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EDITORIAL

Evolving role of the endoscopist in management of gastrointestinal neuroendocrine tumors

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Abstract

Neuroendocrine tumors (NETs) are uncommon gastrointestinal neoplasms but have been increasingly recognized over the past few decades. Luminal NETs originate from the submucosa of the gastrointestinal tract and careful endoscopic exam is a key for accurate diagnosis. Despite their reputation as indolent tumors with a good prognosis, some NETs may have aggressive features with associated poor long-term survival. Management of NETs requires full understanding of tumor size, depth of invasion, local lymphadenopathy status, and location within the gastrointestinal tract. Staging with endoscopic ultrasound or cross-sectional imaging is important for determining whether endoscopic treatment is feasible. In general, small superficial NETs can be managed by endoscopic mucosal resection and endoscopic submucosal dissection (ESD). In contrast, NETs larger than 2 cm are almost universally treated with surgical resection with lymphadenectomy. For those tumors between 11-20 mm in size, careful evaluation can identify which NETs may be managed with endoscopic resection. The increasing adoption of ESD may improve the results of endoscopic resection for luminal NETs. However, enthusiasm for endoscopic resection must be tempered with respect for the more definitive curative results afforded by surgical treatment with more advanced lesions.

Key words: Carcinoid; Gastrointestinal; Endoscopy; Endoscopic submucosal dissection; Neuroendocrine tumor

Core tip: Neuroendocrine tumors (NETs) are uncommon but increasingly recognized gastrointestinal neoplasms. Management of NETs requires full understanding of tumor size, depth of invasion, lymphadenopathy, and location within the gastrointestinal tract. Small NETs can be removed by endoscopic techniques, while NETs > 2 centimeters typically require surgery. For tumors 11-20 mm in size, careful evaluation can

identify which NETs may be managed with endoscopic resection. Endoscopic submucosal dissection has been increasingly used for treatment of luminal NETs. However, enthusiasm for endoscopic resection must be tempered with respect for the more definitive curative results afforded by surgical treatment with more advanced lesions.

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INTRODUCTION

Neuroendocrine tumors (NETs) are an uncommon finding during endoscopic procedures, though the management of these neoplasms requires full understanding of tumor stage and prognosis, often with use of a multidisciplinary approach. Luminal NETs arise within the submucosa of the gastrointestinal (GI) tract and can be underappreciated without a careful examination. Increased recognition of NETs in recent years has been attributed to multiple factors, including improved detection (due to advanced imaging, laboratory and endoscopic techniques), a true rise in tumor incidence and greater awareness of NETs among physicians[1]. This rising incidence along with higher than previously thought mortality rates creates a challenge for gastroenterologists. These tumors have traditionally been characterized by indolent growth and a generally good prognosis, though more recent data illustrates subtypes of NETs with aggressive behavior and poor long-term survival. Treatment of NETs has traditionally been limited to endoscopic removal of small lesions (< 20 mm) and surgical excision of larger lesions, though advances in endoscopic techniques and the increasing use of endoscopic mucosal dissection (ESD) are allowing endoscopic therapy for an increasing proportion of these neoplasms.

EPIDEMIOLOGY

The incidence of NETs has increased over the past several decades in the United States and a similar rise has also been noted in Europe[2-4]. Data obtained from National Cancer Institute (NCI) registries in the United States identified 13715 NETs over 5 decades and the incidence was highest in the GI tract (67.5%)[2]. In addition, a study utilizing data on 35618 subjects with NETs from the Surveillance, Epidemiology, and End Results (SEER) Program registry reported a significant increase in age-adjusted incidence of NETs from 1.09 per 100000 person in 1973 to 5.25 per 100000 person in 2004[5]. Despite the reputation of NETs as relatively benign neoplasms, these large studies revealed an overall 5-year survival rate of only 50%-67.2%[2-3]. A recent SEER based review of gastorenteropancreatic NETs revealed similar overall 5-year survival rate of 68.1%[6]. Survival was lowest in pancreatic NETs (37.6%) and highest in rectal NETs (88.5%) with other sites being in between (colonic 54.6%, gastric 64.1%, small intestinal 68.1%, and appendiceal 81.3%). This marked variability in prognosis according to location has important implications for when surgical or endoscopic treatment should be chosen.

EMBRYOLOGY AND DISTRIBUTION

NETs of the GI tract are heterogeneous tumors and arise from the endocrine system mainly in the gastric submucosa, the small and large intestine and the rectum, as well as in the pancreas. The embryologic origin and vascular supply of NETs play a role in their classification, as some prefer to distinguish them based on origin by embryologic segments such as foregut (lung, stomach, liver, biliary tract, pancreas, the first portion of the duodenum, and the ovaries), midgut (the distal duodenum, small intestine, appendix, right colon, and the proximal transverse colon), and hindgut (the distal transverse colon, left colon, and the rectum)[7]. NETs can be either functional with secretion of hormones into the bloodstream (gastrinoma, glucagonoma, insulinoma, somatostatinoma and VIPoma) or non-functional[8]. Functional NETs may initially be diagnosed based on the patient's symptoms and serologic assays for the secreted hormone (such as the measurement of elevated insulin levels for an insulinoma); endoscopy may then follow as part of the attempt to localize the underlying NET. Nonfunctional NETs are typically discovered incidentally on endoscopy or cross-sectional imaging.

These tumors are not uniformly distributed within the GI tract. In the SEER 17 registry[6], gastorentero-pancreatic NETs made approximately 61% of NETs. In GI tract, the following sites were identified as common locations for NETs: rectum (17.7%), small intestine (17.3%), colon (10.1%), pancreas (7.0%), gastric (6.0%) and appendix (3.1%). This updated analysis showed a continued increase in the incidence of NETs, particularly in locations such as the rectum, stomach and small intestine, areas in which flexible and video capsule endoscopy have been utilized more often by gastroenterologists over the past few decades[6].

ENDOSCOPIC MANAGEMENT

GI NETs may be encountered during endoscopy under several circumstances. The first scenario is during endoscopic localization for an NET diagnosed by serologic or biochemical means (for instance, a suspected gastrinoma based on markedly elevated gastrin level and diarrhea). Secondly, hormonally inactive NETs may be discovered during evaluation of other symptoms such as GI bleeding or abdominal pain

caused by the tumors themselves. Finally, NETs may be incidentally discovered during endoscopy for upper GI symptoms or during screening colonoscopy. Once the diagnosis of a GI NET has been made by biopsy and histologic evaluation, staging must be performed to determine the appropriate treatment. If small and localized, these lesions can be effectively treated with endoscopic therapy. However, failure to recognize the size, depth, local invasion, or lymphatic spread may lead to incomplete treatment with endoscopic means. It is essential to recognize when surgical excision is the superior modality, and multidisciplinary evaluation of GI NETs is recommended prior to treatment.

ESOPHAGUS

Esophageal NETs comprise only 0.2% of GI NETs[6], and thus their endoscopic and histological features are not well characterized. A 2009 review identified only 25 reported cases in the previous 4 decades[9]. There are no established guidelines for treatment, which is thus dictated by provider experience and patient preference. Case reports describe a favorable prognosis in most subjects. Esophageal NETs may present incidentally as discrete polypoid lesions, or in association with adenocarcinoma in the setting of Barrett's esophagus[10,11]. Low-grade carcinoid lesions have been described, and these have a good prognosis following resection. However, atypical esophageal NETs (classified as large cell esophageal carcinoma or small cell esophageal carcinoma) may present at late stages with large fungating masses. These lesions have high mortality within a year despite surgical resection and subsequent chemotherapy[12-14].

Historically surgical resection has been the preferred treatment for esophageal NETs[15], though endoscopic resection is now considered safe and effective for small or superficial lesions. Esophageal NETs limited to the submucosal layer (without involvement of the muscularis propria) can be removed easily and safely[16]. In fact, endoscopic removal has been utilized frequently for esophageal NETs localized to submucosal layer and $\leqslant$ 10 mm in diameter without ulceration or erosion as these lesions had low probability for lymph node metastasis[9]. The threshold of 10 mm as the maximum size recommended for endoscopic resection of esophageal NET is based not on a large body of evidence for this location, but rather on extrapolation of data from gastric and rectal NETs, which have shown higher rates of lymph node metastases when lesions exceed 10 mm in size.

Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) can each be considered for removal of low-grade esophageal NETs. EMR can allow an en bloc resection of a small lesion, though some authors have posited that ESD is preferable as EMR can lead to mechanical damage and limited pathological evaluation of the resected specimen[9]. ESD can enable complete removal of the tumor while maintaining an adequate horizontal margin for histologic review to ensure complete removal. Endoscopic ultrasound is recommended prior to removal to ensure the lesion does not extend to the muscularis propria, though there are no high-quality studies to show the efficacy of endoscopic ultrasonography (EUS) in delineating esophageal NET margins prior to resection.

STOMACH

Gastric carcinoids (GCs) can be asymptomatic and found incidentally. However, in certain subjects they are found during endoscopic evaluation of dyspepsia, abdominal pain or early satiety[17]. They are categorized into three groups in the following order in terms of frequency: Type 1 GCs (75%) and Type 2 GCs (5%-10%), which are well differentiated, and Type 3 GCs (15%-25%) which demonstrate aggressive behavior[17]. Type 1 GCs are typically small and multiple, seen in the setting of chronic atrophic gastritis with resulting stimulation of enterochromaffin cells by elevated gastrin levels. Type 2 GCs are similarly expressed due to excess gastrin levels in the setting of gastrinoma or multiple endocrine neoplasia type 1 (MEN-1). Type 3 GCs are sporadic, typically solitary and often larger when compared to types 1 and 2, and occur in the setting of normal gastrin levels.

GCs have been removed safely with endoscopy both in adults[18] and in children[19]. Various techniques can be used for resection of these lesions. ESD and EMR with utilization of cap aspiration, a ligation device, or grasping forceps are the most commonly used approaches, and all have been successful. However, initial studies comparing EMR and ESD have shown higher en bloc resection of lesions with ESD when compared to EMR[20,21]. In a recent study comparing the vertical and horizontal margins of 12 subjects who underwent either EMR or ESD, horizontal margins were negative in all subjects regardless of technique[22]. However, 66.7% of subjects in the EMR group had positive vertical margins compared to 0% of subjects in the ESD group. This small study suggests the superiority of ESD in complete removal of small GCs. Additional studies will be needed to confirm these findings and determine their clinical importance.

Metastatic progression of type I GCs is exceedingly rare, but has been described, so it is important not to overlook this possibility when considering endoscopic removal. A study examining prognostic factors in 20 patients with Type 1 GCs identified several factors associated with metastasis: tumor size of $\geqslant$ 1 cm, elevated Ki-67 index of tumor proliferation, and high serum gastrin levels (mean value 2138.4 mI/L)[17]. Careful examination to determine tumor size and depth of invasion can help in identifying those rare Type 1 or 2 GCs which should be managed with surgery and lymph node sampling.

Type 3 sporadic GCs are generally managed surgically due to their size and stage at the time of

diagnosis. Endoscopic management is rare but has been described. One center has described a series of 50 cases in which endoscopic resection of NETs confined to the submucosa and < 2 cm in size was attempted (41 EMR, 9 ESD)[23]. Complete removal was achieved in 80% of cases, and in 13-60 mo of follow-up there were no recorded instances of tumor recurrence, regardless of the completeness on initial resection. Another investigation utilized SEER data and identified 984 subjects with localized GCs who had cancer-directed surgery between 1983 and 2005. Results revealed that tumor size and depth predict lymph node metastasis and endoscopic therapy can be an option for intraepithelial GCs < 2 cm and GCs < 1 cm that invades into the submucosa or lamina propria[24]. Societal guidelines such as the National Comprehensive Cancer Network (NCCN) recommend staging of type 3 GC with EUS, multiphasic computerized tomography (CT) or magnetic resonance imaging (MRI), or somatostatin receptor scintigraphy to determine the appropriate stage and treatment modality. If EUS shows no evidence of lymphadenopathy, then surgical wedge resection or endoscopic resections are appropriate; otherwise, radical resection with lymphadenectomy is preferred[25]. The American Society for Gastrointestinal Endoscopy recommends that all type 3 GCs should be considered for surgical removal based on a high incidence of lymph node invasion, and only very small (< 1 cm), well-differentiated lesions should be considered for endoscopic removal[26]. As in other areas of the GI tract, proper assessment and staging of the lesion are critical for determining the threshold for endoscopic versus surgical removal of gastric NETs.

SMALL INTESTINE

The small intestine is one of the most common sites for NETs (17.3%)[6], though a large proportion of these lesions may not be accessible by standard bidirectional endoscopy. Duodenal NETs make only a small percentage of small bowel NETs[27] but can be candidates for endoscopic resection if the lesion is < 1 cm and confined to the mucosa and submucosa. Lesions of the ampulla or the medial wall of the duodenal C-sweep may be easily missed with use of standard forward-viewing endoscopes, and any survey of the duodenum for localization should ideally include use of a side-viewing duodenoscope. Duodenal bulb NETs are particularly likely to be found incidentally and with small size, with a small likelihood of metastatic disease. Although duodenal NETs < 2 cm have been shown to have limited metastatic potential and can be managed with local excision, tumor size alone does not predict risk of metastatic disease or lymphatic spread[28,29]. Cases of duodenal NETs as small as 5 mm with metastatic lymph node lesions have been reported[27,30]. Duodenal carcinoid tumors that are less than 1cm and limited to the submucosa with no evidence of lymphatic or metastatic disease are candidates for EMR or ESD[31,32]. Novel techniques for endoscopic resection include full-thickness resection with the use of an over-the-scope clip[33]. Careful follow-up examination for local recurrence is needed if decision is to remove these lesions with endoscopic resection[31]. When feasible, endoscopic resection is supported by the 2016 NCCN guidelines[25]. Surgical resection has been recommended for duodenal NETs larger than 1 cm, especially when there is imaging evidence of lymph node involvement or higher mitotic index[34]. Once again, careful examination of the lesion by endoscopic ultrasound is important to determine size and depth of invasion, as well as lymph node metastases.

NETs of the jejunum and ileum are classified as midgut tumors. They may be associated with carcinoid syndrome along with other midgut NETs such as appendiceal and cecal NETs[35]. Jejunal or ileal carcinoids may also present with anemia or overt bleeding, in which case they may be identified during video capsule endoscopy, deep enteroscopy, or colonoscopy with intubation of the terminal ileum[36,37]. Larger NETs may present with obstructive symptoms, including retention of video capsule endoscopy requiring retrieval of the capsule[38]. The majority of NETs of the small intestine are located in the distal ileum. Population based studies revealed that only 29% of NETs located in jejunum and ileum are localized and 71% have either regional or distant metastases[35]. Given the multifocal nature and potential technical difficulty of endoscopic resection of midgut small bowel carcinoids, surgical excision is preferred. The role for endoscopy in these NETs is limited to treatment of bleeding, or histologic confirmation by biopsy and localization by tattoo placement adjacent to the lesion[39]. Even with surgery, the 5-year survival rates for NETs located in these regions are 65% if localized and 71% if there is regional involvement[35]. While partial small bowel resection can be considered for proximal tumors, in such cases the remaining small intestine needs to be examined during resection to exclude multifocal disease[40].

COLONIC

Colorectal NETs comprise the majority of GI NETs (27.8%) and rectal NETs have been recognized more frequently over the past decade due to the increased utilization of screening colonoscopy[6]. Colonic NETs are often locally advanced or metastatic at the time of diagnosis, with a poorer prognosis than NETs located in other parts of GI tract. The 5-year survival rate is only 40% to 70% depending on the location and stage[41]. The larger size, invasive features, and (sometimes) anatomically challenging positions are contraindications to endoscopic management of many colonic NETs, similar to lesions in the jejunum and ileum. Endoscopic therapy with ESD has been reported, but only in small case series and with a higher risk of postprocedural

complications and incomplete resection[42]. Thus, surgical resection with lymphadenectomy is the approach recommended by NCCN guidelines and utilized frequently for these NETs.

RECTAL

Surgical resection with removal of associated lymphatic tissue remains the treatment for rectal NETs greater than 20 mm, due to the high risk of lymphatic invasion and metastasis. However, endoscopic resection is used for rectal NETs of < 20 mm without signs of deep invasion or lymphadenopathy. There is extensive experience with EMR of rectal NETs, mainly due to its ease and low complication rates. Conventional freehand EMR, cap-assisted EMR, or band ligation-assisted EMR have all been used with success and with minimal adverse events in NETs of < 1 cm in size[43-45]. However, with rectal NETs of 11-20 mm in size, complete resection of an en bloc specimen may prove more difficult using EMR[46-48]. This has spurred interest in the use of either ESD or modified EMR techniques to improve the rate of R0 resection while maintaining safety. A hybrid technique employing a "circumferential incision to EMR" (CIEMR) has been adapted to treat rectal NETs without regional lymph node enlargement[49]. When compared to conventional EMR in a randomized prospective trial of rectal NETs < 15 mm, procedure time was longer in CIEMR but R0 resection was superior (96.7% in CIEMR group compared to 82.14% in EMR group (P = 0.043)[50]. Other modifications include combining a circumferential mucosal incision with rubber band ligation (ESD-L)[51]. These techniques provide the advantage of a circumferential incision to ensure a clear lateral margin during resection, but allow the endoscopist to skip the time-consuming submucosal dissection in favor of snare-based resection.

ESD was initially pioneered for treatment of superficial gastric neoplasms and provides additional advantages in regards to en bloc removal and complete histological resection[20,52]. A comparison of ESD and EMR in subjects with rectal NETs < 16 mm without lymphadenopathy revealed similar en bloc resection rates in both groups, but a significantly higher histologic R0 resection rate in ESD group (90.3%) compared to EMR group (71%)[53]. Complication rates were similar for both groups. A retrospective analysis of 239 patients with colorectal NETs < 20 mm showed further evidence of the safety and efficacy of ESD; all but 6 of these lesions were located in the rectum. En bloc resection was achieved in all cases, and in all cases no local recurrence was noted over a median follow up period of 52 mo. Of note, distant metastases were noted in 6 patients (2.51%) during follow-up, underscoring the need for accurate assessment of deep invasion and lymphadenopathy prior to endoscopic removal[42]. ESD appears to increase the probability of complete histological resection when compared to EMR, and may provide an advantage in those NETs 11-20 mm where EMR techniques may not reliably provide a complete resection. A recent meta-analysis looked into 14 studies that included 782 subjects to compare the efficacy and safety of EMR or modified EMR (m-EMR) versus ESD for the treatment of rectal NETs[54]. Results revealed significantly higher rates of pathological complete resection among subjects treated with ESD or m-EMR compared to those treated with conventional EMR (OR = 0.42 and OR = 0.10, respectively) but no significant differences between m-EMR versus ESD groups. In summary, current data supports that m-EMR or ESD can be utilized safely in experienced hands for removal of colorectal NETs less than 2 cm without high-risk features.

The feasibility of endoscopic resection of rectal NETs by EMR or ESD is supported by treatment guidelines, as long as accurate staging is performed. The European Neuroendocrine Tumor Society (ENETS) consensus guidelines from 2012[41] note the importance of high risk features and recommended that rectal or colonic NETs larger than 2 cm or with high-risk features (advanced stage, high mitotic index, muscularis propria invasion or nodal disease) be removed surgically. Other NETs were considered to be candidates for endoscopic resection. These recommendations are mirrored by the NCCN, in which transanal surgical resection or endoscopic techniques are both recommended (following examination by MRI or EUS) for rectal NETs < 2 cm in size.

PANCREAS

Pancreatic NETs (PanNETs) make approximately 7% of GI NETs[6]. They have slightly higher predominance in males and Caucasians[55,56] and peak during the sixth and seventh decades of life[3]. They can be categorized into two groups as functioning versus non-functioning depending on the presence or absence of clinical syndromes related to hormone production. Functioning PanNETs have been reported in the following frequencies: Insulinomas (45%), gastrinomas (20%), glucagonomas (13%), VIPomas (10%) and somatostainomas (less than 5%)[54]. Cumulative 5-year survival has been reported to range between 30% to 97% in PanNETs[57]. The wide variability likely reflects heterogeneity of presentation, with hormonally active tumors being diagnosed at earlier stages during investigation of symptoms.

CT and MRI have been utilized frequently as imaging modalities during diagnosis of PanNETs. The sensitivity and specificity of these imaging modalities have been reported to differ in CT (60%-83% and 83%-100%, respectively) depending on lesion size and also in MRI (85%-100% and 75%-100%, respectively)[57]. Endoscopists play a crucial role in identification and evaluation of PanNETs by EUS. EUS provides not only key information about morphological features of these lesions, but also enables tissue

sampling for histopathological evaluation. Due to its high sensitivity for small lesions, EUS can also identify PanNETs undetected by cross-sectional imaging studies. A review of 81 subjects referred for EUS-guided fine-needle aspiration (EUS-FNA) for a suspected PanNET revealed diagnostic yield of EUS-FNA to be 90.1%[58]. Another large, single-center prospective series studied the utility of EUS early in the diagnostic evaluation of subjects with PanNETs who subsequently had surgical confirmation of tumor localization[59]. In this investigation overall sensitivity and accuracy of EUS was 93% and investigators pointed out the role of EUS as a primary diagnostic modality during evaluation and management of PanNETs. Another study of 72 subjects with PanNETs demonstrated EUS to be not only highly accurate in localizing PanNETs but also cost effective when utilized early in the preoperative course by decreasing the need for further invasive tests[60]. Surgical resection is the recommended treatment modality in PanNETs, and type of resection in PanNETs is mainly determined by size and location of the lesion. EUS - in combination with cross-sectional imaging - can provide crucial information regarding the location and stage of PanNETs to optimize treatment planning.

Besides accurately determining the size and characteristics of lesions, EUS also provides key histological information when combined with FNA. In a retrospective study, 75 out of the 81 patients underwent EUS-FNA and the yield of EUS-FNA reached up to 97.3%[58]. In a recent study, the utilization of FNA along with EUS characterized the nature of the pancreatic NETs in all cases[61] by providing accurate pathological information showing the critical role of EUS-FNA in preoperative management of these patients. In addition, the sampling rate for histological diagnosis by EUS-FNA was shown to be 100% and the concordance rate was 87.5% when it was compared with surgical specimens[62]. EUS thus has a crucial role in planning treatment strategies for PanNETs.

Given the importance of staging for luminal NETs prior to treatment, EUS is also a critical tool for evaluating tumor size, depth of invasion, and presence of lymphadenopathy in these lesions. Multiple studies have demonstrated the utility of EUS for accurately determining resectability of small NETs in the stomach, duodenum, and rectum[63]. EUS has been used to confirm a lack of muscular invasion in a case series of ESD for rectal carcinoids as well[64]. The information gleaned by accurate staging allows the endoscopist to choose the correct strategy (endoscopic or surgical) to afford a definitive cure in a minimally invasive fashion.

NOVEL TECHNIQUES

While EMR and ESD remain the most common endoscopic techniques for treatment of luminal NETs, newer techniques have been employed in an attempt to completely excise these submucosal tumors. For example, submucosal tunneling with endoscopic resection can be utilized to resect esophagogastric NETs arising from the deep submucosal layer. Following its initial use[65], investigators have reported several case series which revealed success rates up to 100% without major complications[66]. Another new technique that is limited to pioneering centers with defined protocols is peroral endoscopic tumor resection (POET). As a technique adapted from the successful management of achalasia with per oral endoscopic myotomy (POEM), POET also utilizes submucosal tunneling approach and provides an opportunity for en-bloc removal of the tumor followed by mucosal closure. POET can provide definitive en-bloc resection, excellent long-term results, and can be applied in cases where surgical resection is not an option due to comorbidities, though its use is limited to tumors of the esophagus, GE junction, and gastric cardia[67]. POET requires experience with POEM and ESD, and has only been utilized in specialized centers.

Endoscopic full-thickness resection (EFTR) has been employed for treatment of some gastric submucosal tumors. Case series have described successful resection in all subjects without laparoscopic assistance and success rate for complete resection was 100%[68]. In a different investigation, mean operative times, length of stays and complete resection rates were found to be similar among subjects who had EFTR (n = 32) *vs* laparoscopic surgery (n = 30) for treatment of gastric stromal tumors[69]. Another study that included 48 subjects with mean tumor size of 1.59 cm (largest lesion 4.8 cm) reported successful removal in all cases and there was no early recurrence during the follow-up period[70]. However, these techniques are not widely available and should be applied only by experts in dedicated centers. In addition, EFTR is ideal for tumors arising from the muscularis propria (such as GISTs) and may not provide superior outcomes when compared to ESD, as most GI NETs remain confined to the submucosa. Future studies will define the roles of these techniques in the management of GI NETs.

CONCLUSION

GI NETs are uncommon neoplasms which may represent a therapeutic challenge for the endoscopist. The choice of proper treatment depends on the location of the NET as well as proper evaluation of size, depth of invasion, and local lymphadenopathy. Endoscopic resection techniques continue to evolve, with the growth of endoscopic mucosal dissection showing promising results in achieving complete and safe en bloc resection of lesions as large as 2 centimeters. Despite the improvements in technique, the enthusiasm for endoscopic resection of larger lesions must be balanced against the superior ability of surgical resection to detect and treat lymphatic spread. Future directions for research should focus not only on optimizing the techniques for endoscopic treatment, but improving the recognition of factors that should

prompt surgical referral.

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