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Clinical and long-term oncological outcomes of gastroduodenal neuroendocrine neoplasms after endoscopic resection – a Multinational Western study

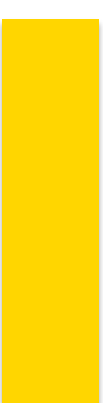
Maria Alípio Gomes

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Eu, Maria Alípio Gomes, abaixo assinado, nº mecanográfico 201906088, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter actuado com absoluta integridade na elaboração do meu trabalho de Dissertação ou Monografia.

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina Clínica

TÍTULO DISSERTAÇÃO

Clinical and long-term oncological outcomes of gastroduodenal neuroendocrine neoplasms after endoscopic resection – a Multinational Western study

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTA TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTA TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTA TRABALHO.	☒

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Eu, Maria Alípio Gomes, abaixo assinado, nº mecanográfico 201906088, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interações (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 13/03/2025

Assinatura conforme cartão de identificação:

Maria Alípio Gomes

Agradecimentos

Ao meu orientador, Dr. Rui Morais, e ao Dr. Francisco Mendes pelo apoio, disponibilidade e incentivo constantes, fundamentais para que a realização deste projeto fosse possível. Do mesmo modo, agradecer a todos aqueles que contribuíram para o trabalho final apresentado.

À minha família pelo apoio, motivação e amor incondicional ao longo de todo o meu percurso de vida. Agradecer pelos conselhos práticos e sensatos e por sempre terem acreditado no meu sucesso. Por todo o orgulho imensurável que sempre partilharam comigo, um enorme obrigada.

Aos meus amigos, que durante 6 anos nunca deixaram de estar presentes e tornaram cada desafio mais leve, agradecer por terem sido uma parte essencial desta jornada.

À Faculdade de Medicina, e a todos os seus Mestres, pelos valiosos ensinamentos que me acompanharão ao longo de toda a minha vida.

A todos os que fizeram parte deste percurso, um obrigada que ultrapassa palavras.

Clinical and long-term oncological outcomes of gastroduodenal neuroendocrine neoplasms after endoscopic resection – a Multinational Western study

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Abstract

Objective

Gastroduodenal neuroendocrine neoplasms (GD-NENs) are being increasingly diagnosed, particularly at stages amenable to endoscopic resection (ER). We aimed to evaluate endoscopic, long-term clinical and oncological outcomes of patients with GD-NENs submitted to ER.

Material and methods

Multinational retrospective study (24 centres, 10 Western countries) that analysed all patients who underwent ER of GD-NENs (January 2014-December 2024). Demographic, clinicopathological and long-term oncological data were collected. A curative resection was defined according to the ENETS guidelines (2023). The cohort was divided in two groups considering the procedure date (2014-2018; 2019-2024) for comparison.

Results

We evaluated 446 patients: 304 gastric (G-NENs) (74.7% type 1) and 142 duodenal (D-NENs). The median lesion size was 10 mm (IQR 6-12). Endoscopic submucosal dissection (ESD) (32.7%) and conventional endoscopic mucosal resection (C-EMR) (26.5%) were the most performed techniques. G-NENs had significantly higher R0 rates (59.8%; 42.3% D-NENs; $p<0.001$). Non-curative ER rate was 58.3% (51.0% G-NENs; 73.9% D-NENs; $p<0.001$). Median follow-up was 37 months (IQR 14-70). Local and distant recurrence rate were 13.2% (14.8% G-NENs; 9.9% D-NENs; $p=0.109$) and 1.8% (1.3% G-NENs; 2.8% D-NENs; $p=0.266$), respectively. Group 2 had a decrease in ESD (37.2%, 29.7%) and increase of band ligation EMR (8.3%, 21.4%) and endoscopic full-thickness resection (1.1%, 5.6%). Group 2 had significantly higher curative resection rates (46.6%; 34.4%; $p=0.011$).

Conclusion

The recurrence of GD-NENs submitted to ER is low, despite suboptimal curative resection rates. The increased curative resection rate in most recent procedures showcases the possibility to optimize patient selection and lesion endoscopic management.

Key-messages

What is already known on this topic:

Endoscopic resection is widely used for small, well-differentiated GD-NENs. Nevertheless, questions remain regarding the efficacy and safety of different endoscopic resection techniques, as well as the long-term outcomes in the follow-up.

What this study adds:

Our findings substantiate that, even with suboptimal curative resection rates, long-term recurrence and tumour-related mortality in patients with GD-NENs remain remarkably low. It also demonstrates that recent advances in endoscopic techniques have significantly improved the rate of curative resections over time.

How this study might affect research, practice or policy:

These results provide critical insights that may refine clinical decision-making and inform future guidelines for the management of GD-NENs. Moreover, these findings lay a robust foundation for prospective studies aimed at elucidating optimal treatment strategies and enhancing long-term outcomes in this patient population.

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumours that arise from the neuroendocrine cells of the diffuse neuroendocrine system. (1, 2) With a relatively slow growth rate, they can develop in a variety of organs, most commonly within the digestive system, with the lung being the second most common site. (1) The majority of NENs occur sporadically, and their risk factors remain poorly understood. However, NENs can also develop as part of inherited genetic conditions, such as the different forms of multiple endocrine neoplasia (MEN), neurofibromatosis type 1, von Hippel-Lindau, and tuberous sclerosis complex. (3) The incidence of gastroenteropancreatic neoplasms (GEP-NENs) has increased significantly over past decades, reaching an estimated global annual age-adjusted incidence rate of 2.39 cases per 100,000 per year. (4, 5) This rise is largely attributed to advancements in endoscopic imaging devices, in association with an increased awareness among endoscopists, which have enhanced the detection of asymptomatic and early-stage tumours, particularly in the stomach and rectum. (4) In light of these developments, there is a growing clinical imperative to refine treatment strategies for early-stage GEP-NENs, underscoring the importance of our study.

Gastroduodenal neuroendocrine tumours (GD-NENs) represent a distinct subset of GEP-NENs with unique clinical behaviours. Specifically, gastric neuroendocrine tumours (G-NENs) account for up to 23% of GEP-NENs. Type I G-NENs, constituting 70-80% of cases, manifests, characteristically, as small, well-differentiated lesions confined to the mucosa or submucosa, with low risk of lymph node metastasis. (6-8) In contrast, the rarer Type II G-NENs (5-6% of cases), usually occurring in the context of Zollinger-Ellison syndrome and MEN-1, display, usually, a similar indolent course despite an increased propensity for nodal metastasis. (9, 10) Type III G-NENs (15-20% of cases), generally exhibit a more aggressive behaviour with mortality rates ranging from 25–30%. (6, 8, 10) Duodenal neuroendocrine tumours (D-NENs) account for approximately 5–8% of cases. Although most D-NEN are small and typically exhibit an indolent clinical course, regional lymph node metastases are observed in 40–60% of cases. (11)

According to the 2019 WHO criteria, NENs are classified into three grades: G1 and G2 (well-differentiated), and G3 (poorly differentiated), based on mitotic count and the Ki-67 proliferation index. (7) The grade of a NEN is a crucial determinant in selecting the most appropriate treatment and serves as a reliable prognostic indicator. However, other lesion characteristics also play a significant role in decision-making and patient outcomes: factors such as the size of the lesion and its anatomical location are equally important

considerations when tailoring treatment strategies and predicting clinical results. (12) Accordingly, endoscopic resection (ER) has been extensively evaluated in the management of GD-NENs. Most guidelines recommend that well-differentiated GD-NENs, measuring typically up to 10–15 mm, should be managed with ER, while larger lesions are more appropriately treated with surgical intervention. (13-17)

Significant gaps persist in the literature regarding the clinical and oncological outcomes following ER of GD-NENs. Although extensive research from Asia has elucidated the benefits of ER for GD-NENs, demonstrating favourable long-term outcomes (18, 19), data from Western populations are markedly sparse. Accordingly, our multinational study was designed to rigorously evaluate the long-term clinical and oncological outcomes following ER of GD-NENs, thereby providing critical insights to optimise patient management strategies.

Methods

Study Design

A retrospective analysis was conducted based on data from 24 Western centres in 10 countries (Portugal, Spain, France, Germany, Belgium, Italy, Austria, Greece, United Kingdom and Australia). Patients consecutively undergoing ER of GD-NEN between January 2014-December 2024 were screened for eligibility. Inclusion criteria included: (i) adult patients undergoing ER of GD-NEN; (ii) at least one follow-up evaluation after ER. Exclusion criteria were: (i) major or minor papilla involvement; (ii) hybrid ER procedures (combination of different ER techniques); (iii) absence of complete histopathological analysis.

Retrospective data was obtained from electronic medical records. Every patient gave written informed consent before ER. This study has subject to approval by the Ethics Committee of the coordinating centre (Unidade Local de Saúde de São João, 289/2024).

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. (20)

Endoscopic Resection Techniques, Histopathological Analysis and Long-term Follow-up

Preoperative evaluation was performed using endoscopic ultrasound (EUS), computed tomography (CT), or Gallium-68 PET/CT, according to each centre's institutional protocol, with the aim of characterising the tumour's size, depth of invasion, and anatomical location, while also excluding regional lymphadenopathy and distant metastatic spread.

All procedures were performed at tertiary reference centres. All procedures were performed by senior endoscopists trained in ER techniques/advanced trainees under supervision. We evaluated the outcomes associated with different ER techniques: Endoscopic Submucosal Dissection (ESD), Conventional Endoscopic Mucosal Resection (C-EMR), Band ligation EMR (B-EMR), Cap-assisted EMR (Cap-EMR), Underwater EMR (U-EMR), Cold-snare Polypectomy, and Endoscopic Full-Thickness Resection (EFTR). Procedure-related adverse events (AEs) (including bleeding and perforation) were also evaluated.

The timing for follow up surveillance endoscopies were defined according to local centre protocols, adjusted to both lesion histopathological analysis, patient characteristics and comorbidities.

Data on long-term outcomes, namely need for surgery/additional treatment after ER, local or distant recurrence, tumour-related and overall mortality was also collected.

Classifications

AEs were defined as any untoward clinical occurrences associated with the procedure and included intraprocedural and/or delayed AEs. Intraprocedural bleeding was defined as persistent bleeding requiring endoscopic hemostasis. Perforation was defined as a loss of continuity in gastric or duodenal wall, recognized during index endoscopy or post-procedure CT. Delayed AEs were eligible if they occurred within 30 days after the index ER. Post-polypectomy bleeding was defined as clinically significant bleeding (hematemesis, melena, or haemoglobin decrease >2 g/dL) resulting in an emergency department visit, admission, or intervention (endoscopy, angioembolization, surgery). Tumour size was determined based on the macroscopic measurement estimated by the gastroenterologist and recorded in the endoscopy report.

Curative resections were defined according to 2023 European Neuroendocrine Tumor Society (ENETS) recommendations (classic criteria) (14). In addition, expanded criteria were also defined, taking into consideration gaps of knowledge in the current literature and highlighted in the previously reported guidelines. Classic and expanded criteria for curative resection for each subtype of GD-NENs are described in [Table 1](#).

Table 1. Curative Resection Criteria for GD-NENs: Comparison of Classic and Expanded Definitions

	Classic Criteria	Expanded Criteria
Type 1 and 2 G-NEN		
Size	<=20 mm	Independent of size in the absence of other risk factors
Resection status	R0 (includes HM0 and VM0)	Rx (HMx and VMx)
Depth of invasion	Mucosa/submucosa	Mucosa/submucosa
Tumour grade	G1-G2	G1-G2
Tumour differentiation	Differentiated	Differentiated
Lymphovascular invasion/lymph node metastasis	Negative	Negative
Type 3 G-NEN		
Size	<10 mm	<=20 mm
Resection status	R0 (includes HM0 and VM0)	Rx (HMx and VMx)
Depth of invasion	Mucosa/submucosa	Mucosa/submucosa
Tumour grade	G1	G1-G2
Tumour differentiation	Differentiated	Differentiated

Lymphovascular invasion/lymph node metastasis	Negative	Negative
D-NEN		
Size	<=10mm	Independent of size in the absence of other risk factors
Resection status	R0 (includes HM0 and VM0)	Rx (HMx and VMx)
Depth of invasion	Mucosa/submucosa	Mucosa/submucosa
Tumour grade	G1	G1-G2
Tumour differentiation	Differentiated	Differentiated
Lymphovascular invasion/lymph node metastasis	Negative	Negative

G-NEN – Gastric Neuroendocrine neoplasm; D-NEN – Duodenal Neuroendocrine neoplasm.

R0 resection implied pathological evaluation with free horizontal and vertical margins (VM and HM), in an *en-bloc* resected specimen. Patients with HMx and VMx resections (due to artefacts that precluded a definite margin evaluation) were considered HM1 and VM1 in the classic curative resection criteria, respectively (except in the expanded curative resection criteria, in which they were considered HM0 and VM0). HM status was only considered in *en-bloc* resections. In patients with more than one NEN, the lesion with more advanced histopathology was considered, for the purpose of statistical analysis.

A systematic approach was followed in each centre to document an accurate histopathological diagnosis, agreed on by expert pathologists, according to international standards (with specimen examination by at least two expert pathologists). Whenever incomplete or incongruent pathological data were evident in the report, the respective centre was contacted, and the histological specimen was re-evaluated for an accurate data collection.

Residual disease was defined as the presence of neoplastic tissue in the ER scar, confirmed by pathological evaluation in the follow-up endoscopy or surgery (parietal residual lesion), and/or as the detection of lymph node metastasis (LNM) in the surgical specimen or in the follow-up.

Local recurrence was defined as histological confirmation of tumour reappearance or persistence at the site of the ER. Distant recurrence was defined as the occurrence of metastatic lesions in anatomical regions remote from the primary tumour site, confirmed histologically. NEN-related mortality was defined as death directly attributable to the NEN, as documented in the patients' clinical records, and distinguished from deaths caused by unrelated factors.

Study Outcomes

The main evaluated outcomes were: (i) the efficacy and safety of different ER techniques in the management of GD-NENs; (ii) the curative resection rate (classic and expanded) after ER; (iii) the rate of residual disease, either in endoscopic/imaging follow-up or in the surgical specimen, after resection.

Additional outcomes included: (i) tumour-related mortality; (ii) overall mortality. In addition, in order to study the trends in ER techniques along the years and its influence in both endoscopic, lesion and patient-related outcomes, the cohort was divided in two groups according to procedure date (1 – 2014-2018; 2 – 2019-2024), for comparison and further analysis.

Data collection and Statistical Analysis

Each participating centre was asked to complete a database including the variables of interest. Categorical variables were described as absolute (n) and relative frequencies (%). Continuous variables were described using medians and interquartile ranges (IQR). Continuous variables were compared using the Mann-Whitney or Student's t-test. On the other hand, categorical variables were compared using the χ^2 test or the Fisher's exact test. Statistical analysis was conducted with the support of IBM SPSS Statistics Version 29 and R.

Results

Demographic Factors of Patients

Demographic characteristics of included patients are described in [Table 2](#). Initially, 537 patients were screened for eligibility. After taking into consideration the inclusion and exclusion criteria, a total of 446 patients with GD-NENs were evaluated: 304 (68.2%) cases of G-NENs and 142 (31.8%) of D-NENs. Among all patients, 51.3% were male, with a median age of 62 years (IQR 53-70). Male sex was significantly more frequent among D-NENs (69.7% vs 42.8%, $p<0.001$). EUS was performed in 42.6% of the patients (34.9% in G-NENs vs 59.2% in D-NENs, $p<0.001$).

Table 2. Demographic Factors of Patients with GD-NEN

	Total (n =446)	Gastric NEN (n=304)	Duodenal NEN (n=142)	p-value
Male Gender, n (%)	229 (51.3)	130 (42.8)	99 (69.7)	< 0.001
Mean age, median (IQR), minimum-maximum, years	62 (53-70), 27-87	61 (51-69), 27-87	65 (58-74), 27-83	0.552
Multiple endocrine neoplasia syndrome, n (%)	25 (5.6)	19 (6.3)	5 (3.5)	0.234
Symptoms at diagnosis (related to hormonal secretion or tumour size), n (%)	104 (23.3)	71 (23.4)	33 (23.2)	0.979
Endoscopic ultrasound performed before endoscopic procedure, n (%)	190 (42.6)	106 (34.9)	84 (59.2)	< 0.001

NEN – Neuroendocrine Neoplasm. n – number. % - percentage value. IQR – interquartile range.

Lesion Data

[Table 3](#) presents a comprehensive summary of the lesion characteristics.

Tumour Location

Among G-NENs, 83.9% were found in the gastric body and 4.9% in the antrum. The majority of D-NENs (79.6%) were found in the duodenal bulb, while 19.7% were located in the second portion of the duodenum, and 0.7% in the third portion of the duodenum.

Tumour Size and Number of Lesions

The median tumour size of the whole cohort was 10.0 mm (IQR 6.0-12.0 mm). G-NENs exhibited a median size of 10.0 mm (IQR 6-14 mm; range 1-50 mm), whereas duodenal lesions were slightly smaller, with a median of 9.0 mm (IQR 7-12 mm; range 1-30 mm)

($p=0.349$). In the gastric cohort, type 1 G-NENs constituted 74.7% of cases. A solitary lesion was observed in 75.1% of cases (95.8% in D-NENs vs 65.5% in G-NENs, $p<0.001$). The incidence of three or more lesions was substantially higher in G-NENs (22.7% vs 0.7%, $p < 0.001$).

Endoscopic Resection Procedure

ESD was performed in 32.7% of cases, at a significantly higher rate in gastric lesions (38.2% vs 21.1%, $p<0.001$). C-EMR was performed in 26.5% of cases, displaying comparable frequencies between groups. Complementary methods included B-EMR (16.1%), cold snare polypectomy (11.4%), Cap-EMR (8.1%), EFTR (3.8%) and U-EMR (1.3%).

Table 3. Lesion Data

Lesion Characteristic		Total (n=446)	Gastric NEN (n=304)	Duodenal NEN (n=142)	p-value
Tumor Location, n (%)	Gastric body	255 (57.2)	255 (83.9)	NA	NA
	Gastric antrum	15 (3.4)	15 (4.9)	NA	
	Gastric, other location	34 (7.6)	34 (11.2)	NA	
	Duodenal bulb	113 (25.3)	NA	113 (79.6)	
	Duodenal, second portion	28 (6.3)	NA	28 (19.7)	
	Duodenal, third portion	1 (0.2)	NA	1 (0.7)	
Tumour size, median (IQR), minimum-maximum, millimetres		10 (6-12), 1-50	10 (6-14), 1-50	9 (7-12), 1-30	0.349
Gastric NEN type, n (%)	Type 1	NA	227 (74.7)	NA	NA
	Type 2	NA	18 (5.9)	NA	
	Type 3	NA	58 (19.1)	NA	
Number of NEN identified at index endoscopy, n (%)	1 NEN	335 (75.1)	199 (65.5)	136 (95.8)	< 0.001
	2 NEN	41 (9.2)	36 (11.8)	5 (3.5)	
	3 or more NEN	70 (15.7)	69 (22.7)	1 (0.7)	
Endoscopic resection procedure, n (%)	ESD	146 (32.7)	116 (38.2)	30 (21.1)	< 0.001
	C-EMR	118 (26.5)	88 (28.1)	30 (21.1)	
	B-EMR	72 (16.1)	46 (15.1)	26 (18.3)	
	Cold Snare polypectomy	51 (11.4)	31 (10.2)	20 (14.1)	
	Cap-EMR	36 (8.1)	16 (5.3)	20 (14.1)	
	EFTR	17 (3.8)	4 (1.3)	13 (9.2)	
	U-EMR	6 (1.3)	3 (1.0)	3 (2.1)	

NEN – neuroendocrine neoplasm; n – number; (%) – percentage; IQR – interquartile range; ESD – endoscopic submucosal dissection; C-EMR – conventional endoscopic mucosal resection; B-EMR – band assisted EMR; Cap-EMR – cap assisted EMR; EFTR – endoscopic full-thickness resection; U-EMR – underwater EMR.

Endoscopic Resection Outcomes According to Tumour Location

ER outcomes, stratified by tumour location, are detailed in [Table 4](#). A detailed subanalysis according to different G-NENs subtypes is reported in [Supplementary Table 1](#).

Procedure-related Adverse Events

AEs were observed in 13.9% of the overall sample, more evident in the gastric group (16.1% vs 9.2%, $p=0.048$). During ER, bleeding was the most frequent AE, occurring in 10.5% of patients (13.2% in gastric vs 4.9% in duodenal lesions, $p=0.032$), followed by perforation in 2.5% (2.3% vs 2.8%).

Resection Analysis

R0 resection was achieved in 54.3% of cases. When stratified by location, R0 resections were attained in 59.8% of G-NENs compared with 42.3% of duodenal lesions ($p<0.001$). The inclusion of Rx cases in curative resections resulted in an expanded R0 resections of 70.4%, ranging between 76.6% in G-NENs and 57.0% in D-NENs.

Based on classic criteria, the curative resection rate differed significantly between groups, with an overall rate of 41.7% (49.0% in gastric vs 26.1% in duodenal lesions, $p<0.001$). Furthermore, the application of expanded criteria increased the overall curative rate to 62.1%, with G-NENs achieving a significantly higher rate (67.4%) compared to D-NENs (50.7%, $p<0.001$).

Table 4. Endoscopic Resection Outcomes (regarding location)

		Total (n=446)	Gastric NEN (n=304)	Duodenal NEN (n=142)	p- value
Procedure Complications					
Procedure related adverse events, n (%)		62 (13.9)	49 (16.1)	13 (9.2)	0.048
Complications observed during endoscopic resection, n (%)		65 (14.6)	50 (16.4)	15 (10.6)	0.032
• Bleeding, n (%)		47 (10.5)	40 (13.2)	7 (4.9)	
• Perforation, n (%)		11 (2.5)	7 (2.3)	4 (2.8)	
• Other, n (%)		7 (1.6)	3 (1.0)	4 (2.8)	
Complications observed after endoscopic procedure, n (%)		6 (1.3)	3 (1.0)	3 (2.1)	0.112
• Bleeding, n (%)		4 (0.9)	1 (0.3)	3 (2.1)	
• Perforation, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
• Other, n (%)		2 (0.4)	2 (0.7)	0 (0.0)	
Lesion Characteristics					
Tumour Grade	Grade 1, n (%)	295 (66.1)	190 (62.5)	105 (73.9)	0.054
	Grade 2, n (%)	45 (32.5)	109 (35.9)	36 (25.4)	

	Grade 3, n (%)	6 (1.3)	5 (1.6)	1 (0.7)	
Tumour	Well differentiated, n (%)	420 (97.0)	287 (97.6)	133 (95.7)	0.271
Differentiation	Poor differentiated, n (%)	13 (3.0)	7 (2.4)	6 (4.3)	
Ki-67 index	Less than 3%, n (%)	252 (58.9)	169 (57.3)	83 (62.4)	0.003
	3-20%, n (%)	167 (39.0)	124 (42.0)	43 (32.3)	
	More than 20%, n (%)	9 (2.1)	2 (0.7)	7 (5.3)	
Invasion Depth	Mucosa / submucosa, n (%)	377 (95.0)	269 (96.1)	108 (92.3)	0.118
	Proper muscular / deeper, n (%)	20 (5.0)	11 (3.9)	9 (7.7)	
Resection Analysis					
Resection	R0, n (%)	242 (54.3)	182 (59.8)	60 (42.3)	<
Margins (R)	R1, n (%)	132 (29.6)	71 (23.4)	61 (43.0)	0.001
	Rx, n (%)	71 (16.1)	51 (16.8)	21 (14.7)	
Horizontal	H0, n (%)	328 (73.5)	225 (74.0)	103 (72.5)	0.713
Resection	H1, n (%)	37 (8.3)	23 (7.6)	14 (9.9)	
Margins (H)	Hx, n (%)	81 (18.2)	56 (18.4)	25 (17.6)	
Vertical	V0, n (%)	253 (56.7)	191 (62.8)	62 (43.7)	<
Resection	V1, n (%)	117 (26.2)	61 (20.1)	56 (39.4)	0.001
Margins (V)	Vx, n (%)	76 (17.04)	52 (17.1)	24 (16.9)	
Lymphovascular invasion, n (%)		29 (7.3)	23 (8.2)	6 (5.1)	0.273
Lymph node metastasis, n (%)		5 (1.4)	5 (2.1)	0 (0.0)	0.130
Curative resection, classic criteria, n (%)		186 (41.7)	149 (49.0)	37 (26.1)	<
					0.001
Curative resection, expanded criteria, n (%)		277 (62.1)	205 (67.4)	72 (50.7)	<
					0.001
Follow up analysis					
Mean follow up, median (IQR), minimum-maximum, months		37 (14-70) 0-120	38 (13-69) 0-120	36 (18-72) 0-120	0.517
Local recurrence, n (%)		59 (13.2)	45 (14.8)	14 (9.9)	0.109
Distant recurrence, n (%)		8 (1.8)	4 (1.3)	4 (2.8)	0.266
Surgery during follow up, n (%)		31 (7.0)	21 (6.9)	10 (7.0)	0.959
NEN-related death, n (%)		2 (0.4)	0 (0.0)	2 (1.4)	0.038
Patient death, n (%)		28 (6.3)	12 (3.9)	16 (11.3)	0.003

NEN – Neuroendocrine Neoplasm. n – number. % - percentage value. IQR – interquartile range.

Surgical Resection Outcomes (regarding location)

As detailed in [Supplementary table 2](#), surgical intervention was required in approximately 7.0% of cases. Specifically, 6.9% of patients with G-NENs underwent additional surgery, with total gastrectomy performed in 42.9% of these cases, while 7% of duodenal lesions necessitated surgery, predominantly via duodenal resection (50.0%). Residual NEN was detected in 61.3% of surgical specimens overall, with a comparable prevalence between groups (p=0.919).

Follow-Up Outcomes

As detailed in [Table 4](#), during a median follow-up of approximately 37 months (IQR 14-70), the incidence of local recurrence was 13.2% overall, with a non-significant trend towards a higher recurrence rate in the gastric group (14.8% vs. 9.9%; $p=0.109$). Distant recurrence was rare (1.8% overall) and similar between groups ($p=0.266$). NEN-related mortality was low overall at 0.4%, with all observed deaths occurring in the duodenal group (1.4% vs 0.0%; $p=0.038$). The overall mortality rate was 6.3%.

[Table 5](#) outlines the long-term oncological outcomes based on curative versus non-curative resections, as defined by both classic and expanded criteria. For Type 1/Type 2 G-NENs, application of classic criteria revealed significant differences between curative and non-curative groups, with local recurrence rates of 9.7% vs 22.3% ($p=0.006$) and distant recurrence rates of 0.0% vs 3.6% ($p=0.027$). In contrast, when the expanded criteria were applied, local recurrence rates were similar between the groups (14.7% vs 17.1%, $p=0.630$), although distant recurrence was significantly higher in non-curative lesions (0.0% vs 5.3%, $p=0.003$). Similarly, for D-NENs, the expanded criteria identified a significantly higher distant recurrence rate in non-curative cases (0.0% vs 5.7%, $p=0.040$). In contrast, Type 3 G-NENs demonstrated similar recurrence profiles across both resection groups.

Table 5. Patient Outcomes Regarding NEN Type (adjusted to classic and expanded criteria)

	Classic Criteria			Expanded Criteria		
	Curative	Non-Curative	p-value	Curative	Non-Curative	p-value
Type 1 / Type 2 Gastric NEN (n=246)						
Local recurrence, n (%)	13 (9.7)	25 (22.3)	0.006	25 (14.7)	13 (17.1)	0.630
Distant recurrence, n (%)	0 (0.0)	4 (3.6)	0.027	0 (0.0)	4 (5.3)	0.003
Surgery during follow up, n (%)	2 (1.5)	12 (10.7)	0.002	4 (2.4)	10 (13.2)	<0.001
NEN in surgical specimen, n (%)	1 (50.0)	8 (66.7)	0.649	3 (75.0)	6 (60.0)	0.597
NEN-related death, n (%)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Type 3 Gastric NEN (n=58)						
Local recurrence, n (%)	2 (13.3)	5 (11.6)	0.861	5 (14.3)	2 (8.7)	0.523
Distant recurrence, n (%)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Surgery during follow up, n (%)	7 (16.3)	0 (0.0)	0.096	1 (2.9)	6 (26.1)	0.008
NEN in surgical specimen, n (%)	4 (57.1)	0 (0.0)	NA	0 (0.0)	44 (66.7)	0.212
NEN-related death, n (%)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Duodenal NEN (n=142)						
Local recurrence, n (%)	2 (5.4)	12 (11.4)	0.291	5 (6.9)	9 (12.9)	0.237
Distant recurrence, n (%)	0 (0.0)	4 (3.8)	0.228	0 (0.0)	4 (5.7)	0.040
Surgery during follow up, n (%)	0 (0.0)	10 (9.5)	0.052	2 (2.8)	8 (11.4)	0.044
NEN in surgical specimen, n (%)	0 (0.0)	6 (60.0)	NA	2 (100.0)	4 (50.0)	0.197
NEN-related death, n (%)	0 (0.0)	2 (1.9)	0.398	0 (0.0)	2 (2.9)	0.149

NEN – Neuroendocrine Neoplasm. n – number. % - percentage value.

Endoscopic Resection Outcomes According to Endoscopic Resection Procedure

Gastric NENs

ER outcomes in G-NENs are described in [Table 6](#).

Cap-EMR and ESD exhibited the highest rates of AEs (31.3% and 28.4% respectively, $p<0.001$). Bleeding was the most frequent AE, occurring in 23.3% of cases in ESD and 25% of cases in Cap-EMR, followed by perforation rates of 3.4% and 6.3%, respectively.

Significant differences were observed in resection margins. U-EMR achieved a R0 rate of 100%, compared to 75.0% with EFTR, 71.7% with B-EMR, 51.1% with C-EMR, 62.1% with ESD, 62.5% with Cap-EMR and 51.56% with cold snare polypectomy, ($p<0.001$).

Using classic criteria, curative resection was achieved in 100% of U-EMR cases, 65.2% of B-EMR cases, and 47.7% of C-EMR cases, whereas ESD achieved 45.7%, ($p=0.106$). When applied expanded criteria, U-EMR achieved complete curative resection in 100.0% of cases, C-EMR in 75%, EFTR in 75.0%, and ESD yielded 57.8%, ($p=0.125$). Despite its lower curative resection rate, ESD demonstrated the second lowest local recurrence rate (6.0%), whereas U-EMR (33.3%) and C-EMR (28.4%) exhibited a statistically significant higher recurrence rate.

Table 6. Endoscopic Resection Outcomes Regarding Endoscopic Technique (Gastric NEN)

Variable		ESD (n=116)	Conventional EMR (n=88)	B-EMR (n=46)	Cold Snare polypectomy (n=31)	Cap-assisted EMR (n=16)	EFTR (n=4)	U-EMR (n=3)	p-value
Major adverse events, n (%)		33 (28.4)	5 (5.7)	3 (6.5)	3 (9.7)	5 (31.3)	0 (0.0)	0 (0.0)	< 0.001
Complications observed during endoscopic resection, n (%)		33 (28.4)	5 (5.7)	3 (6.5)	3 (9.7)	5 (31.3)	0 (0.0)	0 (0.0)	0.017
• Bleeding, n (%)		27 (23.3)	5 (5.7)	2 (4.1)	2 (6.5)	4 (25.0)	0 (0.0)	0 (0.0)	
• Perforation, n (%)		4 (3.4)	0 (0.0)	1 (2.2)	1 (3.2)	1 (6.3)	0 (0.0)	0 (0.0)	
• Other, n (%)		3 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.930
Complications observed after endoscopic procedure, n (%)		0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
• Bleeding, n (%)		0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
• Perforation, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
• Other, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Tumor size, median (IQR), minimum-maximum, years		12 (8-16), 1-50	6 (4-9), 1-21	7 (5-11), 2-18	6 (4-8), 2-12	10 (6-13), 2-15	13 (6-21), 4-25	3 (2-6), 2-6	
Gastric NEN type	Type 1, n (%)	89 (76.7)	67 (76.1)	39 (84.8)	19 (61.3)	9 (56.3)	2 (50.0)	3 (100.0)	0.005
	Type 2, n (%)	10 (8.6)	0 (0.0)	2 (4.3)	5 (16.1)	0 (0.0)	1 (25.0)	0 (0.0)	
	Type 3, n (%)	17 (14.7)	21 (23.9)	5 (10.9)	7 (22.6)	7 (43.8)	1 (25.0)	0 (0.0)	
Tumour Grade	Grade 1, n (%)	61 (52.6)	66 (75.0)	29 (63.0)	22 (71.0)	9 (56.3)	1 (25.0)	2 (66.6)	0.145
	Grade 2, n (%)	52 (44.8)	20 (22.7)	17 (37.0)	9 (29.0)	7 (43.8)	3 (75.0)	1 (33.3)	
	Grade 3, n (%)	3 (2.6)	2 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Tumour Differentiation	Well differentiated, n (%)	111 (98.2)	82 (97.6)	45 (100.0)	26 (89.7)	16 (100.0)	4 (100.0)	3 (100.0)	0.135
	Poor differentiated, n (%)	2 (1.8)	2 (2.4)	0 (0.0)	3 (10.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Ki-67 index	Less than 3%, n (%)	55 (48.2)	60 (71.4)	26 (57.8)	16 (55.2)	10 (62.5)	1 (25.0)	1 (33.3)	0.137

	3-20%, n (%)	58 (50.9)	24 (28.6)	19 (42.2)	12 (41.4)	6 (37.5)	3 (75.0)	2 (66.6)	
	More than 20%, n (%)	1 (0.9)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	
Invasion Depth	Mucosa / submucosa, n (%)	107 (93.9)	74 (97.4)	45 (100.0)	21 (95.5)	16 (100.0)	3 (75.0)	3 (100.0)	0.165
	Proper muscular or deeper, n (%)	7 (6.1)	2 (2.6)	0 (0.0)	1 (4.5)	0 (0.0)	1 (25.0)	0 (0.0)	
Resection Margins (R)	R0, n (%)	72 (62.1)	45 (51.1)	33 (71.7)	16 (51.6)	10 (62.5)	3 (75.0)	3 (100.0)	< 0.001
	R1, n (%)	34 (29.3)	18 (20.5)	11 (23.9)	3 (9.7)	5 (31.2)	0 (0.0)	0 (0.0)	
	Rx, n (%)	10 (8.6)	25 (28.4)	2 (4.4)	12 (38.7)	1 (6.3)	1 (25.0)	0 (0.0)	
Horizontal Resection Margins (H)	H0, n (%)	95 (81.9)	54 (61.4)	39 (84.8)	18 (58.1)	13 (81.3)	3 (75.0)	3 (100.0)	< 0.001
	H1, n (%)	10 (8.6)	5 (5.6)	5 (10.9)	1 (3.2)	2 (12.5)	0 (0.0)	0 (0.0)	
	Hx, n (%)	11 (9.5)	29 (33.0)	2 (4.3)	12 (38.7)	1 (6.2)	1 (25.0)	0 (0.0)	
Vertical Resection Margins (V)	V0, n (%)	76 (65.5)	45 (51.1)	37 (80.4)	16 (51.6)	11 (68.8)	3 (75.0)	3 (100.0)	< 0.001
	V1, n (%)	30 (25.9)	18 (20.5)	7 (15.3)	2 (6.5)	4 (25.0)	0 (0.0)	0 (0.0)	
	Vx, n (%)	10 (8.6)	25 (28.4)	2 (4.3)	13 (41.9)	1 (6.2)	1 (25.0)	0 (0.0)	
Lymphovascular invasion, n (%)		18 (15.9)	0 (0.0)	2 (4.8)	2 (8.0)	1 (6.7)	0 (0.0)	0 (0.0)	0.008
Lymph node metastasis, n (%)		3 (2.8)	0 (0.0)	0 (0.0)	1 (7.7)	1 (7.7)	0 (0.0)	1 (33.3)	0.265
Curative resection, classic criteria, n (%)		53 (45.7)	42 (47.7)	30 (65.2)	14 (45.2)	6 (37.5)	1 (25.0)	3 (100.0)	0.106
Curative resection, expanded criteria, n (%)		67 (57.8)	66 (75.0)	33 (71.7)	23 (74.2)	10 (62.5)	3 (75.0)	3 (100.0)	0.125
Median follow up (IQR), minimum-maximum, months		28 (11-69) 0-120	45 (23-74) 0-120	19 (6-58) 0-100	52 (12-66) 1-120	66 (31-98) 9-120	21 (17-29) 14-35	39 (8-48) 8-48	NA
Local recurrence, n (%)		7 (6.0)	25 (28.4)	4 (8.7)	5 (16.1)	3 (18.8)	0 (0.0)	1 (33.3)	< 0.001
Distant recurrence, n (%)		3 (2.6)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0.622
Surgery during follow up, n (%)		12 (10.3)	5 (5.7)	0 (0.0)	4 (12.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.163
NEN in surgical specimen, n (%)		9 (75.0)	2 (40.0)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.345
NEN-related death, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA

NEN – Neuroendocrine Neoplasm. n – number. % - percentage value. IQR – interquartile range.

Duodenal NENs

ER outcomes in D-NENs are described in [Table 7](#). Major AEs were low, ranging from 0.0% to 10.0% across groups, with no statistically significant differences observed between them. Bleeding emerged as the most frequent complication, occurring in 6.7% of cases in both the ESD and C-EMR groups during ER, ($p=0.864$).

R0 resection was achieved in 73.1% of B-EMR cases and 66.7% of U-EMR cases, which were significantly higher than the 40.0% rate observed in ESD and 26.7% in C-EMR, ($p<0.001$). Curative resection rates using classic criteria were significantly higher with B-EMR (53.8%) compared to 15-30% with other modalities. Under expanded criteria, curative resection rates were 80.0% for cold snare polypectomy, 73.1% for B-EMR, 66.7% for U-EMR, and 53.8% for EFTR, compared to 40.0% and 36.7% for ESD and C-EMR, respectively, ($p=0.002$).

Cap-EMR exhibited the highest local recurrence rate (20.0%) as well as the highest distant recurrence rate (10.0%), though these differences were not statistically significant. During the follow-up period (28 months, IQR 12–60), NEN-related mortality was observed in one patient after ESD (3.3%) and one patient after cold snare polypectomy (5.0%), with no significant differences between groups.

Table 7 – Endoscopic Resection Outcomes Regarding Endoscopic Technique (Duodenal NEN)

Variable		ESD (n=30)	Conventional EMR (n=30)	B-EMR (n=26)	Cap-assisted EMR (n=20)	Cold snare polypectomy (n=20)	EFTR (n=13)	U-EMR (n=3)	p-value
Major adverse events, n (%)		3 (10.0)	3 (10.0)	2 (7.7)	2 (10.0)	2 (10.0)	1 (7.7)	0 (0.0)	0.998
Complications observed during endoscopic resection, n (%)		5 (16.7)	3 (10.0)	3 (11.5)	2 (10.0)	2 (10.0)	0 (0.0)	0 (0.0)	0.864
•	Bleeding, n (%)	2 (6.7)	2 (6.7)	1 (3.8)	1 (5.0)	1 (5.0)	0 (0.0)	0 (0.0)	
•	Perforation, n (%)	0 (0.0)	1 (3.3)	1 (3.8)	1 (5.0)	1 (5.0)	0 (0.0)	0 (0.0)	
•	Other, n (%)	3 (10.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Complications observed after endoscopic procedure, n (%)		1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0.693
•	Bleeding, n (%)	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	
•	Perforation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
•	Other, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Tumor size, median (IQR), minimum-maximum, years		10 (7-12) 4-18	8 (7-11) 3-30	8 (6-9) 4-17	8 (6-10) 5-32	8 (4-14) 2-15	12 (8-13) 1-18	8 (6-10) 6-10	
Tumour Grade	Grade 1, n (%)	19 (63.3)	22 (73.3)	26 (100.0)	11 (55.0)	14 (70.0)	10 (76.9)	3 (100.0)	0.050
	Grade 2, n (%)	11 (36.7)	8 (26.7)	0 (0.0)	8 (40.0)	6 (30.0)	3 (23.1)	0 (0.0)	
	Grade 3, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Tumour Differentiation	Well differentiated, n (%)	29 (100.0)	28 (93.3)	25 (100.0)	17 (85.0)	18 (94.7)	13 (100.0)	3 (100.0)	0.167
	Poor differentiated, n (%)	0 (0.0)	2 (6.7)	0 (0.0)	3 (15.0)	1 (5.3)	0 (0.0)	0 (0.0)	
Ki-67 index	Less than 3%, n (%)	11 (37.9)	19 (67.9)	25 (100.0)	7 (36.8)	10 (62.5)	9 (69.2)	2 (66.7)	< 0.001
	3-20%, n (%)	18 (62.1)	7 (25.0)	0 (0.0)	7 (36.8)	6 (37.5)	4 (30.8)	1 (33.3)	
	More than 20%, n (%)	0 (0.0)	2 (7.1)	0 (0.0)	5 (26.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Invasion Depth	Mucosa / submucosa, n (%)	27 (90.0)	30 (100.0)	18 (94.7)	18 (94.7)	10 (100.0)	9 (69.2)	3 (100.0)	0.039

	Proper muscular or deeper, n (%)	3 (10.0)	0 (0.0)	1 (5.3)	1 (5.3)	0 (0.0)	4 (30.8)	0 (0.0)	
Resection Margins (R)	R0, n (%)	12 (40.0)	8 (26.7)	19 (73.1)	6 (30.0)	6(30.0)	7 (53.8)	2 (66.7)	< 0.001
	R1, n (%)	16 (53.3)	18 (60.0)	5 (19.2)	14 (70.0)	3 (15.0)	4 (30.8)	1 (33.3)	
	Rx, n (%)	2 (6.7)	4 (13.3)	2 (7.7)	0 (0.0)	11 (55.0)	2 (15.4)	0 (0.0)	
	Expanded criteria R0, n (%)	14 (46.7)	12 (40.0)	21 (80.8)	6 (30.0)	17 (85.0)	9 (69.2)	2 (66.7)	
Horizontal Resection Margins (H)	H0, n (%)	28 (93.3)	16 (53.3)	22 (84.6)	18 (90.0)	7 (35.0)	9 (69.2)	3 (100.0)	< 0.001
	H1, n (%)	0 (0.0)	6 (20.0)	2 (7.7)	2 (10.0)	2 (10.0)	2 (15.4)	0 (0.0)	
	Hx, n (%)	2 (6.7)	8 (26.7)	2 (7.7)	0 (0.0)	11 (55.0)	2 (15.4)	0 (0.0)	
Vertical Resection Margins (V)	V0, n (%)	12 (40.0)	8 (26.7)	20 (76.9)	6 (30.0)	6 (30.0)	8 (61.5)	2 (66.7)	< 0.001
	V1, n (%)	16 (53.3)	16 (53.3)	4 (15.4)	13 (65.0)	3 (15.0)	3 (23.1)	1 (33.3)	
	Vx, n (%)	2 (6.7)	6 (20.0)	2 (7.7)	1 (5.0)	11 (55.0)	2 (15.4)	0 (0.0)	
Lymphovascular invasion, n (%)		3 (10.3)	1 (4.5)	1 (4.8)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0.726
Lymph node metastasis, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Curative resection, classic criteria, n (%)		5 (16.7)	6 (20.0)	14 (53.8)	3 (15.0)	5 (25.0)	3 (23.1)	1 (33.3)	0.032
Curative resection, expanded criteria, n (%)		12 (40.0)	11 (36.7)	19 (73.1)	5 (25.0)	16 (80.0)	7 (53.8)	2 (66.7)	0.002
Median follow up (IQR), minimum-maximum, months		28 (12-60) 0-120	60 (21-104) 0-120	34 (18-48) 1-105	89 (59-117) 9-120	29 (7-51) 0-120	18 (5-32) 0-72	25 (0-36) 0-36	NA
Local recurrence, n (%)		0 (0.0)	4 (13.3)	3 (11.5)	4 (20.0)	2 (10.0)	1 (7.7)	0 (0.0)	0.371
Distant recurrence, n (%)		1 (3.3)	0 (0.0)	0 (0.0)	2 (10.0)	1 (5.0)	0 (0.0)	0 (0.0)	0.398
Surgery during follow up, n (%)		1 (3.3)	1 (3.3)	1 (3.8)	3 (15.0)	2 (10.0)	2 (15.4)	0 (0.0)	0.484
NEN present in surgical specimen, n (%)		1 (100.0)	1 (100.0)	0 (0.0)	1 (33.3)	2 (100.0)	1 (50.0)	0 (0.0)	0.399
NEN-related death, n (%)		1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0.680

NEN- Neuroendocrine neoplasm; n – number; (%) – percentage; IQR – interquartile range; ESD – endoscopic submucosal dissection; EMR – endoscopic mucosal resection; B-EMR – band-assisted EMR; Cap-EMR – cap-assisted EMR; EFTR – endoscopic full-thickness resection; U-EMR – underwater EMR.

Temporal Trends in Endoscopic Management (2014–2018 vs 2019–2024)

A temporal comparison was performed between procedures conducted during 2014–2018 (n=180) and those during 2019–2024 (n=266), as shown in [Table 8](#).

Significant changes were observed in the resection techniques employed: the use of ESD decreased from 37.2% to 29.7%, Cap-EMR from 17.2% to 1.9%, and C-EMR from 29.4% to 24.4%, while B-EMR increased from 8.3% to 21.4% and EFTR from 1.1% to 5.6%. AEs dropped significantly from 18.3% to 10.9% (p=0.026).

R0 resection rates increased significantly from 46.1% to 59.8% (p=0.002). The overall curative resection rate increased significantly (from 34.4% to 46.6%, (p=0.011) using classic criteria, and from 55.0% to 66.9%, (p=0.011) using expanded criteria).

Long-term outcomes, including local and distant recurrences and the need for surgery during follow-up, remained stable between the two time periods.

Table 8. Cohort Comparison (according to procedure data)

		2014-2018 (n=180)	2019-2024 (n=266)	p-value
Location, n (%)	Gastric	114 (63.3)	190 (71.4)	0.072
	Duodenal	66 (36.7)	76 (28.6)	
Endoscopic Resection Procedure, n (%)	ESD	67 (37.2)	79 (29.7)	< 0.001
	C-EMR	53 (29.4)	65 (24.4)	
	B-EMR	15 (8.3)	57 (21.4)	
	Cold Snare polypectomy	12 (6.7)	39 (14.7)	
	Cap-EMR	31(17.2)	5 (1.9)	
	EFTR	2 (1.1)	15 (5.6)	
	U-EMR	0 (0.0)	6 (2.3)	
Procedure related adverse events, n (%)		33 (18.3)	29 (10.9)	0.026
Resection Margins (R), n (%)	R0	83(46.1)	159 (59.8)	0.002
	R1	70 (38.9)	62 (23.3)	
	Rx	27 (15.0)	45 (16.9)	
Horizontal Resection Margins, n (%)	H0	126 (70.0)	202 (75.9)	0.046
	H1	22 (12.2)	15 (5.6)	
	Hx	32 (17.8)	49 (18.4)	
Vertical Resection Margins, n (%)	V0	90 (50.0)	163 (61.3)	0.016
	V1	60 (33.3)	57 (21.4)	
	Vx	30 (16.7)	46 (17.3)	
Lymphovascular invasion, n (%)		13 (8.2)	16 (6.7)	0.578
Lymph node metastasis, n (%)		2 (1.4)	3 (1.5)	0.964
Curative resection, classic criteria, n (%)		62 (34.4)	124 (46.6)	0.011
Curative resection, expanded criteria, n (%)		99 (55.0)	178 (66.9)	0.011
Local recurrence during follow-up, n (%)		29 (16.1)	30 (11.3)	0.139
Distant recurrence during follow-up, n (%)		4 (2.2)	4 (1.5)	0.575

Surgery during follow-up, n (%)	14 (7.8)	17 (6.4)	0.572
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n – number; % - percentage; ESD – endoscopic submucosal dissection; EMR – endoscopic mucosal resection; B-EMR – band-assisted EMR; C-EMR – cap-assisted EMR; EFTR – endoscopic full thickness resection; U-EMR – underwater EMR.

Discussion

This study offers a comprehensive analysis of data from 24 Western tertiary centres in 10 countries, with the objective of evaluating long-term clinical and oncological outcomes in patients with GD-NENs managed by ER. Our findings demonstrate that, despite suboptimal curative resection rates, both local recurrence and NEN-related mortality remain exceedingly low. These findings highlight the need for improved patient selection and procedural optimisation in managing GD-NENs, thereby supporting a tailored therapeutic approach that not only enhances oncological outcomes but also minimises treatment-related morbidity.

Regarding G-NENs, multiple studies and guidelines, including the 2023 ENETS recommendations, have established that ER of type 1 G-NENs is a successful treatment option for small (under 20 mm) lesions without *muscularis propria* invasion or LNM, whereas lesions with a size below 10 mm are best managed with periodic endoscopic surveillance. (14, 15, 19, 21-27) For type 2 G-NENs, a tailored treatment strategy is advocated, integrating tumour size, invasion depth and histopathological aggressiveness. (14, 15) In contrast, while surgical resection with lymphadenectomy remains the standard treatment for type 3 G-NENs, emerging evidence suggests that small (under 20 mm), low-grade lesions without LNM, may be amenable to ER. (13-16, 27) Concerning D-NENs, ER has also emerged as a viable alternative. (28) The ENETS guidelines suggest that lesions measuring less than 10 mm, located outside the periampullary region, with no evidence of invasion of the *muscularis propria* and no LNM, can be effectively removed endoscopically. (14) In our study, most lesions met established guideline criteria, as demonstrated by a median lesion size of 10 mm and a predominance of type I G-NENs. Nonetheless, a notable minority exhibited features that extended beyond these conventional parameters, such as a slightly larger size (up to a maximum of 50 mm for G-NENs and 30 mm for D-NENs), poor differentiation (3%), invasion into the *muscularis propria* or deeper (5%) and LNM (1.4%). This distribution enables a direct comparison between our real-world case selection and current guidelines, and suggests that, there is a subset of cases which might benefit from a more tailored therapeutic approach, underscoring the potential need to reassess current treatment guidelines to account for these atypical presentations.

Several studies have sought to elucidate the differences among various endoscopic techniques in the management of GD-NENs. For instance, *Chacchi-Cahuin et al.* and *Kim et al.*, concluded that ESD demonstrated a slight advantage in achieving higher complete resection rates for type 1 G-NENs. (29, 30) In addition, a recent Korean study assessed 103

patients with G-NENs managed by either C-EMR or ESD. The complete resection rate was significantly greater in the ESD group. (31) Regarding D-NENs, *GH Kim et al.*, concluded that ESD achieved a pathological complete resection rate of 100%, markedly exceeding that obtained with C-EMR (56%). However, ESD for D-NENs is technically challenging and is associated with longer procedure times due to the complex duodenal anatomy. (30) In our study, ESD and EFTR were chosen for larger lesions compared with other techniques. In contrast to previous studies, our investigation revealed that while complete pathological resection rates were modest overall, there was a tendency for U-EMR, and B-EMR to yield higher curative resection rates, whereas ESD demonstrated lower resection rates and a greater incidence of AE. It is important to note that these differences did not reach statistical significance, and that an adjusted analysis for lesion-related factors (notably lesion size) was not performed, thereby limiting the strength of our conclusions.

The natural history of GD-NENs, following ER, remains inadequately elucidated, exposing considerable lacunae in current understanding. Nonetheless, a recent retrospective study involving 53 patients with gastrointestinal NENs, comprising gastric, duodenal, and rectal lesions, demonstrated a disease-specific survival rate of 98% over a median follow-up of 44.6 months, with both local and systemic recurrences being exceedingly rare. (17) *Wang et al.* evaluated ER for D-NENs, reporting a median follow-up of 62.6 months with rare local recurrence (6%), despite incomplete resections. (18) Two recent studies on type 1 G-NENs managed by ER reported very promising outcomes: *Uygun A et al.* observed 100% disease-free survival with an 18% recurrence rate in 22 patients, while *Merola et al.* achieved 100% overall survival with no distant recurrence in 33 patients. (19, 32) In our study, the curative resection rate was 41.7% when using classic criteria, whereas the application of expanded criteria raised the curative resection rate to 62.1%. The G-NENs group achieved a significantly higher curative resection rate than the D-NENs group, suggesting that lesion location may significantly influence the efficacy of ER. Notwithstanding the suboptimal resection rates, long-term outcomes, including local recurrence (13.2% overall), distant recurrence (1.8% overall), and NEN-related mortality (0.4% overall) remain remarkably low across both gastric and duodenal groups. The statistically significant differences in local and distant recurrence between curative and non-curative resections suggest that achieving a curative resection is clinically meaningful. These findings support the continued use of ER for GD-NENs, while highlighting the potential benefit of tailoring treatment strategies based on lesion location and refining resection criteria to further optimise patient outcomes.

In our study, we also demonstrated that the evolution of ER techniques over time has resulted in marked improvements in procedural safety and efficacy. Notably, these advances

were associated with a significant reduction in AEs, alongside enhanced resection quality, as reflected by increased R0 resection rates and optimised horizontal and vertical margin statuses. Nevertheless, this increase was not accompanied by a significant decreased in local or distant recurrence rates or even the need for surgery during follow-up, suggesting an opportunity for further improve the endoscopic management of patients with GD-NENs.

Strengths of our study include its robust multinational, multicentre design, encompassing 24 centres across 10 Western countries, and a large cohort, which provides a dataset highly reflective of contemporary clinical practice. Moreover, by stratifying our cohort into two temporal groups, we have been able to elucidate trends in endoscopic management over the past decade, thereby highlighting opportunities for enhanced patient selection and procedural optimisation. Notably, our study also employed a wide range of endoscopic techniques, a feature seldom seen in other studies that typically only compare a few methods.

Nevertheless, some limitations merit consideration. Foremost, the retrospective nature of the study introduces inherent selection biases and potential confounding factors that may not have been fully accounted for. Variability in procedural expertise, technique selection and local management protocols across centres may introduce unmeasured confounding factors that impact the study outcomes. A further limitation of our study is the absence of an adjusted analysis for lesion-related variables which may restrict the robustness of our conclusions. Furthermore, the follow-up protocols were not standardised among patients, which may have led to inconsistencies in the detection and timing of recurrences and other long-term outcomes. Additionally, while the overall cohort is robust, the relatively small numbers for certain techniques, such as EFTR and U-EMR, limit the statistical power for intergroup comparisons and may affect the generalisability of these specific findings. Lastly, despite a median follow-up of 37 months, longer-term outcomes, particularly late recurrences, may not have been fully captured.

In conclusion, our study demonstrates that despite the resection being non-curative in a significant proportion of patients, or even when resection does not meet strict classic curative criteria, the recurrence and tumour-related mortality of GD-NENs remain remarkably low. Consequently, our findings underscore the critical need for further refining patient and lesion selection criteria, which could enhance the benefits of ER.

No funding to be declared.

Conflicts of interest: None.

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Supplementary Table 1. Endoscopic Resection Outcomes (G-NENs)

		Type 1 G-NEN (N=228)	Type 2 G-NEN (n=18)	Type 3 G-NEN (n=58)	p-value
Procedure Complications					
Procedure related adverse events, n (%)		41 (18.0)	1 (5.6)	7 (12.1)	0.250
Complications observed during endoscopic resection, n (%)		41 (18.0)	1 (5.6)	7 (12.1)	0.739
• Bleeding, n (%)		33 (14.5)	1 (5.6)	6 (10.3)	
• Perforation, n (%)		6 (2.6)	0 (0.0)	1 (1.8)	
• Other, n (%)		2 (0.9)	0 (0.0)	0 (0.0)	
Complications observed after endoscopic procedure, n (%)		3 (1.3)	0 (0.0)	0 (0.0)	0.908
• Bleeding, n (%)		1(0.4)	0 (0.0)	0 (0.0)	
• Perforation, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
• Other, n (%)		2 (0.9)	0 (0.0)	0 (0.0)	
Lesion Characteristics					
Tumour Grade	Grade 1, n (%)	149 (65.4)	6 (33.3)	35 (60.3)	< 0.001
	Grade 2, n (%)	78 (34.2)	12 (66.7)	19 (32.8)	
	Grade 3, n (%)	1 (0.4)	0 (0.0)	4 (6.9)	
Tumour Differentiation	Well differentiated, n (%)	221 (98.7)	16 (88.9)	50 (96.2)	0.024
	Poor differentiated, n (%)	3 (1.3)	2 (11.1)	2 (3.8)	
Ki-67 index	Less than 3%, n (%)	132 (59.5)	6 (33.3)	31 (56.4)	0.009
	3-20%, n (%)	90 (40.5)	12 (66.7)	22 (40.0)	
	More than 20%, n (%)	0 (0.0)	0 (0.0)	2 (3.6)	
Invasion Depth	Mucosa / submucosa, n (%)	211 (97.7)	12 (85.7)	46 (92.0)	0.022
	Proper muscular / deeper, n (%)	5 (2.3)	2 (14.3)	4 (8.0)	
Resection Analysis					
Resection	R0, n (%)	138 (60.5)	12 (66.7)	32 (55.2)	0.898
Margins (R)	R1, n (%)	53 (23.2)	3 (16.7)	15 (25.9)	
	Rx, n (%)	37 (16.2)	3 (16.7)	11 (19.0)	
Horizontal	H0, n (%)	170 (74.6)	14 (77.8)	41 (70.7)	0.634
Resection Margins (H)	H1, n (%)	19 (8.3)	0 (0.0)	4 (6.9)	
	HX, n (%)	39 (17.1)	4 (22.2)	13 (22.4)	
Vertical	V0, n (%)	146 (64.0)	12 (66.7)	33 (56.9)	0.713
Resection Margins (V)	V1, n (%)	45 (19.7)	2 (11.1)	14 (24.1)	
	VX, n (%)	37 (16.2)	4 (22.2)	11 (19.0)	
Lymphovascular invasion, n (%)		19 (8.9)	1 (6.3)	3 (6.0)	0.766
Lymph node metastasis, n (%)		2 (1.1)	1 (6.7)	2 (4.7)	0.157
Curative resection, classic criteria, n (%)		56 (24.6)	4 (22.2)	16 (27.6)	0.859
Curative resection, expanded criteria, n (%)		157 (68.9)	12 (66.7)	37 (63.8)	0.758
Follow up analysis					
Mean follow up, median (IQR), minimum-maximum, months		37 (12-70) 0-120	51 (26-66) 1-87	32 (12-66) 0-120	0.057
Local recurrence, n (%)		39 (17.1)	1 (5.6)	7 (12.1)	0.311
Distant recurrence, n (%)		2 (0.9)	2 (11.1)	0 (0.0)	< 0.001

Surgery during follow up, n (%)	13 (5.7)	1 (5.6)	7 (12.1)	0.227
NEN-related death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Patient death, n (%)	9 (3.9)	0 (0.0)	3 (5.2)	0.616

NEN- Neuroendocrine neoplasm; n – number; (%) – percentage.

Supplementary Table 2. Surgical Resection Outcomes (regarding location)

		Total (N=31)	G-NEN (n=21)	D-NEN (n=10)	p-value
Surgery Type					
Total Gastrectomy, n (%)		9 (29.0)	9 (42.9)	NA	NA
Atypical Gastrectomy, n (%)		7 (22.6)	7 (33.3)	NA	
Subtotal Gastrectomy, n (%)		5 (16.2)	5 (23.8)	NA	
Duodenal Resection		5 (16.2)	NA	5 (50.0)	
Subtotal Gastrectomy with Duodenal Resection, n (%)		3 (9.7)	NA	3 (30.0)	
Whipple Procedure		1 (3.2)	NA	1 (10.0)	
Lymph Node Resection		1 (3.2)	NA	1 (10.0)	
Lesion Characteristics					
NEN present in surgical specimen, n (%)		19 (61.3)	13 (61.9)	6 (60.0)	0.919
Tumour Grade	Grade 1, n (%)	13 (68.4)	10 (76.9)	3 (50.0)	0.241
	Grade 2, n (%)	6 (31.6)	3 (23.1)	3 (50.0)	
	Grade 3, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Tumour Differentiation	Well differentiated, n (%)	18 (94.7)	13 (100.0)	5 (83.3)	0.130
	Poor differentiated, n (%)	1 (5.3)	0 (0.0)	1 (16.7)	
Ki-67 index	Less than 3%, n (%)	12 (66.7)	10 (76.9)	2 (40.0)	0.137
	3-20%, n (%)	6 (33.3)	3 (23.1)	3 (60.0)	
	More than 20%, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Invasion Depth	Mucosa / submucosa, n (%)	12 (70.6)	10 (76.9)	2 (50.0)	0.301
	Proper muscular / deeper, n (%)	5 (29.4)	3 (23.1)	2 (50.0)	
Resection Analysis					
Resection	R0, n (%)	16 (84.2)	12 (92.3)	4 (66.7)	0.077
Margins (R)	R1, n (%)	1 (5.3)	1 (6.7)	0 (0.0)	
	Rx, n (%)	2 (10.5)	0 (0.0)	2 (33.3)	
Horizontal	H0, n (%)	14 (87.5)	11 (91.7)	3 (75.0)	0.180
Resection	H1, n (%)	1 (6.3)	1 (8.3)	0 (0.0)	
Margins (H)	HX, n (%)	1 (6.2)	0 (0.0)	1 (25.0)	
Vertical	V0, n (%)	15 (93.8)	12 (100.0)	3 (75.0)	0.074
Resection	V1, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Margins (V)	VX, n (%)	1 (6.2)	0 (0.0)	1 (25.0)	
Lymphovascular invasion, n (%)		9 (29.0)	5 (23.8)	4 (40.0)	0.353
Lymph node metastasis, n (%)		9 (29.0)	5 (23.8)	4 (40.0)	0.353

NEN- Neuroendocrine neoplasm; n – number; (%) – percentage.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Página 1 (Título): “<i>Clinical and long-term oncological outcomes of gastroduodenal neuroendocrine neoplasms after endoscopic resection – a Multinational Western study</i>” Página 4 (Parágrafo 2): “<i>Multinational retrospective study (24 centres, 10 Western countries) that analysed all patients who underwent ER of GD-NENs (January 2014-December 2024).</i>”
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Página 4 (Parágrafo 2): “<i>Multinational retrospective study (24 centres, 10 Western countries) that analysed all patients who underwent ER of GD-NENs (January 2014-December 2024). Demographic, clinicopathological and long-term oncological data were collected. A curative resection was defined according to the ENETS guidelines (2023). The cohort was divided in two groups considering the procedure date (2014-2018; 2019-2024) for comparison.</i>” Página 4 (Parágrafo 3): “<i>We evaluated 446 patients - 304 gastric (G-NEN) (74.7% type 1) and 142 duodenal (D-NEN). (...) G-NEN had significantly higher R0 rates (69.1%; 45.8% D-NEN; $p<0.001$). Non-curative ER rate was 61.4% (59.9% G-NEN; 64.8% D-NEN; $p=0.320$). (...) Local and distant recurrence rate were 14.4% (14.0% G-NEN; 15.1% D-NEN; $p=0.748$) and 1.9% (1.4% G-NEN; 3.0% D-NEN; $p=0.252$), respectively. Group 2 had a decrease in ESD (37.2%, 29.7%) and increase of band ligation EMR (8.3%, 21.4%) and endoscopic full-thickness resection (1.1%, 5.6%). Group 2 had significantly higher curative resection rate (32.2% vs. 42.9%; $p=0.024$).</i>” Página 4 (Parágrafo 4): “<i>The recurrence of GD-NENs submitted to ER is low, despite suboptimal curative resection rates. The increased curative resection rate in most recent procedures showcases</i>

the possibility to optimize patient selection and lesion endoscopic management.”

Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Página 6 (Parágrafo 1): <i>“Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumours that arise from the neuroendocrine cells of the diffuse neuroendocrine system (...) The incidence of gastroenteropancreatic neoplasms (GEP-NENs) has increased significantly over past decades (...) This rise is largely attributed to advancements in endoscopic imaging devices, in association with an increased awareness among endoscopists, which have enhanced the detection of asymptomatic and early-stage tumours, particularly in the stomach and rectum”</i> Página 7 (Parágrafo 2): <i>“Significant gaps persist in the literature regarding the clinical and oncological outcomes following ER of GD-NENs. Although extensive research from Asia has elucidated the benefits of ER for GD-NENs, with studies demonstrating favourable long-term outcomes, data from Western populations are markedly sparse.”</i>
Objectives	3	State specific objectives, including any prespecified hypotheses	Página 6 (Parágrafo 1): <i>“In light of these developments, there is a growing clinical imperative to refine treatment strategies for early-stage GEP-NENs, underscoring the importance of our study.”</i> Página 7 (Parágrafo 2): <i>“Accordingly, our multinational study was designed to rigorously evaluate the long-term clinical and oncological outcomes following ER of GD-NENs, thereby providing critical insights to optimise patient management strategies.”</i>
Methods			
Study design	4	Present key elements of study design early in the paper	Página 8 (Parágrafo 1): <i>“A retrospective analysis was conducted based on data from 24 Western centres in 10 countries (Portugal, Spain, France, Germany, Belgium, Italy, Austria, Greece, United Kingdom and Australia).”</i>

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Página 8 (Parágrafo 1): “<i>A retrospective analysis was conducted based on data from 24 Western centres in 10 countries (Portugal, Spain, France, Germany, Belgium, Italy, Austria, Greece, United Kingdom and Australia). Patients consecutively undergoing ER of GD-NEN between January 2014-December 2024 were screened for eligibility.</i>” Página 8 (Parágrafo 2): “<i>Retrospective data was obtained from electronical medical records.</i>” Página 8 (Parágrafo 6): “<i>The timing for follow up surveillance endoscopies were defined according to local centre protocols, adjusted to both lesion histopathological analysis, patient characteristics and comorbidities.</i>”
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	Página 8 (Parágrafo 1): “<i>Patients consecutively undergoing ER of GD-NEN between January 2014-December 2024 were screened for eligibility. Inclusion criteria included: (i) adult patients undergoing ER of GD-NEN; (ii) at least one follow-up evaluation after ER. Exclusion criteria were: (i) major or minor papilla involvement; (ii) hybrid ER procedures (combination of different ER techniques); (iii) absence of complete histopathological analysis.</i>” Página 8 (Parágrafo 6): “<i>The timing for surveillance endoscopies were defined according to local centre protocols, adjusted to both lesion histopathological analysis, patient characteristics and comorbidities.</i>” N/A. No estudo, os 446 pacientes elegíveis, foram expostos a ressecção endoscópica de tumores neuroendócrinos gastroduodenais.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Página 9 (Parágrafo 2): “<i>AEs were defined as any untoward clinical occurrences associated with the procedure and included intraprocedural and/or delayed AEs. Intraprocedural bleeding was defined as persistent bleeding requiring endoscopic hemostasis. Perforation was defined as a loss of continuity in gastric or duodenal wall, recognized during index endoscopy or post-procedure CT. Delayed AEs were eligible if they occurred within 30 days after the index ER. Post-polypectomy bleeding was defined as</i>

clinically significant bleeding (hematemesis, melena, or haemoglobin decrease >2 g/dL) resulting in an emergency department visit, admission, or intervention (endoscopy, angioembolization, surgery). Tumour size was determined based on the macroscopic measurement estimated by the gastroenterologist and recorded in the endoscopy report.”

Página 9 (Parágrafo 3): “Curative resections were defined according to 2023 European Neuroendocrine Tumor Society (ENETS) recommendations (classic criteria). In addition, expanded criteria were also defined, taking into consideration gaps of knowledge in the current literature and highlighted in the previously reported guidelines. Classic and expanded criteria for curative resection for each subtype of GD-NENs are described in Table 1.”

Página 10 (Parágrafo 1): “R0 resection implied pathological evaluation with free horizontal and vertical margins (VM and HM), in an en-bloc resected specimen. Patients with HMx and VMx resections (due to artefacts that precluded a definite margin evaluation) were considered HM1 and VM1 in the classic curative resection criteria, respectively (except in the expanded curative resection criteria, in which they were considered HM0 and VM0). HM status was only considered in en-bloc resections. In patients with more than one NEN, the lesion with more advanced histopathology was considered, for the purpose of statistical analysis.

Página 10 (Parágrafo 3): Residual disease was defined as the presence of neoplastic tissue in the ER scar, confirmed by pathological evaluation in the follow-up endoscopy or surgery (parietal residual lesion), and/or as the detection of lymph node metastasis (LNM) in the surgical specimen or in the follow-up.”

Página 10 (Parágrafo 4): “Local recurrence was defined as histological confirmation of tumour reappearance or persistence at the site of the ER.

			<i>Distant recurrence was defined to the occurrence of metastatic lesions in anatomical regions remote from the primary tumour site, confirmed histologically.</i> <i>NEN-related mortality was defined as death directly attributable to the NEN, as documented in the patients' clinical records, and distinguished from deaths caused by unrelated factors."</i>
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Página 8 (Parágrafo 4): <i>"Preoperative evaluation was performed using endoscopic ultrasound (EUS), computed tomography (CT), or Gallium-68 PET/CT, according to each centre's institutional protocol, with the aim of characterising the tumour's size, depth of invasion, and anatomical location, while also excluding regional lymphadenopathy and distant metastatic spread."</i> Página 8 (Parágrafo 5): <i>"All procedures were performed at tertiary reference centres. All procedures were performed by senior endoscopists trained in ER techniques/advanced trainees under supervision. We evaluated the outcomes associated with different ER techniques: Endoscopic Submucosal Dissection (ESD), Conventional Endoscopic Mucosal Resection (C-EMR), Band ligation EMR (B-EMR), Cap-assisted EMR (Cap-EMR), Underwater EMR (U-EMR), Cold-snare Polypectomy, and Endoscopic Full-Thickness Resection (EFTR). Procedure-related adverse events (AEs) (including bleeding and perforation) were also evaluated. (...)"</i> Página 9 (Parágrafo 1): <i>"Data on long-term outcomes, namely need for surgery/additional treatment after ER, recurrence, local or distant recurrence, tumour-related and overall mortality was also collected."</i> Página 9 (Parágrafo 2): <i>"Tumour size was determined based on the macroscopic measurement estimated by the gastroenterologist and recorded in the endoscopy report."</i>
Bias	9	Describe any efforts to address potential sources of bias	Página 10 (Parágrafo 2): <i>"A systematic approach was followed in each centre to document an accurate histopathological diagnosis, agreed on by expert</i>

			pathologists, according to international standards (with specimen examination by at least two expert pathologists).”
Study size	10	Explain how the study size was arrived at	Página 12 (Parágrafo 1): “Initially, 537 patients were screened for eligibility. After taking into consideration the inclusion and exclusion criteria, a total of 446 patients with GD-NENs were evaluated: 304 (68.2%) cases of G-NENs and 142 (31.8%) of D-NENs.”
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Página 11 (Parágrafo 3): “Categorical variables were described as absolute (n) and relative frequencies (%). Continuous variables were described using medians and interquartile ranges (IQR). Continuous variables were compared using the Mann-Whitney or Student’s t-test. On the other hand, categorical variables were compared using the χ^2 test or the Fisher’s exact test. Statistical analysis was conducted with the support of IBM SPSS Statistics Version 29 and R.” Página 9: “Table 1. Curative Resection Criteria for GD-NENs: Comparison of Classic and Expanded Definitions” Na variável continua “size”, os limites foram estabelecidos da seguinte forma: para os G-NENs Tipo 1 e 2, o critério clássico define lesões ≤ 20 mm. Para os G-NENs Tipo 3, o critério clássico limita lesões com < 10 mm e o expandido ≤ 20 mm; Para os D-NEN, o critério clássico estabelece o limite de ≤ 10 mm.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions	Página 11 (Parágrafo 3): “Categorical variables were described as absolute (n) and relative frequencies (%). Continuous variables were described using medians and interquartile ranges (IQR). Continuous variables were compared using the Mann-Whitney or Student’s t-test. On the other hand, categorical variables were compared using the χ^2 test or the Fisher’s exact test. Statistical analysis was conducted with the support of IBM SPSS Statistics Version 29 and R.” Página 11 (Parágrafo 3): “Categorical variables were described as absolute (n) and relative frequencies (%). Continuous variables were described using medians and interquartile ranges (IQR). Continuous variables

			were compared using the Mann-Whitney or Student's <i>t</i>-test. On the other hand, categorical variables were compared using the χ^2 test or the Fisher's exact test. Statistical analysis was conducted with the support of IBM SPSS Statistics Version 29 and R."
		(c) Explain how missing data were addressed	Página 10 (Parágrafo 2): "Whenever incomplete or incongruent pathological data were evident in the report, the respective centre was contacted, and the histological specimen was re-evaluated for an accurate data collection."
		(d) If applicable, explain how loss to follow-up was addressed	N/A. No presente estudo, o período de seguimento foi definido como até à última avaliação clínica registada para cada doente, pelo que não se verificaram perdas de seguimento. Desta forma, as análises foram realizadas com base no período de follow-up disponível para cada paciente.
		(e) Describe any sensitivity analyses	N/A. Não foi realizada nenhuma análise de sensibilidade.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Página 12 (Parágrafo 1): "Initially, 537 patients were screened for eligibility. After taking into consideration the inclusion and exclusion criteria, a total of 446 patients with GD-NENs were evaluated: 304 (68.2%) cases of G-NENs and 142 (31.8%) of D-NENs." Página 12 (Parágrafo 1): "After taking into consideration the inclusion and exclusion criteria, a total of 446 patients with GD-NENs were evaluated." Página 8 (Parágrafo 1): "Exclusion criteria were: i) major or minor papilla involvement; (ii) hybrid ER procedures (combination of different ER techniques); (iii) absence of complete histopathological analysis." N/A. O artigo não contempla nenhum flow diagram.

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Página 12 (Parágrafo 1): “<i>Demographic characteristics of included patients are described in Table 2. Initially, 537 patients were screened for eligibility. After taking into consideration the inclusion and exclusion criteria, a total of 446 patients with GD-NENs were evaluated: 304 (68.2%) cases of G-NENs and 142 (31.8%) of D-NENs. Among all patients, 51.3% were male, with a median age of 62 years (IQR 53-70). Male sex was significantly more frequent among D-NENs (69.7% vs 42.8%, $p<0.001$). EUS was performed in 42.6% of the patients (34.9% in G-NENs vs 59.2% in D-NENs group, $p<0.001$).</i>” Página 28 (Parágrafo 3): “<i>Variability in procedural expertise, technique selection and local management protocols across centres may introduce unmeasured confounding factors that impact the study outcomes. A further limitation of our study is the absence of an adjusted analysis for lesion-related variables which may restrict the robustness of our conclusions. Furthermore, the follow-up protocols were not standardised among patients, which may have led to inconsistencies in the detection and timing of recurrences and other long-term outcomes.</i>” Não é indicado diretamente, mas, pelos dados apresentados, na tabela 4 (página 14), tabela 6 (página 19) e tabela 7 (página 22) é possível depreender o número de participantes de cada variável, tendo em conta o tamanho amostral, referido na tabela 2 (página 12). Página 16 (Parágrafo 1): “<i>During a median follow-up of approximately 37 months (IQR 14-70)</i>”
Outcome data	15*	Report numbers of outcome events or summary measures over time	Página 16 (Parágrafo 1): “<i>As detailed in Table 4, during a median follow-up of approximately 37 months (IQR 14-70), the incidence of local recurrence was 13.2% overall, with a non-significant trend towards a higher recurrence rate in the gastric group (14.8% vs. 9.9%; $p = 0.109$). Distant recurrence was rare (1.8% overall) and similar between groups ($p = 0.266$). NEN-related mortality was low overall at 0.4%, with all observed deaths</i>

		occurring in the duodenal group (1.4% vs. 0.0%; $p=0.038$). The overall mortality rate was 6.3%. “ Página 18 (Parágrafo 4): “Despite its lower curative resection rate, ESD demonstrated the second lowest local recurrence rate (6.0%), whereas U-EMR (33.3%) and C-EMR (28.4%) exhibited a statistically significant higher recurrence rate.” Página 21 (Parágrafo 3): “Cap-EMR exhibited the highest local recurrence rate (20.0%) as well as the highest distant recurrence rate (10.0%), though these differences were not statistically significant. During the follow-up period (28 months, IQR 12–60), NEN-related mortality was observed in one patient after ESD (3.3%) and one patient after cold snare polypectomy (5.0%), with no significant differences between groups.” Página 24 (Parágrafo 4): “Long-term outcomes, including local and distant recurrences and the need for surgery during follow-up, remained stable between the two time periods.”
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Página 14 (Parágrafo 1): “ER outcomes, stratified by tumour location, are detailed in Table 4. A detailed subanalysis according to different G-NENs subtypes is reported in Supplementary Table 1. Procedure related AEs were observed in 13.9% of the overall sample, more evident in the gastric group (16.1% vs 9.2%, $p=0.048$). During ER, bleeding was the most frequent AE, occurring in 10.5% of patients (13.2% in gastric vs 4.9% in duodenal lesions, $p=0.032$), followed by perforation in 2.5% (2.3% vs 2.8%). R0 resection was achieved in 54.3% of cases. When stratified by location, R0 resections were attained in 59.8% of G-NENs compared with only 42.3% of duodenal lesions ($p < 0.001$). The inclusion of Rx cases in curative resections resulted in an expanded R0 resections of 70.4%, ranging between 76.6% in G-NENs and 57.0% in D-NENs. Based on classic criteria, the curative resection rate differed significantly between groups, with an overall rate of 41.7% (49.0% in gastric lesions

vs 26.1% in duodenal lesions, $p=0.001$). Furthermore, the application of expanded criteria increased the overall curative rate to 62.1%, with G-NENs achieving a significantly higher rate (67.4%) compared to D-NENs (50.7%, $p<0.001$).”

Página 16 (Parágrafo 1): “As detailed in Table 4, during a median follow-up of approximately 37 months (IQR 14-70), the incidence of local recurrence was 13.2% overall, with a non-significant trend towards a higher recurrence rate in the gastric group (14.8% vs. 9.9%; $p = 0.109$). Distant recurrence was rare (1.8% overall) and similar between groups ($p = 0.266$). NEN-related mortality was low overall at 0.4%, with all observed deaths occurring in the duodenal group (1.4% vs. 0.0%; $p=0.038$). The overall mortality rate was 6.3%. Table 5 outlines the long-term oncological outcomes based on curative versus non-curative resections, as defined by both classic and expanded criteria. For Type 1/Type 2 G-NENs, application of classic criteria revealed significant differences between curative and non-curative groups, with local recurrence rates of 9.7% vs 22.3% ($p = 0.006$) and distant recurrence rates of 0.0% vs 3.6% ($p = 0.027$). In contrast, when the expanded criteria were applied, local recurrence rates were similar between the groups (14.7% vs 17.1%, $p = 0.630$), although distant recurrence was significantly higher in non-curative lesions (0.0% vs 5.3%, $p = 0.003$). Similarly, for D-NENs, the expanded criteria identified a significantly higher distant recurrence rate in non-curative cases (0.0% vs 5.7%, $p = 0.040$). In contrast, Type 3 Gastric NENs demonstrated similar recurrence profiles across both resection groups.”

Página 18 (Parágrafo 18): “ER outcomes in G-NENs are described in Table 6. Cap-EMR and ESD exhibited the highest rates of AEs (31.3% and 28.4% respectively, $p<0.001$). Bleeding was the most frequent AE, occurring in 23.3% of cases in ESD and 25% of cases in Cap-EMR, followed by perforation rates of 3.4% and 6.3%, respectively. Significant differences were observed in resection margins. U-

EMR achieved a R0 rate of 100%, compared to 75.0% with EFTR, 71.7% with B-EMR, 51.1% with C-EMR, 62.1% with ESD, 62.5% with Cap-EMR and 51.56% with cold snare polypectomy, ($p<0.001$). Using classic criteria, curative resection was achieved in 100% of U-EMR cases, 65.2% of B-EMR cases, and 47.7% of C-EMR cases, whereas ESD achieved 45.7%, ($p=0.106$). When applied expanded criteria, U-EMR achieved complete curative resection in 100.0% of cases, C-EMR in 75%, EFTR in 75.0%, and ESD yielded 57.8%, ($p=0.125$). Despite its lower curative resection rate, ESD demonstrated the second lowest local recurrence rate (6.0%), whereas U-EMR (33.3%) and C-EMR (28.4%) exhibited a statistically significant higher recurrence rate.”

Página 21 (Parágrafo 1): “ER outcomes in D-NENs are described in Table 7. Major AEs were low, ranging from 0.0% to 10.0% across groups, with no statistically significant differences observed between them. Bleeding emerged as the most frequent complication, occurring in 6.7% of cases in both the ESD and C-EMR groups during ER, ($p=0.864$). R0 resection was achieved in 73.1% of B-EMR cases and 66.7% of U-EMR cases, which were significantly higher than the 40.0% rate observed in ESD and 26.7% in C-EMR, ($p<0.001$). Curative resection rates using classic criteria were significantly higher with B-EMR (53.8%) compared to 15-30% with other modalities. Under expanded criteria, curative resection rates were 80.0% for cold snare polypectomy, 73.1% for B-EMR, 66.7% for U-EMR, and 53.8% for EFTR, compared to 40.0% and 36.7% for ESD and C-EMR, respectively, ($p=0.002$). Cap-EMR exhibited the highest local recurrence rate (20.0%) as well as the highest distant recurrence rate (10.0%), though these differences were not statistically significant. During the follow-up period (28 months, IQR 12–60), NEN-related mortality was observed in one patient after ESD (3.3%) and one patient after cold snare polypectomy (5.0%), with no significant differences between groups.”

		(b) Report category boundaries when continuous variables were categorized	Página 9: “<i>Table 1. Curative Resection Criteria for GD-NENs: Comparison of Classic and Expanded Definitions</i>” Na variável continua “size”, os limites foram estabelecidos da seguinte forma: para os G-NENs Tipo 1 e 2, o critério clássico define lesões ≤ 20 mm. Para os G-NENs Tipo 3, o critério clássico limita lesões com < 10 mm e o expandido ≤ 20 mm; Para os D-NEN, o critério clássico estabelece o limite de ≤ 10 mm.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A: Neste estudo, os resultados foram apresentados em valores absolutos e em percentagens, acompanhados de valores de p, não tendo sido utilizadas medidas explícitas de risco relativo.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Página 14 (Parágrafo 1): “<i>A detailed subanalysis according to different G-NENs subtypes is reported in Supplementary Table 1.</i>” Página 24 (Parágrafo 1): “<i>A temporal comparison was performed between procedures conducted during 2014-2018 (n = 180) and those during 2019-2024 (n = 266), as shown in Table 8. Significant changes were observed in the resection techniques employed: the use of ESD decreased from 37.2% to 29.7%, Cap-EMR from 17.2% to 1.9%, and C-EMR from 29.4% to 24.4%, while B-EMR increased from 8.3% to 21.4% and EFTR from 1.1% to 5.6%. Procedure-related AEs dropped significantly from 18.3% to 10.9% (p=0.026). Over the study period, R0 resection rates increased significantly from 46.1% to 59.8% (p=0.002). The overall curative resection rate using increased significantly (from 34.4% to 46.6%, p = 0.011 using classic criteria, and from 55.0% to 66.9%, p=0.011 using expanded criteria). Long-term outcomes, including local and distant recurrences and the need for surgery during follow-up, remained stable between the two time periods.</i>”
Discussion			
Key results	18	Summarise key results with reference to study objectives	Página 26 (Parágrafo 1): “<i>This study offers a comprehensive analysis of data from 24 western tertiary centres in 10 countries, with the objective of</i>

evaluating long-term clinical and oncological outcomes in patients with GD-NENs managed by ER. Our findings demonstrate that, despite suboptimal curative resection rates (classic and expanded), both local recurrence and NEN-related mortality remain exceedingly low. These findings highlight the need for improved patient selection and procedural optimisation in managing GD-NENs, thereby supporting a tailored therapeutic approach that not only enhances oncological outcomes but also minimises treatment-related morbidity.”

Página 27 (Parágrafo 2): “Notwithstanding the suboptimal resection rates, long-term outcomes, including local recurrence (13.2% overall), distant recurrence (1.8% overall), and NEN-related mortality (0.4% overall) remain remarkably low across both gastric and duodenal groups. The statistically significant differences in local and distant recurrence between curative and non-curative resections suggest that achieving a curative resection is clinically meaningful. These findings support the continued use of ER for GD-NENs, while highlighting the potential benefit of tailoring treatment strategies based on lesion location and refining resection criteria to further optimise patient outcomes.”

Página 27 (Parágrafo 3): “In our study, we also demonstrated that the evolution of ER techniques over time has resulted in marked improvements in procedural safety and efficacy. Notably, these advances were associated with a significant reduction in procedure-related AEs, alongside enhanced resection quality, as reflected by increased R0 resection rates and optimised horizontal and vertical margin statuses. Nevertheless, this increase was not accompanied by a significant decrease in local or distant recurrence rates or even the need for surgery during follow up, suggesting an opportunity for further improve the endoscopic management of patients with GD-NENs.”

Página 28 (Parágrafo 4): “In conclusion, our study demonstrates that despite the resection being non-

			curative in a significant proportion of patients, or even when resection does not meet strict classic curative criteria, the recurrence and tumour-related mortality of GD-NENs remain remarkably low. Consequently, our findings underscore the critical need for further refining patient and lesion selection criteria, which could enhance the r benefits of endoscopic management.”
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Página 28 (Parágrafo 3): “Nevertheless, some limitations merit consideration. Foremost, the retrospective nature of the study introduces inherent selection biases and potential confounding factors that may not have been fully accounted for. Variability in procedural expertise, technique selection and local management protocols across centres may introduce unmeasured confounding factors that impact the study outcomes. A further limitation of our study is the absence of an adjusted analysis for lesion-related variables which may restrict the robustness of our conclusions. Furthermore, the follow-up protocols were not standardised among patients, which may have led to inconsistencies in the detection and timing of recurrences and other long-term outcomes. Additionally, while the overall cohort is robust, the relatively small numbers for certain techniques, such as EFTR and U-EMR, limit the statistical power for intergroup comparisons and may affect the generalisability of these specific findings. Lastly, despite a median follow-up of 37 months, longer-term outcomes, particularly late recurrences, may not have been fully captured.”
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Página 26 (Parágrafo 3): “Several studies have sought to elucidate the differences among various endoscopic techniques in the management of GD-NENs. For instance, Chacchi-Cahuin et al. and Kim et al., concluded that ESD demonstrated a slight advantage in achieving higher complete resection rates for type 1 G-NENs. In addition, a recent Korean study assessed 103 patients with G-NENs managed by either C-EMR or ESD. The complete resection rate was

significantly greater in the ESD group. Regarding D-NENs, GH Kim et al., concluded that ESD achieved a pathological complete resection rate of 100%, markedly exceeding that obtained with C-EMR (56%). However, ESD for D-NENs is technically challenging and is associated a longer procedure time due to o the complex duodenal anatomy. In our study, ESD and EFTR were chosen for larger lesions compared with other techniques. In contrast to previous studies, our investigation revealed that while complete pathological resection rates were modest overall, there was a tendency for U-EMR, and B-EMR to yield higher curative resection rates, whereas ESD demonstrated lower resection rates and a greater incidence of AE. It is important to note that these differences did not reach statistical significance, and that an adjusted analysis for lesion-related factors (notably lesion size) was not performed, thereby limiting the strength of our conclusions.

Página 27 (Parágrafo 2): The natural history of GD-NENs following ER remains inadequately elucidated, exposing considerable lacunae in current understanding. Nonetheless, a recent retrospective study involving 53 patients with gastrointestinal NENs, comprising gastric, duodenal, and rectal lesions, demonstrated a disease-specific survival rate of 98% over a median follow-up of 44.6 months, with both local and systemic recurrences being exceedingly rare. Wang et al. evaluated ER for D-NENs, reporting a median follow-up of 62.6 months with rare local recurrence (6%), despite incomplete resections. Two recent studies on type 1 G-NENs managed by ER reported very promising outcomes: Uygun A et al. observed 100% disease-free survival with an 18% recurrence rate in 22 patients, while Merola et al. achieved 100% overall survival with no distant recurrences in 33 patients. In our study, the curative resection rate was 41.7% when using classic criteria, whereas the application of expanded criteria raised the curative resection rate to 62.1%, with the G-NENs group achieving a significantly higher curative resection rate than the D-NENs group, suggesting that

lesion location may influence the efficacy of ER. Notwithstanding the suboptimal resection rates, long-term outcomes, encompassing local recurrence (13.2% overall), distant recurrence (1.8% overall), and NEN-related mortality (0.4% overall) remain remarkably low across both gastric and duodenal group. The statistically significant differences in local and distant recurrence observed between curative and non-curative resections suggest that achieving a curative resection is indeed clinically meaningful. These findings support the continued use of ER for GD-NENs while highlighting the potential benefit of tailoring treatment strategies based on lesion location and refining resection criteria to further optimise patient outcomes.”

Página 27 (Parágrafo 3): “In our study, we also demonstrated that the evolution of ER techniques over time has resulted in marked improvements in procedural safety and efficacy. Notably, these advances were associated with a significant reduction in procedure-related AEs, alongside enhanced resection quality, as reflected by increased R0 resection rates and optimised horizontal and vertical margin statuses. Nevertheless, this increase was not accompanied by a significant decrease in local or distant recurrence rates or even the need for surgery during follow up, suggesting an opportunity for further improve the endoscopic management of patients with GD-NENs.”

Página 28 (Parágrafo 4): “In conclusion, our study demonstrates that despite the resection being non-curative in a significant proportion of patients, or even when resection does not meet strict classic curative criteria, the recurrence and tumour-related mortality of GD-NENs remain remarkably low. Consequently, our findings underscore the critical need for further refining patient and lesion selection criteria, which could enhance the overall benefits of endoscopic management.”

Generalisability	21	Discuss the generalisability (external validity) of the study results	Não foi diretamente discutido, no entanto o desenho multinacional e multicêntrico é um ponto a favor da validade externa. Página 28 (Parágrafo 2): <i>“Strengths of our study include its robust multinational, multicentre design, encompassing 24 centres across 10 Western countries, and a large cohort, which provides a dataset highly reflective of contemporary clinical practice.”</i> Contudo, a natureza retrospectiva do estudo, o número baixo de casos em determinadas técnicas e a predominância de lesões pequenas e bem diferenciadas tratadas em centros altamente especializados podem limitar a generalização dos resultados. Página 26 (Parágrafo 2): <i>“In our study, most lesions met established guideline criteria, as demonstrated by a median lesion size of 10 mm and a predominance of type I G-NENs.”</i> Página 26 (Parágrafo 1): <i>“This study offers a comprehensive analysis of data from 24 western tertiary centres in 10 countries”</i> Página 28 (Parágrafo 3): <i>“Additionally, while the overall cohort is robust, the relatively small numbers for certain techniques, such as EFTR and U-EMR, limit the statistical power for intergroup comparisons and may affect the generalisability of these specific findings.”</i>
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Página 28 (Parágrafo 5): <i>“No funding to be declared.”</i>

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

Authors

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- How were patients/the public involved in the design of this study?
- How were they involved in the recruitment to and conduct of the study?
- Were they asked to assess the burden of the intervention and time required to participate in the research?
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GI snapshots report unusual images that make an educational point. Since the aim of these articles is to stimulate the reader to think about the case, the title should be ambiguous and not give away the final diagnosis immediately (e.g. "Recurrent vomiting in 90 year old female"). GI snapshots have two parts:

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Word count: 4000 to 5000 **Unstructured abstract:** up to 250 words **Tables/Illustrations:** 5 or 6 figures, or clear simple diagrams **References:** 30 to 90 We would like you to list key messages, as well as 5 or 6 bullet points for emphasis. Recent advances in clinical practice are aimed at bringing busy clinicians up to date in areas where there have been important advances that are starting to influence clinical practice.

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Word count: up to 1300 words **Tables/Illustrations:** up to 4 **References:** up to 15 You may wish to include any of the following examples in the methodological description (not applicable to all contributions):

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- Main outcomes
- Secondary outcomes
- Study approach
- Device and technique
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- Patient characteristics
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