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ORIGINAL ARTICLE

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Incidental diagnosis of very small rectal neuroendocrine neoplasms: when should endoscopic submucosal dissection be performed? A single ENETS centre experience

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Abstract

Purpose The management of small (≤5 mm) rectal neuroendocrine neoplasms (r-NENs), incidentally removed during colonoscopy, still remains under debate.

Methods All consecutive patients affected by r-NENs from January 2013 to December 2017 were studied. The inclusion criteria were: (1) patients having an incidental pathological diagnosis of very small (≤5 mm) polypoid r-NENs; (2) patients treated with a standard polypectomy as first-line therapy and (3) patients treated by endoscopic submucosal dissection (ESD) as salvage therapy. The primary endpoint was to identify the factors related to residual disease after a standard polypectomy. The secondary endpoint was to calculate the accuracy of endoscopic ultrasound (EUS), grading and size in predicting residual disease.

Results Starting from a prospective database of 123 consecutive patients affected by r-NENs, only 31 met the inclusion criteria. A final pathological examination of an ESD specimen showed residual disease in 7 out of 31 patients (22.6%). A multivariate analysis showed that the size of the polyps was the only independent factor related to residual disease with an odds ratio of 8.7 ± 7.5 ($P = 0.013$) for each millimetre. The accuracy of EUS, grading and tumour size (3.1 mm cut-off point) and area under the curves were 0.661 ± 0.111, 0.631 ± 0.109 and 0.821 ± 0.109, respectively.

Conclusions When the r-NEN polyp was larger than 3 mm, ESD was indicated. Unlike the size of the tumour, grading and EUS features did not accurately predict residual disease.

Keywords Rectal endocrine neoplasm · Endoscopy · Endoscopic submucosal dissection · Endoscopic mucosal dissection

Introduction

Rectal neuroendocrine neoplasms (r-NENs) represent one of most common gastrointestinal endocrine tumours having an incidence rate of ~0.86/100,000/year based on Surveillance, Epidemiology and End Results 17 data [1]. The recently updated European Neuroendocrine Tumour Society (ENETS) guidelines [2] have suggested different management based on three parameters: size of the tumour, endoscopic ultrasound (EUS) staging (T and N) and World Health Organisation (WHO) grading (G1/2 or G3). The ENETS guidelines hypothesised that: (1) macroscopically, all endoscopists should suspect the diagnosis of an r-NEN; (2) all endoscopists should perform at least one biopsy and one EUS before removing the lesion and (3) all endoscopists should choose the technique for polyp removal on the basis of the pathological diagnosis, and the stage and grade

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of the lesion. On the contrary, in clinical practice [3], the physician has to confront a very different clinical scenario: (1) the diagnosis of an r-NEN is usually reached by the pathologist after a standard polypectomy and (2) the decision regarding the removal technique is simply based on endoscopist experience and instrument availability, without prior histology. Moreover, in very small r-NENs (≤5 mm), the decision to perfom second salvage endoscopic therapy, such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) or transanal endoscopic microsurgery (TEMS) is not supported by robust literature [4]. In fact, the same guidelines have suggested that the best endoscopic salvage treatment for very small (≤5 mm) r-NENs remains unclear due to the absence of direct data [2]. The aim of this study was to gather data in order to provide an answer to a simple question: "When is a second look necessary after incidental removal of very small (≤5 mm) r-NENs?".

Materials and methods

This was a retrospective study of a prospective database of 123 consecutive patients affected by r-NENs referred to the ENETS centre of S. Orsola-Malpighi Hospital from January 2013 to December 2017; it was approved by the Ethics Committee of S. Orsola-Malpighi Hospital (RAC 164/2017/O/Oss), with patients giving informed consent. The inclusion criteria were: (1) patients having an incidental pathological diagnosis of very small (≤5 mm) polypoid r-NENs; (2) patients treated with a standard polypectomy as first-line therapy and (3) patients treated using ESD as salvage therapy. Starting with 123 patients, 67 patients were excluded due to size >5 mm or submucosal localisation, 8 because they underwent EMR or ESD directly as a first approach and 17 because they refused ESD after a standard polypectomy. The remaining 31 patients were potentially available for the analysis. The selection process is shown in Supplementary Figure 1. For each patient, data regarding gender, age, site (upper/middle versus lower rectum) and size of lesion, grading of tumour according to the 2017 WHO grading system [5], residual features at EUS, duration of ESD and pathological presence of residual disease after ESDs were collected. The quantification of Ki-67 was obtained by revising all specimens and using digital imaging analysis in order to reduce interobserver disagreement [6]. The details regarding EUS and ESD procedures are described in a Supplementary file (Supplementary Methods). Gender, age, site (upper/middle versus lower rectum) and size of lesion, grading of the residual tumour features at EUS and duration of ESD were studied to verify their ability to predict the presence of residual disease in pathological specimens after ESD. All patients were followed after ESD at 3, 6 and 12 months, and then annually, if disease free. The follow-up consisted of outpatient rectal EUS, endoscopic inspection and biopsy of the scar.

The primary endpoint was to identify the factors related to residual disease after a standard polypectomy in very small r-NENs. The secondary endpoint was to calculate the accuracy of EUS, grading and size in predicting residual disease.

Statistical analysis

Frequencies with percentages were used to describe the discrete variables. The continuous values were reported as medians and 95% confidence intervals (CIs). Univariate and multivariate models were built. For the univariate analysis, the Fischer's exact test and the Mann–Whitney test were used. The multivariate analysis was carried out using logistic regression reporting the results as odds ratios (ORs). In order to reduce the risk of bias due to the small sample size, the standard error was calculated using non-parametric bootstrap estimation (50 replication) [7]. A non-negligible effect of the covariates was identified by a P value <0.05 in both the univariate and the multivariate models. Finally, a receiver operating characteristic (ROC) curve was built Sensitivity, specificity and area under the curve (AUC) were reported. The statistical analyses were computed using the STATA software (StataCorp. 2011, College Station, TX, USA: StataCorp LP).

Results

The baseline characteristics of the 31 patients with an incidental diagnosis of r-NEN are reported in Supplementary Table 1. There were 21 (67.7%) males and 10 (32.3%) females having a median age of 48 years (38–72 years). The median size of the lesion was 3 mm (2–5 mm); 7 (22.6%) were located in the upper/middle rectum, while 24 (77.4%) were located in the lower rectum. All patients underwent a standard polypectomy: 8 (25.8%) in our hospital and 23 (74.2%) in other hospitals who were subsequently referred to our ENETS centre. In the first reports, the polyps were described as sessile, without worrisome features (depression erosion or ulceration) before removal.

At the first pathological examination, the majority of the patients had a G1 r-NEN (24, 77.4%). After EUS evaluation, 10 (32.3%) had an ultrasonographic pattern suspicious for residual disease. All patients underwent ESD with a median duration of 20 min (15 to 25 min) without major immediate or delayed complications. Only one (1.3%) patient presented fever 2 h after the procedure without signs of perforation. The median hospital stay was 1 day (1 to 1 day). The final pathological examination of the ESD

specimen showed residual disease in 7 out of 31 patients (22.6%). Briefly, among the patients with residual disease, there were four (57.1%) females and three (42.9%) males having a median age of 48 years (38–69 years). The median size was 4 mm (2–5 mm) with a similar distribution between the upper/medium rectum and the lower rectum (3, 42.9 and 4 57.1%, respectively). There were four (57.1%) and three (42.9%) patients with NENs G1 and G2, respectively. At the time of the procedures, only four patients had EUS features suspicious for residual disease. The median duration of the procedures was 20 min (15–23 min). All patients with residual disease were followed up with EUS and scar biopsies as previously described. No relapse recurrence was reported, and thus all patients are still alive and disease free, with a median follow-up of 30 months (3–57 months).

All patients were followed after ESD at 3, 6, and 12 months, and then annually, if disease free. The follow-up consisted of outpatient rectal EUS, endoscopic inspection and biopsy of the scar.

Table 1 shows the results of the univariate analysis; in patients who had residual disease in the ESD specimen, the median size of the initial polyps was 4 mm (2–5 mm), while, in those who had a "free" ESD specimen, the median size was 3 mm (2–4 mm). This difference can be seen in Fig. 1 and is statistically significant ($P = 0.001$). Gender, age, site and grading of the lesion, EUS features and duration were related to the presence of residual disease. Multivariate analysis (Table 1) confirmed that the size of the polyps was the only independent factor capable of predicting residual disease with an OR of 8.7 ± 7.5 ($P = 0.013$) for each millimetre. The probabilities of residual disease are described in Table 2. Tumours from 0.1 to 1 mm and those from 1.1 to 2 mm had a statistically negligible probability of residual disease after a standard polypectomy (0.1 and 1.4%, respectively). Tumours from 3.1 to 4 mm had a low risk of residual disease after a standard polypectomy (14.1%; 0–28.9%; $P = 0.060$). Tumours >4 mm presented a statistically non-negligible risk of incomplete excision after a standard polypectomy: 60.1% (12.7–100; $P = 0.011$) and 93.6% (68.2–100; $P < 0.001$). The postestimation probabilities of residual disease are plotted in Fig. 2. The EUS, grading and tumour size ROC curves are plotted in Fig. 3. The sensitivity of the EUS, the grading and the tumour size (3.1 mm cut-off point) were 57.1, 42.9 and 71.4%, respectively. The EUS, the grading and the tumour size (3.1 mm cut-off point) specificity were 75, 83.3 and 95.8%,

Table 1 Univariate and multivariate analysis of factor predicting residual disease in asymptomatic, incidentally discovered r-NEN, removed with standard endoscopy

Characteristics	Histopathological presence of r-NEN in ESD specimen				
	Univariate			Multivariate	
	No (%)	Yes (%)	*P* value	OR ± bootstrap SE	*P* value
Sex					
Female	6 (25)	4 (57.1)	0.172[a]	Referent	0.553[c]
Male	18 (75)	3 (42.9)		2.3 ± 251	
Age (years, median, 95% CI)	48.5 (35–78)	48 (38–69)	0.923[b]	0.9 ± 15[d]	0.364[c]
Size (mm, median, 95% CI)	3 (2–4)	4 (2–5)	0.001[b]	8.7 ± 7.5[d]	0.013[c]
Site of lesion					
Upper/medium rectum	4 (16.7)	3 (42.9)	0.302[a]	Referent	0.707[c]
Lower rectum	20 (83.3)	4 (57.1)		0.5 ± 509	
2017 WHO classification					
G1	20 (83.3)	4 (42.9)	0.302[a]	Referent	0.873[c]
G2	4 (16.7)	**3 (57.1)**		1.3 ± 108	
Features suspect for disease residual at EUS					
No	18 (75)	3 (42.9)	0.172[a]	Referent	0.858[c]
Yes	6 (25)	4 (57.1)		0.7 ± 181	
Duration of ESD procedure (min, median, 95% CI)	19.5 (15–30)	20 (15–23)	0.824[b]	0.9 ± 44[d]	0.767[c]

All patients underwent a second endoscopic look with ESD

95% CI confidence interval at 95%, *r-NEN* rectal neuro-endocrine neoplasm, *WHO* World Health Organisation, *ESD* endoscopic sub-mucosa excision, *OR* odds ratio

[a]Fischer's exact test

[b]Mann–Whitney test

[c]Logistic regression; OR

[d]For each unit of covariate

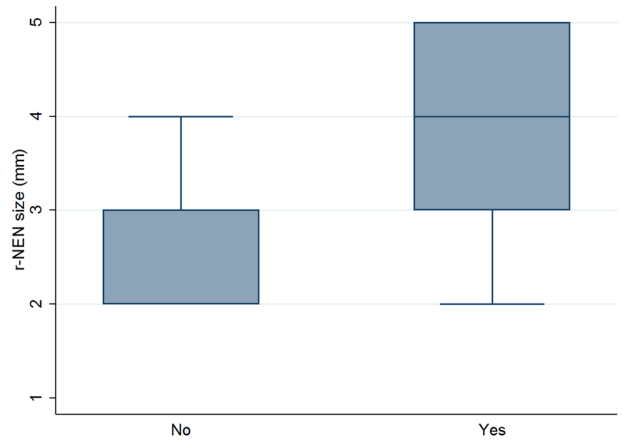

Fig. 1 Box and whiskers plot showing the relationship between the size of the tumour and residual disease: the boxes represent the interquartile ranges, and the lines within the boxes show the median values. The whiskers represent the extreme values. The r-NEN size of the patients without residual disease is represented in the right box, while the r-NEN size of those with residual disease is represented in the left box. r-NEN: rectal neuro-endocrine neoplasm

Table 2 Postestimation values of cut-off size in predicting residual disease after standard polipectomy

Size (mm)	Probability (%) of residual disease After a standard polipectomy (95% CI)	*P* value
0.1–1	0.1 (0–0.7)	0.723[a]
1.1–2	1.4 (0–5.8)	0.525[a]
2.1–3	14.1 (0–28.9%)	0.060[a]
3.1–4	60.1 (12.7–100)	0.011[a]
4.1–5	93.6 (68.2–100)	<0.001[a]

95% CI 95% confidence interval

[a] Logistic regression

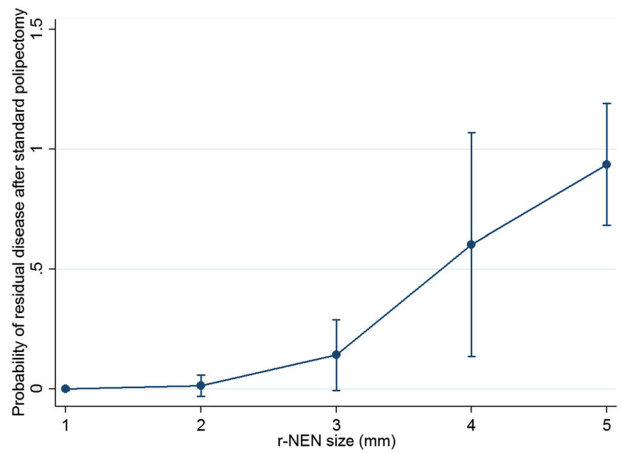

Fig. 2 Probability of residual disease based on r-NEN size: the blue circles represent each cut-off point; the connected blue line indicates the relationship between the probability of residual disease and size. The whiskers represent the values of the probabilities at a confidence interval of 95%. r-NEN: rectal neuro-endocrine neoplasm

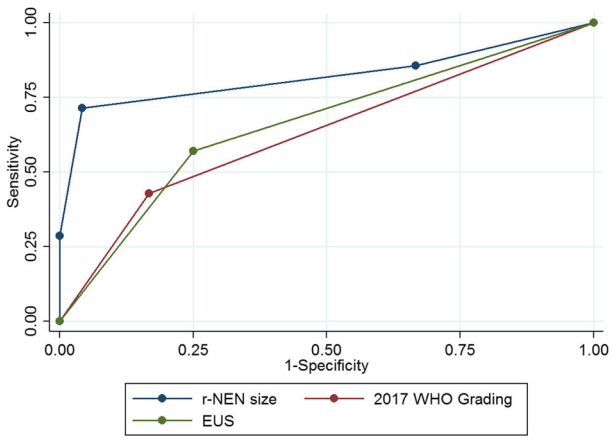

Fig. 3 EUS, grading and size ROC curves: r-NEN: rectal neuro-endocrine neoplasm. WHO: World Health Organisation; EUS: endoscopic ultra-sound; ROC curve: receiver operating characteristic curve

respectively. The AUCs of the ROC curves were 0.661 ± 0.111, 0.631 ± 0.109 and 0.821 ± 0.109 for EUS, grading and tumour size (3.1 mm cut-off point), respectively. EUS, grading and tumour size (3.1 mm cut-off point) correctly classified 71, 74 and 90% of patients, respectively.

Discussion

The 2016 ENETS guidelines provide a well-structured algorithm for managing small (<10 mm) r-NENs [2]. In clinical practice, any decision regarding the therapeutic approach is based on the size, grading and EUS findings of the tumour. However, these guidelines hypothesised that the r-NENs were macroscopically suspected at the time of the first colonoscopy and were biopsied and morphologically studied with EUS [4]. This scenario is very different from clinical pratcice, especially when the r-NEN is a very small (<5 mm) polyp. In fact, the endoscopic appearance of rectal NENs can be indistinguishable from a hyperplastic polyp when the lesion is 5 mm or less in diameter. In this scenario, the endoscopist treats the small polyp in a standard way using a forcep or a snare to remove the lesion, and the pathologist reaches the unexpected diagnosis of r-NEN. In the series in the present study, all the rectal polyps were removed using snare, even when very small because the recent literature data [8] has suggested that polyps should be removed with a forcep only if a single shot guarantees complete removal. Thus, the physician faces a very difficult dilemma, that is, whether or not to perfom salvage therapy? Therefore, the knowledge derived from the literature still remains unclear. A recent review [9] has suggested that, for r-NENs <5 mm, a standard polypectomy could also be considered curative. However, several other reports [10, 11] have recommended first-line EMR, but, at the same time,

have reported an incomplete excision rate of ~25–30% based on margin evaluation. However, after a standard polypectomy, the margin status evaluation is very difficult for the pathologist. In our series, salvage ESD was always performed, and a rate of residual disease of 22.6% was observed. These data suggested that the risk of incomplete excision existed and was not negligible even for very small r-NENs. Moreover, the only factor related to incomplete resection was the size of the lesion, and postestimation values suggested that the probability of residual disease was very high (60–90%) when the r-NEN size was >3 mm. On the contrary, in this study, the EUS features of the scar or the grading of the r-NEN removed did not significantly predict the risk of residual disease. These results can be very useful for the physician who comes up against this clinical scenario; after the removal of an incidental R-NEN, any choice based on grading or EUS finding could be worse than that based on the original tumour size (cut-off 3.1 mm). In particular, the scar, altering the normal wall stratification, makes impossible a correct local staging by EUS.

In fact, the data in the present study suggested that, in polyps smaller than 3 mm, a follow-up programme can be safely recommended, while ESD should be reserved only for tumours >3 mm. In the present series, ESD was a safe and quick procedure without major complications. Similar data regarding ESD, comparing the technique to EMR and a standard polypectomy, have been reported by several authors [12, 13]. Endoscopic submucosal dissection was the salvage therapy of choice in the patients in this study, even though the authors realised it was not the only possible approach when facing this scenario. After incidental removal of an r-NEN, the clinician has some options. The follow-up option, without additional treatment, would seem to be appropriate for relatively low aggressive tumours, such as rectal NETs [2]. This choice is not always appreciated by the patient, especially if relatively young. Data regarding follow-up are comforting but the long-term natural history of these lesions is unknown. The second option is surgical radicalisation, which can be achieved with a rectal anterior resection (RAR) or TEMS [2]. The former surgical approach guarantees complete radicality, but considering the very low rate of micrometastasis in rectal NENs <5 mm, it should be considered overtreatment. On the contrary, TEM is a more conservative approach as compared to RAR, but it still requires general anaesthesia, and is performed in the operating room, thus increasing costs. Moreover, it also has some limitations, such as the technical difficulty regarding lesions close to the anal verge or those located in the peritoneal rectum, and the need for anal divulsion with a certain rate of faecal incontinence after the procedure [14].

The third option is endoscopic treatment. Endoscopic submucosal dissection allows achieving complete local radicality, even in lesions involving the submucosal layer, sparing the muscle layer with total organ preservation in terms of anatomy and function [15]. Other well-known advantages are that it is performed in a day hospital or on an outpatient basis, without general anaesthesia. In fact, the procedure in the rectum can be performed with conscious sedation [16]. All these factors could contribute to cost reduction and improve patient compliance with the procedure.

In the present study, all the patients were treated with conscious or deep sedation, without orotracheal intubation, and the procedure was well tolerated. Only one mild complication (post-procedural fever) was observed. The operating time was relatively short; this was due to the size of the scar, which, in this scenario, was always of only a few millimetres. In the treatment of naive lesions, the use of the EMR technique, especially if CAP or band assisted, is often the best choice, especially when the size is inferior to 5 mm and the r-NEN is known. On the contrary, in the setting of salvage therapy on a scar, EMR is almost always not feasible because the site and the anelasticiy of the scar do not allow creating adequate lifting of the lesion with saline or with suction.

This study obviously has some limitations; it was monocentric and involved a small sample size. Nevertheless, the most recent large experience [10, 11] included fewer small polyps. In fact, Kim et al. [10] reported only 22 polypoid r-NENs <5 mm. In addition, the use of bootstrap replication reduced the risk of bias in logistic regression and permits obtaining robust results [17]. Moreover, all studies [10–13] based the evaluation of complete resection on the EMR margin status rather than on second salvage therapy with ESD. Finally, this is the first study carried out in a western country, which included only very small polyps (<5 mm) removed before a diagnosis of r-NEN.

In conclusion, this study provided new information in a real clinical setting, answering the very simple question of how to manage a patient when, after standard excision of a small rectal polyp, an incidental diagnosis of r-NEN comes back from the pathologist. Based on the present data, regardless of the grading of the tumour removed or the EUS findings on the scar, if the initial lesion was >3 mm, salvage ESD should be performed. Additional multicentric, prospective well-designed studies are necessary in order to confirm these data.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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