow-up 22.9 mo.

Because ESD is time consuming, requires more training and expertise, along with higher complication rates and since good outcomes have also been achieved with EMR, the utility of ESD in small lesions has been questioned. Terheggen *et al*[76] randomized 40 patients with BE HGD and IMC to EMR or ESD. Disease free margins were achieved more frequently with ESD compared to EMR (10 of 17 *vs* 2 of 17; $P = 0.01$). However, there was no difference in complete remission from neoplasia at 3 mo (ESD 15 of 16 *vs* EMR 16 of 17; $P = 1.0$). During a mean follow-up period of 23 mo, recurrence of cancer was observed in 1 case in the ESD group. The study concluded that though there are theoretical advantages to ESD, it has little clinical relevance as additional treatment is performed for residual BE after EMR.

ESD has a much steeper learning curve compared to EMR.

Complications

In a meta-analysis, the pooled estimates for perforation and bleeding were 1.5% (95%CI: 0.4%-3.0%) and 1.7% (95%CI: 0.6%-3.4%), respectively. Esophageal stricture rate was 11.6% (95%CI: 0.9%-29.6%)[75]

WHERE DO WE GO FROM HERE?

Endoscopic eradication therapy has proven to be a highly effective and durable technique for the management of BE associated neoplasia with minimal morbidity. It is the standard of care in management of BE with HGD, confirmed and persistent LGD and IMC and can be considered in selected cases of submucosal cancer. In spite of high eradication rates, three concerns remain: resistance, progression and recurrence. Patients with persistent metaplasia or dysplasia after three sessions of ablation are considered to be resistant and can contribute up to 21% of patients presenting for EET[77]. In these patients esophageal acid exposure needs to be assessed and adequate control can be achieved by increasing acid suppressive regimen or fundoplication. Alternative eradication methods such as cryotherapy[32] or EMR can be tried. Secondly progression to worse grade of dysplasia occurs in 1.7%-3.6% of patients during EET[14,18]. Endoscopists need to be vigilant of this fact and counsel the patients accordingly. Recurrence of IM or dysplasia after CE - IM occurs at an annual rate of 4.8% and 2% respectively[20]. Hence, ongoing surveillance is strongly recommended in post ablation period.

The European society of gastrointestinal endoscopy recommends that BE expert centers should meet the following criteria: annual case load of $\geqslant$ 10 new patients undergoing endoscopic treatment for HGD or early carcinoma per BE expert endoscopist; endoscopic and histological care provided by endoscopists and pathologists who have followed additional training; at least 30 supervised endoscopic resection and 30 endoscopic ablation procedures to acquire competence in technical skills, management pathways, and complications[78].

Finally, one of the main areas of future research is identifying BE patients who are at high risk for progression and therefore may benefit from prophylactic EET. Accurate risk stratification models including clinical and endoscopic features and biomarkers need to be developed to identify these patients.

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