EXPERT REVIEWS

Endoscopic resection for gastrointestinal neuroendocrine tumors

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Gastrointestinal (GI) and neuroendocrine tumors (NETs) can be treated by mini-invasive endoscopic resection when localized in the superficial layers of the bowel wall and their size is <20 mm. Endoscopic diagnosis of NETs is usually incidental or suspected after clinical, laboratory or imaging findings. Endoscopic mucosal resection is the most commonly used technique for NET removal, endoscopic submucosal dissection is indicated in selected cases, while papillectomy is feasible for ampullary lesions. Histopathologic assessment of the resection margin (circumferential and deep) is important for staging. Incidence of endoscopic mucosal resection-/endoscopic submucosal dissection-related complications for removal of GI NETs are similar to those reported for other GI lesions. Endoscopic follow-up is based on histopathologic characteristics of the resected NETs and its site. NETs >20 mm in size, with penetration of the muscle layer and/or serosa are at high risk for metastases and surgical approach is recommended when feasible.

Keywords: ampullectomy • endoscopical mucosal dissection • endoscopic mucosal resection • gastrointestinal • neuroendocrine tumors

Neuroendocrine tumors (NETs), previously referred as 'carcinoids' (carcinoma-like), are a heterogeneous group of neoplasia that originates from the neuroendocrine cells. These cells are widely dispersed throughout the body with a regulatory function due to the secretion of biogenic amines. Most commonly NETs are localized in the GI tract. Other localizations include the bronchopulmonary tree and less often ovaries and testes [1]. More often NETs are sporadic and single, but they can also be multiple and be part of familial syndromes such as MEN1, von Hippel–Lindau or neurofibromatosis type 1.

Their clinical manifestation is diverse. 'Nonfunctioning' tumors are initially asymptomatic due to the small dimensions of the primary tumor (<20 mm). Uncommonly they can produce obstruction (bile duct or bowel), perforation or bleeding in the GI tract. They become symptomatic later in their course due to the mass effect of the primary tumor and/or when distant metastases occur [2,3]. When 'functioning', they can be discovered even when they are small due to the symptoms caused by the biogenic amines that they produce. The typical carcinoid syndrome (constellation of symptoms due to the secretion of bioactive products) is characterized by diarrhea, flushing and bronchospasm [4]. These biogenic amines can also cause carcinoid disease of the heart (right-sided cardiac valve disease) [4,5]. But this syndrome is relatively uncommon in localized disease, and when present the disease is usually advanced. These symptoms can also contribute to misdiagnosing the actual disease as they can be attributed to conditions that are more common (irritable bowel syndrome, food allergy etc.).

In the USA, the prevalence of gastroenteropancreatic NETs has been calculated at 35 per 100,000 tumors [6]. Previously under-recognized, their prevalence has increased in the last years due to the increased use of computed tomography (CT) and endoscopy. Endoscopical diagnosis of NETs of the gut is more commonly incidental, or based on previous clinical suspicion. Different modalities of treatment are available (endoscopic, surgical and pharmacological) and treatment approach is dependent on the tumor site, size, type, histological grade, stage and symptoms.

Endoscopic diagnosis

The primary NET tumor is most often localized in the GI tract. Within the GI tract, the small intestine is the most frequent site (34%), then

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the rectum (23%), colon (19%), stomach (7.7%), pancreas (7.5%) and appendix (6.6%). Upper GI endoscopy detects NETs localized in the esophagus, stomach, duodenum and periampullary lesions. Lower GI endoscopy detects lesions in the colo-rectum and terminal ileum. Capsule endoscopy and push-enteroscopy are suitable for detection of lesions in the small intestine. While capsule endoscopy is more comfortable option for the patient, it lacks biopsy capabilities [7].

Upon endoscopical examination of the GI tract, NETs appear as polypoid lesions of various dimensions, usually <20 mm, and can be solitary or multiple. Most commonly they are covered with normal mucosa. Rarely overlying mucosa is ulcerated or bleeding. Endoscopy can be indicated upon clinical, laboratory or imaging studies or more frequently these lesions represent incidental findings.

Definitive diagnosis is made by histological examination of bioptic samples from the lesion, preferably obtained with deep biopsy. Further immunohistochemical analysis for specific neuroendocrine cell markers is necessary, like immunostaining for chromogranin A (CgA) and/or synaptophysin (Figure 1). Assessing the proportion of proliferative cells (mitotic count and Ki-67 index) is important regarding the prognosis.

The diagnostic work-up of GI NETs also includes biochemical tests, radiological contrast studies, nuclear imaging and endoscopic ultrasound. A very sensitive marker of NETs is the plasma level of CgA [8]. It correlates well with the tumor burden but is also very useful for monitoring for recurrence of the disease [9]. Though sensitive, it lacks specificity as this marker can be elevated in other neoplastic diseases like cancers of the pancreas, lung or prostate [10] and in conditions such as atrophic gastritis and renal impairment. Treatment with proton pump inhibitors also results in elevated values of CgA [11]. Other biochemical tests that help in refining the diagnosis of NETs are assessment of serotonin degradation product such as urinary 5-hydroxyindole-3-acetic acid (5-HIAA), and other specific amines and peptides secreted by NETs (serotonin, histamine, gastrin, vasoactive intestinal peptide and tachykines). The other diagnostic modalities, CT, magnetic resonance, nuclear imaging techniques, PET and somatostatin receptor scintigraphy (SRS), are helpful for diagnosis, staging and follow-up.

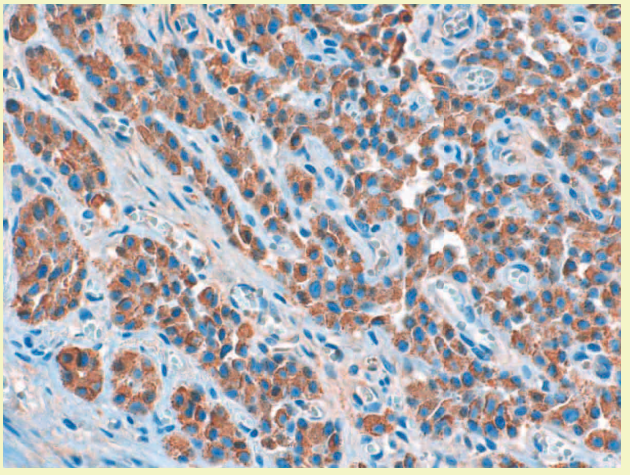

Figure 1. Extensive positivity for chromogranin A (immunoperoxidase).
Figure provided courtesy of F Inzani (Università Cattolica del Sacro Cuore-Policlinico A, Rome, Italy).

On endoscopic ultrasound (EUS), NETs accessible for EUS present as hypoechoic masses in the submucosa with or without invasion. With EUS, it can be readily determined the layer of origin and wall layer involvement (submucosa vs muscularis propria), and thus aid in the decision of treatment approach (endoscopic vs surgical). Since the accuracy of EUS in differentiating malignant from benign lesions is limited [12], definitive diagnosis still relies on pathological confirmation after removing the lesion *in toto*.

The current recommended classification system for gastroenteropancreatic (GEP) NETs was developed and published in 2000 [13] by the WHO and updated in 2010 [14]. This classification is based on tumor site of origin, clinical syndrome (functional and non-functional tumors), tumor grade and differentiation. The grading system for NETs is based on the rate of proliferation defined by the mitotic rate and Ki-67 index [15]. Accordingly, high proliferative indices are characteristic for high-grade tumors associated with aggressive behavior, while low proliferative indices are characteristic for low-grade tumors that are considered to be indolent in nature [16]. According to the differentiation, GEP NETs are classified into well-differentiated and poorly differentiated NETs. Differentiation of the tumor correlates with the grade of the tumor; the poorly differentiated NETs being usually of high grade, while well-differentiated are usually of low or intermediate grade [14,16]. A detailed assessment of the histological characteristics of the tumor as well as the extent of local spread is of great importance regarding prognosis and therapy determination. Therefore, every pathological report should include minimum data set as proposed by the US consensus document on the pathology of NETs [17].

Endoscopic resection

All GI NETs, despite tumor size, should be considered potentially malignant and warrant detail evaluation of the organ wall involvement as well as the presence of distant metastases. Two endoscopical organ-sparing treatment modalities that result in whole lesion removal are endoscopic mucosal resection (EMR) and endoscopic mucosal dissection (ESD). They can be offered for early malignant lesions as for benign lesions, both of which are limited to the superficial layers of the organ wall. Generally, they are suitable choice for GI NETs with small dimensions (≤20 mm) and in the absence of penetration of the muscularis propria and metastases. Those GI NETs showing deep wall involvement, beyond the muscular layer and/or dimensions >20 mm carry high risk for metastases [18–20]. NETs of the ampulla, duodenum, small bowel and rectum even at size ≤11 mm are considered to be at high risk for deep infiltration and metastases [20]. A better evaluation of the lesion is achieved by performing EUS before endoscopic resection, upon determining extent of invasion, tumor size and site of origin.

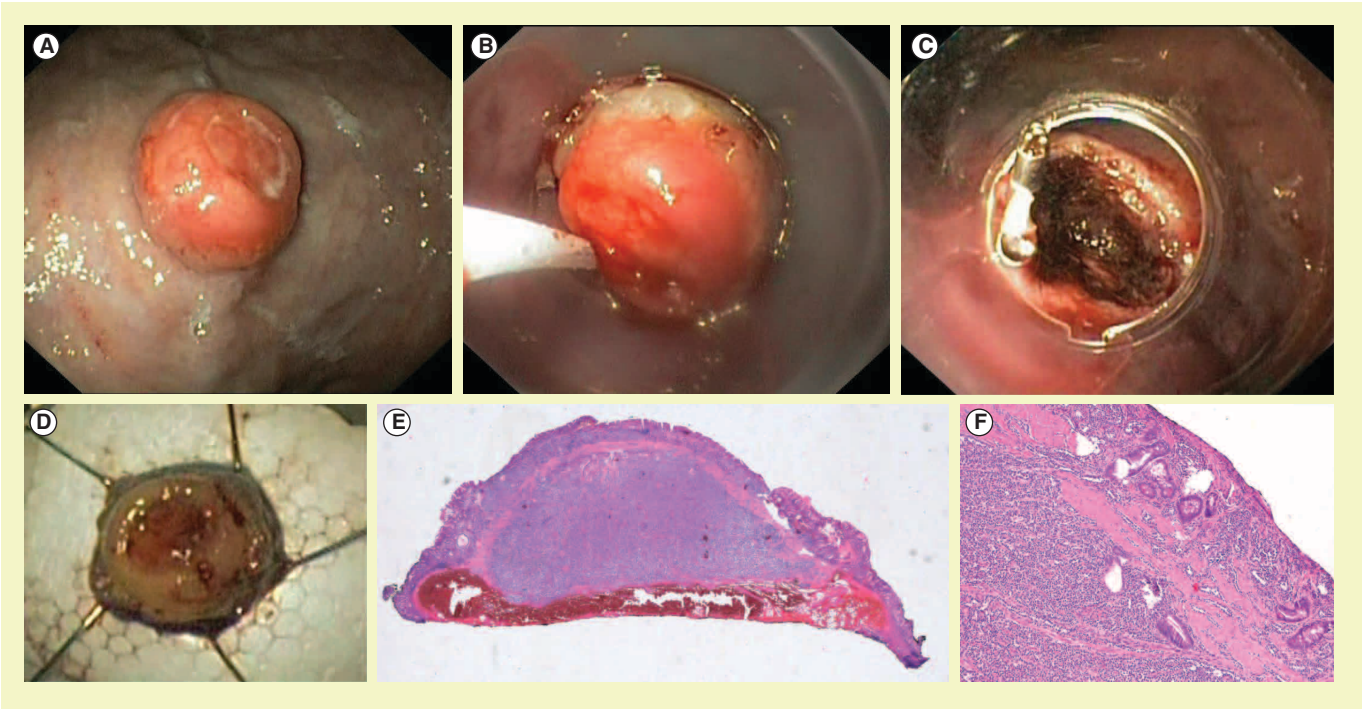

Figure 2. Cap-assisted mucosectomy for gastric neuroendocrine tumor. (A) Endoscopic appearance of the lesion. **(B)** The 'safety cushion' was created injecting saline with adrenaline and indigo carmine. **(C)** Endoscopic appearance after mucosectomy. **(D)** The resected tumor. **(E)** Microscopic image if the lesion. **(E)** One of the serial sections performed on endoscopical mucosal resection with neoplasia invading lamina propria and deep submucosal. **(F)** Well-differentiated neuroendocrine tumor is associated with chronic atrophic gastritis with intestinal metaplasia and shows a typical thinly trabecular structure formed by relatively monomorphic cells. Figures **(E)** and **(F)** provided courtesy of F Inzani (Università Cattolica del Sacro Cuore-Policlinico A, Rome, Italy).

Accordingly, the choice of endoscopic treatment for GI NETs is highly dependent on size as well as site and location of the lesion into the wall layers. EMR is suitable for lesions ≤10 mm [21–26], while ESD for larger lesions (≤20 mm) [27–29]. Small ampullary NETs (<10 mm) are indication for papillectomy.

Endoscopic mucosal resection

EMR is an endoscopic technique used for removal of small lesions limited to the mucosa/submucosa. Three modalities of EMR are used; injection-, cap- or ligation-assisted EMR.

In injection-assisted EMR a 'safety cushion' is created with injection of solution into the submucosa, followed by removal of the lesion with electrocautery snare in en-bloc or piecemeal manner (depending on size of the lesion). This 'safety cushion' prevents deep mechanical or electrocautery damage, and in the same time facilitates the removal as it lifts the lesion.

Cap-assisted EMR (EMR-C) (Figure 2) is performed with the use of caps on the tip of the endoscope. These caps are cylindrical, made of transparent plastic and can be soft or rigid. Caps are available with oblique (for esophageal lesions) or flat circular tip (for gastric and rectal lesions) with outer dimensions from 12.9–18 mm [30]. In cap mucosectomy a 'safety cushion' is also created. After the endoscope is positioned over the lesion, a retraction of the lesion into the cap is achieved by applying suction. Then with closing the snare, a resection with electrocauterization of the lesion is made. The electrocautery snares used in this type of EMR are specially designed crescent-shaped snares, that when opened, are positioned on the inner circumferential ridge at the tip of the cap [30].

In ligation-assisted EMR (EMR-L) a standard variceal band ligation device is used. Submucosal injection is also an option in this procedure, however it is rarely performed [27,30,31]. When the endoscope is positioned over the lesion, the band is released after retraction of the lesion by suction. Afterward, a safe resection with electrocautery snare is made below the band.

Papillectomy

Removal of the ampullary lesions is usually done with standard polypectomy snare (Figure 3). Submucosal injection of solutions is

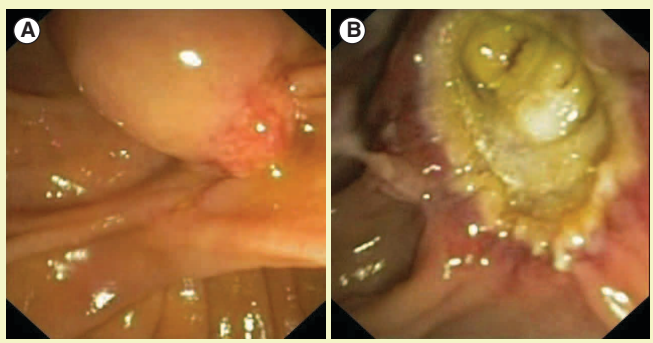

Figure 3. Ampullary neuroendocrine tumor. Endoscopic appearance **(A)** before and **(B)** after snare papillectomy.

dependent on local expertise and the characteristics of the lesion. It is recommended that this type of lesions should be managed by endoscopist experienced also in ERCP as proper drainage of the pancreatic and bile duct is necessary after papillectomy.

Endoscopic submucosal dissection

ESD allows complete 'en bloc' submucosal resection of lesions, which allows an accurate thorough histopathological assesment. The margins (deep and lateral) of the resected specimens can be more adequately examined for lymphovascular infiltration and depth of invasion [32–35]. ESD is characterized by three steps: creating submucosal cushion by injecting fluid in the submucosa, cutting the surrounding mucosa in circumferential manner and subsequent dissection of the submucosa beneath the lesion. Afterward, the specimen is placed on a plate of rubber or wood with the submucosal side facing the plate; the periphery is fixed with thin needles; then the specimen is immersed in formalin and is sent for histological evaluation (Figure 4) [30]. However ESD is also characterized with some disadvantages that include the following: the requirement of a high level of technical skills, it is time-consuming and there is higher risk of complications [32–35].

Submucosal injection solutions

Creating 'safety cushion' with submucosal injection warrants bigger safety during endoscopic resection, either ESD or EMR. The injected solution separates the lesion from the muscularis propria thus prevents perforation and thermal damage to the underlying tissue. The most widely used solution is normal saline solution (0.9%).

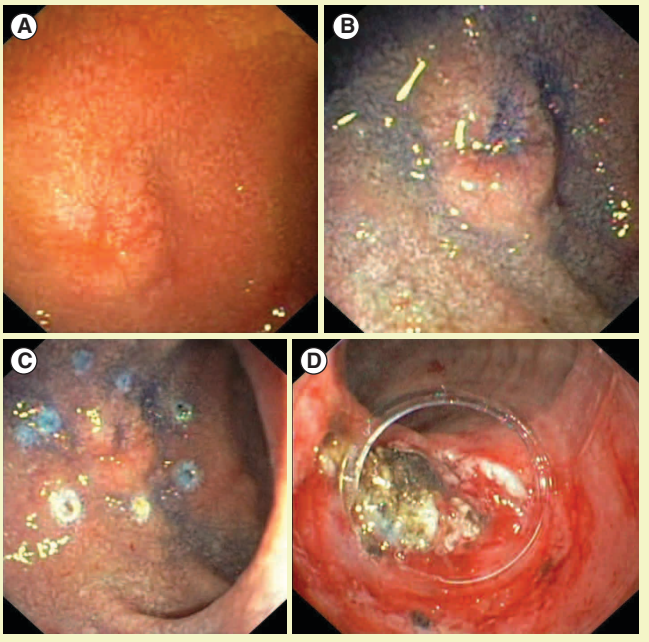

Figure 4. Endoscopic submucosal dissection (ESD) for duodenal neuroendocrine tumor. (A) Endoscopic appearance of a duodenal neuroendocrine tumor. **(B)** Endoscopic appearance after coloration with methylene blue dye.**(C)** The lesion was marked with argon plasma before ESD. **(D)** Final endoscopic appearance after ESD.

Commonly, staining dye (e.g, indigo carmine or methylene blue) is added to help in better identification of the deep margins while resecting [36]. In some instances, epinephrine is added to reduce the risk of bleeding. During the endoscopic resection several injections of saline are necessary as the solution undergoes penetration and diffusion in the surrounding tissue and the mucosal lift is lost.

Studies in recent years showed that several other agents such as sodium hyaluronate (HA), hydroxypropyl methylcellulose, mannitol, glycerol and fibrinogen produce longer-lasting mucosal elevation [37–41]. Extended mucosal elevation is particularly important when ESD is performed. One study showed that injection of solution of 0.4% sodium hyaluronate diluted with the same volume of normal saline resulted in improvement in ease of submucosal injection and ease of snearing in colorectal EMR [42]. Disadvantages like high cost and difficult administration limits their use in routine endoscopy. Some studies reported tissue damage and local inflammatory reactions when hydroxypropyl methylcellulose, hypertonic sodium chloride (3.75%), and hypertonic dextrose (>20%) are used [39]. There are concerns about the use of HA because of possible stimulation of tumor growth which inhibits its general use [43,44]. Investigations with autologous blood products and whole blood have given promising results [45,46]. They are readily available cheap alternatives without risk of transmission of infectious agents. Injection of whole blood showed superiority in height and durability of the safety cushion and favorable effects like promoting local hemostasis compared to other solutions [46]. The promising role of autologous whole blood in EMR or ESD and its preparation requires further *in vivo* studies in humans.

Esophagus

Esophageal NETs are uncommon. These tumors have a more distal distribution in the esophagus, corresponding to the distribution of the NE cells in this organ. They arise from the mucosal lamina propria or the submucosa. They are usually diagnosed by upper GI endoscopy due to the symptoms they cause, such as: pain, weight loss, fatigue, dysphagia, heartburn and melena [47]. On endoscopic examination they present as polypoid lesions. Invasion through the muscularis propria and lymph node metastases are not uncommon, so careful evaluation is imperative [47,48]. EUS is a useful diagnostic method for defining the degree of invasion through the esophageal wall which in turn helps planning the treatment (endoscopy or surgery). Possible endoscopic treatment modalities for esophageal NET are EMR (also cap-assisted EMR) and ESD. In a recent report in the literature, mid-esophageal NET was successfully resected using the EMR technique [49].

Stomach

Gastric NET represent about 7.7% of all the GI NET. Over the past years their observed incidence has risen due to the widespread use of gastroscopy and improved diagnostic histopathological techniques. These tumors usually derive from the histamine-secreting enterochromaffin-like (ECL) cells, the most common gastric neuroendocrine cell type. They differ among themselves

according to their pathogenesis and pathological findings, thus they are characterized with different biological behavior. Crucial to their appropriate management is defining their type according to their pathophysiological background which influences therapeutic approach. The extent of the disease (involvement of lymph nodes, metastases) is further assessed with EUS, CT or MRI and somatostatin scintigraphy.

The NETs of the stomach are generally categorized as well differentiated and poorly differentiated neoplasms (the later regarded as neuroendocrine carcinoma) [50]. Well-differentiated NETs of the stomach are also called gastric carcinoids (GC) and they are further subclassified according to their relationship to gastrin.

Type 1 gastric NETs, which represent 75% of all gastric carcinoids [51] occur in the setting of hypergastrinemia. This hypergastrinemia is a physiological response to a chronic low-acid state such as chronic atrophic gastritis (CAG), pernicious anemia [50,52] and other autoimmune diseases [53] that cause destruction of gastric parietal cells. The chronically elevated level of gastrin leads to ECL cells hyperplasia and subsequent dysplasia and neoplastic transformation [54]. Recent epidemiological data and case reports support the potential role of long-term proton pump inhibitor induced hypergastrinemia and the development of gastric type 1 NETs [55,56]. Clinically type I NETs are usually asymptomatic and found incidentally on gastroscopy performed for other reasons [51]. The lesions are polypoid (<10 mm), commonly multiple [52], in the gastric fundus/body [50], with local growth confined to the mucosa and submucosa, low Ki67 index, without angioinvasion and low tendency for metastases. When the lesions have bigger dimensions than 10 mm, the rate for lymph node invasion and distant metastasis is slightly elevated, 3–8% and 2% respectively [57,58]. Though benign behavior is the usual pattern [59], in the course of the disease they might become less-differentiated and with high proliferation rate [60]. When appropriately managed, type 1 GCs are associated with excellent prognosis and 5-year survival rate is estimated at 96.1% [52].

Endoscopic resection is one of the treatment options for these lesions, beside surgical resection (local wedge excision, antrectomy) and pharmaceutical intervention. Endoscopic mucosal resection is appropriate for intraepithelial tumors <20 mm and for tumors <10 mm invading into the lamina propria/submucosa [61]. Recent studies showed that endoscopic management for type 1 GC is safe and effective method with 100% survival rate [60].

Type 2 gastric NETs are also gastrin dependent. They are associated with hypergastrinemia due to autonomous gastrin secretion from a gastrinoma in the setting of multiple endocrine neoplasia (MEN1). Since the parietal sells are intact, type 2 gastric carcinoids are associated with low intraluminal pH and the development of multiple duodenal mucosal ulceration characteristic of Zollinger-Ellison syndrome [50]. Clinically they can manifest with symptoms due to hyperacidity (serious peptic ulcer disease). On endoscopy they are small multiple lesions (<10 mm) in the gastric fundus/body [52], they can be locally invasive with deep infiltration and metastasis occur in about 12% [50]. The prognosis is good for type 2 gastric carcinoids with 5-year survival rate of 60–75% and is dependent on the course of MEN1 gastrinoma [62]. These tumors can be safely treated with endoscopic resection when tumor size is <20 mm [15].

Type 3 gastric NETs and poorly differentiated gastric NEC are gastrin-independent lesions that arise in normal gastric mucosa. Type 3 NETs develop as solitary ulcerating tumors (>10 mm), from well differentiated to poorly differentiated, demonstrate aggressive local behavior with deep penetration in the gastric wall with frequent invasion of blood and lymph vessels and high incidence (24–55%) of metastasis [50]. Poorly differentiated NECs often are larger than 20 mm [63]. These two types of gastric NET often contain other endocrine cells [63] other than ECL cells or cells of non-neuroendocrine origin [64]. They can also occur with concurrent gastric adenocarcinoma [63,65]. Type 3 and gastric NECs should be surgicaly managed [15]. Their prognosis is poor, with an overall 5-year survival rate of <50% [66].

When endoscopically managed, either by EMR [25,26] or traditional polypectomy, the resected specimen must be histologically assessed for signs of angionvasion. If margins show positive then partial gastrectomy and/or local resection should be performed [67]. At present there are no published studies on ESD in the treatment of gastric carcinoids, although ESD has been proposed for en bloc R0 resection of gastric NETs [68].

Duodenum

The duodenum is less frequent primary location for GI NET. Primary duodenal NET represents less than 2% of all GI NET [69]. Duodenal NET are classified in five types based on their patohistological characteristics: duodenal gastrinomas, duodenal somatostatinomas, non-functioning duodenal NETs, poorly differentiated neuroendocrine carcinomas (predominantly ampullary) and duodenal gangliocytic paragangliomas [70].

Doudenal gastrinomas are the most common type, accounting for 50–60% of all duodenal NET. They can be either sporadic or associated with MEN1 syndrome [71], located in the first or second portion of the duodenum. Lymph node metastasis is not uncommon at the time of diagnosis even though they are usually <10 mm and limited to the mucosa or submucosal [72]. Duodenal somatostatinomas are second in frequency and often with periampullary localization. Non-functioning duodenal NETs metastatise only when the tumor has invaded the submucosa. They have a more favorable prognosis. Poorly differentiated neuroendocrine carcinomas are predominantly periampullary located. They present with involvement of the regional lymph nodes and metastasis in the liver. Duodenal gangliocytic paragangliomas are also found at the ampulla or in the periampullary region and are characterized with benign course.

Most duodenal NET are diagnosed on upper endoscopy performed for unrelated symptoms. Ampullary carcinoids more frequently present with jaundice. Hormonally active duodenal NET may develop Zollinger-Ellison syndrome, Cushing syndrome and even acromegaly, while very few patients present with the classical carcinoid syndrome.

Three independent risk factors for metastases are identified for primary duodenal NET: invasion of the muscularis propria,

tumor size >20 mm and presence of mitotic figures [73]. Tumor staging and localization is assessed with EUS, the conventional imaging methods (CT and MRI) as well as Octreoscan and the new and sensitive method ^{68}Ga-DOTATOC-PET/CT [74].

In general, primary duodenal NET can be endoscopicaly resected when <10 mm, in absence of invasion of the muscularis layer, no evidence of distant metastasis and located outside the periampullary region. Endoscopic resection with EMR for lesions <10 mm is considered safe and effective [75,76], though there is a case report on EMR of 12 mm duodenal carcinoid [77]. ESD in the duodenum is technically more difficult because of the thin wall, and longer resection time is needed with high risk of perforation [78]. Recent study showed that ESD can also be an option for duodenal lesions <10 mm, showing invasion up to the submucosal layer; while ESD is associated with extremely high risk of perforation for tumors with a wide inferior margin close to the muscularis propria layer and pathological diagnosis of a deep resection margin is less certain [79]. Papillary NETs are rare. There are small number of cases (105) in the literature and an optimal treatment is not established [80]. The preferred management is surgical with pancreaticoduodenectomy, given the serious consequences they can cause by obstructing the bile and pancreatic duct [81]. Clinically they can present with nonspecific symptoms like epigastric discomfort [82] or with jaundice (53%), pain (24%), pancreatitis (6%) and weight loss (3.6%) [83] and rarely bleeding [84]. They can be diagnosed with forward viewing endoscope [82], however better visualization is achieved with side-viewing endoscope. Additional investigation with ERCP and EUS can rule out involvement of the bile or pancreatic duct.

Although radical surgery was the traditional treatment for these lesions, endoscopic resection is also an alternative approach. Lesions suitable for endoscopic treatment are those with mainly intraluminal growth, larger than 20 mm, absent deeper invasion and no lymph node involvement and distant metastasis [81,85–87]. Although, well differentiated adenomas or carcinomas *in situ* are successfully treated with endoscopic papillectomy, there are scarce data for the possible role of papillectomy in treating NETs. In recent case report an ampullary NET was en bloc resected with the ESD method using duodenoscope; no residual lesion on follow up and no complications related with the procedure were reported [82]. ESD provides resection of the whole lesion and thus more accurate histopathological assessment of the tumor margins [88]. ESD is more advantageous because it is also less invasive than surgical treatment. However this procedure is associated with high risk of perforation and bleeding, great difficulty in operation and its success also depends on operator. ESD can be recommended in selected cases of ampullary NETs, and should be managed by skilled endoscopists.

Small bowel

Endoscopy for small bowel NETS is used mostly as diagnostic tool and rarely as therapeutic approach. These tumors are usually diagnosed late when they present with complications of advanced stage of the disease like bleeding, intestinal obstruction or bowel perforation. The typical 'carcnoid syndrome' is rare with NETs that involve the small intestine which contributes to their late diagnosis [89]. They are characterized with aggressive local behavior (transmural invasion and extensive fibrosis) and give distant metastases [90]. They can be found on capsule endoscopy or enteroscopy performed for diagnosis of unexplained intestinal bleeding or distant metastasis from unknown origin.

Small bowel NETs can be associated with concomitant or subsequent development of other neoplasms of the GI tract or from other origin like lung, ovary and prostate. This association is also observed for rectal NET and appendiceal NET [91]. Although GI evaluation is reasonable following the diagnosis of intestinal NET, there are no clear recommendations for a long-term surveillance.

Colon

NET of the colon and rectum (rectal NETs are discussed below) derive from the enterochromaffin cells (so-called Kulchitsky cells) of the gut found in the crypts of Lieberkühn. Their clinical presentation depends on the site of origin although most often is nonspecific. Carcinoid syndrome is rare with colorectal NET (<5%) and when present suggests liver metastases.

The cecum and the ascending colon are the most frequent localizations for primary colonic NETS. Due to the bigger diameter of this part of the colon compared with that of the descending and sigmoid colon, right-sided colonic NETs tend to present later. At the time of diagnosis more than two thirds are metastatic [92,93]. The 5-year survival rate is 61.8% [91]. Symptoms when present include abdominal pain, change in bowel habits, anorexia, bleeding, weight loss and weakness. NETs of the colon are identified on colonoscopy and definitive diagnosis is made by biopsy or after endoscopic resection.

Since colonic NETs are most often diagnosed when they have reached dimensions >20 mm and with regional lymph node metastases, the treatment is commonly surgical (segmental colectomy with wide regional lymphadenectomy) [94,95]. Endoscopic approach in treatment can be offered for lesions <20 mm, located in the mucosa, submucosa and absence of metastasis. Endoscopic treatment modalities are standard polypectomy and EMR, while ESD is technically more difficult in the colon and associated with high risk of perforation.

Rectum

Like for other GI NETs, the number of cases of rectal NETs over the past years has increased. This increase in incidence is most likely due to greater use of endoscopy and endoscopic screening [96]. Endoscopically they have characteristic features which can lead to early diagnosis, although definite diagnosis relies on histologic results. Usually they are small (<10 mm), submucosal nodules or focal areas of submucosal thickening, covered with yellow-discolored mucosa. These lesions are mobile and on conventional endoscopy they will slide compared with the muscle layer, but not with the mucosal layer. EUS helps in the early diagnosis of rectal carcinoids where they appear as hypoechoic

nodules with origin of the lesion from the lamina propria without an obvious boundary with the mucosa.

'Carcinoid syndrome' is rare in their clinical presentation [97]. Frequent complaints are changes in bowel habit, discomfort in the anorectal area, pruritus ani, bleeding [98] and rectal pain as a late symptom. The frequency for metastases increases with the tumor size [99]. When tumors are less than 10 mm, the actual risk is extremely low. For rectal NETs measuring 10–19 mm metastatic frequency is 5–15%, but for tumors of 20 mm or larger the frequency increases up to 80% [98].

Endoscopic treatment can result in complete excision for lesions that are <10 mm, with absent penetration in the muscularis propria and no lymph node metastases. The choice of endoscopic treatment though is a matter of debate and standardized treatment is still not established. Conventional polypectomy is less likely to achieve pathologically complete resection [100]. The reason for this is that these tumors arise from the deep portions of the mucosa, penetrate the muscularis propria and then form a submucosal nodule. Complete resection for EMR of rectal NETs varies from 28.6–51.7% [33,23,101]. This led to investigations of the success of more advanced endoscopic techniques in achieving tumor-free resection margins [100–103]. In one retrospective analysis, cap assisted EMR was shown to be highly effective compared to EMR [102]. EMR-C was also shown as a good alternative for ESD as this method is technically challenging [102]. In another retrospective analysis, EMR, ESD and endoscopic submucosal resection with a ligation device (ESMR-L) were compared based on therapeutic efficacy and safety [103]. The results in the study showed superiority of ESD and ESMR-L compared to EMR in treating rectal carcinoid. ESMR-L showed as a suitable treatment option as is readily available, minimally invasive and easy to perform.

For tumors that are not suitable for endoscopic resection, surgical resection or other trans-anal excision are treatments of choice.

Complications

Complications of endoscopic treatment of GI NETs are mostly related to the endoscopic treatment technique. Complications include pain, bleeding, perforation and stricture.

Pain is most likely to develop after esophageal ESD. Bleeding is more common and ranges from 1% to 45% [30]. It can be endoscopically managed with hemostasis of appearing vessels which also prevents post-procedural bleeding. Hemostasis can be achieved by different measures (hemostatic forceps, coagrasper, argon plasma coagulation and endoclips) [104]. Urgent surgery is rarely needed for the management of the bleeding. The rates of perforation are much higher for ESD (4–10%) compared to those for EMR (0.3–0.5%) [30]. The risk of perforation is bigger for the small intestine and the colon since their wall is much thinner. Small perforations during the procedure if recognized immediately can be successfully managed without emergency laparotomy [105,106]. The perforation can be sealed with endoclips and the subsequent treatment is conservative with nasogastric suction, fasting and antibiotics [105,106]. Larger perforations should be managed surgically to prevent peritonitis [36]. ESD is also associated with the development of stricture when creating big ESD ulcer in the esophagus or pyloric area [104]. Repeated bougie or balloon dilatation are often applied to prevent passage obstruction [107–109].

Papillectomy on the other hand can be complicated with post-procedure pancreatitis. Prophylactic stenting of the pancreatic duct allows proper drainage and prevents pancreatitis [110].

'Carcinoid crisis' is a rare condition precipitated by the mechanical manipulation of GI NETs. It is manifested as hemodynamic instability with flushing, tachycardia/bradycardia, bronchospasm or complete vasomotor collapse [111]. It can be prevented with administration of octreotide. The doses and the route of administration are variable and are mostly related to the operation time of the procedure [111–114].

Follow-up

NETs are slowly growing tumors that may recur many years after resection. Therefore a long-term surveillance is necessary. Endoscopic follow-up it's still not standardized, although is usually done at 3 and 12 months and then annually. The site of resection can be tattooed so it can be easily found many years after. Monitoring for recurrence should be performed through biopsy of the site of resection on follow-up endoscopic exams. If recurrence is found, endoscopical treatment can be repeated. Endoscopical follow-up (including EUS) should be supplemented with additional radiological and biochemical examinations.

Expert commentary & five-year view

GI NETs are a complex disease that requires site-specific therapeutic approach. Advanced endoscopic techniques can be recommended for small lesions confined to the mucosa and submucosa and no signs of lymph node involvement and distant metastases.

Lesions suitable for endoscopic management should be referred to tertiary centers where multidisciplinary approach can be guaranteed. The choice of endoscopic treatment modality depends on the characteristics of the lesion and the local expertise. EMR and ESD have emerged as safe and effective therapeutic alternatives for GI NETs. Complications, of which bleeding and perforation are most common, can be endoscopically treated without the need of urgent surgery.

Long-term endoscopic surveillance is recommended as GI NETs are slow growing tumors. Measurement of the plasma CgA can aid in the monitoring for recurrence of the disease. Endoscopic resection can be repeated for local recurrence of the lesion at the site of excision.

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Key issues

- Choose the best approach: generally surgical approach is recommended in neuroendocrine tumors (NETs) >20 mm in size. Endoscopical treatment is the better choice in NETs <20 mm in size and in absence of penetration of the muscularis propria and metastases.
- Endoscopic treatment for gastrointestinal NETs is highly dependent on size, as well as site and location in the wall layers: endoscopic mucosal resection is suitable for lesions ≤10 mm, while endoscopic submucosal dissection is suitable for larger lesions (≤20 mm).
- Complications of endoscopic treatment include pain, bleeding, perforation and strictures.
- Papillectomy is indicated in small ampullary NETs (<10 mm).
- Papillectomy can be complicated with post-procedure pancreatitis and/or bleeding.
- The risk of perforation is bigger for the small intestine and the colon since their wall is much thinner.
- After endoscopic resection of gastrointestinal NETs, long-term endoscopic surveillance is recommended together with measurement of the plasma chromogranin A.

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