ORIGINAL ARTICLE

Endoscopic treatment of rectal neuroendocrine tumors in a 13-year retrospective single-center study: are we following the guidelines?

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KEY WORDS

endoscopic submucosal dissection, mistakes, polypectomy, rectal neuroendocrine neoplasms, transanal endoscopic microsurgery

ABSTRACT

INTRODUCTION Rectal neuroendocrine neoplasms (rNENs) are potentially metastatic lesions. False endoscopic diagnosis and subsequent treatment may lead to nonradical resection and metastases.

OBJECTIVES This study aimed to analyze the clinical characteristics of rNENs, investigate whether the lesion origin was suspected by endoscopists during examination and if those lesions were subsequently removed using the appropriate method, and assess the outcomes of patients after curative and noncurative resections.

PATIENTS AND METHODS We analyzed the records of patients hospitalized in our department (2006–2019) with a diagnosis of rNENs. We included 40 patients with rNENs, evaluated their clinical characteristics, and investigated whether the neuroendocrine origin of the lesions was suspected on endoscopy. We compared the outcomes of patients treated with the proper method (endoscopic submucosal dissection/endoscopic mucosal resection [ESD/EMR]) and those treated with polypectomy.

RESULTS Abnormalities appeared as typical, yellowish subepithelial lesions (n = 24), lesions resembling hyperplastic polyps (n = 12), or tumors with central depression (n = 4). The median size was 5.5 mm and most of them were G1 lesions (n = 36). Only 14 of them were suspected to be of neuroendocrine origin at the first endoscopic examination, and 12 were removed by ESD/EMR. The remaining tumors (n = 26) were removed using polypectomy. Most of the patients were disease-free at follow-up, but 2 patients after polypectomy and a single patient after nonradical ESD developed metastases.

CONCLUSIONS In most cases, the origin of the lesion was not suspected on colonoscopy and subsequently the tumor was removed using an inappropriate method. Endoscopists do not follow the guidelines when dealing with patients with rNENs and more emphasis should be placed on education on the management of rNENs.

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INTRODUCTION Rectal neuroendocrine neoplasms (rNENs) are small tumors that are currently being found at an increasing frequency during colonoscopy examinations.[1] These are usually G1 lesions, of less than 10 mm in diameter, derived from the muscularis mucosa, which grow into the submucosa and deeper layers. Their subepithelial origin is the reason why simple snare or biopsy forcep polypectomy is usually an ineffective method of treatment. Thus, more advanced methods such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), transanal endoscopic microsurgery (TEM), or surgery should be used to achieve R0 resections and prevent metastasis.[1,2] The natural course of G1 tumors is usually indolent, but ineffective treatment can lead to metastatic spread.[3-5] According to the literature, rNENs can be suspected during the endoscopic examination in most cases based on the macroscopic features of the lesion.[1,3] In typical cases, rNENs manifest as small subepithelial lesions of yellow or white appearance.

WHAT'S NEW?

Rectal neuroendocrine neoplasms (rNENs) refer to subepithelial lesions, which are increasingly frequently found on colonoscopy nowadays. In most cases, diagnosis can be established based on the evaluation of endoscopic features. In the majority of cases, proper treatment leads to curative resection and good prognosis. Our study shows that compliance with guidelines is poor. Endoscopists do not recognize rNENs on endoscopy and thus treat them with polypectomy, which is associated with noncurative resections and may lead to metastatic spread. Our study demonstrates the malignant potential of small rrNENs and the need to educate physicians on the diagnosis and treatment of those lesions.

The rationale for the present study came from the results of previous studies, our impressions that endoscopists do not follow the guidelines when dealing with rNENs, and the fact that the suspicion of rNENs, even in typical cases, is not noted on endoscopy yet on the basis of the histopathological examination.[3,6] Therefore, we aimed to investigate the clinical, endoscopic, and pathological characteristics of rNENs and determine whether the neuroendocrine origin of lesions is suspected by endoscopists during the examination and subsequently removed using an appropriate method. We also analyzed the outcomes of patients after simple polypectomy and EMR / ESD.

PATIENTS AND METHODS We evaluated all colonoscopic, endoscopic ultrasound (EUS) examinations and pathological results after polypectomy and ESD / EMR in patients hospitalized in our department at the university hospital between 2006 and 2019 to identify those with rNENs.

We retrospectively identified 52 patients with rNENs in medical records. The main inclusion criterion was the endoscopic treatment of an rNEN with curative or noncurative resection. We excluded 3 patients with surgically treated G3 tumors and another patient with a G3 tumor who had metastatic spread and died soon after the diagnosis. Eight patients were lost to follow-up (FIGURE 1). Thus, 40 patients with rNENs who underwent endoscopic treatment were included in the study. We collected data on patients' age, sex, symptoms, lesion appearance on endoscopy, method of endoscopic resection, tumor stage, and World Health Organization classification[7] from the patients' medical records.

We compared the patients treated with EMR / ESD with those undergoing simple polypectomy, considering the aforementioned clinical features. Patient outcomes were evaluated by a follow-up visit and the analysis of the results of the last follow-up examinations (computed tomography, EUS, and endoscopy).

Statistical analysis Statistical analysis was performed using the Statistica software, version 13.3 (Tibco, Palo Alto, California, United States). The nonparametric Mann–Whitney test was used to compare patients' age, tumor size, and length of follow-up, and the χ^2 test was used to compare patients' sex. Data were expressed as number (percentage), median (interquartile range), and range, as appropriate. A P value less than 0.05 was considered significant.

Due to the retrospective and noninterventional design of the study, ethics board approval was not required. Despite that, all living patients were informed about the study and they provided their written consent to participate.

RESULTS Forty patients (24 women and 16 men; median age, 52.5 years; range, 27–70 years) with rNENs who underwent endoscopic treatment were included in the study. Twenty-five patients (62.5%) were asymptomatic. The symptoms reported by the others included abdominal pain, distension, diarrhea, and bleeding. None of the patients had carcinoid syndrome. Thirty-one patients (77.5%) had coexisting disorders: hypertension (15 [37.5%]), thyroid gland disease (hypothyroidism, hyperthyroidism, or nodular goiter; 7 [17.5%]), rectal varices (5 [12.5%]), irritable bowel syndrome (4 [10%]), or ulcerative colitis (1 [2.5%]). Two patients (5%) had other malignancies (urothelial urinary bladder cancer and melanoma), and 7 patients (17.5%) had colonic epithelial polyps. Endoscopically, lesions had 3 main types of appearance: typical, yellowish smooth polyps (24 [60%]; FIGURE 2), small lesions similar to hyperplastic polyps (12 [30%]; FIGURE 3), or atypical lesions with central depression (erosive or ulcerated; 4 [10%]; FIGURE 4). The median lesion size was 5.5 mm (range, 3–12 mm) and most lesions were G1 tumors (n = 36), with only 4 G2 lesions. Only 14 of the lesions (35%) were suspected to be of neuroendocrine origin on endoscopy, and 12 of them (30%) were removed using ESD / cap-assisted EMR, with R0 resection achieved in 11 of them. In 2 cases, endoscopists removed the tumor by hot-snare polypectomy despite a suspicion of rNEN based on macroscopic features. The remaining lesions (n = 26) were removed by polypectomy using biopsy forceps (n = 9; no R0) or hot snare (n = 17; R0 achieved in 7 cases; in 5 cases, it was not possible to assess resection margins).

When we evaluated the appearance of the tumors and the methods of resection, we observed that, even in the group of tumors with a typical appearance, simple polypectomy was performed in the majority of patients (17 out of 24 [70.8%]), and ESD / EMR, only in 7 patients (29.2%). A scheme showing the macroscopic appearance of the lesions in relation to the endoscopic treatment performed is presented in FIGURE 5.

We also identified a relevant group of a small rNENs (12 out of 40 [30%]) that resembled hyperplastic polyps. In that group, only 2 out of 12 lesions (16.7%) were removed with ESD, and the rest (10 out of 12 [83.3%]) by simple polypectomy. In the group of rNENs with central

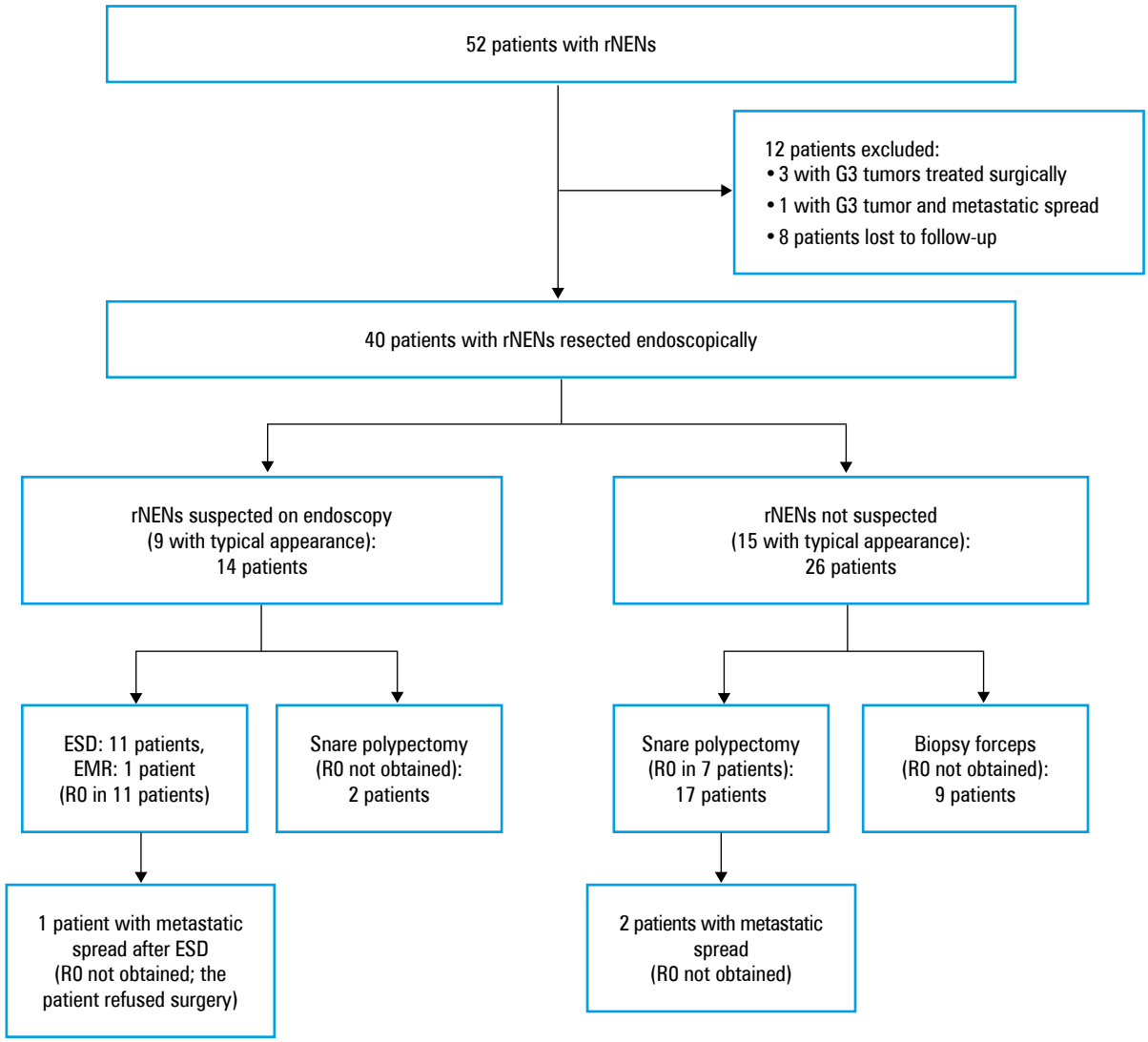
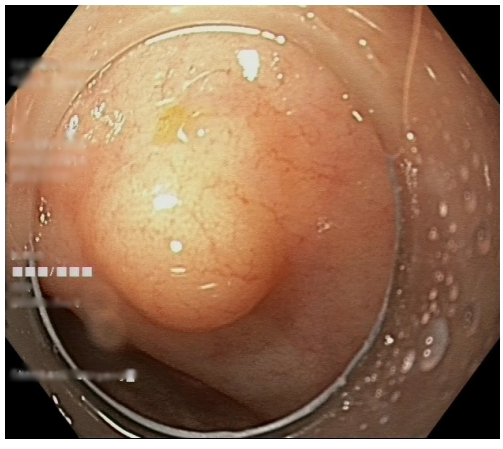


FIGURE 1 Flowchart of the patients enrolled in and excluded from the study, methods of treatment, follow-up, and outcomes after resection
Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; rNENs, rectal neuroendocrine neoplasms

FIGURE 2 Typical rectal neuroendocrine neoplasm



depression, 4 out of 5 lesions (80%) were removed by ESD, and the remaining lesion, by polypectomy.

A comparative analysis of the groups treated with EMR / ESD and the group treated with polypectomy (TABLE 1) showed similar patients' age, duration of follow-up, and sex distributions, with significant differences in tumor size (larger in the ESD group; $P = 0.004$). In the ESD / EMR (7 out of 12 [58.3%]) and polypectomy (15 out of 28 [53.6%]) groups, most lesions had a typical appearance. R0 resection was more often achieved in the group treated with ESD / EMR (11 out of 12 patients) than in the group treated with polypectomy (7 out of 28 [92% vs 25%]). The median length of follow-up was slightly yet nonsignificantly ($P = 0.42$) longer in the patients treated with ESD / EMR (50.2 months) than in those undergoing polypectomy (35.3 months). The overall median follow-up was 39.4 months.

Most of the patients were disease-free at follow-up, with 3 exceptions. Two patients treated with snare polypectomy for G2 and G1 tumors (8 and 9 mm in size, respectively) developed metastases 27 and 53 months afterwards, respectively, and died. A single patient treated with ESD for a 15-mm tumor showing risk features (G2 with central depression) refused surgery (proposed because of the infiltration of the vertical margin) and developed metastases to the liver after 69 months. At the time of writing, the patient was treated with chemotherapy.

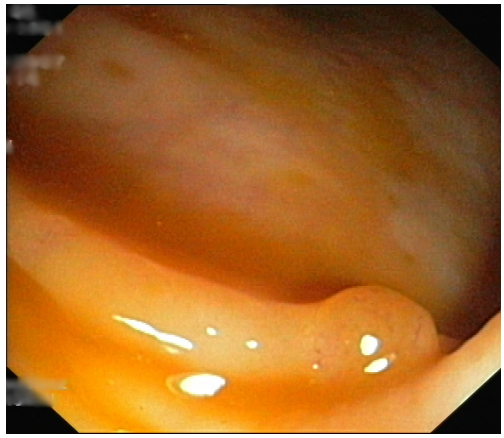


FIGURE 3 Atypical neuroendocrine neoplasm similar to hyperplastic polyp

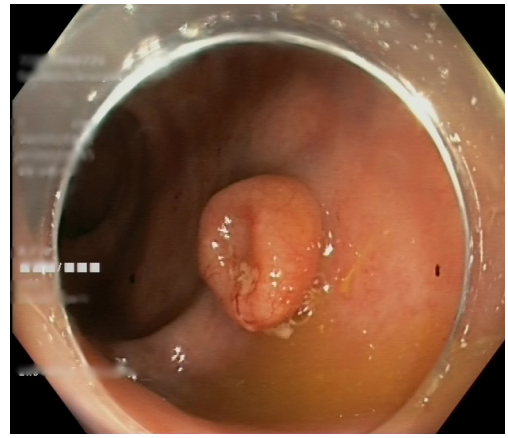


FIGURE 4 Atypical rectal neuroendocrine neoplasm with ulceration

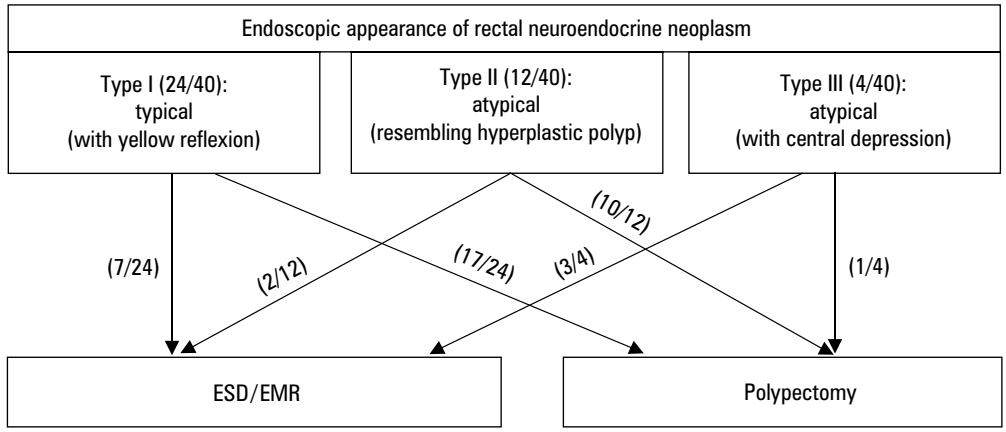


FIGURE 5 Flowchart presenting the endoscopic appearance of the lesions and the methods of resection applied
Abbreviations: see FIGURE 1

TABLE 1 Clinical features and comparative analysis of patients treated with endoscopic submucosal dissection, mucosal resection, and polypectomy

Parameter		Polypectomy (n = 28)	ESD / EMR (n = 12)	All (n = 40)	*P* value
Age, y		53 (48–60.5)	47 (43–56.3)	52.5 (44.8–60)	0.12
Tumor size, mm		4.75 (3–7.3)	10 (6.75–10)	5.5 (3–10)	0.004
Follow-up, mo		35.3 (15–104.9)	50.2 (15.1–71.6)	39.4 (15.1–81)	0.42
Sex	Male	11 (39)	5 (42)	16 (40)	0.08
	Female	17 (61)	7 (58)	24 (60)	
Type	Typical	15 (54)	7 (58)	22 (55)	–
	Atypical	13 (46)	5 (42)	18 (45)	
Grading	G1	26 (93)	10 (83)	36 (90)	–
	G2	2 (7)	2 (17)	4 (10)	
R0 resection		7 (25)	11 (92)	19 (48)	–
Patient outcomes		Metastases and death (2 patients), local recurrence and metastases (1 patient), distant metastases (1 patient)	Metastases (1 patient with high risk rNEN who refused surgery)	Metastases (3 patients), death (2 patients)	–

Data are presented as number (percentage) of patients or median (interquartile range).

Abbreviations: see FIGURE 1

DISCUSSION Rectal NETs are subepithelial lesions with a metastatic potential, which have been recently detected with a growing frequency.[1] The key points in the management of those tumors include a proper diagnosis based on endoscopic features and removal of the tumor using EMR, ESD, TEM, or surgery (for lesions with risk features) to achieve R0 resection and prevent the development of metastases.[1,2,8,9]

The purpose of our study was to determine whether the neuroendocrine origin of rNENs is suspected at the initial endoscopic examination and which methods are used by endoscopists to remove them, as well as to assess patient outcomes after radical and nonradical resection of rNENs. We aimed to answer the emerging question: are we following the guidelines when dealing with rNENs? The European Neuroendocrine Tumor Society (ENETS) guidelines (2008, 2012, and 2016)[2,8,10] represented the points of reference in our study (depending on the year in which the endoscopic procedure was performed); all updates recommended complete endoscopic resection in the case of small rNENs. The 2016 ENETS guideline update directly indicated ESD,TEM, or EMR as a method of treatment, while the previous ones suggested the use of band-snare resection, aspiration lumpectomy, strip biopsy. or transanal methods and justified that by nonradical outcomes of snare polypectomy.

Rectal neuroendocrine neoplasms are typically described as small, smooth G1 lesions with an intact covering mucosa and a yellow appearance.[11,12] This is in line with our observation showing that most of those tumors were graded G1 and were of similar appearance. Symptoms were present in more than a quarter of patients in this study, but according to the literature they are present in up to 50% of cases.[13] Those most commonly reported included abdominal pain, distension, diarrhea, and bleeding and, as in other studies, no patients had clinical symptoms of carcinoid syndrome.[14] In our opinion, in the majority of cases, symptoms were more frequently related to coexisting disorders (ie, rectal varices in the case of bleeding or rectal discomfort and irritable bowel syndrome in the case of distension or abdominal pain) than to the presence of small rNENs.

The majority of patients had comorbidities, mainly hypertension and/or thyroid gland disease, rectal hemorrhoids, and irritable bowel syndrome. Case reports and studies have reported the presence of synchronous colorectal adenocarcinoma and other primary malignancy in up to 14.5% of patients with neuroendocrine tumors.[15,16] Here, we could not identify patients with coexisting colon adenocarcinoma, but 2 patients had a secondary malignancy and a single patient had ulcerative colitis.

The typical endoscopic appearance (yellowish subepithelial lesion) in our study group, which is similar to that observed in other studies (eg, in 96% of patients reported by Lee et al[17]), was the most common manifestation of rNENs in our study. However, we could also distinguish further 2 patterns: atypical tumors resembling hyperplastic polyps and atypical lesions with central depression.

Notably, only 12 of 40 rNENs (30%) and 7 of 24 lesions (29.2%) in the group with a typical lesion appearance were removed using the appropriate method (FIGURE 5). Neuroendocrine origin was suggested during endoscopy in 14 out of 40 patients (35%), but 2 lesions were removed by snare polypectomy. In our opinion, these findings show either a problematic routine pattern or lack of education on decision making in the diagnosis and treatment of rNENs. Unfortunately, it did not seem to be a local problem. A study from the French Group of Endocrine Tumors on 345 rNENs revealed that a suspicion of a subepithelial lesion was noted during the initial endoscopy in only 24% of cases, and in 18%, the neuroendocrine origin of the tumor was suggested by an endoscopist.[3] Yet, one-third of those suspected tumors were removed by simple polypectomy.[3]

Justifying some of endoscopists' decisions, there was also a relevant group of small rNENs (FIGURES 2 and 5). When we retrospectively analyzed lesion images, it was difficult to distinguish them from hyperplastic polyps on routine white-light endoscopy. A better characterization of small polyps using advanced methods of visualization could be a solution. Regrettably, studies assessing more advanced methods of imaging have focused mainly on epithelial lesions,[18] with only a few case reports showing their potential in determining rNENs.[19] A better characterization of rNENs would be an interesting area of study, as, similar to the gastric NETs in the study by Lahner et al,,[20] it might help prevent mistakes in the treatment of small and atypical rNENs.

In our study, 3 patients developed metastases; 2 of them had 8- and 9-mm G2 and G1 tumors, respectively, (the G1 tumor case has been recently described in *Polish Archives of Internal Medicine*)[21] with typical morphology, which were removed by snare polypectomy. The other patient had a 15-mm G2 tumor with central depression and refused surgery, but he was treated with ESD (nonradical resection). The patient then refused salvage surgery and developed metastases after 69 months. What is important from the educational point of view, 2 of our patients with small tumors developed metastases, which showed the malignant potential of small rNENs, generally perceived as indolent lesions.[22,23] This finding contrasts with other studies reporting indolent behavior and no metastases of rNENs smaller than 10 mm.[22-24] It suggests that a size of 10 mm (not 5 mm as in the ENETS guidelines) should be an indication for EUS.[24,25] Our findings are in line with those of other studies showing the metastatic potential of rNENs smaller than 10 mm, including studies

by Gleeson et al[26] (metastases were present in 3% of patients), Kasuga et al[27] (in 4.9%), Konishi et al[28] (in 7%), and case reports.[21,29,30]

Risk factors for metastases, except tumor size, include tumor grade, lymphovascular infiltration, muscular invasion, presence of metastases, and endoscopic appearance (surface changes and ulceration).[1,9,26,28] However, in our 2 patients from the group treated with polypectomy who developed metastases, we could not identify any factor, apart from size greater than median (but still smaller than 10 mm and G2 grading in a single patient, that would differentiate them from the remaining patients who underwent nonradical resection and did not develop metastases. Those patients had rNENs of typical appearance, without surface changes, which were removed nonradically by hot-snare polypectomy. It shows that we cannot always predict the disease course of small tumors without risk features, or predict which tumor will metastasize. Our observations point to the need for reliable, commonly available for clinical use, and economical biomarkers that would enable the prediction of the disease course. A recent study by Gut et al[31] showed that the levels of serum serotonin in patients with small intestine neuroendocrine tumors and carcinoid syndrome differ depending on the tumor grading, staging, and extent of liver involvement. The usefulness of some markers in predicting the course of rNENs has been reported in the literature: Mitsuhashi et al[32] showed that molecular biomarkers such as CpG island methylator phenotype and microRNA 885-5p upregulation positively correlate with lymphovascular invasion. The expression of cyclin A and human embryonic stem cell marker 77 (HES77) positively correlated with the presence of metastases and shorter survival in patients with rNEN according to the studies by Jernman et al.[33,34]

A tumor size smaller than 10 mm increases the risk of metastases.[1] In the study by Gleeson et al,[26] metastases were present in 66% of tumors measuring 10 to 20 mm and in 73% of those of 20 mm in size or greater.

The prognosis of patients with rNENs is good, with an overall 5-year survival of 80%,[30] considering that the presence of metastases shifts the prognosis to that of adenocarcinoma.[28] The natural history of rNENs shows that removing a tumor by an inappropriate method may lead to metastasis and patients' death.[3,4,35,36] In the study by Fine et al,[3] the recurrence of rNENs after treatment occurred in 5% of patients, and 8 patients had metastatic spread (median time, 59 months), which led to death in 2 individuals. These observations are similar to those from our study and provide an additional argument in the ongoing debate on the need for salvage therapy and close follow-up with both endoscopy and abdominopelvic computed tomography or magnetic resonance imaging and/or EUS after nonradical resections by snare polypectomy.[4,23]

Additional evidence supporting this approach comes from data showing that simple polypectomy is associated with a high percentage of nonradical resections (80% in the study by Onozato et al,[22] 69% in the study by Son et al,[37] and up to 83% in the study by Fine et al[3]), the presence of remnant disease in a scar (up to 43%),[38-41] and the risk of local recurrence or metastatic spread,[3,5,42] even several years after the endoscopic resection.[4]

The outcomes of patients from the ESD group who developed metastases emphasize the problem of risk features, which according to the literature are a size of 20 mm or greater, grading of G2 or higher, invasion of the muscularis propria, infiltration of vessels, and the presence of ulceration and metastases.[1,43,44] Moreover, atypical features (shape, color, and surface changes) are related to lymph node metastases.[45] Therefore, according to the guidelines,[1,8] tumors of 20 mm in size or greater or those of 10 mm or greater showing risk features and those removed incompletely by endoscopic resection should be treated surgically. Our patient with the 15-mm G2 tumor not radically removed by ESD should therefore have been treated with salvage surgery, but the patient refused further treatment.

Limitations Our study had several limitations including the retrospective design, the small number of patients (a consequence of involving a single center and the rarity of rNENs), and the small size of the analyzed tumors (a consequence of the inclusion criterion of the endoscopic treatment of rNENs). Furthermore, apart from patients who underwent colonoscopy and endoscopic treatment in our department, we also included 9 patients who underwent simple polypectomy elsewhere and were referred to our department for follow-up rectal EUS.

Despite these limitations, our study showed the need for educating endoscopists on the diagnosis and treatment of rNENs, which can be typically suspected based on the macroscopic appearance. Our findings also confirmed previous observations showing that even small rNENs have a metastatic potential. This underlines the problem of risk factors for metastatic spread, which should always be considered when making clinical decisions about rNENs, and the need for salvage therapy and follow-up after nonradical resections.

Conclusions Rectal neuroendocrine neoplasms are mostly small lesions with a low potential for malignancy yet some risk of metastatic spread.[1,46] In the majority of cases, the origin of the lesions is not suspected by endoscopists on colonoscopy (even despite a typical appearance) and subsequently those lesions are removed using inappropriate methods. Endoscopists do not follow the guidelines when dealing with patients with rNENs and greater emphasis should be placed on their education on rNEN diagnosis and therapy.

The prognosis of rNENs is favorable when patients are treated according to the guidelines, whereas improper management may lead to metastatic spread and death.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT KD conceptualized and designed the study, collected and analyzed data, and wrote the manuscript. NR-R and KM collected data and wrote the manuscript. AB performed ESD/EMR and critically revised the manuscript. EU analyzed histopathological findings and critically revised the manuscript. BK-K critically revised the manuscript and followed up the study patients. TS designed the study and wrote and critically revised the manuscript. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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