

Endoscopic Resection of Gastrointestinal Neuroendocrine Tumors: Safe and Effective

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Keywords

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Ressecção endoscópica de tumores neuroendócrinos gastrointestinais: segura e eficaz

Palavras Chave

Tumores neuroendócrinos · Ressecção endoscópica · ressecção endoscópica da mucosa · Dissecção endoscópica da submucosa

Gastrointestinal neuroendocrine tumors (GI-NETs) are being increasingly diagnosed, particularly at earlier stages of disease, where endoscopic resection (ER) is a well-known treatment alternative [1, 2]. The appropriate management of GI-NETs requires a complete understanding of tumor size, depth of invasion, lymph node metastasis status, and location within the gastrointestinal tract. In general, small superficial NETs can be managed by either standard endoscopic mucosal resection (EMR), modified EMR (cap or band assisted), or endoscopic submucosal dissection (ESD). Several studies have described

ER as safe and effective alternative with favorable outcomes; however, most of the studies include a small number of patients, are retrospective in nature, and lack direct comparison of different ER techniques. In this issue of *GE – Portuguese Journal of Gastroenterology*, we will find 3 new studies that provide further evidence of the safety, feasibility, and favorable outcomes of different ER methods for GI-NETs.

First, João et al. [3] present a prospective cohort study evaluating the efficacy and safety of cap-assisted EMR (EMR-C) for small (≤ 10 mm) low-grade rectal NETs (r-NETs). In this single-center cohort study, 13 patients were included during a 4-year period (January 2017 until September 2021), with a 100% complete ER rate and a 92% complete pathological resection (CPR) rate (median lesion size of 6 mm). These results are consistent with the largest retrospective studies on the outcomes of EMR-C for small r-NETs. Yang et al. [4] and Lee et al. [5] report a 94% and 83% complete histological resection rate, respectively. These results are encouraging and, as stated by the authors, EMR-C had higher rates of CPR than conventional EMR (77%), and similar results with ESD, with the advantage of significant lower procedural times [4]. There was only one adverse event (7.6%) reported by the authors corresponding to a case of intraprocedural bleed-

ing, similar to previously reported, rendering EMR-C a safe ER method [4, 5]. There was no evidence of residual or recurrent lesions during a median follow-up of 6 months, which was expected due to the excellent prognosis of small r-NETs. In fact, GI-NETs guidelines state that small, completely resected r-NETs do not warrant regular follow-up [2]. In 2 cases, EMR-C was used for recurrent r-NETs with endoscopic and histological success, reaffirming the benefit role of salvage EMR.

ESD is another minimally invasive technique that has been described for the treatment of GI-NETs, although it is still controversial which lesions benefit from this more demanding technique with also higher risk of adverse events. Manta et al. [6], in a multicenter retrospective study, evaluated the efficacy and safety of ESD in a cohort of 84 patients with esophageal ($n = 13$), gastric ($n = 61$), and duodenal ($n = 10$) gastrointestinal subepithelial tumors. Despite the 95.5% overall CPR rate, this rate was lower (75%) when applied specifically to GI-NETs. These results are similar to reported for overall ESD for foregut GI-NETs (69–96.6%) and the high variability of CPR rates most likely reflects the inclusion of all organs, grade, size, morphology, and depth of invasion of included lesions and merits careful interpretation [7, 8]. Regarding complications (8.3%), only one major bleeding was observed while no cases of perforations were reported, further emphasizing the safety of ER.

Even though CPR is the ultimate goal in every ER modality, in the specific case of GI-NETs, the true impact of incomplete pathological resections for both recurrence and overall survival remains unclear. Pimentel-Nunes et al. [7] present the first study that focused specifically on the long-term outcomes of different ER methods for the treatment of luminal GI-NETs. More specifically, the authors showed the short- and long-term outcomes after different ER methods of gastric, duodenum, and rectal GI-NETs, namely, standard endoscopic mucosal resection (sEMR), EMR-C, and ESD. In this single-center retrospective analysis, 53 patients with GI-NETs were included (25 gastric, 15 duodenal, and 13 rectal), with a complete ER in all cases (sEMR = 21; EMR-C = 19; ESD = 13) and a 68% overall CPR with no difference between ER techniques. The patients were followed for a mean of 45 months and during this period there were only 3 distant recurrences and 1 local recurrence. Distant recurrence occurred in 2 cases of gastric NETs (type 1 and type 3) and one duodenal NET. Only 1 patient had positive margins on the first resection. Endoscopic and histopathological lesion size of ≥ 12 mm and 20 mm, respectively, were considered as risk factor for distance recurrence in

univariate analysis. Also, only one death was noted after the distance recurrence, due to surgical complications. These results demonstrate that, for small lesions (≤ 12 mm on endoscopy and ≤ 20 mm on histopathology), regardless of the ER technique and margins at histopathological examination, as long as the lesions are completely resected, local and distance recurrence is rare and the overall global prognosis is very favorable. For larger lesions, multidisciplinary decision is advised, and if ER is pursued, a more intensive follow-up may be required. Previous studies also highlighted the favorable outcome even with histological positive margins for GI-NETs. For example, in the retrospective study by Matsueda et al. [9] of ER (sEMR, band-ligation EMR, and ESD) of nonampullar duodenal NETs, 97% of the 34 lesions were completely resected, but CPR rate was only 59%. However, there was no local or distant recurrence after a median follow-up of 47.9 months. Sivandzadeh et al. [10] also showed an absence of distant recurrence during a mean follow-up of 64 months in 36 patients with endoscopically resected GI-NETs (sEMR, band-ligation EMR) where only 38.9% had a CPR. For small r-NETs, a meta-analysis also demonstrated no difference in long-term outcomes between different EMR techniques (modified EMR, ESD, and sEMR), with local and distant recurrences being exceedingly rare even after incomplete pathological resection [11]. Finally, in the study of Pimentel et al. [7] EMR-C was surprisingly associated with a significantly higher complication rate (EMR-C 32%, ESD 8%, and EMRs 0%, $p = 0.01$), with 3 cases of perforations (2 duodenal and 1 gastric), mostly managed endoscopically with surgery being needed in only 1 patient after duodenal ESD.

These new 3 studies provide new evidence and strengths that ER is a safe and highly effective therapy for small luminal GI-NETs and should be the first-line therapy for lesions < 15 – 20 mm, depending on the location, and as recommended by the most current guidelines. For most small gastric, duodenal, and rectal lesions, EMR probably should be favored over ESD if lesion characteristics suggest that en bloc complete ER is feasible. ESD appears to be the best option for lesions that cannot be removed en bloc with EMR, and the comparable outcomes of EMR and ESD may also reflect the inclusion of more difficult lesions in the latter technique. To note, EMR-C and ESD are associated with higher risk of major complications, specifically in duodenum, even when performed by skilled operators. However, multicenter, prospective randomized trials are still warranted to confirm and support these results.

Statement of Ethics

Ethics approval was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Joana Carvão and Nélia Abreu contributed equally to the conception, writing, and critical revision of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

- 1 Carvão J, Dinis-Ribeiro M, Pimentel-Nunes P, Libânio D. Neuroendocrine tumors of the gastrointestinal tract: a focused review and practical approach for gastroenterologists. *GE Port J Gastroenterol*. 2021;28(5):336–48.
- 2 Delle Fave G, O’Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, et al. ENETS consensus guidelines update for gastroduodenal neuroendocrine neoplasms. *Neuroendocrinology*. 2016;103(2):119–24.
- 3 João M, Alves S, Areia M, Elvas L, Brito D, Saraiva S, et al. Cap-assisted endoscopic mucosal resection for rectal neuroendocrine tumors: an effective option. *GE Port J Gastroenterol*. 2022:1–8.
- 4 Yang DH, Park Y, Park SH, Kim KJ, Ye BD, Byeon JS, et al. Cap-assisted EMR for rectal neuroendocrine tumors: comparisons with conventional EMR and endoscopic submucosal dissection (with videos). *Gastrointest Endosc*. 2016 May;83(5):1015–22;quiz 1023–e6.
- 5 Lee J, Park YE, Choi JH, Heo NY, Park J, Park SH, et al. Comparison between cap-assisted and ligation-assisted endoscopic mucosal resection for rectal neuroendocrine tumors. *Ann Gastroenterol*. 2020 Jul–Aug;33(4):385–90.
- 6 Manta R, Zito FP, Pugliese F, Caruso A, Mangiafico S, D’Alessandro A, et al. Endoscopic submucosal dissection for subepithelial tumor treatment in the upper digestive tract: a western, multicenter study. *GE Port J Gastroenterol*. 2022:1–6.
- 7 Pimentel-Nunes P, Ortigão R, Afonso LP, Bastos RP, Libânio D, Dinis-Ribeiro M. Endoscopic resection of gastrointestinal neuroendocrine tumors: long-term outcomes and comparison of endoscopic techniques. *GE Port J Gastroenterol*. 2022:1–9.
- 8 Li QL, Zhang YQ, Chen WF, Xu MD, Zhong YS, Ma LL, et al. Endoscopic submucosal dissection for foregut neuroendocrine tumors: an initial study. *World J Gastroenterol*. 2012 Oct 28;18(40):5799–806.
- 9 Matsueda K, Kanesaka T, Kitamura M, Shichijo S, Maekawa A, Yamamoto S, et al. Favorable long-term outcomes of endoscopic resection for nonampullary duodenal neuroendocrine tumor. *J Gastroenterol Hepatol*. 2021 Dec;36(12):3329–36.
- 10 Sivandzadeh GR, Ejtehadi F, Shoaee S, Aminlari L, Niknam R, Taghavi AR, et al. Endoscopic mucosal resection: still a reliable therapeutic option for gastrointestinal neuroendocrine tumors. *BMC Gastroenterol*. 2021 May 24;21(1):238.
- 11 Zhang HP, Wu W, Yang S, Lin J. Endoscopic treatments for rectal neuroendocrine tumors smaller than 16 mm: a meta-analysis. *Scand J Gastroenterol*. 2016 Nov;51(11):1345–53.