83663_Auto_EditedC.docx

Rectal neuroendocrine tumours and the role of emerging endoscopic techniques

Keating E *et al*. Endoscopic management of rectal NETs

Eoin Keating, Gayle Bennett, Michelle A. Murray, Sinead Ryan, John Aird, Donal B. O'Connor, Dermot O'Toole, Conor Lahiff

Abstract

Rectal neuroendocrine tumours represent a rare colorectal tumour with a 10 fold increased prevalence due to incidental detection in the era of colorectal screening. Patient outcomes with early diagnosis are excellent. However endoscopic recognition of this lesion is variable and misdiagnosis can result in suboptimal endoscopic resection with subsequent uncertainty in relation to optimal long-term management. Endoscopic techniques have shown particular utility in managing this under-recognized neuroendocrine tumour.

Keating E, Bennett G, Murray MA, Ryan S, Aird J, O'Connor DB, O'Toole D, Lahiff C. Rectal neuroendocrine tumours and the role of emerging endoscopic techniques. *World J Gastrointest Endosc* 2023; In press

Core Tip: Rectal neuroendocrine tumours (r-NETs) are increasingly detected during colorectal screening. Endoscopists may not accurately distinguish r-NETs from other

polyps and inadvertent resection attempts result in significant post resection challenges. r-NETs have an unpredictable metastasis pattern, requiring appropriate pre-resection assessment. Accurate endoscopic assessment and resection provides an effective option in the management of r-NETs.

INTRODUCTION

Neuroendocrine tumours (NETs), previously described as carcinoid tumours, describes a classification of neoplastic cells originating from a neuroendocrine cell lineage. NETs can occur in multiple organ systems throughout the body and have a specific classification criteria according to the World Health Organization (WHO)[1]. These criteria include a grading of tumours based on mitotic counts and Ki-67 proliferation index (G1/G2/G3). The gastroenteropancreatic tract is the most common site for NETs (GEP-NETs), accounting for 73.7% of all NETs[2]. Overall, colonic NETs remain a rare occurrence compared to colorectal adenocarcinoma incidence rates, accounting for only 1.5% of all colorectal cancers[3].

Rectal neuroendocrine tumours (r-NETs) are one of the most frequent sites of GEP-NETs, representing 27% of GEP-NETs and 18% of all NETs[4]. The incidence of r-NETs is estimated to have risen 10 fold over the past 4 decades, attributed to increased incidental detection during colorectal cancer screening[5]. Weinstock *et al*[6] demonstrated that the majority of r-NETs are asymptomatic, with only a minority reporting symptoms such as altered bowel habit (12.8%), rectal bleeding (6.4%) or unexplained weight loss (2.1%). The carcinoid syndrome of flushing or diarrhoea is rarely associated with r-NETs[7].

The primary prognostic factor for r-NETs is driven by the disease stage at diagnosis. Five year survival for localised disease is excellent with rates of 94%-100%[8]. Regional and metastatic spread are uncommon as 75%-85% of r-NETs are localised at time of diagnosis[9]. According to the WHO grading criterion, r-NETs are predominantly G1 or G2 due to low proliferative activity.

The risk factors for nodal involvement or metastatic disease include lymphovascular invasion, muscularis propria involvement and tumour size/grade[8-10]. Pre-resection staging with endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI) is necessary to adequately assess for regional or metastatic disease. Multiple approaches to achieve R0 resection may be utilised, primarily depending on lesion size, such as endoscopic mucosal resection (EMR, band or ligation approach), endoscopic submucosal dissection (ESD), combination approaches [*e.g.*, knife-assisted snare resection (KAR)] or

surgical approaches such as transanal resection (*e.g.*, Transanal endoscopic microsurgery) or radical resections.

The classical described endoscopic appearance of r-NETs is of a small, typically < 20 mm, solitary nodule with a yellow coloration, embedded in the rectal submucosa. However, the correct endoscopic diagnosis of r-NET is not always achieved by the endoscopist, demonstrated by Fine *et al*[11], to be as low as 18%. As prognosis in r-NETs is dependent on the appropriate resection method, lack of recognition may result in a compromised initial resection, affecting patient prognosis.

PLANNED RECTAL NEUROENDOCRINE TUMOUR MANAGEMENT

Endoscopic diagnosis and inspection of r-NETs

The standard description of an r-NET at endoscopy is of a solitary nodular structure, appearing to be embedded in the normal rectal mucosa, and most often associated with a yellow coloration. r-NETs can be endoscopically differentiated from rectal adenomas by the presence of overlying normal rectal mucosa. The majority of r-NETs are < 20 mm in size[6] and increasing tumour size is also associated with increased risk of metastasis, especially once size exceeds 20 mm[12]. Lesion size is thus a primary consideration in planning excision strategies.

However, metastatic disease has been confirmed in small r-NETs of < 10 mm diameter[13], indicating that tumour size cannot be used in isolation. Therefore close inspection of the surface mucosa at endoscopy is required as the presence of overlying ulceration, depression or erosions is also associated with tumour metastasis[14].

Pre-intervention management

If r-NET is suspected at time of endoscopy, the European Neuroendocrine Tumour Society (ENETS) guidelines, published in 2012 and revised in 2016, recommends completing a pre-intervention workup with a rectal EUS to establish tumour size, tumour depth (including involvement of muscularis propria) and evidence of lymphovascular involvement[5,9,15]. EUS accuracy of tumour depth is high, with rates of 91-100%

correlation with post-resection findings reported[16,17]. Accurate, pre-intervention EUS is therefore essential in determining r-NET stage and selection of optimal resection strategy.

r-NETs of > 10 mm in size are also recommended to undergo MRI pelvis examination to assess for muscularis propria invasion and lymphovascular involvement. If muscularis propria involvement or nodal positivity is confirmed, a surgical approach with anterior resection and total mesenteric excision is recommended[9].

Beyond a lesion size of 20 mm, the risk of r-NET metastasis is significant and evaluation with CT thorax, abdomen and pelvis, in addition to MRI pelvis is required, prior to surgical management[8,9].

Endoscopic resection approaches
As outlined above, resection approach for r-NETs depends on accurate assessment of size, grade (if biopsies completed) and locoregional involvement. Complete excision of r-NETs < 10 mm is considered the gold standard and can be safely achieved using advanced endoscopic techniques[5,8].

Strategies to excise r-NETs of 10-19 mm in size have not reached consensus acceptance and there are no comparative studies of endoscopic resection *vs* surgical outcomes for this size cohort[9,15,18]. The requirement for a general anaesthetic for surgical approaches such as transanal endoscopic microsurgery may favour advanced endoscopic techniques in a selection of patients. A metastatic risk of 10%-15% is quoted for this category[10]. Therefore, a case-by-case strategy may be required for r-NETs 10-19 mm in size, based on patient characteristics (*e.g.*, comorbidities), in addition to the EUS and/or MRI findings predicting potential locoregional spread or metastatic disease.

The ENETS 2012 guideline stipulates that the only guaranteed curative option is complete resection in a localised lesion[9]. Pathological interpretation of r-NET margin clearance is therefore of primary importance to determine risk of locoregional spread. En-bloc resections are preferential to piecemeal resection to aid pathological assessment. The goal of achieving en-bloc pathology specimens influences the choice of advanced endoscopic technique employed to resect the r-NET (Table 1).

EMR

EMR is widely used in the safe and successful resection of large non-pedunculated colorectal polyps (LNPCPs) by Western endoscopists[19]. Conventional EMR (C-EMR) en-bloc resection rates in Western centres, across all polyp sizes, approach 35%[20]. En-bloc resections have significantly lower rates of recurrence over piecemeal EMR[21]. In relation to r-NETs therefore, caution must be exercised in lesion assessment, to ensure that an en-bloc resection is feasible.

C-EMR

The ENETS guidelines endorse the use of C-EMR for r-NET lesions < 10 mm in size, once muscularis propria involvement has been out ruled with rectal EUS[15]. However, Nakamura *et al*[22] demonstrated that C-EMR had complete resection rates of 36.4% and curative resection rates of only 27.3%.

Modified EMR

In the same Nakamura study, modified EMR (M-EMR) strategies such as band ligation EMR or cap assisted EMR achieved significantly higher complete resection and curative resection rates, 88.0% and 69.4% respectively. Additionally, M-EMR achieved a 100% en-bloc resection rate. While this study was limited by a small number of EMRs (n = 11), its results are consistent with other studies regarding EMR resection of r-NETs outcomes and support the use of M-EMR over C-EMR for resection of r-NETs < 10 mm.

With regard to cap-assisted EMR (EMR-C), it is superior to EMR in complete histologic resection rates (94.1% *vs* 76.8%) without significant additional perforation or bleeding risks[23]. Similarly for band ligation EMR, complete resection rates outperform C-EMR, 93.3% *vs* 65.5% respectively, again without additional procedural times or complication rates[24].

M-EMR is restricted in its use to lesions < 10 mm in size, due to the specifications of the band or cap diameter of the equipment. M-EMR outcomes, for r-NETs < 10 mm in

diameter, approach the resection results of ESD[5], and may be more accessible to Western endoscopists who lack suitable ESD exposure. A recent Japanese study demonstrated superior M-EMR complete resection rates and lower recurrence rates *vs* ESD, but this did not reach significance[25]. Yang *et al*[23] have also demonstrated that EMR-C histologic resection rates approach those of ESD (94.1% *vs* 93.8%) , but again, this did not reach significance.

The ENETS 2016 guidelines, factoring the improved en-bloc resection rates, recommend M-EMR, and specifically band ligation EMR, for r-NET resections of lesions < 10 mm[15].

ESD

ESD uses an endoscopically deployed thermal-knife to dissect the submucosal plane, facilitating en-bloc resection and aiding pathological interpretation. ESD was pioneered in Japan for the resection of gastric neoplasia and consequently, there are significant differences in the R0 outcomes and exposure to ESD practice between Asian and non-Asian countries[26].

ESD affords excellent r-NET en-bloc resection rates ranging from 98.2% to 100% and high R0 resection rates (90.38%-90.9%) for lesions < 20 mm[27,28]. Due to these superior outcomes, systematic reviews have recommended ESD over EMR for the resection of r-NETs < 10 mm and for ESD consideration in lesions < 20 mm[27,29].

Analysing the utility of ESD, there are several limitations to consider. Colonic ESD for LNPCPs is associated with higher complication rates including perforation and post-polypectomy bleeding (PPB) when compared to EMR[30]. Specifically considering r-NETs, there is a non-significant trend towards perforation and PPB but this is limited by small sample sizes[31]. Increased endoscopist experience is associated with a reduction in ESD complication rates[27]. Another consistent limitation of ESD is the increased procedural time required *vs* EMR[29,31].

Chen *et al*[27] also highlighted the coagulation or burn effect on normal tissues at time of ESD and potential effects on R0 pathologic interpretation. To counter this

phenomenon, Yoshii *et al* demonstrated an "underwater" ESD approach which afforded a heat sink effect, successfully limiting burn artefact[32].

Hybrid technique-KAR

ESD requires extensive training and procedural exposure to perform safely and effectively with a significant learning curve[33]. As demonstrated above, ESD outcomes differ between Asian and non-Asian endoscopists. Attempting to accelerate the learning curve of ESD for Western endoscopists has led to the development of a hybrid technique, combining familiar EMR practices with elements of ESD.

KAR described by Bhattacharya *et al* in the resection of LNPCPs incorporates standard submucosal injection, followed by circumferential submucosal dissection[34]. Once a circumferential margin has been established, a snare is deployed to facilitate en-bloc resection. The study achieved a 53% en- bloc resection rate in polyps < 50 mm in size and demonstrated a recurrence rate of 4.3% for en-bloc specimens. The KAR technique was subsequently shown to be effective in the management of scarred polyps with previous EMR[35].

Lisotti *et al*[36] applied the KAR technique for two < 5 mm r-NETs in a case series, successfully achieving en-bloc resections and negative resection margins. The following case report from our institution further illustrates the utility of KAR in this context.

We present the case of a 33-year-old male with a background history of cystic fibrosis, referred for consideration for lung transplantation. During a pre-transplantation screening colonoscopy at a local hospital a 6mm submucosal lesion was identified 3 cm above the anorectal junction (Figure 1A). Re-evaluation at our institution included EUS, which confirmed a hypoechoic, homogenous, well circumscribed lesion, arising from the submucosa and consistent with a r-NET (Figure 1B). Submucosal injection (gelofusion and methylene blue) was followed by hybrid KAR to successfully achieve en-bloc resection (Figure 1C and D). Histopathological examination confirmed a grade 1, well-differentiated neuroendocrine tumour, with no evidence of lymphovascular involvement and negative margins (Figure 1F). After multidisciplinary discussion, and corresponding

to 2012 ENETs guidelines on sub-centimetre r-NETs, surveillance was not considered necessary for this 6mm lesion and the patient has been listed for transplantation.

Surveillance post resection

ENETS guidelines for surveillance post r-NET resection are determined by size, in addition to mitotic grade[9]. Follow-up modalities recommended include colonoscopy, rectal EUS and cross sectional imaging. G1 or G2 r-NETS, < 10 mm in size, with no evidence of lymphovascular invasion or muscularis propria involvement are not recommended for follow-up at present. All r-NETs 10-20 mm require annual endoscopic follow up. r-NETs > 20 mm require intensive follow-up due to the risk of metastasis.

The surveillance guidelines have generated debate, particularly for r-NETs of <10mm in diameter. The reported metastatic risk of these small r-NETs has varied from 0% to 10%[16,37,38]. Holinga et al[38], proposed an intensive EUS surveillance programme at 3 mo post resection, in addition to 6 moly EUS for the 3 years post resection.

MANAGEMENT OF INCIDENTAL OR UNRECOGNISED R-NETS

Prevalence

Fine et al[11] confirmed that the real time endoscopic recognition of r-NETs is low at only 18%. Of 284 unsuspected r-NETs in the French study, 190 (67%) underwent attempted resection, primarily by standard polypectomy (n = 148/190, 78%)[11]. The successful R0 resection rate for patients who underwent polypectomy at initial colonoscopy was only 17%. As the prognosis of r-NETs depends on the successful complete excision of the lesion, salvage therapies such as EMR, ESD or trans-anal endoscopic microsurgery were required.

Surveillance

The retrospective diagnosis of r-NET poses a challenge in determining appropriate surveillance. Polypectomy or piecemeal EMR are often associated with R1 pathology as well as difficulty assessing for lymphovascular invasion, a key factor in surveillance

algorithms. Therefore, appropriate surveillance for these cases is yet to be determined and results in local variation in practice. Such difficulties can largely be avoided by accurate index endoscopic assessment.

CONCLUSION

Rectal neuroendocrine tumours represent a rare colorectal tumour, with increasing prevalence due to incidental diagnosis during standard colorectal screening. Accurate endoscopic recognition rates of r-NETs are disappointing and the area requires increased focus in endoscopy training to improve specificity. Endoscopist education on the differentiation of rectal adenomas from r-NETs is a priority in this regard. Management strategies for diagnosed r-NETS are well established. Advanced endoscopic resection techniques have resulted in improved outcomes and can be an effective alternative for surgical resection for intermediate (10-19 mm) r-NETs but further studies are required. Newer techniques such as KAR may be valuable but require further study. International surveillance guidelines are clear but adherence to guidelines is variable and need to be more consistently applied.

83663_Auto_EditedC.docx

PRIMARY SOURCES

1   "UEG Week 2016 Poster Presentations", United European Gastroenterology Journal, 2016   21 words — 1%
Crossref

2   Moon, Chang Mo, Kyu Chan Huh, Sung-Ae Jung, Dong Il Park, Won Hee Kim, Hye Mi Jung, Seong-Joon Koh, Jin-Oh Kim, Yunho Jung, Kyeong Ok Kim, Jong Wook Kim, Dong-Hoon Yang, Jeong Eun Shin, Sung Jae Shin, Eun Soo Kim, and Young-Eun Joo. "Long-Term Clinical Outcomes of Rectal Neuroendocrine Tumors According to the Pathologic Status After Initial Endoscopic Resection: A KASID Multicenter Study", The American Journal of Gastroenterology, 2016.   21 words — 1%
Crossref

3   www.ncbi.nlm.nih.gov   14 words — 1%
Internet

4   Andreas Probst, Annette Schneider, Tina Schaller, Matthias Anthuber, Alanna Ebigbo, Helmut Messmann. "Endoscopic submucosal dissection for early gastric cancer: are expanded resection criteria safe for Western patients?", Endoscopy, 2017   12 words — < 1%
Crossref

5   Elettra Merola, Andrea Michielan, Umberto Rozzanigo, Marco Erini et al. "Therapeutic strategies for gastroenteropancreatic neuroendocrine   10 words — < 1%

neoplasms: State-of-the-art and future perspectives", World
Journal of Gastrointestinal Surgery, 2022
Crossref

6   assets.researchsquare.com   10 words — < 1%
Internet

7   www.jove.com   9 words — < 1%
Internet

8   "Advanced Endoscopic Techniques", Journal of
Gastroenterology and Hepatology, 2020   7 words — < 1%
Crossref

9   Xiao-Xin Ma, Li-Sheng Wang, Luo-Lin Wang, Ting
Long, Zheng-Lei Xu. "Endoscopic treatment and
management of rectal neuroendocrine tumors less than 10 mm
in diameter", World Journal of Gastrointestinal Endoscopy, 2023   7 words — < 1%
Crossref

EXCLUDE QUOTES   OFF   EXCLUDE SOURCES   OFF

EXCLUDE BIBLIOGRAPHY   OFF   EXCLUDE MATCHES   OFF