Endoscopic resection with ligation using a multi-band mucosectomy system in Barrett's esophagus with high-grade dysplasia and intramucosal carcinoma

Yasser M. Bhat, Emma E. Furth, Colleen M. Brensinger and Gregory G. Ginsberg

Abstract:

Background: Endoscopic therapy for early neoplasia in Barrett's esophagus (BE) is evolving. Endoscopic resection has an increasing role. We wanted to evaluate the safety and efficacy of multi-band ligation/resection [ER-L] without pre-injection in BE with high-grade dysplasia [HGD] and intramucosal carcinoma [IMCA].

Methods: A cohort of 65 consecutive patients from a single academic medical center, who underwent ER-L as part of endoscopic eradication therapy for BE with HGD/IMCA were studied. ER-L was performed after endoscopic mapping and endoscopic ultrasound (EUS). Subsequently, adjunctive ablative therapies including photodynamic therapy, argon plasma coagulation and radiofrequency ablation were applied to achieve complete eradication of all BE. Thereafter biopsy surveillance was performed per protocol. All patients were prescribed a proton-pump inhibitor. Main outcome measurements: Change in histopathological stage; eradication of BE and HGD/IMCA; adverse events.

Results: The median number of ER-L applications in each session was 4 (range 1–6) and the mean total number of ER-L sessions was 1.5. Compared with prior forceps biopsy, histopathology from the ER-L specimen changed in 24 (37.5%, $p = <0.0001$). With median follow-up of 15 months (range 8–42), complete and durable BE eradication was achieved with ER-L alone in 36 (60%) and the remainder with adjunctive ablation therapies. There were nine complications (four (6%) acute bleeding, five (7.5%) strictures, zero perforations).

Conclusions: ER-L without submucosal (SM) pre-injection is safe and effective when applied selectively for eradication of BE with HGD/IMCA. There is significant change in pathological stage after ER-L conferring a diagnostic and staging advantage. ER-L may be used adjunctively with ablation therapies.

Keywords: Barrett's esophagus, early esophageal cancer, endoscopic treatment of Barrett's esophagus

Introduction

A variety of endoscopic ablative therapies have been proposed for eradication of dysplastic Barrett's esophagus (BE) including contact and noncontact thermal coagulation [multipolar electrocautery, laser, argon plasma beam and radiofrequency ablation (RFA)], photodynamic therapy (PDT) and cryotherapy [Gossner *et al.* 1999; Overholt *et al.* 1999; Pasricha *et al.* 1999;

Tsai *et al.* 1999; Van Laethem *et al.* 1998; Sampliner *et al.* 1996]. However, ablative modalities are limited because they lack confirmation of completeness of eradication, crucial to determining treatment adequacy.

Endoscopic resection (ER), also called endoluminal resection or endoscopic mucosal resection, has also been proposed for eradication of

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dysplastic Barrett's alone or combined with ablative therapies [Ell *et al.* 2007, 2000; Buttar *et al.* 2001]. ER holds an advantage over ablative therapies because it provides a histopathological specimen and is particularly useful for the evaluation and management of nodular Barrett's [Larghi *et al.* 2005]. Compared to forceps biopsy tissue sampling alone, ER leads to a change in histopathology stage in up to 40% of instances [Ginsberg, 2003; Nijhawan and Wang, 2000]. When intramucosal carcinoma (IMCA) is present, the endoscopic resection specimen provides important histopathologic prognosticators: degree of cancer differentiation; presence or absence of lymphovascular invasion; depth of cancer invasion; and the distance of cancer from the deep and lateral resection margins. These criteria aid in determining suitability of curative endoscopic therapy. The low-risk criteria are: absence of submucosal (SM) invasion, low or moderately differentiated cancer, no lymphovascular invasion, clear margins, and size less than 2 cm.

Published ER techniques that have been used for Barrett's include 'simple snare resection', 'inject and cut', cap-assisted endoscopic resection (ER-C), and endoscopic resection with ligation (ER-L) [Seewald *et al.* 2007]. In 'simple snare resection' a stiff monofilament snare is used to grasp tissue without pre-injection while decompressing the lumen. The 'inject and cut' technique employs pre-injection into the SM with a saline solution with or without diluted epinephrine to create a bleb that is then entrained by a standard braided-wire snare. In ER-C a transparent suction cap is fitted to the tip of the endoscope, SM pre-injection is performed, aspiration is applied and the targeted tissue is sucked into the chamber, whence a waiting snare closes around it for transection [Inoue *et al.* 1993]. ER-L is a simple and easy method employing a modification of the variceal band ligation technique [Fleischer *et al.* 1996]. With or without SM pre-injection, targeted tissue is sucked into the banding chamber and a ligation band is deployed. This creates a pseudopolyp that is then resected by snare polypectomy technique.

ER-C and ER-L are the most commonly used techniques in dysplastic Barrett's and have been shown to have comparable safety and efficacy [May *et al.* 2003]. This report describes a large, single-center experience with the ER-L without pre-injection in the evaluation and management

of Barrett's with high-grade dysplasia (HGD)/IMCA.

Patients and methods

All patients were referred to a single investigator (G.G.G.) for management of HGD or IMCA in the setting of specialized intestinal metaplasia (SIM) of the esophagus and esophagogastric junction. We maintain a protocol whereby each such patient undergoes a 'mapping' esophagogastroduodenoscopy (EGD) with repeat biopsies and endoscopic ultrasound (EUS). All patients are offered surgical consultation. Patients with EUS and ER evidence of HGD and IMCA are offered 'curative' endoscopic eradication therapy. Endoscopic eradication therapy employed ER (ER-C and/or ER-L) and/or ablation therapies [argon plasma coagulation (APC), PDT, RFA] individualized based on the length and configuration of the Barrett's metaplasia, presence of HGD and/or mucosal cancer, and presence or absence of dysplastic mucosal irregularities that permitted targeted ER. Patients with EUS and/or ER evidence of cancer invasion beyond the mucosa (T1sm or higher) or lymphadenopathy on EUS suspicious for malignancy are recommended operative resection or 'palliative' endoscopic eradication therapy. Patients undergo endoscopy with eradication therapies every 6–12 weeks until eradication of all SIM is achieved based on 'post-treatment surveillance' endoscopy inspection with targeted, plus four-quadrant biopsies from the neosquamocolumnar junction, residual/recurrent Barrett's appearing mucosa, and previous Barrett's involved segments. Thereafter, post-treatment surveillance endoscopy is performed as follows: every 6 months for 2 years and then annually thereafter (for HGD alone) and every 3 months for the first year, every 6 months for the second year and then annually (for IMCA).

Results of the mapping, eradication, and post-treatment surveillance endoscopies, histopathological findings and adverse events are entered into a database. In August 2004 we began incorporating ER-L into our treatment armamentarium. We reviewed the database for a period of 39 months (from August 2004 to November 2007) to identify only those patients that underwent ER-L using the Duette Multiband Mucosectomy kit during this period. The Institutional Review Board (IRB) of the University of Pennsylvania School of Medicine approved the study.

Pre-ER-L assessment

Informed consent was obtained in all patients. Mapping endoscopy with biopsies was carried out with the therapeutic channel endoscope (GIF-1T 160, Olympus, Center Valley, PA). Mapping of the esophagus was performed with four-quadrant biopsies every 2 cm in the Barrett's segment and targeted biopsies of any macroscopically recognizable lesions (i.e. mucosal irregularity) using a 'jumbo' biopsy forceps. An expert pathologist reviewed the pathology specimen (E.E.F.). As such, the length and configuration of the SIM, uni- or multifocality of the HGD/IMCA, and localization of any macroscopic lesions was established.

EUS was performed with a mechanical radial system with a water-filled balloon for acoustic coupling (GF-UM160, Olympus, Center Valley, PA) at 5–20 MHz frequencies. Tumor (T) staging and node (N) staging was routinely performed. All patients were placed on acid suppressive medications if not taking them. High-dose, twice daily proton pump inhibitors were administered to all patients and maintained for the duration of the study. All patients with a diagnosis of cancer underwent computed tomography scans of the chest and abdomen for staging.

ER-L technique

The majority of patients were sedated with a combination of intravenous midazolam and fentanyl. Anesthesia assistance with propofol was used only in those patients who had demonstrated intolerance to standard sedation. The patients were asked to fast on the day of the procedure. A therapeutic endoscope, with a 3.7 mm working channel, (GIF 1T 160, Olympus, Center Valley, PA) was used. The Duette Multiband Mucosectomy kit (Cook Medical, Bloomington, IN) includes a modified multiband ligator and a hexagonal polypectomy snare measuring 1.5×2.5 cm made of braided wire (Figure 1). This device is a modification of the original Saeed Six-shooter Multiband ligator (Wilson-Cook Medical, Winston-Salem, NC) in that it facilitates the maintenance of the polypectomy snare in the accessory channel during use to permit rapid repeated sequencing of tissue targeting, aspiration, ligation and resection. After the device is loaded on the endoscope and passed into the esophagus, up to six band resections per device can be performed. Electrosurgical energy used was pure coagulation current at 35 W (Valleylab, Boulder, CO).

Figure 1. Duette mucosectomy kit loaded on the endoscope with the snare in the working channel.

The mucosa to be resected was sucked into the banding chamber and the ligation band was deployed to create a pseudopolyp. No SM pre-injection was performed. The pseudopolyp was then resected using the snare, which was intended below the band. The next application was performed on mucosa directly adjacent to the prior margin of resection. The number of applications, length and circumference of resectate, and immediate and delayed adverse events were recorded (Figures 2 and 3). The extent of ER-L was individualized depending on length and configuration of SIM and/or macroscopic lesions and uni- or multifocality of HGD and/or IMCA. ER-L specimens were initially advanced into the stomach. After completing ER-L, forceps biopsies were obtained from the ER margins and residual Barrett's appearing mucosa. The resected specimens were collected from the stomach with a Roth Net (US Endoscopy, Mentor, OH) and fixed in formalin solution for histopathology. Patients were discharged on the same day after recovery from sedation, maintained on their proton-pump inhibitor and a regular diet.

Pathology

Pathology assessment included description of the adequacy of the specimen for histopathological interpretation, presence of SIM, and grade of dysplasia when present. When cancer was

Figure 2. Pre-endoscopic resection with ligation (ER-L) appearance of the esophagus in a patient with Barrett's esophagus with nodular IMCA.

Figure 3. Post-endoscopic resection with ligation (ER-L) appearance of the esophagus in the same patient.

identified, the interpretation included depth of tumor invasion, grade of differentiation (poor to well differentiated), lymphatic or vascular invasion, and the adequacy of the deep margins of resection. Adequacy of lateral margins could not be assessed in patients that underwent piecemeal resection. T1A (mucosal cancer) was defined as cancer with maximum depth of invasion limited to the muscularis mucosa and it was called T1B (SM cancer) if there was extension into the SM but not the muscularis propria.

ER-L histopathology was compared to prior forceps biopsy specimens and any changes in pathology were classified. For the purposes of this study only, 'upgrade' was defined as change in pathological staging from HGD to IMCA or from IMCA to SM invasion on ER specimens. 'Downgrade' was defined as change from IMCA to HGD or from HGD to LGD. Dysplasia eradication (DE) was defined as elimination of all detectable dysplasia and complete eradication (CE) was elimination of all dysplasia and SIM. These determinations were made by endoscopic and pathologic assessment.

Adjunctive treatments

Single session wide-area ER-L alone was applied when Barrett's mucosal extended <3–5 cm and incorporated no more than 50–75% of the luminal circumference. Incremental two-session wide-area ER-L incorporating up to 50% of the luminal circumference per session was performed when the Barrett's extent was circumferential. For patients with residual SIM after ER-L, complete eradication was attempted with photodynamic therapy (PDT), radiofrequency ablation (RFA) or argon plasma beam coagulation (APBC). PDT was delivered after injection of 2 mg/kg porfimer sodium (Photofrin, Axcan Pharma, Mount-Saint-Hilaire, Quebec, Canada) with red light at 630 nm wavelength from a diode laser (Diomed; Axcan) at a light dose of 150 J/cm². Beginning in September 2007 RFA was performed with the HALO³⁶⁰ system (BARRX Medical, Sunnyvale, CA), which is a balloon-based ablation electrode that can rapidly deliver preset RF energy density (12 J/cm²) at 300 W to the desired mucosa. It requires measurement of the esophageal luminal diameter with a sizing balloon prior to treatment. APBC was used for smaller areas of residual BE and was performed at 60 W and 1 l/min flow (ConMed Corp., Utica, NY). Post-treatment surveillance endoscopy was performed as described in the methods section.

Statistical analysis

Categorical variables were summarized using counts and percentages, while continuous variables were summarized using means, medians, standard deviations, and ranges. McNemar's test for paired data was used to compare the change in histopathology between the biopsy and ER-L specimen. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Table 1. Patient characteristics.

Patients, <i>n</i>	65
Male/Female, <i>n</i> (%)	53(82)/12(18)
Age (mean $\pm$ SD)	67 $\pm$ 11
Operative candidate Y (%)	33 (51)
Follow-up in months (median; range)	15; 8–42
BE length in cm (mean $\pm$ SD)	4.2 $\pm$ 3.4
SSBE/LSBE (<i>n</i> [%])	36(55)/29(45)
BE confluent/ nonconfluent, <i>n</i> (%)	36(55)/29(45)
Pre-ER-L diagnosis	
HGD alone, <i>n</i> (%)	65 (100)
HGD with IMCA, <i>n</i> (%)	26 (40)
Unifocal/multifocal	32(49.2)/33(50.8)
HGD or IMCA, <i>n</i> (%)	

BE, Barrett's esophagus; SSBE, short-segment Barrett's esophagus; LSBE, long-segment Barrett's esophagus; ER-L, endoscopic resection with ligation; HGD, high-grade dysplasia; IMCA, intramucosal carcinoma.

Results

During the study period, 65 patients underwent ER-L with the Duette mucosectomy system and constitute the study population. The patient characteristics are described in Table 1. Of the 65 patients, 33 (50%) were deemed fit operative candidates, 36 (55%) had short-segment Barrett's esophagus (SSBE) (≤ 2 cm) and 29 (45%) had long-segment Barrett's esophagus (LSBE) (≥ 3 cm). BE was confluent in 36 (55%) with a mean length of 4.2 cm. HGD was present in all patients and HGD with IMCA in 26 (40%) on initial biopsy. HGD and IMCA were multifocal in 32 (49.2%) and unifocal in 33 (50.8%).

ER-L procedure and complications

A total of 94 ER-L sessions were performed for eradication of BE (one session in 38 patients, two in 19 patients and three in six patients). The mean number of sessions per patient was 1.5. A median number of four (range 1–6) resection applications were performed per session. Procedures were carried out in the outpatient setting for all but one patient who was admitted for overnight observation after minor bleeding.

Acute bleeding was noted in four (6%) patients (Table 2). All were minor bleeding treated with endoscopic therapy alone. Bleeding episodes were not hemodynamically destabilizing and did not require transfusion. Three instances were treated with local injection of diluted epinephrine (1:10,000 cm³) alone and one with a combination of epinephrine injection and placement of

Table 2. Application and complications with the multi-band mucosectomy kit.

Number of ER-L band applications/session (median; range)	4 (1–6)
Number of ER-L sessions (Mean $\pm$ SD)	1.5 $\pm$ 0.7
Complications	
Acute bleeding (<i>n</i> [%])	4(6)
Strictures (<i>n</i> [%]), –treatment (patients [no. of dilations])	5(7.7) 2(1) and 3(3)
Perforation	0(0)
Deaths	0(0)
Dysplasia eradication (<i>n</i> = 60)	
ER-L alone (<i>n</i> [%])	60 (100)
Complete eradication of BE (<i>n</i> = 60)	
ER-L alone (<i>n</i> [%])	36(60)
ER-L + APC	17(28)
ER-L + PDT	5(8)
ER-L + RFA	2(4)

ER-L, endoscopic resection with ligation; BE, Barrett's esophagus; APC, argon plasma coagulation; PDT, photodynamic therapy; RFA, radiofrequency ablation.

two hemoclips. This last patient was admitted for overnight observation, fasting and IV fluids as a precautionary measure. No recurrent or delayed bleeding, perforations or procedure-related deaths were reported in any patient. Five (7.7%) patients developed symptomatic strictures. All strictures occurred in the initial phase of our experience and when resection encompassed $>75\%$ of the luminal circumference. Two of these patients were treated with a single session of dilation with the Savary bougie and the other three patients required three sessions each for complete response. In two patients, the endoscope with band-ligation cap could not be passed into the esophagus. In these two instances, an esophageal overtube (Guardus Overtube, US Endoscopy, Mentor OH) was placed, thus permitting ease of insertion and withdrawal of the instrumentation.

Long-term follow-up and outcomes

Two patients with nodular unifocal IMCA were found to have SM tumor invasion on ER-L pathology specimens and elected to have esophagectomy. Final pathology from surgical specimen demonstrated no IMCA in the esophagus in either patient. Another patient with IMCA had poor prognosticating factors on ER-L pathology (SM invasion, lymphovascular invasion) but was considered a poor surgical candidate and was treated with palliative chemoradiotherapy. This patient is alive at 20 months post-treatment with no

evidence of residual or recurrent cancer. Finally, two elderly patients (ages 87, 88) with IMCA and poor prognosticating factors on ER-L were considered poor candidates for both surgical and oncologic therapy. They are enrolled in a protocol of palliative endoscopic resection for macroscopic disease and continue to survive at 12 months postdiagnosis.

Therefore, 60 patients were considered for curative therapy with a goal of complete eradication. Using ER-L as monotherapy, dysplasia (HGD/IMCA) was eradicated in all patients and complete SIM eradication (CE) was achieved in 36 (60%) patients. Patients with remaining SIM underwent adjunctive ablation therapies (APC in 28%, PDT in 8% and RFA in 4%) for complete eradication of all SIM. All patients are alive at a median follow-up of 15 months (range 8–42 months) from resection date.

Histopathology examinations

The results of pathologic examination of ER-L specimens showed a change from the pre-ER biopsy specimens in 24 of 65 patients ($p = <0.0001$; Tables 3 and 4). In five patients there was a 'downgrade' of pathology from HGD to low-grade dysplasia (LGD). None of these patients have had recurrent HGD on surveillance biopsies.

In 19 patients, an 'upgrade' in with was seen. Eight showed evidence of SM invasion on ER-L as compared to IMCA only on forceps biopsy

Table 3. Endoluminal resection specimen pathology as compared to jumbo forceps biopsy specimen pathology.

Pathology	Number (%)	<i>p</i> value
'Upgrade'	19 (30)	<0.0001
'Downgrade'	5 (7.8)	0.0253
Any change	24 (37.5)	<0.0001

Table 4. Change in pathology on Endoluminal resection as compared to forceps biopsy ($n = 24$).

'Downgrade' ($n = 5$)	HGD to LGD (5) HGD to IMCA (9)
'Upgrade' ($n = 19$)	Indeterminate to HGD (2) IMCA to IMCA with submucosal invasion (8)
HGD, high-grade dysplasia; LGD, low-grade dysplasia; IMCA, intramucosal carcinoma; SM, submucosa.	

pathology and EUS. Five patients underwent management as described above (surgery, chemotherapy and palliative ER-L). Three patients with superficial SM invasion (Tsm1) elected not to have surgery and complete eradication of dysplasia and BE was achieved with endoluminal therapy. None have shown any recurrence of HGD or IMCA on surveillance (24–36 months) to date. All patients with SM invasion had focal nodular lesions on endoscopy and had been examined by endosonography (5–20 Mhz) and were all staged N0. In the remaining 11 patients, ER-L showed an 'upgrade' from HGD to IMCA in nine and from indeterminate to HGD in two.

Discussion

BE is the presence of SIM in the esophagus and esophagogastric junction (EGJ) [Spechler, 2002]. BE is clinically significant because it is associated with an increased risk for the development of adenocarcinoma of the distal esophagus and the EGJ [Hamilton and Smith, 1987]. The Barrett's cancer risk is estimated at 0.5% per year, at least a 30-fold increased risk over that of the general population. BE progresses through stages of dysplasia to cancer. Patients without dysplasia or with LGD have low rates of disease progression. Although the fate of HGD is variable, there is a 5-year risk of esophageal carcinoma exceeding 30% [Spechler, 2002].

Operative esophagectomy has been the standard treatment offered to patients with IMCA and HGD in Barrett's mucosa [Enzinger and Mayer, 2003]. Although this achieves a cure in majority of these patients, it is associated with considerable morbidity and mortality, especially when performed at less-experienced centers [Birkmeyer *et al.* 2002]. Many patients with IMCA and HGD are elderly or have comorbid medical conditions that make them unfit for esophagectomy. Further, many patients with HGD will not develop cancer in their lifetimes and surgery may be deferred until it is detected on surveillance examinations [Schnell *et al.* 2001]. Many patients would prefer to avoid esophagectomy in favor of an equally efficacious nonoperative alternative. Therefore, the emergence of safe and effective endoscopic therapies for HGD and IMCA is attractive for selected patients.

Early esophageal neoplasia includes tumors that are staged T1N0M0 and does not differentiate

between cancer involving the mucosa *versus* deep SM invasion. To better consider lesions amenable to nonoperative therapy this classification has been further subdivided into T1m cancer and T1sm with predicted rates of concurrent lymph node metastasis of 1–3% *versus* 5–40% respectively [Pech *et al.* 2003; Rice *et al.* 1998]. Therefore, a substantial percentage of patients with T1sm disease are not reliably amenable to curative endoscopic resection given the variable rate of lymph node involvement. In contrast, patients with HGD and T1m disease have negligible risk of concurrent lymph node metastasis and no greater than that of mortality associated with operative esophagectomy [Enzinger and Mayer, 2003]. Endoscopic therapy has shown considerable promise as a minimally invasive approach to patients with HGD and T1m cancer [Ell *et al.* 2007; Larghi *et al.* 2005; Soetikno *et al.* 2003; Pech *et al.* 2003]. Accurate staging is therefore critical when considering the management options for patients with BE and HGD/IMCA.

We found the ER-L method without pre-injection to be safe, easy to apply and well tolerated. All procedures were completed on an outpatient basis and only one patient was admitted overnight for minor bleeding. None of the patients reported postoperative pain. We encountered no major complications and the rate of minor complications (bleeding, strictures) in our series is similar to others in this group of patients [Ell *et al.* 2007; Larghi *et al.* 2007].

The quality of the resected and retrieved specimens was satisfactory to designate depth of invasion of superficial neoplasia as T1a (mucosal level) *versus* T1b (SM invasion). Further, cancer invasion just through the muscularis mucosa into the superficial SM could be distinguished from the deeper SM invasive cancer. Our analysis showed there was a change in pathologic staging in 24 of 65 patients in the study. Five patients who had low-grade dysplasia on ER-L specimen as compared to HGD on forceps biopsy underwent no further therapy. They have demonstrated no HGD on surveillance biopsies. Nine of 39 (23%) patients with HGD only on forceps biopsy had IMCA on ER-L. There was no invasion of the SM in any of these patients. This result confirms the high incidence of mucosal carcinoma in patients with HGD and is similar to experiences of other investigators. However, SM invasion was seen on

ER-L specimens in 8 of 26 (30%) patients with IMCA on biopsy and EUS. Similar results have been noted in other series [Larghi *et al.* 2005; Nijhawan *et al.* 2000].

Knowledge of the depth of tumor invasion influenced our approach in determining individual patient management. We recommended esophagectomy in our eight patients with SM cancer but only two were able to or chose to undergo it. One patient underwent chemo-radiotherapy and two were considered unfit for chemotherapy and underwent palliative ER-L. Both patients are alive at 12 months follow-up. The three remaining patients with T1sm cancer on ER-L histopathology have undergone successful curative endoluminal eradication therapy with no evidence of cancer at 24–36 months follow-up.

ER-L using the DuetteTM multi-band mucosectomy resection system is safe and effective as part of evaluation, staging, and endoscopic eradication of BE with HGD/IMCA. It can be applied without pre-injection of SM solution, on an outpatient basis, using sedation with analgesia, and with no interruption in patient's oral intake. Wide-area, piecemeal confluent resections can be performed quickly. Resected specimens enhance accuracy of diagnosis and staging. Symptomatic strictures were uncommon, responded to dilation therapy, and occurred only when greater than 50% of the luminal circumference was resected. Immediate bleeding was uncommon, occurred predominantly early in our experience, was treated endoscopically, and was nearly eliminated when a pure coagulation current was used. Further, our treatment multimodality treatment protocol resulted in eradication of Barrett's mucosa in all 60 patients who were considered candidates for curative resection. Moreover, ER-L can be safely and effectively incorporated as the initial phase of multi-modal endoluminal eradication therapy with the application of broad-field ablation techniques for residual HGD and non-dysplastic BE.

Conflict of interest statement

The authors, Yasser M. Bhat, MD, Emma E. Furth, MD, Colleen M. Brensinger, MS, Gregory G. Ginsberg, MD report that we have no conflict of interest – financial or otherwise – associated with this manuscript.

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