Consortium guidelines update for colorectal neuroendocrine neoplasms (NEN)


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A more extensive paper on colorectal NEN is provided in the 2012 ENETS guidelines and 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 NEN are commonly (but not exclusively) small and generally low to intermediate grade (Grades 1 or 2 [G1, G2]) whereas colonic NEN are often aggressive, poorly differentiated and higher grade (G3). Rectal NENs have become more frequent than small intestine NETs since 2000.

There are some differences between USA and Korea as demonstrated by publications from Taghavi et al. (1) and Jung et al. (2).

a) Rectal NETs are more common in women in a US-population (OR 1.196), however, more likely in men (OR 1.92) in Korea. In USA the highest incidence was in Asians (OR10) and Blacks OR 1.96, confirmed by paper from Taghavi et al (1); a new finding is of a high incidence in Hispanics (OR 2.6)

b) it has been shown that ulceration occurs in tumors larger than 2 cm from the report of Yanyong et al. (3) on 284 cases less than 2 cm vs. 28 greater than >2 cm

c) In a single centre retrospective series from Baltimore, USA (Gleeson et al. (4)), no metastases were seen in lesions 9 mm or less, and this follows the previous ENETS recommendations guiding both investigations, outcomes and therapeutic options based on cut-off sizes of 10 and 20 mm. The occurrence of multiple rectal NEN was also noted by Park et al (5) who recommend full comonoscopy in the presence of one colorectal NEN. (Park et al (5))

**Screening**

Colonoscopy screening programmes are picking up NEN of colon and terminal ileum.

Incidence at screening is 0.17% (2). The appearance is of yellowish polyoid or flat doughnut-shaped lesion 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/tumour 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 metastases and metastases continue to be examined, in view of uncertainty over whether recurrence is likely to occur in resected colorectal NEN.

Natour et al (6) examined the SEER data of 929 patients with localized colonic NEN which were all treated surgically. They found that tumour size and depth predict lymph node metastasis and showed that intramuosal tumors <1cm have a 4% risk of lymph node metastasis. Tumours <10mm had a 3% risk of metastases in the Baltimore group and while the risk is not zero for small tumours, the majority of patients appear cured once full resections of small (<10 mm rectal NEN with favourable biology is 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 >1cm but no discrimination was seen with regard to prognosis between 1-2 vs >2 cm of size. This group also found a small risk of metastasis in tumors <1cm (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 NE carcinomas, Smith et al (7) in 126 patients with high grade tumours hinted that a more favourable prognosis may be present if there is an adenocarcinoma component on histology.
3. Classification
The WHO 2010 classification was found to be superior to WHO 2000 with regard to prediction of short-term prognosis by Lee et al. (9), and the ENETS staging system was validated by survival analysis (7).

4. Therapy
Endoscopy/ Surgery
Endoscopic resection of rectal tumours 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 <10mm and no involvement of muscularis propria, EMR is adequate once complete but EMR band-assisted ligation may improve the number of complete resections (10). If EMR results in incomplete resection then ESD or TEMS may be indicated as salvage therapy; these date emanated from inference 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 best option but TEMS does lead to more complications. (Jeon et al (11), Lee et al (10), Wu et al (12)). Patients with incomplete resection from snare polypectomy (that is not recommended), EMR or other techniques should be discussed on a case-per-case basis at centres of excellence in treating NEN. EUS is recommended for most rectal NEN except for perhaps very small (<5mm) lesions that have been completely removed where it may be not be necessary.

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

Smith et al (8) provide evidence that resection of 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 Ayta et al (15) confirms these findings and introduces the issue of radiotherapy for rectal high grade NEC, but without conclusive evidence of benefit.

The combination of everolimus and octreotide has been reported in the Radiant 2 trial (Pavel et al Lancet. 2011 Dec 10;378(9808):2005-12). In a post hoc analysis, there was improved progression-free survival compared to placebo in radiant 2 study; there may therefore be some rationale for using this combination in well-differentiated G1/G2 colorectal NEN but this remains to be verified (16).

Similarly, use of somatostatin analogues – somatuline autogel, was tested in a phase III study (Clarinet study) but as there were only 14 cases of colorectal NEN it is impossible to predict real benefit in colorectal NEN (even in patients with overexpression of somatostatin receptors).

Summary.
There are some changes to the previous guidelines as a result of some large series clarifying risk of recurrence and different methods of therapy in these tumours 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 consensus guideline updates for other gastro-entero-pancreatic (GEP) neuroendocrine tumours [17-22, this issue].
References
6 Al Natour RH, Saund MS, Sanchez VM, Whang EE, Sharma AM, Huang Q, Boosalis VA, Gold JS. Tumor size and depth predict rate of lymph node metastasis in colon carcinoids and can be used to select patients for endoscopic resection. J Gastrointest Surg. 2012 Mar;16(3):595-602.
Fig. 1. Algorithm for treating rectal neuroendocrine tumours