



NEN Gain or NEN Loss: Endoscopic Resection for Rectal Neuroendocrine Neoplasms < 15 mm

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Rectal neuroendocrine neoplasms (rNENs), which represent 12–27% of all gastrointestinal NENs [1], are the second-most common site of gastrointestinal NENs [1]. An increasing incidence of rNENs has been reported over the past few years, likely related to the discovery of asymptomatic tumors during screening colonoscopy [1]. The optimal management of localized rNENs is not yet standardized, particularly for lesions 10–19 mm in diameter. This size range is considered the “sweet spot” for advanced resection methods for rNENs as will be discussed in further detail below; this size range is based on an extensive literature that suggested that 15 mm should be considered the optimal size cut-off to predict the risk of metastases [2–4]. rNENs comprise a heterogeneous group of neoplasms that are not entirely indolent, as they have traditionally been considered, having a risk of metastatic disease ranging from 3 to 60% [5]. Among these, tumor size has traditionally been considered the most important factor in predicting aggressive disease. In this context, neoplasms < 10 mm are associated with a low risk of metastasis (< 3%), whereas lesions > 20 mm are generally metastatic in 60–80% of cases [5]. In between, patients with rNENs measuring 10–19 mm develop synchronous or metachronous metastases in 4–20% of cases [5]. In this context, some authors have attempted to define a more precise cut-off to predict the risk of metastasis and/or recurrence. In the study by Concors et al. [2], which assessed a total of 4893 rNENs, the authors reported that an increase in tumor size was associated with a higher likelihood of pathologically confirmed lymph node involvement. Both size and

degree of differentiation were independently associated with a higher likelihood of distant metastatic disease. For well and moderately differentiated tumors, tumors > 15 mm were associated with a higher risk of distant metastases. These data notwithstanding, it is extremely important to remember that size alone has limited accuracy [6] and does not represent the only factor that influences tumor behavior. As recently reported [6], tumors ≤ 10 mm can be both at stage IV or G3, suggesting that, more important than size alone, the European Neuroendocrine Tumor Society (ENETS) TNM staging accurately predicts prognosis in patients with rNENs.

Furthermore, the most appropriate endoscopic resection technique for localized small rNENs is a topic of ongoing debate. The available endoscopic techniques include endoscopic mucosal resection (EMR), modified EMR (mEMR), endoscopic submucosal dissection (ESD), and, more recently, full-thickness endoscopic resection (EFTR). Each technique is dependent on the expertise of the endoscopist, the patient’s preference, tumor location, muscular layer invasion, the presence of metastases, lymphovascular involvement, and histological grade. Though EMR is considered a relatively safe and effective technique for the removal of small, superficial rNENs confined to the mucosa and submucosal layer, it has some limitations, such as the inability to achieve *en bloc* resection (the gold standard for tumor resection) and a higher rate of local recurrence compared with other techniques. Its application to rNENs remains controversial since mEMR and ESD have superior *en bloc* resection rates and histologically complete resection rate [7]. mEMR is considered more advanced and has a higher *en bloc* resection rate and a lower local recurrence rate, but it is also associated with a higher risk of complications and a longer procedure time. In detail, endoscopic submucosal resection with a ligation device (ESMR-L) is only applicable for tumors < 10 mm due to the short diameter of the caps fitted to colonoscopes. ESD is considered an effective technique for the *en bloc* resection of slightly invasive

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gastrointestinal lesions particularly useful for treating rectal lesions, but is associated with a higher risk of complications and a longer procedure time. EFTR is a relatively new technique that has a high *en bloc* resection rate and a low local recurrence rate.

In this issue of *Digestive Diseases and Sciences*, Hamada et al. [8] report the results of a retrospective study that includes 139 rNENs < 15 mm, concluding that endoscopic resection has favorable short- and long-term outcomes in this specific subgroup of rNENs. One of their key findings is that ESMR-L and ESD were the two best endoscopic techniques for rNENs < 10 mm and 10–14 mm, respectively, highlighting the importance of selecting the appropriate endoscopic technique based on the size of the tumor. Overall, their results provide further evidence of the safety and effectiveness of endoscopic resection for small rNENs. The use of ESMR-L and ESD for rNENs confirms that endoscopic resection can achieve *en bloc* resection, reducing the risk of recurrence. Nevertheless, the article does not discuss EFTR, likely since it is not typically the first choice for tumors < 15 mm. Yet, in the case of small NENs, invasion beyond the submucosa can be present. On the other hand, EFTR is becoming increasingly popular among gastrointestinal specialists since it enables the complete removal of the tumor, including the surrounding layers of the rectal wall, which may increase the chances of achieving a more complete resection for small neoplasms that grow beyond the submucosa. Although the benefits of EFTR for rNENs are not well established in the literature, this technique can overcome the limitations related to the deep infiltration of rNENs. Nevertheless, prior to widespread adoption, the performance of these techniques will have to be carefully compared to EMR, mEMR, and ESD. Since no significant differences have been reported between ESD and mEMR and among the mEMR variants, [9] there are no recommendations for the selection of any specific endoscopic resection technique for rNENs < 15 mm. Nevertheless, endoscopic resection is indicated if there is no evidence of invasion beyond submucosa and any presence of locoregional disease since it aims to achieve a complete oncological resection. Even though endoscopic ultrasound (EUS) is generally suggested for the staging of all rNENs [10], for small (≤ 10 mm) rNENs, the use of EUS is more controversial [11], probably due to its lower accuracy for small tumors [12]. As a consequence, in clinical practice, EUS is not routinely performed for all rNENs before resection [13].

In summary, the study by Hamada et al. [8] highlights the efficacy of endoscopic resection as a treatment option for small rNENs, helping address the optimal endoscopic resection technique for localized small rNENs. As reported [8], rNENs < 15 mm that appear to show a low metastatic potential might theoretically be treated via endoscopic resection in the absence of other factors

related to metastasis, including lymphovascular involvement, increased mitotic rate, and muscular layer invasion. Nevertheless, the results should be cautiously interpreted; of note, as stated by the authors [8], the small number of patients with rNENs > 10 mm (21 patients out of a total of 139 lesions with 118 tumors being < 10 mm in size) together with the retrospective nature of the study and the lack of staging EUS in all included patients complicate any conclusions drawn. Furthermore, it is likely that in the near future, EFTR techniques will also be among the endoscopic treatment options, especially in those cases with deep infiltration beyond the submucosa, or as a second step after an incomplete EMR or ESD, or again as a valuable option for patients who are not surgical candidates. Meanwhile, it might be advisable to stage all rNEN patients with EUS as per current guidelines [10] and in selected patients with neoplasms < 15 mm who have low metastatic risk (i.e. low grade, no lymphovascular involvement nor muscular layer invasion), an endoscopic resection might be suggested. In absence of clear-cut recommendations, the choice of a single endoscopic technique should be based on tumor characteristics (i.e. ESD for tumors > 10 mm) and personal expertise. Referral to tertiary centers with consolidated expertise in the multidisciplinary management of NENs remains the goal for the optimal management of these tumors.

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