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Endoscopic management of rectal neuroendocrine tumours. How to avoid a mistake and what to do when one is made?

Krzysztof Dąbkowski[1], *Marek Szczepkowski*[2], *Beata Kos-Kudła*[3], *Teresa Starzyńska*[1]

[1]*Department of Gastroenterology, Pomeranian Medical University, Szczecin, Poland*
[2]*Clinical Department of Colorectal, General, and Oncological Surgery, Centre of Postgraduate Medical Education, Warsaw, Poland*
[3]*Department of Endocrinology and Neuroendocrine Tumours, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland*

Abstract

Rectal neuroendocrine tumours are subepithelial lesions that are potentially malignant. Although the biology of these lesions has become increasingly understood and their management has been established, the endoscopic management of these tumours remains controversial. Recent studies demonstrated that compliance with guidelines is poor, and the majority of rectal neuroendocrine tumours are removed by an improper method, making management more complex and putting patients at risk of metastatic spread. Thus, there is a need to educate physicians who care for patients with these disorders. Our review has some tips and pointers for preventing mistakes in primary treatment and salvage therapy after polypectomy. **(Endokrynol Pol 2020; 71 (4): 343–349)**

Key words: *rectal neuroendocrine tumours; endoscopic ultrasound; endoscopic submucosal dissection; transanal endoscopic microsurgery*

Introduction

Rectal neuroendocrine neoplasms (rNENs) are subepithelial lesions that are diagnosed with increasing frequency. They are typically small tumours with low malignant potential, but risk of metastasis [1], which depends inter alia on the tumour mitotic index, vessel infiltration, and size [1]. The endoscopic management of rNENs has been established, but controversies remain [1–5]. Taking into account their subepithelial origin and malignant potential, they should be removed either by endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), transanal endoscopic microsurgery (TEM), or surgery [5]. The removal of these lesions with a snare or biopsy forceps results in an unacceptably high rate of incomplete resections [6, 7]. The natural history of rNENs shows that using an improper method to remove the tumour puts patients at risk of metastases development, resulting in repeated follow-up radiologic, endoscopic examinations and the need for salvage therapy [8, 9].

Recent studies have shown that the majority of lesions are removed by an improper method, even when typical endoscopic features are present, and diagnoses are made retrospectively based on histopathological assessment [9, 10]. Thus, there is still a need to educate physicians caring for patients with rNENs, so that accurate diagnoses are made before the "simple" polypectomy (mistake) is done, and to broaden the knowledge of the management after ineffective treatment [11]. Herein, we review the key points of endoscopic management, from diagnosis to treatment.

Clinical and endoscopic characteristics of rectal neuroendocrine tumours: diagnosis, management, and avoiding mistakes

Rectal NENs constitute about 1% of rectal neoplastic lesions, and they are often accidental findings in colonoscopy [5]. Symptoms including changes in bowel habits, rectal bleeding, and abdominal pain, which are present in 50% of individuals; however, they can be attributed more to other underlying diseases (e.g. haemorrhoids, irritable bowel disease) than to the presence of the tumour itself [5]. Moreover, hormonal activity and symptoms of carcinoid syndrome, in contrast to small intestinal neuroendocrine tumours (NETs), are rare [1].

Rectal NETs are usually small (< 10 mm in diameter) single lesions located 5–10 cm from the dental line [2]. Typically, they manifest as regular lesions with yellow or white reflexion and smooth intact covering mucosa

Krzysztof Dąbkowski, Department of Gastroenterology, Pomeranian Medical University, ul. Unii Lubelskiej 1, 71–252 Szczecin, Poland, tel/fax: (+48) 91 425 32 11; e-mail: dabkowskikrzysztof@wp.pl

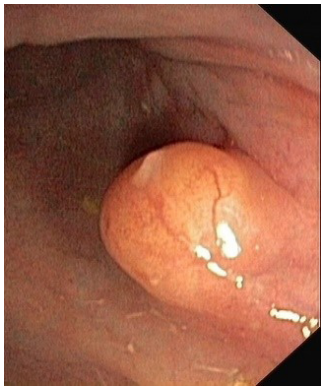

Figure 1. *Typical rectal neuroendocrine tumour with yellow reflexion*

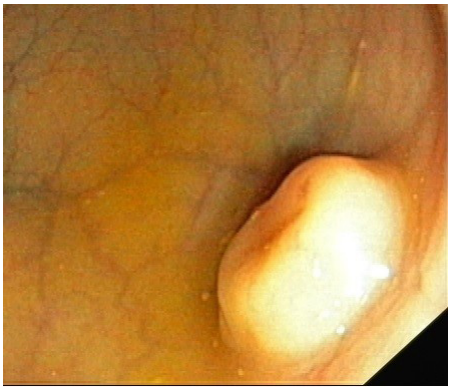

Figure 2. *Subepithelial lesion with central depression*

(Fig. 1) [1, 2]. Atypical manifestations include lesions with central depression/ulceration/scar (Fig. 2), and lesions with central hyperaemia or flat seating small polyps that are hard to distinguish from hyperplastic polyps. The key issue in the initial management of these lesions is to suspect rectal NEN based on macroscopic features before mistakenly performing routine snare polypectomy. A retrospective analysis by Lee et al. [11] showed that it was possible to suspect a NET by macroscopic appearance, on endoscopy, in 95.9% of cases (94/98 lesions) [12]. These tumours are also described as hard and movable, and some authors suggested checking these features with a biopsy forceps as a helpful diagnostic tool [12].

We postulate that in cases of tumours with typical morphology, the reason why rNENs are removed with a polypectomy is either routine or poor compliance with management guidelines. In a minority of cases, rectal NENs present as small lesions, just slightly protruding from the mucosa, making them hard to distinguish from other polypoid lesions (they resemble hyperplastic polyps), and they are routinely removed with biopsy forceps or a snare. An outstanding question is whether any tools are available that allow physicians to avoid a mistake in cases of such small lesions.

Since Kudo's pit pattern and endoscopic classifications (e.g. Narrow-band Imaging International Colorectal Endoscopic [NICE] classification) for colorectal neoplasms were presented with the use of video chromoendoscopy — narrow-band imaging (NBI) — we are able to predict the histopathology of epithelial lesions [13]. In the NICE classification colour for lesions, surface (pit pattern) and vessel patterns are assessed to differentiate benign hyperplastic polyps from adenoma, and adenoma from cancer. According to the meta-analysis by McGill et al., the differential diagnosis of neoplastic and non-neoplastic polyps with the use of NBI can be made with 91% specificity and 83% sensitivity [14]. To the best of our knowledge, only a few studies (mainly related to gastric lesions) and case reports have assessed NETs with NBI [15, 16]. In the study by Lahner et al. all gastric type I NETs showed an abnormal surface pattern (tubulovillous or irregular), but with no specific features that distinguished them from other lesions [15]. In the case report by Lin et al., round pits larger than those seen in hyperplastic polyps surrounded by honeycomb brown microvessels were typical features of rNEN [16]. Taking into account the fact that the basis for endoscopic diagnosis is shifting from histopathology to advanced methods of imaging, the use of NBI and other methods of advanced imaging may be an interesting area of research, and hopefully will be a solution for characterising small rectal neuroendocrine polyps before they are removed by polypectomy.

Another area of controversy is the issue of taking a biopsy on initial endoscopy. We believe that routine biopsies from subepithelial lesions that look typical should be avoided, which would not significantly change the management strategy (EMR/ESD/TEM/surgery, preceded by endoscopic ultrasound [EUS]). Biopsy should only be considered in doubtful cases (atypical features) and in tumours that are more than 2 cm in size (according to the guidelines, these patients should be referred to surgery). The advantage of taking biopsies is the significantly high percentage of positive histopathological results compared to other subepithelial lesions, whereas the disadvantage is that it can lead to fibrosis and blur the tumour borders, making further endoscopic treatment more complicated from a technical viewpoint [1, 12]. In the study by Lee et al. biopsy of rNENs on initial endoscopy was the only factor that was significantly related to the risk of incomplete tumour resection [12]. The authors underlined not only the aspect of uncertain tumour borders, which can lead to the problems with snaring and targeting the lesion, but also of preceding biopsy-related fibrosis, which can disturb the ESD or EMR [12].

The endoscopic treatment of lesions more than 5 mm in size should be preceded by other modalities. An endoscopic ultrasound, according to European Neuroendocrine Tumour Society (ENETS) guidelines, is indicated for lesions more than 5 mm in size, to identify muscular layer invasion and the presence of enlarged mesorectal lymph nodes [4, 5]. Studies have shown high concordance, reaching more than 90% (even 100% in the study by Ishii et al.) between the assessment of depth of invasion in EUS and postoperative histopathology [17, 18]. This high accuracy allows for treatment planning (i.e. involvement of the muscular layer shifts treatment from ESD to TEM or surgery when surgery for enlarged lymph nodes is indicated). Rectal NENs in EUS typically present as hypoechoic, homogenous lesions derived from the submucosal layer. Some recent studies show low potential of malignancy and indolent behaviour of small rNENs [19–22], suggesting that EUS may not be essential before endoscopic treatment of rNENs < 10 mm in size [19, 21]. This approach that shifts the indications for EUS (from 5 to 10 mm), taking into account earlier observations showing metastatic potential of well-differentiated and small rNENs, remains, in our opinion, controversial [23].

The recommended methods of treatment are either EMR, ESD, TEM, or surgery, depending on tumour size and the presence of unfavourable features such as advanced histology (G2, G3), lymphangio invasion, infiltration of muscular layer, lymph nodes, and distant metastases. It should be underlined that the indications for endoscopic and surgical treatment proposed by different author guidelines differ slightly, as presented in Table 1.

Various endoscopic methods have been proposed as effective and safe for the treatment of rectal NENs, but an important issue is that of which method should be offered to patients. When making decisions the percentage of R0 resections, complications and the presence of muscle layer infiltration, and enlargement of lymph nodes in EUS should be taken into account. Studies have shown that the R0 resection rate is obtained more commonly with TEM (97.6–100%) than with ESD (81.1–100%) and EMR (47.8–80%) (Tab. 2). The respectively low R0 resection rate is the reason why EMR is generally recommended for small (< 10 mm) lesions, and when used, modified methods (cap or ligation band EMR) of resection should be applied [5]. The meta-analysis by Zhou et al. comparing ESD and EMR for the treatment of rNENs demonstrated higher efficacy of ESD in terms of complete resection rate, with no significant differences between ESD and modified EMR [24]. There was also no statistically significant difference in complication risk; bleeding and perforation occurred in similar numbers in both groups of patients (6/209 in the ESD group and 6/418 in the EMR group) [24].

The percentage of reported complications of rNENs treatment from ESD (0–9%) is slightly lower than that in patients treated with TEM (2.6–13%) (Tab. 1). In both methods, the majority of adverse events can be treated endoscopically or conservatively with no need for open surgical intervention. The advantage of TEM (compared to ESD), apart from the higher R0 resection rate, is that it can be used as a salvage treatment after non-radical therapy (after polypectomy and EMR as well as ESD), also allowing for sampling of perirectal lymph nodes. The disadvantages are the aforementioned complications, invasiveness of the procedure, and the need for anaesthesia and an operating room [25].

Recently, a new method of endoscopic treatment for colorectal tumours was presented, with the use of an endoscopic full-thickness resection device (FTRD) [26, 27]. The study by Meyer et al. on 40 patients with rectal NENs showed not only the feasibility (median time, 18.5 min) and safety (no major adverse events), but also the effectiveness of this method (R0 resection rate in 95%) [26]. Moreover, in all reported case reports of rNEN, FTR showed its effectiveness and safety, both for the treatment of primary rectal NEN and as a salvage therapy after polypectomy [28–30]. Thus, FTR is a promising alternative to the aforementioned methods; however, comparative studies in larger groups of patients are needed to confirm its safety and efficacy.

We believe that the treatment method should be discussed with the patient, taking into account the aforementioned issues (R0 resection rate, complications, invasiveness), the EUS results, and the experience of the centre. The data comparing methods used for the treatment of rectal NENs, including R0 resections and complications, are presented in Table 2.

Management after simple polypectomy (what to do when a mistake is made)

The ENETS guidelines recommend that all rectal NENs be removed with EMR/ESD/TEM or surgery [1, 4, 5]. This statement is based on the assumption that the diagnosis is made on endoscopy, and then the patient is referred for treatment, preceded by EUS. Unfortunately, this scenario is far from what occurs in real life, and in many cases, the neuroendocrine origin of the lesion is not suspected on endoscopy and the diagnosis is made retrospectively by a pathologist [10]. In the study by Fine C et al. on a large group of 329 patients with small rNEN the suspicion of rNEN on endoscopy was made only in 18% of cases; despite

Table 1. *Indications for surgical and endoscopic treatment of rectal neuroendocrine neoplasms (rNENs) according to the guidelines*

Guideline	Recommended treatment
ENETS 2012 [4]	Surgery:
	• > 2 cm
	• 1–2 cm with muscularis invasion, nodal positive, G2 T3, T4, G3
	TEM:
	• < 1 cm with muscularis invasion, G2, G3
	• 1–2 cm without muscularis invasion, nodal negative, G2, T1–T2
	• Endoscopy (ESD, EMR < 10 mm):
	• < 1 cm without muscularis invasion, G1, G2
	• 1–2 cm without muscularis invasion G1
NCCN 2019 [37]	Surgery
	• T2–T4 > 2 cm
	• 1–2 cm with muscularis propria invasion node positive
	TEM or endoscopy:
	• ≤ 2 cm without muscularis invasion, node negative
	• Endoscopic resection (method not specified):
	• < 1 cm
NANETS 2010 [38]	Surgery
	• > 2 cm
	• 1–2 with muscularis invasion, nodal positive
	TEM:
	• 1–2 cm without muscularis invasion, nodal negative
	• consider in T2 tumours, when lymph node metastases are excluded
	• Endoscopic resection (method not specified)
	• < 1 cm without muscularis invasion
	• consider in tumours < 1–2 cm confined to the mucosa/submucosa (T1)
Polish Network of Neuroendocrine Tumours 2017 [1]	Surgery
	• > 2 cm
	• 1–2 cm with risk factors (TEM in individual cases)
	Endoscopic resection (ESD):
	• < 1 cm
	• 1–2 cm without risk factors

ENETS — European Neuroendocrine Tumour Society; NANETS — North American Neuroendocrine Tumour Society; NCCN — National Comprehensive Cancer Network; TEM — transanal endoscopic microsurgery; ESD — endoscopic submucosal dissection; EMR — endoscopic mucosal resection

T1— tumor invades the lamina propria or submucosa; T2 — tumour invades the muscular layer or is ≥ 2 cm in size; T3 — into subserosal tissue; T4 — invades serosa and/or adjacent organs — American Joint Committee on Cancer (AJCC) 8th edition [39]

this, one third of those that were correctly recognised were removed by polypectomy [10]. Polypectomy of rectal NENs leads to an unacceptably high incomplete resection rate (69.1–83%) and the risk of a presence of remnant residual tumour [6, 7, 31, 32]. Endoscopic or surgical therapy after non-curative treatment is termed salvage therapy. It is based on performing more advanced treatment than the prior procedure (finding and removing the scar or remnant tumour with ESD or TEM) or removing the rectum and mesorectal lymph nodes with surgery. This adjunct treatment, the same as in primary excision, should be preceded by EUS to look for the remnant tumour and the presence of lymph node metastases.

The perception of salvage therapy has evolved from views that small tumours (< 1 cm) with typical features can be removed with snare polypectomy, and in cases of incomplete resection, adjunct therapy is recommended [1, 17]. This statement has been justified by the presence of a high percentage of residual tumours in patients who undergo salvage therapy, the risk of metastatic spread related to the natural biology of rectal NENs,

Table 2. *Data comparing R0 resection rates and complications after endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and transanal endoscopic microsurgery (TEM)*

Author/year	Method	Patients no.	R0 resection (%)	Complications
Kinoshita et al. 2007 [40]	TEM 14 primary 13 secondary	27	100%	Transient soilage Mild dehiscence (8.3%)
Park et al. 2010 [41]	ESD	31	90,3%	Perforation (3.2%), bleeding (3.2%)
	EMR	62	71%	Perforation (1.8%), bleeding (6.5%)
Yamaguchi et al. 2010 [42]	ESD	20	90%	Perforation (5%)
Zhou et al. 2009 [43]	ESD	20	100%	Perforation (5%)
	EMR	23	47,8%	No
Lee et al. 2010 [44]	ESD	46	82,6	Bleeding + perforation (6.3%)
	EMR	28	64.3	Bleeding (3.6%)
Ishii et al. 2010 [18]	ESD	22	100%	Bleeding (9%)
Kumar et al. 2010 [33]	TEM	24	100%	Urinary retention Entrance to peritoneal cavity (8.3%)
Kim et al. 2012 [45]	TEM	38	97,6%	Urinary difficulty (2.6%)
Zhao et al. 2012 [46]	ESD	10	100%	Bleeding (20%)
	EMR	10	80%	Bleeding (30%)
	EMR-C	10	100%	No
Kim et al. 2013 [47]	ESD	44	97.7	No
	EMR	33	77.4	No
	ESMR-L	40	100%	Perforation (2.5%)
Chen et al. 2015 [34]	TEM	38 primary 21 secondary	100%	Perforations (3.4%) Fever (13.6%)
Kaneko et al. 2016 [48]	ESD	24	100%	No
	EMR-L	22	63%	No
Shao et al. 2017 [35]	TEM	90 66 primary 24 secondary	100%	6.7%
Zhang et al. 2019 [49]	LCEMR	22	86,3%	No
	ESD	12	91,67%	No
Meier et al. 2019 [26]	FTR	40	95%	Minor bleeding (10%) Rupture of FTRD snare (2.5%) (procedure finished with conventional snare)

EMR-C — cap assisted endoscopic mucosal resection; ESMR-L — endoscopic submucosal resection with a ligation device; LCEMR — endoloop ligation after cap-endoscopic mucosal resection; FTR — full-thickness resection; FTRD — full-thickness resection device

and long-term observations describing disease recurrence after polypectomy [8]. However, the evidence supporting this management is not very strong due to the lack of large comparative studies comparing the outcomes of patients after non-curative endoscopic resection who did not undergo adjunct therapy and those who underwent salvage treatment.

Cha et al. followed up a group of 322 patients who underwent endoscopic resection of rNENs and found that only 31% (44/142) of the patients who did not fulfil the criteria of R0 resection underwent salvage therapy [11]. Eleven of these patients underwent surgery, and lymph node metastases were found in six patients, while there were no features of disease progression in the remaining patients [11]. The study by Fine et al. in patients with rNENs showed a generally favourable natural history, and recurrence after endoscopic resection was only observed in 5% of cases (16/345) in the

median follow-up of 32 months; however, in two cases it led to patient death [10]. This study also revealed that the neuroendocrine origin of the polyps is suspected in a minority of cases on endoscopy, before the polypectomy is conducted, and even when the diagnosis is suspected, many of rNEN are removed with a snare polypectomy, justifying the continuous education of endoscopists in this field [10]. This conclusion is in accordance with the results of our study, which showed that endoscopists suspected polyps of neuroendocrine origin in only 37.5% of cases (9/24 lesions) [9].

In studies analysing the pathological results of salvage therapies, the presence of remnant tumour in resected scars was reported in a significant number of cases (4/27 in the study by Kumar et al. [33], 9/21 in the study by Chen et al. [34], 10/24 in the study by Shao et al. [35], and in 7/31 cases in the study by Pagano N et al. [36]). In the study by Pagano et al. the authors stated that the only independent factor related to residual disease (present in 22.6% of patients treated with ESD as salvage therapy) was the size of the polyps, and they showed that ESD was indicated in lesions larger than 3 mm (60–90% probability of residual disease) [36].

In a previous study, the authors performing TEM as salvage therapy recommended tattooing the scar with an ink before the procedure because they postulated that it leads to better visualisation, facilitates FTR, and results in a higher percentage of curative resections [33]. The disadvantage of scar marking is that it can lead to fibrosis and make adjunct endoscopic treatment more difficult. The decision on which method (ESD/TEM) should be used as optimal for salvage therapy in patients who do not meet the criteria for surgery should be made individually, taking into account the same factors as those noted for primary treatment.

Summary and Conclusions

The compliance with guidelines is poor, justifying the education of physicians, particularly endoscopists, dealing with rNENs, in terms of primary treatment and salvage therapy after polypectomy. The polypectomy of rectal NETs results in unacceptably high non-curative resection rates. The diagnosis of typical submucosal lesion should be made on endoscopy, and patients should be referred for more advanced treatment (EMR/ESD/TEM), preceded by EUS. An endoscopic mucosal resection should be reserved for small (< 10 mm) rectal NENs, and when possible, modified methods of EMR should be applied.

ESD and TEM are optimal methods for the treatment of rectal NENs that do not qualify for surgery, both of which can be used as primary treatment and salvage therapy. Comparative studies and meta-analysis are needed to determine which method is optimal for treatment in primary and secondary settings.

R0 resection rates, complications, patient preference, and experience of the centre are factors that should be taken into account when making decisions about therapy.

Taking into account the feasibility, safety, and effectiveness FTR seems to be a promising alternative to the aforementioned methods in terms of both primary and salvage therapy for rNENs.

Disclosure

The authors declare no conflict of interest.

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