Review Article

Endoscopic treatments for early gastroesophageal lesions

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Abstract: Gastroesophageal (GEJ) carcinoma is well-recognized since the 1970s and has shown 2.5-fold increase in incidence since then. There still exists much controversy and ambiguity in the literature about the occurrence and recurrence of these lesions post-treatment. This has been attributed to the variability in the terms and definitions used in these junctional lesions. Despite this, great strides have been made in the treatment of early lesions decreasing morbidity and mortality from surgical treatment options. The current modalities involve ablation [like radiofrequency, cryo or argon plasma coagulation (APC)] and/or resection [endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)] depending on the type and nature of lesion. These techniques are an effective tool demonstrating high rates of complete eradication of metaplasia or dysplasia (CE-IM/CE-D). It is crucial that the endoscopists are mindful about meticulous examination of the GEJ and Cardia as well as partake in appropriate surveillance post-endoscopic eradication. In addition, appropriate documentation of the location and type of lesion is also extremely important. This review aims to compare current endoscopic techniques in their efficacy, need for expertise and risk of complications when used in the treatment of early junctional lesions. Future studies and guideline recommendations to standardize definitions, diagnoses and post-treatment surveillance are needed.

Keywords: Endoscopy; endoscopic mucosal resection (EMR); endoscopic submucosal dissection (ESD); radiofrequency ablation (RFA); gastroesophageal (GEJ)

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Introduction

Gastroesophageal junction (GEJ) is the anatomic junction between the end of the tubular esophagus and the start of the stomach i.e. the gastric cardia. Another commonly used terminology is top of gastric folds (TGF), which is an endoscopic landmark at the transition between the smooth esophagus to the gastric rugae. This usually coincides with the attachment of the diaphragm. In the absence of a hiatus hernia, the GEJ also correlates with the histological transition from the esophageal squamous epithelium to the columnar/glandular gastric cells (squamo-columnar junction, SCJ or z-line) (1).

Barrett's esophagus (BE), a pre-cancerous condition that involves intestinal metaplasia of the squamous epithelium is suspected endoscopically when the z-line appears to be proximal to TGF. Multiple studies use these terminologies interchangeably sometimes leading to confusion, heterogeneity and misrepresentation of the location being

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described.

Adding to the complexity, is the term neo-squamous columnar junction (NSCJ) which is applicable in cases where Barrett's esophagus has been subjected to endoscopic therapy (BET) leading to scarring of the original SCJ. It becomes imperative that accurate descriptions be used to depict locations of lesions based on the definitions above not only research settings but also in clinical practice.

GEJ lesions also known as junctional lesions have gained a lot of attention recently since the incidence of GEJ adenocarcinoma has risen by 2.5 folds since 1970, with this being more prominent in the elderly white males in the western hemisphere (2,3). Early detection of these lesions and prompt management with continued surveillance will be key in preventing advanced disease and its associated morbidity and mortality.

Definition, classification and diagnosis of GEJ lesions

GEJ is at the cusp of 2 organs-end of the tubular esophagus and the beginning of the gastric cardia. Given the anatomical and histological differences of these 2 adjacent organs, there is the dilemma of whether to treat these lesions similar to esophageal or gastric lesions.

There have been efforts to classify these lesions using the Siewert and TNM classifications to guide treatment:

(I) Based on location: Siewert et al. in 1987 (4) classified these lesions based on the epicenter of the lesion.
   (i) Type I/distal esophageal: epicenter 2–5 cm above the GEJ;
   (ii) Type II/true GEJ: epicenter within 2 cm (above or below) of the GEJ;
   (iii) Type III/subcardial tumors: epicenter 2–5 cm distal to the GEJ.

(II) TNM classification (5): in 2016, the TNM (tumor, lymph node, metastasis) Classification of Malignant Tumors (9th and 10th editions) defined junctional cancer as all tumors in which the center is found 2 cm proximal or distal to the junction. Cancers involving the GEJ and with an epicenter within the proximal 2 cm of the cardia (Siewert types I/II) are staged as esophageal. Cancers whose epicenter is more than 2 cm distal from the GEJ are staged using the stomach cancer TNM staging, even if the GEJ is involved.

(III) Based on histology/early *vs.* advanced: similar to BE, these lesions can also be classified as early when metaplasia or low-grade dysplasia is noted and advanced if high-grade dysplasia, intramucosal carcinoma or adenocarcinoma is noted.

(IV) Based on morphology: superficial GEJ lesions can be classified as polypoid (Ip, Is) and non-polypoid (IIa, IIb, IIc and III) depending on their endoscopic appearance relative to the surrounding mucosa according to the Paris classification (6).

Proper diagnosis of true GEJ lesions is challenging since they may originate from two distinct etiologies, with some being esophageal adenocarcinomas probably arising from Barrett's esophagus and the others being gastric adenocarcinomas associated with H pylori infection and atrophic gastritis. It's been suggested that the key to differentiated whether an esophageal or gastric origin is not the histology of the cancer itself but both the histology of the non-cancerous stomach and the history of reflux symptoms. Gastric cancers are strongly associated with mucosal atrophy, intestinal metaplasia body-predominant H pylori gastritis in a patient without reflux history. In contrast, esophageal adenocarcinomas occur in subjects with reflux symptoms having a healthy non-atrophic gastric mucosa (7).

Upper GI endoscopy with careful examination of the GEJ with white light as well as with image enhanced technologies like narrow band imaging (NBI) and blue light imaging (BLI) needs to be carried out to characterize mucosal and vascular patterns of non-dysplastic, high grade and cancer lesions (8). Biopsies should be obtained from any visible raised or flat lesions. Endoscopic ultrasound (EUS) might be necessary to evaluate the depth of the lesion and EUS-guided FNA can be considered to obtain biopsy of suspicious regional/non-regional lymph nodes without traversing the primary tumor.

According to the current guidelines, early lesions and with a staging of T1aN0 can be treated with BET. This includes endoscopic resection of raised, visible lesions using endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) or submucosal tunneling endoscopic resection (STER) and ablation of the remaining/flat BE mucosa with goal of complete eradication of all metaplasia (CE-IM), dysplasia (CE-D) or neoplasia (CE-N). All lesions that would stage higher than T1aN0 would warrant surgical and/or chemotherapy. T1b lesions could be considered for BET especially in the setting of favorable features: no lympho-vascular invasion, sm1 involvement only and well differentiated lesions.

Table 1 Resection and ablation-based endoscopic therapies

Endoscopic modality	Technique	Types	Efficacy
Resection methods			
EMR	Endoscopic resection of the involved mucosa	Suck and cut (suction) (multiband mucosectomy; cap assisted); lift and cut (non-suction) using submucosal injection (saline, dextrose, hyaluronate, gelatin etc.)	CE-N: 94–100%, CE-IM: 76–100%
ESD	Involves injecting fluid into the submucosa and creating an incision around the perimeter of the lesion, and then carefully dissecting the lesion from the deeper layers	Variant: endoscopic muscularis excavation (if the subepithelial tumor arises from the muscularis propria)	Complete resection rates: 79–98%
STER	Involves incision in the mucosal membrane to create a submucosal tunnel and separating the tumor from the surrounding tissue		Complete resection rates: 94–100%
Ablative methods			
RFA	Directed and controlled heat energy is used for ablation	Circumferential ablation: Barrx 360; focal ablation: Barrx 90, Barrx 90 ULTRA and Barrx 60	CE-D: 91–100%, CE-IM: 71–93%
Cryotherapy	Involves application of cryogen leading to rapid freezing and death of the esophageal cells	Cryospray: liquid nitrogen (–196 ℃); polar wind: CO_2 gas (–78 ℃); cryoballoon: focal and Swipe[90] ablation systems	CE-D: 87–97%, CE-IM: 42–81%
APC	Involves application of thermal energy to the target tissue via ionized argon gas	Hybrid APC: combination of APC with submucosal saline injection	CE-D: 40–77%, CE-IM: 52%

APC, argon plasma coagulation; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; RFA, radiofrequency ablation; STER, submucosal tunneling endoscopic resection.

Endoscopic treatment modalities

A comparative description of the modalities, the types and their efficacy are shown in *Table 1*. *Table 2* lists all the systematic reviews that have evaluated the efficacy and safety of all the modalities described below.

Resection modalities

These techniques described below are used for lesions that are raised/nodular.

EMR

EMR was a technique first described in Japan (20) for the management of early gastric cancer and since been used for a variety of other gastrointestinal lesions. This involves as the name indicates, resection of the involved mucosa using an endoscopic technique (*Figure 1*). Broadly, this technique can be used with suction (suck and cut) or without (lift and cut). It has the advantage of being able to aid in the staging of the disease as compared to its ablative counterparts. While studies have shown up to 100% CE-IM and CE-N, a systematic review in 2018 (14) suggested CE-IM of 85% and CE-N of 96.6%. Stricture (37.4%), bleeding (7.9%) and perforation (2.3%) are the main complications. A drawback of this technique is the inability to resect a large lesion en bloc. This technique while effective, needs expertise and additional training. Currently, the most widely used ER technique for Barrett's neoplasia is multiband mucosectomy (MBM). In this technique the esophageal mucosa is sucked into the cap, captured in a rubber band, and resected with a snare using electrocautery. Because the rubber bands are not strong enough to hold the proper muscle layer, MBM is associated with a low risk of perforations even without prior submucosal lifting (21). Both the Duette device (Cook Medical, Limerick, Ireland) and the Captivator EMR device (Boston Scientific, Marlborough, Mass) appears to be equally effective to remove early Barrett's neoplasia in expert hands (22,23).

Table 2 Systematic reviews with meta-analyses reporting efficacy of various modalities

Study	Therapy	Number	Efficacy/success	Complications	Recurrence
Hamade 2019 (9)	Cryotherapy as first line for all BE	6 studies; 282 patients	CE-IM: 69.35%; CE-N: 97.9%	Stricture formation 4.9%	Persistent dysplasia 7.3%; recurrence of neoplasia 10.4/100 patient years; recurrence of IM 19.1/100patient years
Dan 2019 (10)	EMR-EMR cap vs. MBM for early/pre-cancerous lesions	5 studies; 405 patients	Complete resection rate of EMR-cap vs. MBM OR =2.09 [95% confidence interval (CI): 0.78–5.60, P=0.14]	Lower bleeding rate (OR =0.45, 95% CI: 0.24–0.83, P=0.01), similar perforation rate (OR =0.55, 95% CI: 0.15–2.06, P=0.37), similar stricture rate (OR =0.77, 95% CI: 0.10–5.84, P=0.80)	Similar local recurrence rate (OR =0.50, 95% CI: 0.09–2.67, P=0.42)
Mohan 2019 (11)	Liquid nitrogen cryotherapy for all BE (as a primary modality or in combination)	9 studies; 386 patients	CE-IM 56.5% (in patients who failed RFA CE-IM-58.4%); CE-D 83.5%; CE-HGD 86.5%	Any AE 4.7%	Any BE recurrence 12.7%
Pandey 2018 (12)	RFA in LGD	8 studies; 619 patients	CE-IM 88.17%; CE-D 96.69%		Recurrence of IM 5.6%; recurrence of dysplasia 9.66%
Visrodia 2018 (13)	Cryotherapy for persistent IM after RFA	11 studies; 148 patients	CE-IM 45.9%; CE-D 76%	Any AE 6.7%	
Tomizawa 2018 (14)	EMR for BE	8 studies; 676 patients	CE-IM 85%; CE-N 96.6%	Stricture 37.4%; bleeding 7.9%; perforation 2.3%	Recurrence of IM 15.7%; recurrence of neoplasia 5.8%
Desai 2017 (15)	Focal EMR + RFA for HGD/ EAC/IMC	9 studies; 774 patients	CE-IM 73.1%; CE-N 93.4%	Stricture 10.2%; bleeding 1.1%; perforation 0.2%	Recurrence of IM 16.1%; recurrence of dysplasia 2.6%; recurrence of EAC 1.4%
	Stepwise or complete EMR for HGD/EAC/IMC	11 studies; 751 patients	CE-IM 79.6%; CE-N 94.9%	Stricture 33.5%; bleeding 7.5%; perforation 1.3%	Recurrence of IM 12.1%; recurrence of dysplasia 3.3%; recurrence of EAC 0.7%
Lv 2017 (16)	STER for UGI submucosal tumors	28 studies	Complete resection 97.5%; en bloc resection 94.6%	Subcutaneous emphysema and pneumomediastinum 14.8%; pneumothorax 6.1%; pneumoperitnoeum 6.8%; perforation 5.6%	
Park 2015 (17)	ESD for GEJ cancers	6 studies; 359 GEJ cancers	Complete resection 98.6%; en bloc resection 87%	Stenosis 6.9%	269 curative resections no local/ metastatic recurrences; 90 non-curative lesions 3 local and 2 metastatic recurrences
Chadwick 2014 (18)	RFA vs. complete EMR in BE	28 studies; 1,087 patients; (532 EMR and 555 RFA)	CE-D (EMR) 95%; CE-D (RFA) 92%	Adverse events (EMR/RFA); any short-term AE (12%/2.5%); esophageal strictures (38%/4%)	EMR (23-month follow-up) 5%; RFA (21-month follow-up) -6%
Orman 2013 (19)	RFA for BE	18 studies; 3,802 patients	CE-IM 78%; CE-D 91%	Stricture 5%	Recurrence of IM 13%

AE, adverse events; BE, Barrett's esophagus; CE-D, complete eradication of dysplasia; CE-IM, complete eradication of intestinal metaplasia; CE-N, complete eradication of neoplasia; CI, confidence intervals; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGD, high grade dysplasia; IMC, intra-mucosal carcinoma; LGD, low grade dysplasia; MBM, multiband mucosal ligation; OR, odds ratio; RFA, radiofrequency ablation; STER, submucosal tunneling endoscopic resection; UGI, upper gastrointestinal.

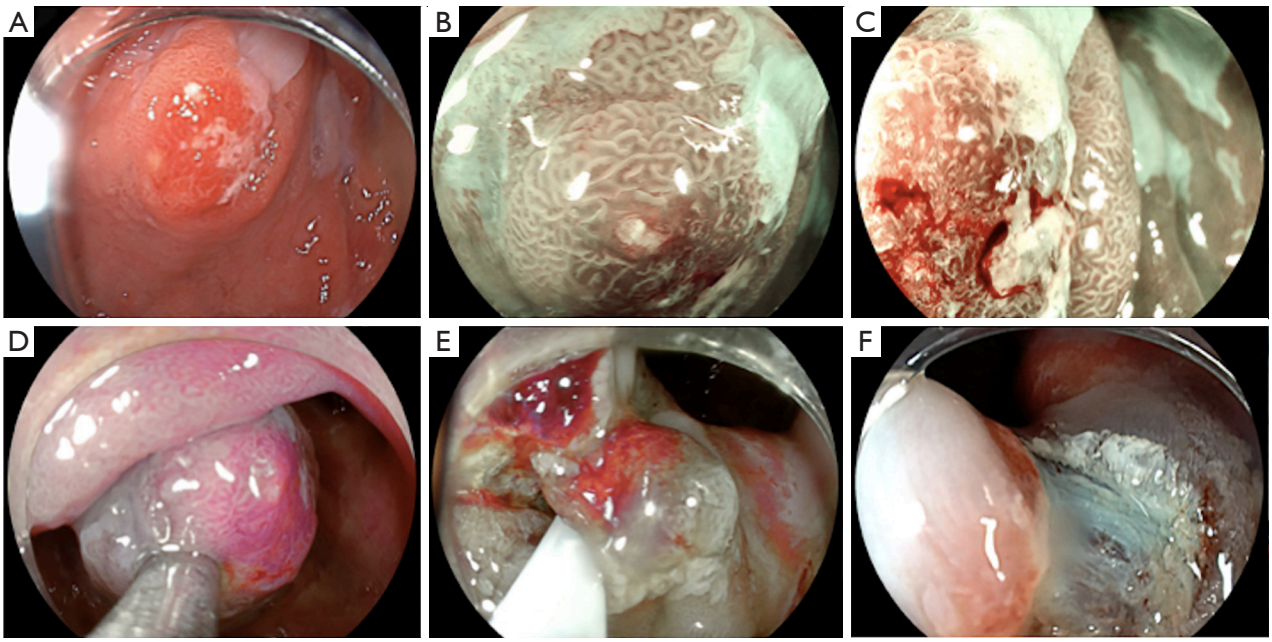

Figure 1 EMR for a high grade dysplastic lesion of the EGJ. (A) White light image shows a 0-IIa lesion, 10 mm in diameter located in the anterior quadrant of the EGJ at 34 cm from the incisors. (B) BLI shows a darker central area surrounded by intestinal metaplasia. (C) BLI with magnification shows microstructure irregularity and easy bleeding. (D) Submucosal injection using a mixture of normal saline solution, indigo carmine dye and epinephrine. (E) Mucosal resection using a 10 mm polypectomy snare. (F) Ulcer post-resection. Histopathology revealed high grade dysplasia surrounded by Barrett's epithelium and negative horizontal margin.

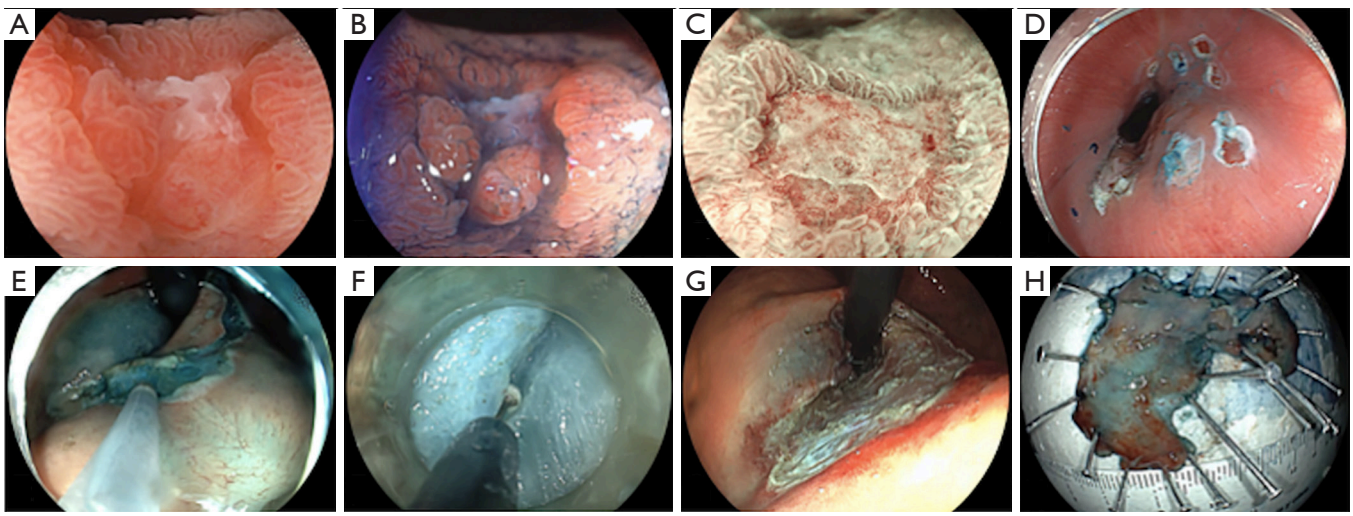

Figure 2 ESD for early adenocarcinoma of the EGJ. (A) White light image shows a 0-IIc lesion 12 mm in diameter located 1.5 cm below the EGJ at the upper third of the lesser curvature of the stomach, area 23. (B) Indigo carmine dye spraying clearly revealed the margin of the lesion. (C) BLI with magnification revealed microvascular and microstructure irregularity and, a positive demarcation line suggesting early gastric cancer. (D) Proximal marking at the oral side. (E) Circumferential incision and submucosal injection using a mixture of normal saline solution, epinephrine, indigo carmine dye and hyaluronic acid. (F) Submucosal dissection using the IT-Knife2. (G) Ulcer post-ESD. (H) The lesion is fixed before immersion in formaldehyde. Histopathology revealed a diffuse and well differentiated (mixed type) intramucosal adenocarcinoma, 12 mm in size, without lymphovascular invasion and with negative margin.

ESD

ESD was first described in 2002 (24) to address issues of resectable size and precision with EMR. In this technique, fluid is injected into the submucosa to provide a lift and then an incision is placed around the perimeter of the lesion followed by careful dissection of the lesion from the deeper layers (*Figure 2*). Asian studies have shown resection rates of 79–98% and specifically a systematic review was done to review rates in GEJ cancers in 2015 (17). Complete resection rate of 98.6% was reported in this review with stricture and stenosis (6.9%) being the main complication. An important advantage of this method, in addition to its high resection rate is the rate of recurrence. Although a challenging procedure with scarce case reports published in the literature (25), circumferential ESD for early Barrett's neoplasia can provide both tumor curability and complete removal of IM, thereby, avoiding subsequent ablation procedures. In a recent western study of true GEJ tumors, 10 and 2 gastric and Barrett's adenocarcinomas were treated by ESD, respectively. En bloc, en bloc tumor-free margin, and curative resection rates were 100%, 75%, and 50%, respectively. All ESDs for Barrett's adenocarcinoma resulted in curative resection. Non-curative resection was found, however, in 6 (60%) of gastric tumors and, all were associated with submucosal deep invasion. Perforation was found in 1 (8%) case that underwent successful endoscopic closure. There were no cases of delayed bleeding in this consecutive study. Noteworthy, the mean tumor size of non-curative gastric adenocarcinoma cases was lower, 13.8 mm than that of curative cases, 15.5 mm (NS) suggesting that tumor differentiation regardless of size may be the main predictive factor for non-curative resection of gastric type adenocarcinomas at the GEJ (26).

The ESD technique involves specialized skills and needs additional training as well. A modification of this technique with tunneling in the submucosa to dissect the tumor is STER (submucosal tunneling endoscopic resection).

Ablative modalities

These techniques below are used for flat lesions or in combination after completion of resection modalities to eradicate any remnant/recurrent lesions, mainly the flat BE mucosa.

Radiofrequency ablation (RFA)

RFA involves the application of directed and controlled heat energy to ablate lesions. Current devices allow circumferential or focal application of RF to ablate lesions according to their extent. It is a relatively safe an effective modality with good CE-IM (71–93%) and CE-D (91–100%) rates. A systematic review in 2018 (12) for RFA in LGD reported a CE-IM of 88.17% and CE-D of 96.69% with recurrence rates of 5.6% (IM) and 9.6% (dysplasia). Similar results were also noted in a comparative review with EMR (18) where CE-D rates of 92% were noted. In this study, esophageal stricture was around 4% and was the main complication with very minimal rates of bleeding or perforation. While it is readily available and easy to use, the requirement of multiple (usually 2–4) sessions, cost and the destructive effect of this ablative technique are the main drawbacks.

Cryotherapy

Cryotherapy involves the application of cryogen to the abnormal mucosa leading to the rapid freezing and thawing that leads to the death of the cells. Cryogen can be applied as a spray or using a balloon with the spray nozzle in the center. This modality can be used to treat focal lesions as well as larger segments as well. While it has not been evaluated systematically compared to RFA, rates of CE-IM up to 81% and CE-D up to 97% are reported. A recent systematic review of cryotherapy as a first line modality (9) demonstrated CE-IM of 69.35% and CE-N of 97.9%. Stricture rates was 4.9% with recurrence of IM and neoplasia reported at 19.1 and 10.4 per 100 patient-years. Another systematic review in 2018 (13) reviewed the role of cryotherapy for persistent IM after RFA and CE-IM and CE-D rates of 45.9% and 76% respectively were reported. This methodology has the advantage of ease of use and cost-effectiveness, but also requires multiple sessions with lower eradication and higher recurrence rates as compared to RFA.

APC and hybrid argon plasma coagulation (APC)

APC is an ablative modality that involves the application of thermal energy to the target tissue via ionized argon gas. Due to the high rates of complications to the underlying tissues, hybrid APC was developed whereby a submucosal saline injection is performed to provide a protective cushion before APC is applied. It has fairly acceptable rates of CE-IM (69%) and CE-D (67–86%). Interim data from 2017 (27) of 80 patients showed CE-BE of 92.5% with fever (11.25%), bleeding (2.5%) and perforation (1.25%) as the main complications.

Limitations of current studies

While there is growing evidence for the efficacy and safety of all these modalities in treating BE, studies have not focused specifically on treating GEJ lesions and tend to lump these lesions with either distal esophagus or with cardia lesions. While it is known that intestinal metaplasia can occur in the tubular esophagus, GEJ and cardia, it is essential to know the occurrence, progression of the disease in the junctional area and the efficacy of these modalities in the junctional lesions. It must also be pointed out that while the numbers and studies described in this review are applicable to GEJ, they were only few studies and reviews that specifically reported this data. A recent review undertaken by our group (unpublished at the time of this manuscript) evaluating the location of recurrence of BE after BET noted that 4 out of the 21 studies included reported data separately for GEJ, NSCJ and cardia. In total, 55.6% (pooled estimate; 95% CI, 43.7–67.5%) of the BE recurrences and 54.1 (38.5–69.6%) of the HGD-EAC recurrences were in the GEJ/NSCJ/Cardia area. These results underscore the importance of accurate nomenclature and documentation of the exact location of the junctional occurrence.

Future directions

Advances in endoscopic techniques have ushered in a new era in the treatment of early GEJ lesions. This has offered patients treatment options with less morbidity and mortality than was previously available with surgical resection. There is still a lack of well-designed studies that accurately define and report on these lesions. Future efforts should focus on using the standardized terminology described to better define GEJ lesions, and determine their rates of progression, outcomes, and recurrences to better delineate this entity.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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