

# ENETS Consensus Guidelines Update for Colorectal Neuroendocrine Neoplasms

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## Introduction

A more extensive paper on colorectal neuroendocrine neoplasms (NENs) is provided in the 2012 ENETS Guidelines, additional information over the past 2 years and/or expert opinions have thus been incorporated into this guideline update.

## Epidemiology

It is becoming clearer that rectal NEN is a different disease to colonic NEN. Rectal NENs are commonly (but not exclusively) small and generally low to intermediate grade [grades 1 or 2 (G1 or G2)], whereas colonic NENs are often aggressive, poorly differentiated and higher grade (G3). Rectal NENs have become more frequent than small intestine neuroendocrine tumors (NETs) since 2000.

There are some differences between the USA and Korea as demonstrated by publications from Taghavi et al. [1] and Jung et al. [2]:

- 1 Rectal NETs are more common in women in a US population (OR 1.196); however, they more likely in men in Korea (OR 1.92). In the USA, the highest incidence was in Asians (OR 10) and Blacks (OR 1.96), confirmed by a paper from Taghavi et al. [1]; a new finding is the high incidence in Hispanics (OR 2.6).
- 2 The report by Yangong et al. showed that ulceration occurs in tumors >2 cm [3] (in 284 cases with tumors <2 cm vs. in 28 cases with tumors >2 cm).
- 3 In a single-center retrospective series from Baltimore, Md., USA [4], no metastases were seen in lesions ≤9 mm, and this follows the previous ENETS recommendations guiding investigations, outcomes and thera-

For an alphabetical list of all other Vienna Consensus Conference participants, see Appendix.

peutic options based on cut-off sizes of 10 and 20 mm. The occurrence of multiple rectal NENs was also noted by Park et al. [5] who recommended full colonoscopy in the presence of one colorectal NEN.

## Screening

Colonoscopy screening programs are picking up NENs of the colon and terminal ileum. The incidence rate at screening is 0.17% [2]. They appear as yellowish polypoids or flat doughnut-shaped lesions, but there may be central ulceration. Ideally, lesions should be tattooed at the time of removal if thought to be a NET, since further therapy may be needed. A referral should be made to NET MDM/tumor board for further management. The incidence of rectal NET is positively associated with young age, male gender, alcohol and LDL levels.

### *Predictors of Outcome*

Factors predicting lymph node involvement and metastasis continue to be examined, in view of uncertainty over whether recurrence is likely to occur in resected colorectal NENs.

Al Natour et al. [6] examined the SEER data of 929 patients with localized colonic NEN which were all treated surgically. They found that tumor size and depth predicted lymph node metastasis and showed that intramucosal tumors <1 cm have a 4% risk of lymph node metastasis. Tumors <10 mm had a 3% risk of metastasis in the Baltimore group [4], and while the risk is not zero for small tumors, the majority of patients appear cured once full resections of small (<10 mm) rectal NENs with favorable biology are performed. Predictors of survival were further examined by Weinstock et al. [7] who showed that stage was the strongest predictor of survival in multivariate analysis and that grade, size, symptoms and treatment modality were only significant in univariate analysis. In this study, discrimination of size as a predictor was confirmed between <1 and >1 cm, but no discrimination was seen with regard to prognosis between 1 and 2 versus >2 cm in size. This group also found a small risk of metastasis in tumors <1 cm (1%), and the majority of tumors >2 cm had metastasized (60%) [7]. Size of the primary, therefore, remains a less than totally reliable discriminator of prognosis.

When examining high-grade neuroendocrine carcinomas in 126 patients, Smith et al. [8] suggested that a more favorable prognosis may be present if there is an adenocarcinoma component on histology.

## Classification

With regard to prediction of short-term prognosis, the WHO 2010 classification was found to be superior to the WHO 2000 classification by Lee et al. [9]; and the ENETS staging system was validated by survival analysis [7].

## Therapy (fig. 1)

### *Endoscopy and Surgery*

Endoscopic resection of rectal tumors can be by: simple polypectomy, endoscopic mucosal resection (EMR) with modified EMR band ligation, endoscopic submucosal dissection (ESD) and transanal endoscopic microsurgery (TEMS). For lesions <10 mm and no involvement of the muscularis propria, EMR is adequate once complete, but EMR band-assisted ligation may improve the number of complete resections [10]. If EMR results in an incomplete resection, then ESD or TEMS may be indicated as salvage therapy; these data came from inferences within citations, as there are no actual recurrences in this situation. It is not clear from the literature whether rescue or salvage therapies are really required and if so, which of these is the best option, but TEMS leads to more complications [10–12]. Patients with an incomplete resection from snare polypectomy (this technique is not recommended), EMR or other techniques should be discussed on a case-per-case basis at centers of excellence in treating NEN. Endoscopic ultrasound is recommended for most rectal NENs except perhaps for very small (<5 mm) lesions that have been completely removed where it may not be necessary.

Determining the cut-off size has also been challenged by recent data. As minimally invasive procedures gather momentum and improve in completeness of excision, cut-off sizes may need to be revised. In the series by Gleeson et al. [4], no metastases were seen in lesions ≤9 mm, and local resection was deemed safe in lesions between 10 and 16 mm according to McDermott et al. [13] (this was, however, a pooled analysis with data quality scoring low/moderate for all series included). In the series of rectal lesions by Yangong et al. [3], no recurrence was seen in 248 cases after transanal resection and endoscopic polypectomy. Similarly, Shigeta et al. [14] questioned whether radical resection is better than local resection for rectal carcinoids for tumor sizes 10–20 mm with and without positive lymph nodes and found that radical surgery reduces quality of life. Although these series are reassuring that recurrence is uncommon, further evidence is needed to conclude that local resection is safe for these intermediate tumors.

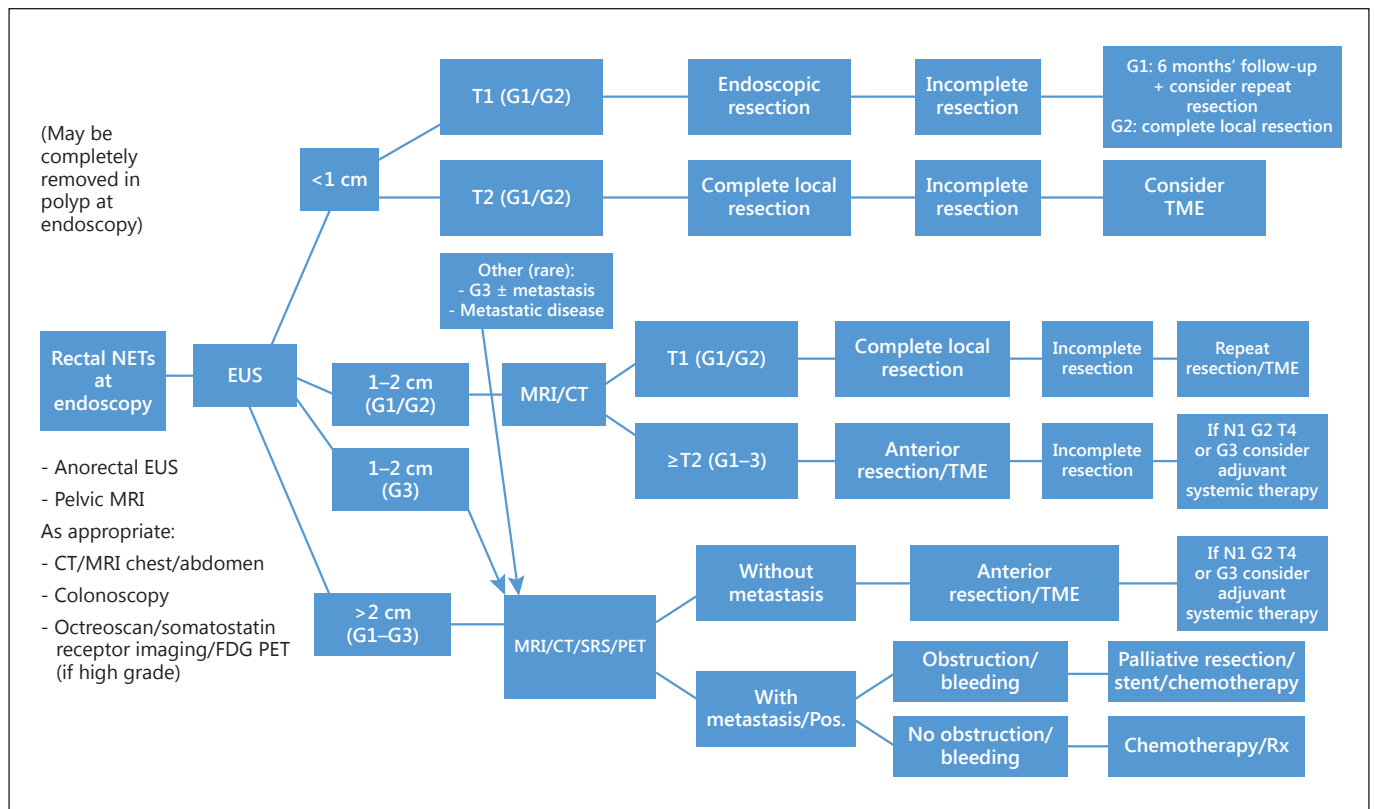


Fig. 1. Algorithm for treating rectal NETs.

Smith et al. [8] provided evidence that resection of the primary in high-grade colorectal NENs with or without metastases does not result in improved prognosis (median survival 13 months). This is in contrast to adenocarcinoma and is more in keeping with small cell lung cancer in terms of prognosis and outcomes of surgery. A smaller study by Aytac et al. [15] confirmed these findings and introduced the issue of radiotherapy for rectal high-grade neuroendocrine carcinoma, but without conclusive evidence of benefit.

The combination of everolimus and octreotide has been reported in the RADIANT-2 trial [16]. In a post-hoc analysis, there was improved progression-free survival compared to placebo in the RADIANT-2 study; there may, therefore, be some rationale for using this combination in well-differentiated G1/G2 colorectal NENs, but this remains to be verified [17]. Similarly, the use of somatostatin analogues – somatuline autogel – was tested in a phase III study (CLARINET study), but as there were only 14 cases of colorectal NENs, it is impossible to predict real benefit (even in patients with overexpression of somatostatin receptors).

## Summary

There are some changes to the 2011 Guidelines as a result of some large series clarifying the risk of recurrence and introducing different methods of therapy in these tumors which are increasingly common. It is important that clinicians throughout the wide ranges of disciplines treating these cases are aware of these updates.

Please also refer to the consensus guideline updates for other gastroenteropancreatic neuroendocrine tumors [18–23, this issue].

## Appendix

### All Other Vienna Consensus Conference Participants

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