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Position Paper

Endoscopic management of gastric, duodenal and rectal NETs: Position paper from the Italian Association for Neuroendocrine Tumors (Itanet), Italian Society of Gastroenterology (SIGE), Italian Society of Digestive Endoscopy (SIED)

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ABSTRACT

The present paper reflects the position of the Italian Association for Neuroendocrine Tumors (Itanet), the Italian Society of Gastroenterology (SIGE), and the Italian Society of Digestive Endoscopy (SIED) regarding the management of patients affected by gastric, duodenal, and rectal neuroendocrine neoplasms (NENs) amenable to endoscopic treatment. The key questions discussed in this paper are summarized in Table 1. Data were extracted from the MEDLINE database through searches; expert opinions and recommendations are provided in accordance with the available scientific evidence and the authors' expertise. Recommendations are presented alongside a level of evidence and grade of recommendation based on the GRADE system. This paper specifically focuses on subgroups of NENs considered suitable for endoscopic management according to current international guidelines: i. well-differentiated gastric neuroendocrine tumors (gNET) type 1 < 2 cm and selected cases of type 3; ii. well-differentiated duodenal, non-functioning, non-ampullary NET with size < 2 cm; and well-differentiated rectal NET with size < 2 cm.

1. Introduction

Neuroendocrine neoplasms (NENs) often arise from the gastrointestinal tract and range from slow-growing tumors to aggressive carcinomas. The WHO classifies them as neuroendocrine tumors (NET) when they are well-differentiated (further divided into G1 with mitotic count <2 in 2 mm^2 and/or Ki-67 index <3%, G2 with mitotic count between 2 and 20 in 2 mm^2 and/or Ki-67 index between 3% and 20%, and G3 with mitotic count >20 in 2 mm^2 and/or Ki-67 index >20%) and as neuroendocrine carcinomas (NEC) when the morphology is poorly differentiated [1]. Most gastric, duodenal and rectal NENs are well-differentiated NETs.

Gastric NETs (gNETs) are further categorized into three subgroups: type 1, which represent 75–80%, are associated with chronic atrophic gastritis (CAG) and appear as small polyps during esophagogastroduodenoscopy (EGD), with low metastatic risk and excellent prognosis; type 2 accounts for 5% of gNETs and is linked to Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1 (MEN-1); type 3 constitutes 15–25% of gNETs, presenting as more aggressive and larger lesions not associated with hypergastrinemia (Table 1). Correct gNET classification requires CAG assessment, through multiple biopsies from key locations on the lesser and greater curvatures of the antrum, the lesser curvature of the

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Table 1
General features of gastric, duodenal and rectal NETs amenable to endoscopic resection.

	Type 1 gNET	Type 3 gNET	dNET	rNET
Typical endoscopic and histological characteristics	75–80% of gNETs Often multiple tumors Small size (usually < 1 cm, rarely > 2 cm) Usually low grade (G1 or G2 with low Ki67)	15–25% of gNETs Single tumor Variable size, often > 1 cm Variable grade (G1–G3)	Single tumor Usually < 1 cm, large lesion possible Variable grading (usually G1 or G2 with low Ki67)	Usually sessile with yellowish mucosa Single tumor Usually < 1 cm, large lesion possible Variable grading (usually G1 or G2 with low Ki67)
Risk of metastases	Negligible for tumors < 1 cm	> 50%	40–60% for tumors > 1 cm	Negligible for tumors < 1 cm
Main indication for endoscopic resection*	Tumor size < 2 cm	Tumor size < 1 cm and G1 grade	Tumor size < 1 cm	Tumor size < 1 cm
Preferred endoscopic technique for resection	EMR (m-EMR) or ESD	EMR (m-EMR) or ESD	EMR (m-EMR)	EMR (m-EMR) or ESD

* Additional factors need to be considered before planning endoscopic resection (see text for details).

corpus, the middle portion of the greater curvature of the corpus, and the incisura angularis, as outlined in the Sydney system [2]. Assessing fasting serum gastrin levels is also required in the initial assessment of type 1 gNETs, which are associated with hypergastrinemia. This contrasts with sporadic type 3 gNETs, in which gastrin levels are typically normal. Narrow-band imaging (NBI), a form of electronic chromoendoscopy, is highly effective for diagnosing precancerous conditions, with over 85–90% accuracy in detecting intestinal metaplasia and dysplasia. It effectively differentiates adenomas from hyperplastic polyps by analyzing mucosal patterns and identifies type 1 gNETs by their central erosion, often with a clear demarcation line [3,4] (Fig. 1).

Duodenal NETs (dNETs) account for 2–3% of all gastrointestinal NENs. Approximately 90% of these lesions are non-functional tumors, typically small polypoid growths within the mucosa or submucosa [1]. Additionally, they are usually categorized based on their specific anatomic location as either ampullary or non-ampullary tumors, with the latter group generally considered less aggressive than the former (an example of dNET is shown in Fig. 2)

Rectal NETs (rNETs) are generally well-differentiated NET G1 or G2 with a 5-year survival rate of 75% [5]. They are categorized into non-l-cell and l-cell phenotypes, the latter marked by specific l-cell markers rather than chromogranin A, which when present, indicates a worse prognosis (Fig. 3) [6,7]. While rNETs tend to be slow-growing, the metastatic risk varies significantly (3–60%), with tumor size as a critical prognostic factor [8,9]. No absolute tumor size cutoff can predict metastasis (however, tumor size < 10 mm is associated with a very low rate of metastases), but lymphovascular invasion and tumor grade are key metastasis predictors (Table 1) [10,11].

Several techniques are available for endoscopically resecting gastric, duodenal, and rectal NETs. Endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and endoscopic full-thickness resection (EFTR) are primary methods. EMR involves creating a submucosal fluid cushion before snare resection, aiming for “en-bloc” removal but sometimes resulting in “piecemeal resection”, although achieving “en-bloc” resection is frequent in lesions < 15 mm [12]. Modifications to EMR include underwater EMR (using water for layer separation), cap-assisted EMR (using a cap to ensnare the lesion), circumferential incision EMR (CI-EMR, with prior circumferential cutting), and ligation-assisted EMR (L-EMR, using a band for tissue elevation). ESD entails the use of a knife for initial lesion marking and subsequent dissection of the submucosal layer under direct visualization following the injection of a solution beneath the lesion [13,14]. EFTR is a resection technique that allows for the removal of the mucosa, submucosa, muscular layer, and also serosa in a significant proportion of cases. This is achieved first by traction of the lesion, followed by the release of an over-the-scope clip to close the defect in the muscular layer, and ultimately, the lesion is removed using a polypectomy snare. Endoscopic ultrasound (EUS) is a minimally invasive technique that merges endoscopy and high-frequency ultrasound to provide detailed views of the gastrointestinal (GI) tract and surrounding structures [15]. It utilizes radial array echoendoscopes for a 360-degree view, linear array scopes with Color-Doppler for sagittal imaging and interventions (thanks to their instrument channels), and high-frequency mini probes for more detailed imaging through a standard endoscope [15,16]. Since its advent in 1980, EUS has become essential for diagnosing and staging GI tumors, examining subepithelial lesions, and performing complex therapeutic interventions, including tissue sampling via fine needle aspiration or biopsy [17].

This position paper presents recommendations from Italian Association for Neuroendocrine Tumors (Itanet), Italian Society of Gastroenterology (SIGE), and Italian Society of Digestive Endoscopy (SIED) for the endoscopic management of NENs considered suitable for endoscopic management according to current international guidelines: i. well-differentiated gastric gNET type 1 with size < 2 cm and selected cases of type 3; ii. well-differentiated, non-functioning, non-ampullary dNET with size < 2 cm; and well-differentiated rNET with size < 2 cm.

2. Materials and methods

Three representatives from each participating scientific society contributed to the development of this work. Following an initial web meeting, a total of 16 questions were identified pertaining to gastric, duodenal, and rectal NETs (Table 2). High-grade tumors (NET G3 or NEC) and non-sporadic tumors arising in the context of hereditary syndromes (e.g., type 2 gNETs) were not addressed in this manuscript, as they were deemed beyond the scope, which focused on providing practical clinical guidance for the endoscopic management of patients. For this reason, the term “NET” will be used throughout the manuscript, as only well-differentiated tumors will be covered.

For each question, a dedicated working team was formed, drawing on the specific expertise of each society. A literature search of the PubMed database was conducted, focusing on gastric, duodenal, and rectal NETs in conjunction with endoscopic management. The GRADE system was employed to evaluate the strength of recommendations and the level of evidence [18].

The initial draft underwent revisions through a series of textual email exchanges in May 2023, followed by a virtual meeting of the working teams in October 2023. The draft was further refined until a consensus was reached. The final, revised draft underwent external review and received endorsement from the executive boards of all three scientific societies.

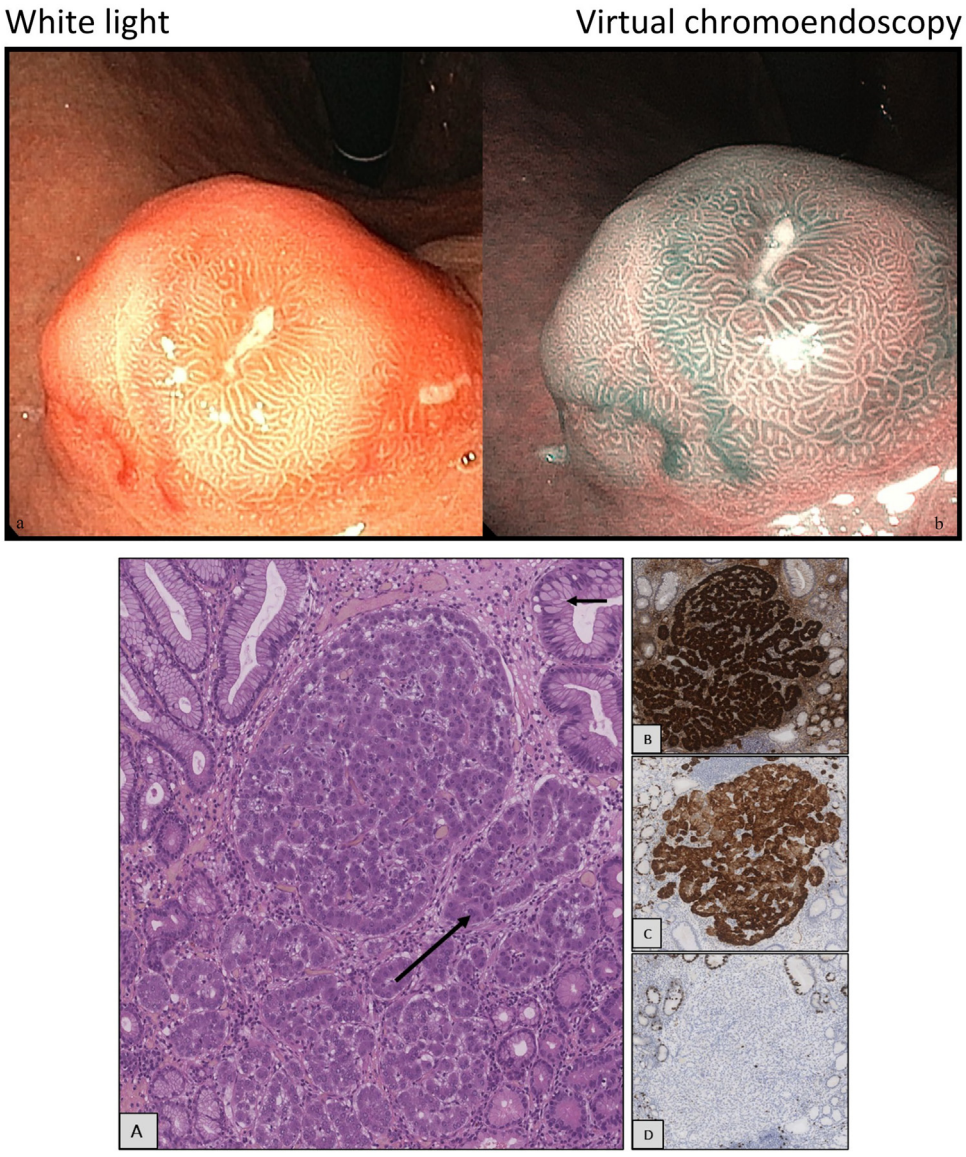

Fig. 1. Endoscopic appearance of a type-1 gastric NET in white light (a) and virtual chromoendoscopy (b). Histological features: well differentiated neuroendocrine tumor with a typical small trabecular architecture without necrosis (A). It is composed of well differentiated cells with abundant eosinophilic cytoplasm and monomorphic round nuclei that lack prominent nucleoli (A,arrow). The general neuroendocrine markers Chromogranin-A (B) and Synapthophysin (C) are strong and diffusely expressed in 100% of neoplastic cells. Most of ECL cell NET G1, Ki-67<2% (D).

Table 2
List of questions.

Gastric NETs – type 1
Q1: Should type 1 gastric NET always be resected?
Q2: Is EUS necessary before planning endoscopic resection?
Q3: Which is the best endoscopic technique to achieve a complete R0 resection?
Q4: How to manage patients with incomplete R1 endoscopic resection?
Q5: What is the timing of follow-up after a complete R0 endoscopic resection?
Gastric NETs – type 3
Q6: When may type 3 gastric NETs be removed by endoscopy?
Q7: Is disease staging (by radiology/nuclear medicine/EUS) required before planning endoscopic resection?
Duodenal NETs
Q8: Which are the tumor features to select candidates for endoscopic resection?
Q9: Is EUS necessary before planning endoscopic resection?
Q10: Which is the best endoscopic technique to acheive complete R0 resection?
Q11: How to manage patients with incomplete R1 endoscopic resection?
Q12: Is disease staging (radiology/nuclear medicine/EUS) required before planning endoscopic resection?
Rectal NETs
Q13: Is it necessary and, if yes, how to recognize a rectal NET at endoscopy?
Q14: Is EUS necessary before planning endoscopic resection?
Q15: Which is the best endoscopic technique to achieve a complete R0 resection?
Q16: How to manage patients with incomplete R1 endoscopic resection?

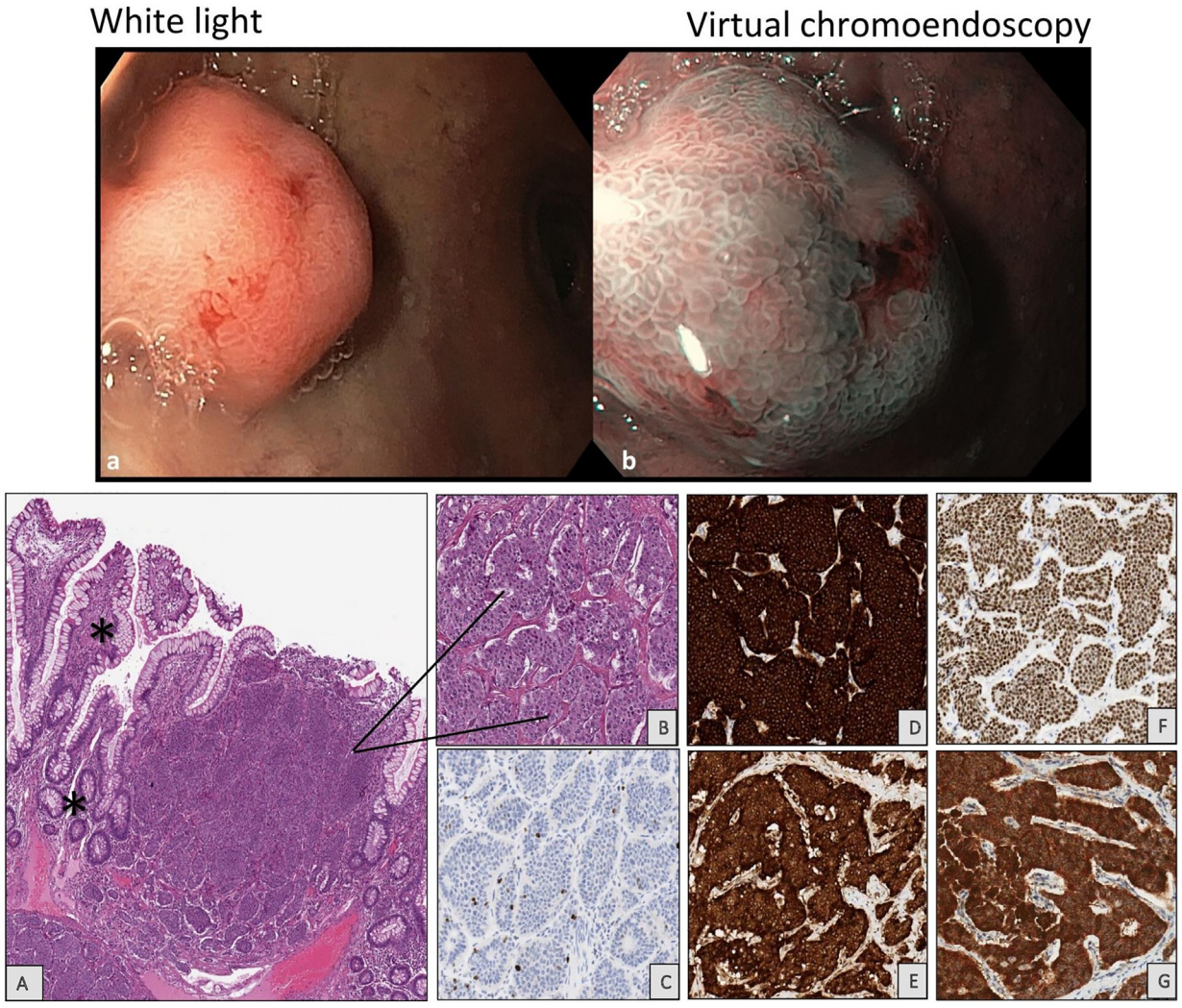

Fig. 2. Endoscopic appearance of a duodenal NET in white light (a) and virtual chromoendoscopy (b). Histological features: duodenal well-differentiated neuroendocrine tumor (NET), duodenal EC-cell NET is composed of nests of uniform neuroendocrine cells separated by fibrovascular tissue and with peripheral palisading (A,B). Normal intestinal villi (A, star) or with hyperplastic aspects (A, star) are present next to neoplasia. Small intestinal NET is usually G1, Ki67:1,2% (C) and is characterized by diffuse and strong expression of general neuroendocrine markers Synaptophysin (D) and Chromogranin A (E). Duodenal serotonin-producing EC-cell NET is also positive for CDX2 (F) and Serotonin hormone (G), both useful to support the small bowel origin of neoplasia in metastatic setting.

3. Statements

3.1. Gastric NETs – type 1

3.1.1. Q1: Should type 1 gastric NET always be resected?

Type 1 gNETs are classified as indolent tumors, characterized by a nearly 100% long-term survival rate, a minimal risk of tumor-related mortality, and a metastasis risk of less than 5%, which typically occurs in larger tumors (greater than 2 cm) (Table 1) [1]. The primary prognostic determinant for the development of metastases in type 1 gNETs is tumor size. The established threshold of 10 mm is widely accepted as a crucial factor in decision-making [19]. Specifically, tumor resection is recommended for tumors larger than 10 mm, while a non-interventional endoscopic surveillance program is deemed safely acceptable for smaller tumors.

Tumor grading, typically quantified by the Ki67 value, holds significant prognostic weight in NETs overall [20]. However, its role in the context of type 1 gNETs is less firmly established, with conflicting findings regarding its practical clinical utility. This discrepancy is largely attributed to the relatively low number of patients with intermediate-to-high Ki67 values (G2-G3 type 1 gNETs) in the patient cohorts examined in the available scientific literature, making a comprehensive analysis of its prognostic role challenging. Nevertheless, despite the absence of robust data on this matter, it appears reasonable to consider the removal of G2-G3 tumors regardless of their size, given their potential for more biologically aggressive behavior compared to G1 NETs.

Lastly, the presence of multiple tumors should be taken into account when managing these patients. It is well recognized that gNETs can occur in multiples [21], making it technically challenging to achieve complete endoscopic resection of all visible lesions.

3.1.2. Recommendations

Endoscopic resection is recommended for single tumors, or a limited number of tumors, larger than 1 cm. Although data are sparse for tumors specifically in the 1–2 cm size range, resection is still advised for these tumors to mitigate the potential risk of further growth and subsequent metastasis. However, for lesions > 2 cm, endoscopic resection is not advised due to the high risk of potential existing metastatic lesions. (2b/A)

For single tumors < 1 cm, a decision between endoscopic resection or surveillance should be based on clinical and pathological

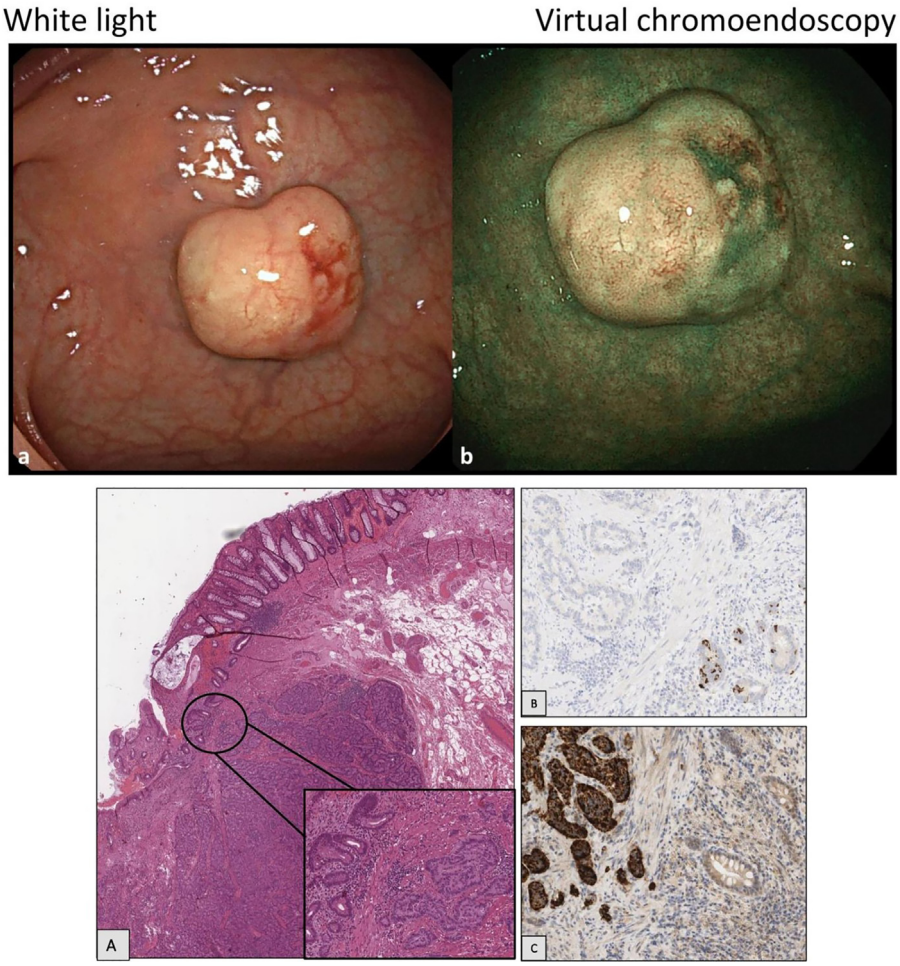

Fig. 3. Endoscopic appearance of a rectal NET in white light (a) and virtual chromoendoscopy (b). Histological features: l-cell NETs are usually observed in the rectum and typically display a characteristic 'ribbon-like' architectural pattern (box). NET cells show bland features with mild to moderate atypia and monomorphic nuclei with salt-and-pepper chromatin. Necrosis is usually absent. l-cell phenotype present negative immunoreactivity for Chromogranin-A (B) but positive immunoreactivity for l-cell markers, including chromogranin-B (C), glucagon-like peptide 1 and pancreatic peptide YY.

factors (e.g. patient's age and comorbidity, tumor grading, specific anatomic site, previous history of recurrent gNET). (2b/B)

In cases with multiple polyps, a personalized multidisciplinary discussion is essential to determine the potential role of endoscopy in comparison to other therapeutic options, including endoscopic surveillance, medical treatment with somatostatin analogs, or surgical approach in very selected cases. (4/A)

3.1.3. Q2: Is EUS necessary before planning endoscopic resection?

While various endoscopic techniques are available for treating these neoplasms [22], EUS provides the advantage of accurately assessing lesion size, depth of invasion, and regional lymph node involvement—critical factors in determining the suitability for endoscopic resection [23]. According to ENETS guidelines [1], EUS staging is recommended for lesions > 10 mm to confirm the appropriateness of different endoscopic techniques for removal.

However, there is a lack of concrete evidence that using EUS before endoscopic resection improves eradication rates, nor is it clear that endoscopic eradication is always the necessary approach. Considering the tumors' generally slow progression and low metastasis risk, EUS might not be essential. Omitting EUS could lower healthcare costs and streamline endoscopic services, possibly decreasing waiting times and enhancing care access. For small lesions, less than 10 or even 15 mm, clinical decision-making could potentially rely solely on endoscopic findings, streamlining the preoperative planning process [24]. Additional data are strongly recommended to demonstrate the actual impact of EUS on the management of patients with type 1 gNETs, given the current lack of robust evidence supporting when and how EUS should be utilized in these patients.

3.1.4. Recommendations

The decision to utilize EUS in preoperative planning for type 1 gNETs should be made on an individual basis, taking into account specific patient factors and tumor characteristics. (5/A)

EUS should be performed before planning endoscopic resection for lesions larger than 10 mm (or even a threshold of 15 mm may be considered, although it is not firmly established). (5/A)

3.1.5. Q3: Which is the best endoscopic technique to achieve a complete R0 resection?

Selecting the optimal endoscopic technique for resecting type 1 gNETs remains a complex decision. Various approaches are employed in clinical practice, ranging from biopsy forceps to ESD [1].

In a systematic review [25], ESD demonstrated a slightly superior capacity for complete tumor removal; specifically, the proportion of R1 margins (tumor-free clear vertical and lateral margins without tumor invasion) was 2.6% in ESD-treated patients compared to 7.7% in those treated with EMR ($p = 0.2$). The proportion of complete resections was 98.7% for ESD versus 96.3% for EMR ($p = 0.6$), respectively. However, ESD exhibited a higher complication rate of 11.7% versus 5.4% with EMR ($p = 0.2$). It's important

to note that only one study included in this systematic review directly compared the two techniques [26], reporting a higher rate of complete resection for ESD (94.9%) compared to EMR (83.3%), albeit with higher complication rates (23.1% vs. 10.4%). Recently, no significant difference in terms of achieving complete resection between EMR and ESD in gastric NETs was reported, particularly for lesions < 15 mm [27,28].

Generally, using forceps or a simple snare for polypectomy is not recommended for gNETs due to the elevated risk of incomplete R1 endoscopic resection and significant risk of recurrence. Both EMR and ESD appear to be effective techniques for removing type 1 gNETs, and EFTR shows promise with high R0 resection rates. Nevertheless, randomized controlled trials are necessary to validate these findings. Snare polypectomy may be acceptable for small (< 1 cm), multiple tumors when performing multiple EMR or ESD might be technically challenging.

3.1.6. Recommendations

Using biopsy forceps or snare polypectomy for resection is not the preferred choice due to the high risk of incomplete R1 resection. (2b/B)

EMR (or mEMR) and ESD are the recommended techniques for removing type 1 gNETs (2a/A). While EFTR shows promise, further data are required before it can be routinely recommended.

3.1.7. Q4: How to manage patients with incomplete R1 endoscopic resection?

Managing patients with incomplete R1 endoscopic resection of type 1 gNETs necessitates a comprehensive multidisciplinary strategy. Despite the availability of various endoscopic techniques, the overall risk of achieving an incomplete tumor resection (R1) after an endoscopic procedure (considering all the available endoscopic techniques) is approximately 36% [29].

Evaluating a step-up approach is recommended following the initial procedure if visible residual tumors or positive R1 margins are identified [1]. Additional endoscopic interventions, such as sequential resection techniques (EMR followed by ESD, potentially followed by EFTR), should be considered [30].

In cases where further endoscopic treatment does not achieve complete eradication and new R1 margins are detected, it is essential to assess tumor characteristics (e.g., tumor grade, size, number, and vascular involvement documented during the initial resection). This evaluation helps identify patients who may benefit from disease staging through cross-sectional imaging and [68Ga]Ga-DOTATOC PET scans to rule out the presence of metastatic disease [31].

If complete endoscopic eradication is not achievable and high-risk tumor features are present, a multidisciplinary team should discuss the potential need for additional measures, including systemic therapies like somatostatin analogs [32] or surgical mini-invasive wedge resection with nodal sampling. It is important to note that while somatostatin analog therapy yields a high rate of complete response, relapse is often observed after discontinuation [32,33].

Surgical resection, always recommended for tumors larger than 20 mm, may also be indicated in smaller lesions, provided high-risk features are present (e.g., invasion beyond the muscular propria, G2 NET with high Ki67 [specific cutoff not specified], or G3 tumors, evidence of lymphovascular invasion) [1]. However, the impact of residual R1 disease on clinical outcomes, in terms of improving survival or reducing the risk of distant metastasis, remains uncertain, especially in small tumors [34]. Long-term follow-up studies are necessary to provide more definitive evidence.

An individualized and integrated approach, involving regular surveillance, targeted interventions, and collaboration among gastroenterologists, oncologists, and surgeons, is crucial for the effective management of patients with incomplete endoscopic resection of R1 type 1 gNETs, particularly in the presence of high-risk factors.

3.1.8. Recommendations

In the event of an R1 incomplete resection, it is advised to employ a step-up endoscopic approach, progressing from less to more advanced techniques (EMR > ESD > EFTR), especially when risk factors such as size > 1 cm, lymphovascular invasion, or G2 tumors (with the Ki67 cut-off level not specified) are present. (3a/B)

It is crucial to carefully weigh the risks associated with the procedure against the likelihood of achieving an R0 resection. This consideration is essential due to the uncertain clinical significance of residual microscopic disease, particularly in small tumors (< 1 cm). (3b/A)

3.1.9. Q5: What is the timing of follow-up after a complete R0 endoscopic resection?

The timing of follow-up after complete R0 endoscopic resection is a critical aspect in the management of type 1 gNETs. It aims to ensure early detection of potential recurrences and evaluate the long-term effectiveness of the procedure. Despite type 1 gNETs being relatively indolent neoplasms, they carry a high recurrence rate, ranging from 20% to 60% [32,35,36].

Generally, the initial follow-up after R0 endoscopic resection should primarily focus on confirming the completeness of the resection and ensuring there is no residual tumor. Therefore, it is typically scheduled within 6–12 months after resection, depending on the certainty of the complete endoscopic removal. Subsequent follow-up intervals should be set every 12 months until a negative EGD without evidence of NET is obtained. However, for certain high-risk cases (such as size >10 mm, G2 tumors, or lymphovascular invasion), more frequent follow-up may be considered reasonable [1]. Repeating biopsies during follow-up EGD for potentially identifying ECL-cell dysplasia and/or non-visible microcarcinoids, as well as in re-staging the degree of mucosal atrophy and/or intestinal metaplasia is advised. The ideal follow-up interval should take into account various factors, including tumor type, size, grading, and individual patient characteristics [37]. Beyond the first year and after negative follow-up results, the frequency of endoscopic surveillance can be shifted to surveillance for the underlying condition, i.e., CAG, with a gastroscopy every 3 years [38,39]. However, it is important to note that endoscopic surveillance has not been validated in prospective studies, and clear evidence regarding the benefits of specific schedules is currently lacking.

Moreover, beyond NET resection, the necessity of conducting follow-up in patients with CAG is also justified by the risk of developing gastric adenocarcinoma.

3.1.10. Recommendations

An initial EGD should be performed 6–12 months after complete resection of gNETs. Subsequent EGDs are scheduled yearly until a negative examination (no tumor identified) is obtained; at that time, patients would undergo regular endoscopic follow-up as indicated fro CAG surveillance. In case of residual NET < 1 cm not requiring further endoscopic resection (see Q1), endoscopic surveillance should be maintained yearly. 3b/B

3.2. Gastric NETs – type 3

3.2.1. Q6: When may type 3 gastric NETs be removed by endoscopy?

In general, surgical resection has traditionally been considered the gold standard therapeutic approach for type 3 gNETs. However, recently, endoscopic resection has been proposed in selected cases with small size and low Ki67, provided that staging by EUS, contrast-enhanced CT, and [68Ga]Ga-DOTATOC PET has excluded

the presence of deep-wall involvement or nodal or distant metastases [1]. Endoscopic resection of type 3 gNETs G1 < 10 mm appears to be safe and effective [40], and it could also be considered for selected cases of small, low G2 (Ki67 cut-off not defined) type 3 gNETs (although a specific cut-off size level is not established, a tumor size <15 mm is reasonable), particularly in patients who are unfit for surgery or have a high risk for surgical resection [41]. Regarding the endoscopic resection technique, as in type 1 gNETs, EMR and ESD have been the most commonly used techniques (Table 1). In a recent systematic review, a complete resection rate was observed in 72–80% of patients, reaching 87% in the largest series [41–45]. However, current evidence does not provide clear guidance on the best endoscopic resection technique for type 3 gNETs.

3.2.2. Recommendations

In patients with small (< 1 cm) G1 (and selected cases of G2 tumors with low Ki67—cut-off not established), sporadic type 3 gNETs, endoscopic resection should be considered as a valid alternative to a surgical approach, particularly in patients at high risk for surgical procedures. (3a/B)

For patients with larger tumors and/or high-risk features (G2 tumors—cut-off not established or lymphovascular invasion), a surgical approach is recommended. (2b/A)

3.2.3. Q7: Is disease staging (by radiology/nuclear medicine/EUS) required before planning endoscopic resection of type 3 gastric NETs?

Type 3 gNETs have consistently been considered aggressive tumors due to their metastatic potential, although they can display significant heterogeneity [37], which makes their management challenging. In the modern era, thanks to the widespread use of EGD [22], tumors are increasingly being identified and treated at an early stage, often small in size. Conservative approaches, ranging from endoscopic treatment to sparing surgical resection, have become more prevalent in managing such cases [41–45].

As a result, thorough disease staging has become essential before considering an endoscopic approach. Various modalities are available for disease staging, including EUS, computed tomography (CT), magnetic resonance imaging (MRI), and [68Ga]Ga-DOTATOC PET for evaluating distant metastasis. Additionally, FDG-PET might be useful for staging high-grade tumors [1].

Given that tumor size and lymphovascular invasion appear to be the primary factors influencing patient management and outcome in low-grade type 3 gNET [41,43], EUS plays a crucial role in stratifying patients with lesions larger than 10 mm and determining the appropriate treatment approach [23], as it is the most sensitive technique for evaluating tumor size, infiltration beyond the submucosal layer, and nodal involvement [1].

3.2.4. Recommendations

Disease staging through contrast-enhanced CT (or MRI) and [68Ga]Ga-DOTATOC PET is advised prior to planning the resection of type 3 gNETs, whether through endoscopic or surgical means. (4/A)

EUS is recommended for tumors deemed suitable for endoscopic resection in order to assess gastric wall involvement and rule out local nodal metastases. (5/A)

3.3. Duodenal NETs

3.3.1. Q8: Which are the tumor features to select candidates for endoscopic resection?

Duodenal NETs present a unique challenge due to their potential for malignancy and variable clinical behavior [45–47]. The optimal management of dNETs depends on several factors that need to be considered before planning treatment, including tumor size, anatomic location, depth of duodenal wall invasion, grade and morphology, endoscopic appearance, hormone secretion status, patient age, and performance status. Therefore, a comprehensive evaluation encompassing histology, local and distant staging through EUS, CT (or MRI), and [68Ga]Ga-DOTATOC PET is mandatory to determine the appropriateness of endoscopic resection [48].

In general, the endoscopic approach is limited to non-functioning, non-ampullary dNETs. It is recommended to stratify the lesions into three categories based on tumor size before planning endoscopic resection [1]: i. Very small non-functioning lesions (5 mm or less) are commonly removed after a lifting injection or biopsy before any histological diagnosis is made, and these lesions do not usually recur or metastasize. ii. Small lesions < 1 cm (up to 15 mm in some reports, although the cut-off level is not standardized) should be managed through an endoscopic approach [1], as most of these lesions are G1 and do not invade the muscle layer. iii. There is potential for endoscopic resection for tumors 1–2 cm in size, although patients need to be carefully selected and treated in centers skilled in the resection of duodenal lesions.

Tumors larger than 2 cm and/or those with lymph node involvement should be treated with surgical resection (i.e., limited duodenectomy or extended pancreaticoduodenectomy according to the surgeon's technical opinion) [1,49].

It is imperative to exercise significant caution and avoid categorizing dNETs as mere "irrelevant findings," as these tumors can harbor regional lymph nodes and distant metastases in as many as 40–60% of cases, regardless of the tumor size (Table 1) [50].

Unless the patient is unfit for surgery, endoscopic resection has no role in the management of functioning dNETs, even in localized disease without metastases, due to the unclear ability of endoscopic resection to resolve hormonal secretion. Thus, surgery remains the primary option for these cases. Syndromic cases (linked to hereditary conditions like gastrinoma in MEN-1 or somatostatinoma in neurofibromatosis type 1) demand comprehensive approaches due to multifocality and heightened malignancy risks [51],52.

3.3.2. Recommendations

Endoscopic management should not be considered for functioning or peri–ampullary lesions, irrespective of tumor size, due to the risk of tumor metastases. (3b/A)

Endoscopic resection is the preferred therapeutic option for tumors < 1 cm and, in highly selected cases, even when the size is 1–2 cm. (3b/A)

3.3.3. Q9: Is EUS necessary before planning endoscopic resection?

It is crucial to thoroughly assess the involvement of the duodenal wall and the presence of lymph node disease to plan the most appropriate endoscopic treatment, considering the high risk of complications (e.g., bleeding or perforations) associated with deep endoscopic resections due to the thickness of the duodenal wall [53]. EUS demonstrates good diagnostic accuracy in detecting primary tumors, especially when they are small, and in identifying lymph node disease, as well as in assessing the involvement of the layers [15,54,55]. Additionally, EUS appears to have a detection rate of 63% for dNETs and lymph node disease, which is crucial for accurate staging of locoregional lymph node metastasis, known to occur in up to 40–60% of cases, although the risk for lesions < 1 cm is much lower [1,15,56].

Given that tumor size is one of the most critical prognostic factors associated with an increased incidence of lymph node metastasis, especially for lesions >10 mm, guidelines recommend performing EUS for dNETs measuring 5–10 mm [1,57].

3.3.4. Recommendations

EUS is recommended for dNETs measuring 5–10 mm for treatment planning and local staging purposes, and for lesions 10–20 mm that are considered for endoscopic resection. (5/B)

3.3.5. Q10: which is the best endoscopic technique to achieve a complete R0 resection?

Due to the complexity of managing complications, the resection of dNETs should be conducted in experienced centers, especially when utilizing advanced endoscopic techniques.

Snare polypectomy has shown limited effectiveness, with a positive R1 margin observed in 90% of cases [58]. Even with EMR, a relatively high positive R1 margin of around 66% has been reported [59]. Modified EMR techniques have demonstrated lower rates of R1 resections: l-EMR showed a positive R1 margin in 31% of dNETs, while CI-EMR was around 29% [60–62]. As for ESD, it should only be considered in expert advanced centers following a multidisciplinary decision due to the high risk of complications. However, with regard to the risk of R1 resection, one study reported a 100% R0 resection rate [63]. ETFR could also be considered as an additional therapeutic option, despite the lack of solid scientific data. If endoscopic therapy carries a high risk of complications or a high risk of R1 resection, surgery should be considered [1].

3.3.6. Recommendations

EMR (and modified EMR) is the preferred technique for endoscopic resection of dNETs (3b/B)

Snare polypectomy should be avoided due to the high risk of incomplete R1 resection (3b/B)

ESD should only be considered in expert advanced centers. (4/A)

3.3.7. Q11: How to manage patients with incomplete R1 endoscopic resection?

Given the potential for malignancy in all dNETs, the decision regarding additional surgery or endoscopic surveillance in cases of R1 margins after endoscopic resection should be made after carefully considering surgical risk and the presence of risk factors for metastasis (such as lymphovascular invasion, high tumor grade, and invasion of proper muscle) [64].

The rate of complete histologic resection ranges between 45% and 57.1%, with no significant differences observed between available endoscopic techniques [65,66]. Therefore, R1 finding is not uncommon. The assessment of residual disease requires a thorough evaluation through imaging techniques such as EUS, [68Ga]Ga-DOTATOC PET, and CT (or MRI). Depending on the size, location, and proximity of the residual disease to critical structures, additional endoscopic interventions may be considered in a step-up approach [1]. Currently, there are no established evidence-based approaches as the definitive standard for managing cases of incomplete dNETs R1 endoscopic resection. Consideration of tumor characteristics and the potential for procedure-related complications is essential, bearing in mind that the application of deep endoscopic resections is limited by the thinness of the duodenal wall [27]. In cases where further endoscopic interventions are not feasible or have limited efficacy, surgery may be required. However, this area requires further investigation as the recurrence rate and overall survival did not show clear differences between endoscopic and surgical treatment [66–69].

Nevertheless, the exact significance of R1 resection in relation to the clinical outcomes of dNETs remains elusive. While a 'wait and watch' strategy has been suggested as potentially safe for localized, $\leq$10 mm, G1, non-functioning, non-ampullary dNETs [70], it is still premature to endorse this strategy, given the current lack of definitive understanding regarding the natural history of patient prognosis and disease progression [71]. On the other hand, it must be taken into account that microscopic R1 residual disease does not always translate into tumor progression. Therefore, the pursuit of more advanced endoscopic resection should be carefully evaluated, also keeping in mind the potential adverse events related to the specific anatomic site in the duodenum. A multidisciplinary approach involving gastroenterologists, oncologists, and surgeons is crucial to assess the patient's overall characteristics and the features of the resected dNET [47].

3.3.8. Recommendations

In cases of R1 resection of dNET, attempting to achieve complete resection by repeating endoscopic resection is recommended. (3b/B)

Extreme caution should be exercised when planning deep endoscopic resection (i.e., ESD), given the high risk of complications (e.g., bleeding and perforation). (4/A)

When a complete R0 resection cannot be achieved, an endoscopic surveillance program in combination with radiological abdominal imaging is mandatory. (3b/A)

3.3.9. Q12: Is disease staging (radiology/nuclear medicine/EUS) required before planning endoscopic resection?

Given the biological heterogeneity of dNETs, precise disease staging before planning endoscopic resection is imperative for optimal patient management [47]. It is worth noting that there is a propensity for understaging, observed in up to 38% of cases [50]. Despite their diminutive size, dNETs have the potential for distant or loco-regional metastatic dissemination, reported in a range between 19% and up to 40% of cases in some instances [72]. This trend is particularly notable in ampullary tumors (not discussed in this paper), which are associated with significantly worse disease-specific patient survival [73]. This underscores the pivotal significance of employing meticulous staging methodologies to accurately evaluate the likelihood of metastatic dissemination. Complete disease staging by CT (or MRI) and [68Ga]Ga-DOTATOC PET should be performed in any dNET with a size $>$ 1 cm, given the relatively high risk of metastases in this subgroup of patients.

Endoscopic examination plays a crucial role in evaluating the primary tumor and accurately determining its location, size, and relationship with the papilla of Vater. Concurrently, EUS facilitates the comprehensive evaluation of tumor depth and contiguous lymph nodes [23], although it has a limited detection rate for loco-regional nodes in the presurgical context of dNETs [50]. Complementarily, CT (or MRI) and [68Ga]Ga-DOTATOC PET offer essential insights into tumor size, location, and potential metastatic involvement, although a portion of micrometastases might remain undetected [50]. The integration of staging data facilitates the identification of suitable candidates for endoscopic resection, thereby mitigating the propensity for incomplete resections and guiding subsequent therapeutic strategies.

3.3.10. Recommendations

Disease staging by radiological examination and [68Ga]Ga-DOTATOC PET is recommended in dNETs $>$ 1 cm before planning treatment. (4/A)

3.4. Rectal NETs

3.4.1. Q13: Is it necessary and, if yes, how to recognize a rectal NET at endoscopy?

Typically, rNETs manifest as rounded, sessile polypoid lesions with yellowish mucosa. In this context, the absence of the "pillow sign" elicited by forceps biopsy is instrumental in distinguishing rNET from lipomas [8]. On rare occasions, they can present as semi-pedunculated or multiple. Distinguishing them from hyperplastic or adenomatous polyps can be quite challenging. In rare

cases, they may exhibit irregular surfaces, hyperemia, ulceration, or central depression (generally when larger than 1 cm), which may indicate more aggressive behavior [8,74].

Tumor size, grading, atypical endoscopic appearance, and lymph node status are the most significant risk factors for metastasis [5,8,9,11,74], and both endoscopic appearance and size can be easily assessed during colonoscopy. In cases of uncertainty, EUS is a valuable tool for distinguishing rNET from other polypoid lesions. On EUS, rNETs appear as well-defined nodules with homogeneous echoes located at an average depth of 7.5 cm from the anus in the submucosa or deeper layers [75].

Unfortunately, rNETs' neuroendocrine nature is often overlooked, and they are not yet sufficiently recognized by endoscopists (only 18% of cases according to a recent national study from the French group of endocrine tumors) [76]. Consequently, resection by hot or cold snare polypectomy is performed too frequently, resulting in incomplete or uncertain removal in over 50% of cases [77]. Assessing margin status can be very challenging; Pagano et al. demonstrated the low accuracy of EUS in detecting residual disease after standard polypectomy [78].

3.4.2. Recommendations

Recognition of neuroendocrine tumors during endoscopy is imperative to avoid standard polypectomy with incomplete removal (rNETs typically present as solitary, yellowish, submucosal polypoid lesions, usually with a regular surface). (3b/A)

The presence of hyperemia or pseudodepression suggests a higher risk of nodal or metastatic involvement, suggesting performing tumor staging before planning endoscopic resection. (3b/B)

3.4.3. Q14: Is EUS necessary before planning endoscopic resection?

EUS may aid in determining the appropriate technique for endoscopic resection [5], but its role in staging remains a topic of debate. Recent ENETS guidelines do not specifically mention EUS but place it in the broader category of "full imaging," which is recommended for lesions ≥10 mm [74]. Previous guidelines recommended EUS for all lesions, regardless of size [10]. It is worth noting that these guidelines often group rectal and colonic NET together, despite their significant biological and clinical differences.

Rectal NETs, which are typically small and well-differentiated, tend to have a lower metastatic potential [79]. Additionally, small rNETs are often incidentally discovered during screening colonoscopies [79]. Therefore, routinely performing EUS for all lesions larger than 10 mm before endoscopic resection may conflict with the recommendations of endoscopy societies, which recommend polypectomy upon detecting any polypoid lesion on screening colonoscopy [80].

EUS use should be individualized, as its impact on outcomes lacks evidence. Indications may include assessing resection techniques for lesions >10 mm, decision-making for lesions 10–20 mm, and local staging when complete resection is unattainable.

3.4.4. Recommendations

In rNETs, EUS is recommended for lesions > 10 mm before planning endoscopic resection and for local staging purposes. (5/B)

3.4.5. Q15: Which is the best endoscopic technique to achieve a complete R0 resection?

Endoscopic management is recommended for rNETs < 1 cm, while an upfront surgical approach is required for lesions > 2 cm (Table 1). Managing rNETs within the 1–2 cm range is challenging, and the optimal strategy for these patients is not well defined. ENETS suggests considering endoscopic resection in these cases, provided that comprehensive disease staging has ruled out nodal involvement. However, these cases should be discussed in a multidisciplinary setting within a referral NET center before treatment planning.

Appropriate resection technique selection is critical for rNETs to avoid R1 resections and positive margins, as evidenced by recent studies [81]. While there is no universal consensus on the preferred method for endoscopic resection, the choice is often guided by lesion size, a key factor in the risk of lymph node involvement [74,82,83].

EMR is the most commonly used method. However, it was noted early on that a limitation of this method was the high rate of positive vertical margins (up to 50%) [84]. This led to the development of modified EMR techniques (e.g., with band ligation l-EMR, with cap C-EMR, and with pre-cutting P-EMR), which achieved better results in terms of complete resection without increasing adverse events or recurrence risk [85]. These methods have resulted in resections with free margins (R0) ranging from 50% to 100%. In a meta-analysis, ESD was found to be superior to conventional EMR in terms of complete resection rate (89% vs. 75%, p <0.001), and m-EMR demonstrated complete resection in 91% of patients [86]. However, a recent meta-analysis including 18 studies and 1168 patients found that for rNETs < 1 cm, the outcomes of EMR were comparable to those of ESD in terms of safety and efficacy [87].

Furthermore, a recent randomized trial comparing cap-assisted EMR and ESD in rNETs showed similar efficacy between the two techniques, with a complete resection rate of 97.4% and 92.7%, respectively. An additional advantage of cap-assisted EMR was the shorter operation time, along with a similar safety profile [88].

3.4.6. Recommendations

EMR (modified EMR, cap-assisted preferred) or ESD are equally effective and are recommended for the removal of rNETs (2a/A).

Snare polypectomy should be avoided due to the high risk of incomplete R1 resection (3b/A).

3.4.7. Q16: How to manage patients with incomplete R1 endoscopic resection?

Managing rNETs following incomplete R1 endoscopic resection requires careful consideration. Essential is a detailed histopathologic analysis of the excised tissue to evaluate residual tumor burden and histologic grade. In the case of a histological diagnosis performed in a non-expert center, revision in a referral NET center is strongly advised [89]. The risk of incomplete R1 resection for rNETs is 12–27% depending on the technique used (a lower risk is reported for ESD, whereas it can be up to 80% after snare polypectomy) [29]. The significance of incomplete pathologic resection is unclear. Predominantly retrospective studies with brief follow-up [90–94] indicate a low recurrence risk post-incomplete endoscopic R1 resection. Current data do not conclusively show if additional treatments are warranted following R1 resection, given that positive margins are not reliably prognostic for recurrence or long-term outcomes [29]. However, if the tumor was 1–2 cm in size, resection of the scarred area should be performed either by deep endoscopic techniques, such as ESD or EFTR, or by transanal minimally invasive surgery (TAMIS) [74]. A recent retrospective analysis demonstrated that in patients with residual R1 disease, systematic scar resection through ESD or EFTR is highly effective in achieving complete R0 tumor removal, with an almost 100% success rate. Additionally, a proportion of confirmed residual tumor was identified in 43% of cases [95]. Indeed, in the absence of safety data on non-invasive approaches (wait-and-watch approaches), options usually encompass repeat endoscopic resection using ESD or EFTR [29]. TAMIS may be particularly beneficial for cases in which repeated endoscopic resection may be technically difficult.

In patients with non-resectable R1 residual disease, a wait-and-see strategy may be considered after patient consultation, ac-

Table 3
Dos and Don'ts in gastric, duodenal, and rectal NETs.

Dos

Gastric NETs
- Investigate the presence of CAG by multiple biopsies of the gastric antrum and body before planning any endoscopic treatment of gNET to assess tumor type.
- Perform EMR (preferably modified) or ESD for planning endoscopic resection of gNET to minimize the risk of incomplete R1 resection.
- Perform EUS before endoscopic resection when tumor size is > 1 cm.
- Refer CAG patients to a specific follow-up program for endoscopic surveillance, given the risk of type 1 gNET recurrence, and the risk of gastric adenocarcinoma.

Duodenal NETs
- Perform full disease staging (using CT or MRI and [68Ga]Ga-DOTATOC PET) when tumor size is > 1 cm.
- Choose the proper endoscopic technique with the intent to achieve R0 resection, balancing the risk of the procedure and the patient's condition.

Rectal NETs
- Perform full disease staging (using CT or MRI and [68Ga]Ga-DOTATOC PET) when tumor size is > 1 cm.
- Perform EMR (preferably modified) or ESD for planned endoscopic resection of rNET to minimize the risk of incomplete R1 resection.

Don't

Gastric NETs
- Do not attempt endoscopic resection for tumors larger than 2 cm due to the high likelihood of pre-existing metastatic disease.
- Do not remove gNETs by forceps or snare polypectomy, given the high risk of obtaining incomplete R1 resection.
- Never remove gNET before assessing tumor type (type 1 - CAG-related vs type 3 - sporadic).

Duodenal NETs
- Do not remove dNETs by ESD unless you have specific experience with this technique in the duodenal site.
- Do not plan endoscopic resection when tumor size is > 1 cm without consulting an experienced surgeon.

Rectal NETs
- Do not remove polyps which have the appearance of a neuroendocrine tumor lesion by biopsies or snare polypectomy, given the extremely high risk of incomplete R1 resection.
- Do not plan endoscopic resection when tumor size is > 2 cm due to the high likelihood of pre-existing metastatic disease.

knowledging the uncertain but non-zero recurrence risk. For lesions under 1 cm, repeat endoscopic or TAMIS may be proposed to mitigate recurrence risk, despite unclear long-term outcome effects. Ongoing surveillance through endoscopic and imaging studies is crucial for monitoring, although optimal duration and discontinuation remain undefined.

3.4.8. Recommendations

A step-up approach using more advanced endoscopic techniques (EMR > ESD > EFTR) or TAMIS is recommended in rNETs after incomplete R1 endoscopic resection, although the real clinical meaning of residual R1 resection remains unclear. (2b/B)

Leaving microscopic R1 residual disease is acceptable in selected patients at high risk of repeating advanced endoscopy or surgery after removing smaller (< 1 cm) G1 rNETs. (4/B)

4. Conclusion remarks

The present paper represents an effort to merge the current knowledge and perspective from three scientific societies that are directly involved in real-world practice in the management of gastric, duodenal, and rectal NETs. One of the main conclusions of this cooperative work is the awareness of the lack of scientific evidence supporting the available literature, which is mainly based on retrospective studies, often evaluating small groups of patients. This seems to be the result of a combination of the rarity and the heterogeneity of the NET diseases. Several unmet needs remain unsolved: i. the identification of clear prognostic factors needs to be established beyond the tumor size; ii. differently from NETs from other anatomic sites, the prognostic role of Ki67 is unclear; iii. the real impact of microscopic residual R1 disease after endoscopic resection is not known; iv. there is not sufficient data to establish which is the best endoscopic technique, in terms of efficacy to achieve complete resection and safety, to remove gastric, duodenal, and rectal NETs. Further multicenter studies performed by sharing the collaboration among the referral centers, specifically designed in a prospective way, are warranted to better understand these issues. However, some relevant clinical messages may be taken from this position paper, which might be helpful for gastroenterologists facing these peculiar diseases (Table 3).

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Conflict of interest

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