BMC Gastroenterology

RESEARCH

Open Access

Endoscopic resection of rectal neuroendocrine tumors: zero disease-related deaths during a 10-year follow-up period

Yasuyo Hayashi[1], Haruei Ogino[1*], Yosuke Minoda[1], Yoshimasa Tanaka[1], Yoshitaka Hata[1], Masaru Kubokawa[2], Seiichiro Sakisaka[3], Kazuhiro Haraguchi[4], Shin-ichiro Fukuda[5], Soichi Itaba[6], Daisuke Yoshimura[7], Shunsuke Takahashi[8], Munehiro Tanaka[9], Hiroaki Kubo[10], Shinichi Somada[11], Eikichi Ihara[1] and Yoshihiro Ogawa[1]

Abstract

Background Gastrointestinal neuroendocrine tumors (GI-NETs) are slow-growing tumors with the potential for malignancy that originate from neuroendocrine cells. Therefore, early diagnosis and treatment of GI-NETs are necessary to prevent metastasis. The widespread use of colonoscopy, which allows early detection of rectal neuroendocrine tumors (rNETs) that are small enough to be treated endoscopically, has resulted in an increasing rate of endoscopic resection of rNETs. However, whether the long-term prognosis of endoscopically resected rNETs is favorable has not yet been determined. This study aimed to assess whether endoscopically resected rNETs affect the long-term prognosis of patients.

Methods We retrospectively reviewed the medical records of 163 consecutive patients with rNETs who underwent endoscopic resection at 11 hospitals in Japan between 1999 and 2012. The primary analysis focused on 47 patients with 51 rNETs who underwent ≥ 10 years of follow-up. The secondary analysis focused on patients who underwent less than 10 years of follow-up.

Results The median follow-up period of patients included in the primary analysis was 12.3 years (range, 10–19.1 years). The median lesion size was 5 mm (range, 2–12). Three lesions were treated using conventional endoscopic mucosal resection (EMR). Twenty-nine lesions were treated using modified EMR. Nineteen lesions were treated using endoscopic submucosal dissection. The R1 resection rate and lymphovascular invasion rate were 15.7% and 25.5%, respectively. The curative resection (CR) rate and non-CR rate were 66.7% and 33.3%, respectively. Two patients with lesions treated with non-CR underwent radical surgery. None of the 47 patients experienced lesion recurrence during the 10-year follow-up period. Two patients whose lesions were treated with CR died of other diseases.

Conclusions Death attributable to rNETs did not occur among patients who underwent at least 10 years of follow-up after endoscopic resection.

Keywords Rectal neuroendocrine tumors, Endoscopic resection, Risk factors, 10-year follow-up, Prognosis

*Correspondence:
Haruei Ogino
ogino.haruei.600@m.kyushu-u.ac.jp

Full list of author information is available at the end of the article

Background

Gastrointestinal neuroendocrine tumors (GI-NETs), which originate from neuroendocrine cells in the deep mucosal layer and were referred to as benign carcinoid tumors [1], are now classified as neuroendocrine neoplasms with metastatic potential [2–4]. Consequently, GI-NETs detected by endoscopic and imaging modalities generally require treatment. GI-NETs are mainly observed in the small intestine and rectum; however, they are also observed in the colon, stomach, and appendix [5]. The most common sites of GI-NETs in Caucasian and Asian patients are the midgut and rectum, respectively [6–8]. Rectal neuroendocrine tumors (rNETs) comprise 60–89% of GI-NETs in Japanese patients [9]. Because of the recent widespread use of screening endoscopy, the rNET detection rate has increased [10]. rNETs differ from other GI-NETs such as midgut NETs because of their slower development. Additionally, because lesions are often found in the anal region, surgery may require a stoma, thus potentially influencing treatment. Endoscopic resection is the first choice of treatment for patients with rNETs smaller than 10 mm [11]. However, risk factors for rNET metastasis, including tumor size, tumor grade, muscle invasion, positive resection margins, and lymphovascular invasion (LVI), should be considered [12–16].

According to the guidelines in Japan, indications for the endoscopic treatment of rNETs include grade 1 lesions, lesions smaller than 10 mm, and lesions located in the submucosal layer [12]. Because of the risk of metastasis, the criteria in Japan for endoscopic treatment, especially lesion size, are quite strict compared with those in Europe and the United States [17, 18]. However, recent studies have proposed a 15-mm threshold as a critical predictor of metastasis of intermediate tumors (10–19 mm), particularly in Western countries, where endoscopic resection is often recommended for lesions up to 20 mm [19, 20]. In contrast, the guidelines in Japan propose a stricter size criterion of ≤ 10 mm to prioritize patient safety. Importantly, even for tumors ≤ 10 mm, the accurate assessment of risk factors such as LVI and resection margins, which are critical to determining the risk of recurrence, is challenging. Therefore, thorough evaluation and refinement of management strategies for tumors ≤ 10 mm are essential before the adoption of broader criteria, such as the 15-mm threshold proposed by recent studies, can be considered.

One concern associated with the criteria in Japan is the potential positivity of resection margins during endoscopic treatment that can be attributed to the predominant development of rNETs within the submucosal layer. Another concern is the possibility of LVI rates associated with additional monoclonal antibody D2-40 and Elastica van Gieson (EVG) staining that are higher than that associated with hematoxylin–eosin (HE) staining. The positivity rate of LVI observed with HE staining for rNETs ≤ 10 mm ranges from 0 to 8.1%; however, that observed with immunohistochemical analyses for rNETs ≤ 13 mm ranges from 22.4 to 46.7% [21–24]. In Japan, the indications for endoscopic resection of rNETs are based on the histological findings of HE staining; however, the effects of D2-40 and EVG staining on their diagnosis are unclear.

Endoscopically resected rNETs in patients with the aforementioned risk factors generally require radical surgery, and such patients often undergo follow-up without further intervention to avoid unnecessary extensive procedures because of their small size and proximity to the anal region. However, the optimal duration of follow-up not only for lesions with positive risk factors but also for those deemed suitable for endoscopic resection is unclear. In Japan, the duration of follow-up varies across institutions, and some patients do not undergo follow-up after treatment. Because few reports of long-term follow-up periods have been published, whether the long-term prognosis of patients with endoscopically resected rNETs is affected by conventional risk factors or the absence of these factors is unclear. Therefore, it is necessary to determine whether endoscopically resected rNETs affect the long-term prognosis. Because rNETs develop slowly, an assessment of the long-term prognosis for more than 5 years is crucial. Consequently, this study aimed to examine the prognosis of patients with rNETs who were followed-up for at least 10 years after endoscopic resection.

Materials and methods

Study design and ethics

We retrospectively reviewed the medical records of 163 consecutive patients with rNETs who underwent endoscopic resection between March 1999 and December 2012 at the Department of Medicine and Bioregulatory Science of Kyushu University, Aso Iizuka Hospital, Kitakyushu Municipal Medical Center, National Hospital Organization Kyushu Medical Centre, Saiseikai Fukuoka General Hospital, Hara Sanshin Hospital, Kyushu Rosai Hospital, National Hospital Organization Fukuoka-higashi Medical Centre, National Hospital Organization Beppu Medical Center, Social Insurance Nakabaru Hospital, or Fukuoka City Hospital. The primary analysis focused on patients who underwent follow-up for at least 10 years. To provide additional insights, the secondary analysis focused on patients who underwent follow-up for less than 10 years. The study protocol was approved by the Ethics Committee of Kyushu University (approval no. 2020 – 722; approval date: April 3, 2021). Additionally, the ethics committee of each participating hospital approved the study protocol. This study was conducted in accordance with the Declaration of Helsinki. Because

of the retrospective nature of this study, it was difficult to obtain individual consent; therefore, information about this study was made public on the website.

Patients

Patients who met the following inclusion criteria were enrolled in the study: rNETs were resected via an endoscopic procedure in accordance with the indications for endoscopic resection and tumors were pathologically evaluated. Of the total cohort of 163 patients, 47 patients with 51 rNETs were included in the primary analysis and 116 patients with 127 rNETs were included in the secondary analysis. Radical surgery was recommended for all patients whose endoscopic specimens exhibited risk factors for metastasis. The final treatment decision was determined based on the patients' wishes.

Endoscopic procedures

Endoscopic procedures for rNETs were classified as conventional endoscopic mucosal resection (cEMR), modified EMR (mEMR), and endoscopic submucosal dissection (ESD). cEMR was defined as EMR with hot snare resection after submucosal injection, and mEMR was defined as either ligation-assisted EMR or cap-assisted EMR.

Pathological diagnosis

All specimens were evaluated histologically at each hospital to determine the tumor size, tumor grade, invasion depth, margin status, LVI, synaptophysin level, chromogranin A level, necrosis, and neural invasion. The specimens were re-evaluated histologically at the Department of Anatomic Pathology, Kyushu University. D2-40 and EVG staining were performed retrospectively as part of this study to evaluate LVI. However, these staining results were not available at the time of treatment; therefore, they did not influence the clinical decisions regarding additional surgery or follow-up strategies. All data were analyzed using the 2019 World Health Organization classification [25].

We also evaluated the various resection rates. En bloc resection was defined as resection of the lesion in one piece. R0 resection was defined as en bloc resection with negative margins. R1 resection was defined as resection with positive margins. Curative resection (CR) was defined as resection of a grade 1 tumor with negative LVI and negative margins.

Follow-up

Basic follow-up after endoscopic resection included colonoscopy to allow surveillance of local recurrence and either chest and abdominal computed tomography (CT) or chest radiography and abdominal ultrasonography to allow surveillance of local recurrence and metastatic recurrence. The follow-up period and surveillance frequency were based on the recommendations of the attending physicians. Imaging frequency during follow-up was not standardized across institutions; instead, it was performed according to the discretion of the attending physicians and based on the patient's clinical condition and institutional protocol.

Outcome measurements

The primary endpoint of this study was overall survival (OS). The date of survival confirmation was the date of death or last evaluation, which was confirmed in the medical records and was not limited to an evaluation performed in the gastroenterology department.

Statistical analysis

Categorical variables (expressed as numbers and percentages) were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables (expressed as medians and ranges) were analyzed using the Mann–Whitney U test. The Kruskal–Wallis test was performed to compare the continuous variables of the three treatment groups. The OS rate was calculated using the Kaplan–Meier method. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP Pro version 16 (SAS Institute, Cary, NC, USA).

Results

Clinical and pathological characteristics of the patients and lesions followed-up for at least 10 years after endoscopic resection

A total of 47 patients (26 men, 21 women) with 51 rNETs were included in the primary analysis (Fig. 1). The clinical and pathological characteristics of the patients are summarized in Table 1. The median patient age was 57.0 years (range, 24–77 years). The occurrence rate of single lesions was 93.6%, and that of two lesions was 6.4%. Two lesions (6.4%) exhibited central depression. The median tumor diameter was 5 mm (range, 2–12 mm); only three lesions had a diameter ≥ 10 mm. Three (5.9%) lesions were treated using cEMR, 29 (56.9%) lesions were treated using mEMR, and 19 (37.2%) lesions were treated using ESD. All lesions were classified as grade 1 and located in the submucosal layer. The en bloc resection rate was 100%. The R0 and R1 resection rates were 84.3% and 15.7%, respectively. During HE staining, no lesions exhibited lymphatic invasion (0%), whereas four lesions displayed venous invasion (8%). However, the addition of immunohistochemical staining revealed three (6%) lesions that exhibited lymphatic invasion, 11 (21.6%) lesions that exhibited venous invasion, and 13 (25.5%) lesions that exhibited LVI. The CR and non-CR rates

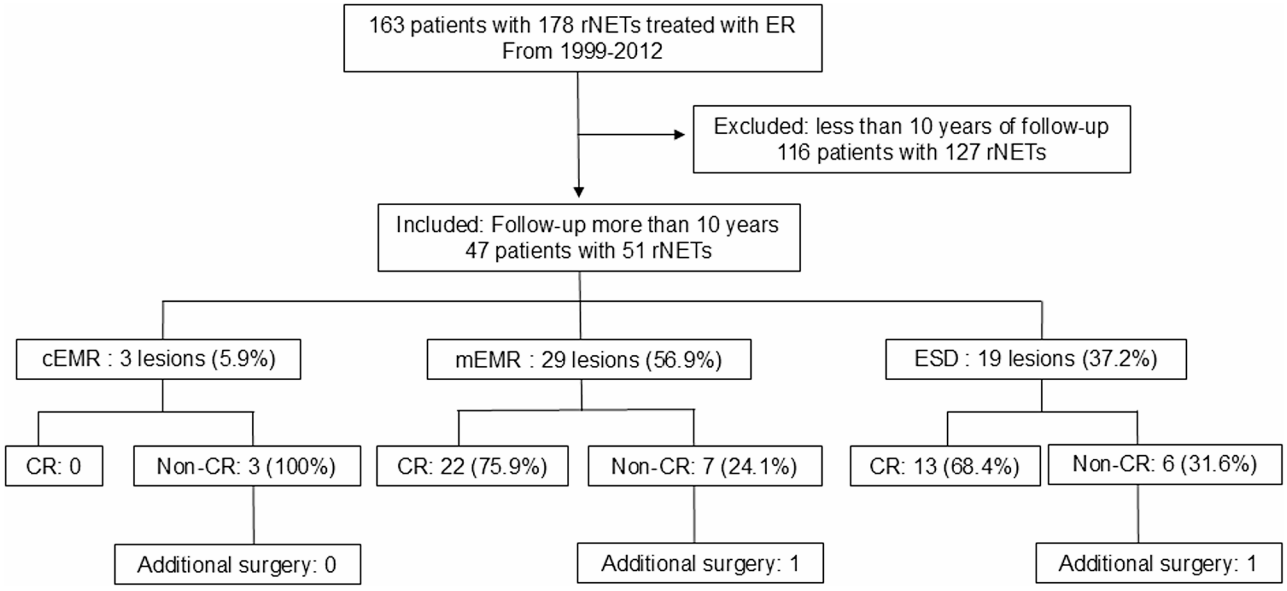

Fig. 1 Study flow chart. An illustration of the study flow chart of patients with rNETs in this study. cEMR, conventional endoscopic mucosal resection; CR, curative resection; ER, endoscopic resection; ESD, endoscopic submucosal dissection; mEMR, modified endoscopic mucosal resection; rNET, rectal neuroendocrine tumor

were 66.7% and 33.3%, respectively. Forty-one (80.4%) lesions had positive chromogranin results, and 48 (94%) lesions had positive synaptophysin results. One (2%) lesion exhibited necrosis and one (2%) lesion exhibited neural invasion.

Comparison of the clinical and pathological characteristics of the three treatment groups included in the primary analysis

The endoscopic treatment outcomes are summarized in Table 2. The tumor size and margin status were significantly different among the three groups. The en bloc resection rate for all three groups was 100%. The R0 resection rates were 0% (3/3) for the cEMR group, 86.2% (25/29) for the mEMR group, and 94.4% (18/19) for the ESD group. LVI was detected in two (66.7%) cEMR specimens, six (20.7%) mEMR specimens, and five (26.3%) ESD specimens. The CR rates were 0% (3/3) for the cEMR group, 75.9% (22/29) for the mEMR group, and 68.4% (13/19) for the ESD group. One patient in the mEMR group and one patient in the ESD group with lesions treated with non-CR underwent radical surgery. Among the two patients who underwent additional surgical resection, one had venous invasion detected with HE staining and one had positive resection margins. These findings were considered risk factors for disease recurrence; therefore, additional surgery was recommended. Procedure-related complications occurred in one patient who underwent ESD and experienced delayed bleeding.

Long-term clinical outcomes of patients included in the primary analysis

Death attributable to rNETs did not occur during the follow-up period. Two patients died of other diseases. The median follow-up period of 47 patients with 51 lesions was 12.3 years (range, 10–19.1 years). The Kaplan–Meier OS curve during the follow-up period after endoscopic resection is shown in Fig. 2. Data observed during the follow-up period are presented in Table 3. Forty (78.4%) lesions were followed-up for 10–15 years, and 11 (21.6%) lesions were followed-up for more than 15 years. Recurrence and metastasis did not develop during the follow-up period; however, imaging evaluations were not performed for some patients. The median follow-up period after endoscopic treatment of 51 lesions was 9 years (range, 0–16 years). Endoscopic follow-up was performed for 5 years for 33 (64.7%) lesions and for 10 years for 22 (43.1%) lesions. The median follow-up period of 51 lesions observed using imaging modalities such as endoscopy, abdominal CT, chest radiography, and abdominal ultrasonography was 10 years (range, 0–18 years). Forty-two (82.4%) and 29 (56.9%) lesions were followed-up for 5 years and 10 years, respectively, using imaging modalities.

Outcomes of rNETs followed-up for less than 10 years included in the secondary analysis

To further evaluate the outcomes of endoscopically resected rNETs, we conducted a secondary analysis that included patients who underwent follow-up for less than 10 years. Initially, 116 patients with 127 rNETs

Table 1 Clinical and pathological characteristics of 47 patients with 51 rNETs

Characteristics	
Age, years, median (range)	57 (24–77)
Sex, male/female	26/21
Single tumor, n (%)	44 (86.2%)
Multiple tumors, n (%)	7 (13.7%)
Tumor size, mm, median (range)	5 (2–12)
Tumor size (%)	
<10 mm, n (%)	48 (94.1%)
≥10 mm, n (%)	3 (5.9%)
Central depression of the tumor	2 (3.9%)
Type of endoscopic resection	
cEMR	3 (5.9%)
mEMR	29 (56.9%)
ESD	19 (37.2%)
Margin status	
R0, n (%)	43 (84.3%)
R1, n (%)	8 (15.7%)
Endoscopic curability	
CR, n (%)	34 (66.7%)
Non-CR, n (%)	17 (33.3%)
Tumor depth, submucosa, n (%)	51 (100%)
NET G1	51 (100%)
Ki-67 labeling index (%)	
Mean ± SD	0.44 ± 0.47
Range	0-1.7
Mitotic counts (per 10 HPF)	
Mean ± SD	0
Range	0
Lymphatic invasion, n (%)	
Negative	48 (94%)
Positive	3 (6%)
Venous invasion, n (%)	
Negative	40 (78.4%)
Positive	11 (21.6%)
Lymphovascular invasion, n (%)	
Negative	38 (74.5%)
Positive	13 (25.5%)
Chromogranin, n (%)	
Negative	10 (19.6%)
Positive	41 (80.4%)
Synaptophysin, n (%)	
Negative	3 (6%)
Positive	48 (94%)
Necrosis, n (%)	
Negative	50 (98%)
Positive	1 (2%)
Neural invasion (%)	
Negative	50 (98%)
Positive	1 (2%)

cEMR, conventional endoscopic mucosal resection; CR, curative resection; ESD, endoscopic submucosal dissection; HPF, high-power field; LVI, lymphovascular invasion; mEMR, modified endoscopic mucosal resection; NA, not available; rNET, rectal neuroendocrine tumor; SD, standard deviation

Table 2 Comparison of clinical and pathological outcomes of the three treatment groups

Characteristics	cEMR, *n* = 3	mEMR, *n* = 29	ESD, *n* = 19	*P* value
Tumor size (%)				0.08
<10 mm, n (%)	3 (100%)	29 (100%)	16 (84.2%)	
≥10 mm, n (%)	0	0	3 (15.8%)	
Lesions				0.17
Single tumor, n (%)	2 (66.7%)	27 (93.1%)	15 (79%)	
Multiple tumors, n (%)	1 (33.3%)	2 (6.9%)	4 (21%)	
En bloc resection, n (%)	3 (100%)	29 (100%)	19 (100%)	1
Margin status				0.002
R0, n (%)	0	25 (86.2%)	18 (94.7%)	
R1, n (%)	3 (100%)	4 (13.8%)	1 (5.3%)	
LVI, n (%)				0.2
Negative	1 (33.3%)	23 (79.3%)	14 (73.7%)	
Positive	2 (66.7%)	6 (20.7%)	5 (26.3%)	
Endoscopic curability				0.04
CR, n (%)	0	22 (75.9%)	13 (68.4%)	
Non-CR, n (%)	3 (100%)	7 (24.1%)	6 (31.6%)	
Complications	0	0	1 (5.6%)	0.43
Additional surgery, n (%)	0	1 (3.5%)	1 (5.3%)	1

cEMR, conventional endoscopic mucosal resection; CR, curative resection; ESD, endoscopic submucosal dissection; LVI, lymphovascular invasion; mEMR, modified endoscopic mucosal resection; NA, not available; R0, en bloc resection with negative margins; R1, resection with positive margins

were identified; however, two patients (2 lesions) were excluded because of missing data. Therefore, a total of 114 patients with 125 rNETs were included in the analysis (Supplemental Fig. 1).

The clinical and pathological characteristics of these patients are summarized in Supplemental Table 1. The median age of the patients was 55 years (range, 24–80 years). This cohort included slightly more men than women. The median tumor size was 5 mm (range, 2–12 mm), and all lesions were classified as grade 1 and located in the submucosal layer. LVI was observed with 13 lesions (10.4%), and the overall R0 resection rate was 84.8%.

Treatment outcomes differed among the three resection methods (Supplemental Table 2). A total of eight (6.4%) lesions were treated with cEMR, 80 (64%) lesions were treated with mEMR, and 37 (29.6%) lesions were treated with ESD. The CR rates were 37.5% for cEMR, 70% for mEMR, and 67.6% for ESD. Additional surgery was required for three cases treated with cEMR and two cases treated with ESD. Further interventions were not necessary for cases treated with mEMR.

During the short-term to mid-term follow-up period (median follow-up, 6.7 years; range, 1–9.9 years), disease-related deaths did not occur and recurrence and metastasis were not observed. These findings highlight the safety and efficacy of endoscopic resection of small rNETs, even during a shorter follow-up period. In particular,

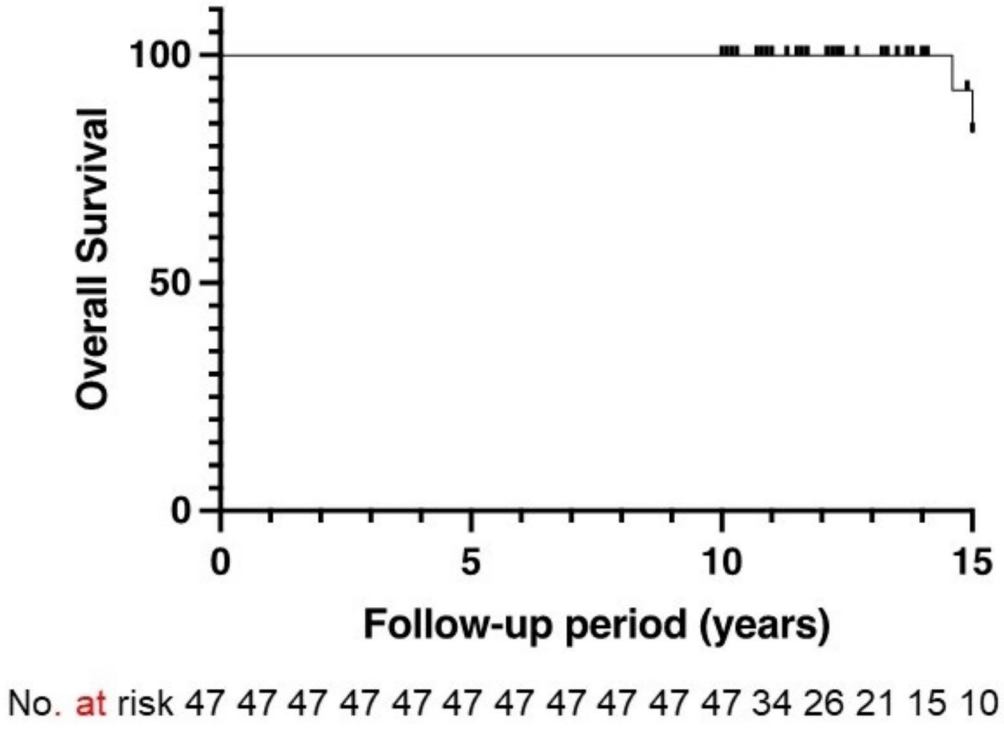

Fig. 2 Kaplan–Meier curve. Overall survival of patients who underwent follow-up after endoscopic resection

Table 3 Characteristics of 51 lesions during follow-up

Characteristics	Lesions
Follow-up period, years, median (range)	12.3 (10-19.1)
10–15 years of follow-up, n (%)	40 (78.4%)
> 15 years of follow-up, n (%)	11 (21.6%)
Endoscopic follow-up period, years, median (range)	9 (0–16)
Endoscopic follow-up for 5 years, n (%)	33 (64.7%)
Endoscopic follow-up for 10 years, n (%)	22 (43.1%)
Follow-up comprising imaging modalities, years, median (range)	10 (0–18)
Follow-up comprising imaging modalities for 5 years, n (%)	42 (82.4%)
Follow-up comprising imaging modalities for 10 years, n (%)	29 (56.9%)

Imaging modalities included endoscopy, abdominal computed tomography, chest radiography, and abdominal ultrasonography

mEMR and ESD demonstrated favorable outcomes with high CR rates and minimal need for additional surgical interventions.

Discussion

A follow-up period of approximately 5 years after treatment is the gold standard for rapidly growing epithelial tumors; in contrast, rNETs, which are slow-growing tumors, require a follow-up period of at least 10 years. However, only a few studies have evaluated the long-term prognosis of endoscopically resected rNETs for at least 10 years. During the current study, the 10-year survival rate of endoscopically resected rNETs was favorable, and additional surgery was not performed for patients with risk factors for disease recurrence. This study provides valuable insights regarding follow-up strategies for endoscopically resected rNETs.

Other indications for endoscopic resection are believed to affect the prognosis of rNETs. Because endoscopic resection was performed for lesions smaller 10 mm and confined to the submucosal layer, our analysis mainly focused on risk factors such as positive margins and LVI. During this analysis, 66.7% of the patients had no risk

factors for metastasis and 33.3% had positive risk factors for metastasis.

Endoscopic resection, which includes cEMR, mEMR, and ESD, has a significant effect on the incidence of positive margins. Notably, the positive margin rate associated with cEMR was higher than that associated with mEMR and ESD [26–30]. Although the number of cases in this study that underwent endoscopic resection was limited, the positive margin rate associated with cEMR was 100%, consistent with the findings of previous studies. In contrast, the short-term outcomes of mEMR and ESD were promising because of the high R0 resection rate. Additionally, complication rates of 0% and 5.6% were observed with mEMR and ESD, respectively. At our institution, mEMR and ESD are the established standard treatments for patients with diagnosed or suspected rNETs. Consequently, during the current study, cEMR was exclusively performed for rNETs misdiagnosed as epithelial tumors. Rossi et al. reported a 5.3% recurrence rate after endoscopic resection of rNETs ≤ 10 mm; this rate was primarily attributable to local recurrence after incomplete resection, particularly with cold snare polypectomy [31]. In contrast, recurrence was not observed during the long-term follow-up period of our study. The discrepancy in the recurrence rates of our study and others is likely attributable to differences in endoscopic techniques. We predominantly used advanced techniques such as mEMR and ESD, which result in complete resection (R0) rates that are higher than those of cold snare polypectomy. This highlights the importance of selecting the appropriate resection technique to minimize local recurrence. Because positive margins may lead to local recurrence, follow-up endoscopy is necessary. During this study, follow-up endoscopy for R1 resection cases was performed for a median of 6 years (range, 0–16 years).

LVI is a risk factor for lymph node metastasis [13, 14]. However, recent studies have found that using specific immunohistochemical staining increases the detection rate of LVI compared with that of simple HE staining [32]. The significance of LVI (i.e., whether it is truly a risk factor) identified using specific immunohistochemical staining has not yet been determined. All patients in the present study underwent additional specific immunohistochemical staining, resulting in an increased positive rate of lymphatic invasion (from 0 to 6%). Similarly, the positive rate of vascular invasion increased from 8 to 22%. A treatment strategy for cases with positive D2-40/EVG staining results despite negative HE staining results has not been established. At our institution, radical surgery is generally recommended for patients with positive D2-40/EVG staining results. However, in this study, only two of 17 such patients underwent surgery. This may have been attributable to the limited evidence of specific immunohistochemical staining and concerns regarding the invasiveness of radical surgical treatments.

In this study, most patients with rNETs who underwent endoscopic resection were followed-up even though the pathological analysis revealed risk factors for recurrence. These patients were observed for at least 10 years, but neither the absence nor the presence of risk factors affected the prognosis. The rate of additional surgical resection in our study was lower than that of previous studies, possibly because of patient-specific and treatment-specific factors. At the time of this study, robotic-assisted surgery was not widely available, and lesions near the anal region were often associated with a significant risk of permanent colostomy; therefore, physicians prioritized observation to preserve the quality of life. Additionally, LVI was assessed retrospectively; therefore, if LVI was not detected using HE staining, then such cases may have been considered low-risk, thus leading to the preference for observation rather than surgery. These factors illustrate the real-world complexities of clinical decision-making during follow-up.

The patients in this study were observed for at least 10 years, but neither the absence nor the presence of risk factors affected the prognosis. These findings have important implications for the development of future treatment strategies. For instance, follow-up may be acceptable for older patients, such as those older than 70 years, with underlying diseases because of the invasiveness of radical surgery and potential decrease in the quality of life caused by colostomy [33, 34]. Currently, the C-NET study in Japan is prospectively investigating the recurrence, metastasis, and prognosis of rNETs, which were treated not only with endoscopic resection but also with surgery [35]. The primary aim of the current study was to evaluate recurrence using colonoscopy and abdominal CT at 1, 5, and 10 years after treatment; however, the secondary aim was to evaluate long-term outcomes. The C-NET study, which is ongoing, could provide insights regarding the need for examinations and appropriate follow-up durations. Although registration for the C-NET study has been completed, the results are pending. Nevertheless, to formulate strategies, data regarding the long-term prognosis are crucial. The results of the current study can be used to support clinical decision-making, especially for lesions indicated for endoscopic resection, while awaiting the results of the C-NET study. Furthermore, by comprehensively considering the results of both of these studies, a more thorough understanding of the long-term prognosis of patients with rNETs could be achieved. Therefore, the results of our retrospective study have significant value.

This study had some limitations. This was a retrospective study with a relatively small sample size, and some enrolled patients did not undergo follow-up imaging. The actual examination rates were 82.4% at 5 years and 56.9% at 10 years (Table 1). The retrospective nature of this study inherently limited control over the follow-up procedures and introduced variability across institutions. Follow-up

imaging and endoscopic surveillance were performed based on the discretion of the attending physicians, thus leading to differences in the frequency of observation and modalities used. These factors may have influenced the consistency of data collection and interpretation of outcomes. Despite these limitations, the long-term follow-up data provide valuable insights regarding the real-world clinical management of rNETs. Many examinations conducted 10 years after endoscopic resection were motivated by the evaluation of other medical conditions. According to a consensus in Western countries, follow-up may not be necessary for cases indicated for endoscopic resection [35]. In the present study, 10.6% (5/47) of the patients who had indications for endoscopic resection did not undergo any imaging examinations. We also acknowledge the potential for selection bias in this study because our primary analysis included only patients with a follow-up period ≥ 10 years. To address this, we performed a secondary analysis of patients who underwent follow-up for less than 10 years (114 patients with 125 rNETs). Importantly, rNET-related death was not observed during this shorter follow-up period. These results are consistent with those of the long-term follow-up group, thereby further supporting the favorable prognosis of endoscopically resected small rNETs across different follow-up durations. This study reflects a real-world clinical scenario in which some patients do not undergo frequent imaging examinations. These findings suggest that even in actual clinical settings in which comprehensive follow-up may be challenging, valuable insights can be obtained.

Conclusion

In this study, none of the patients who were followed-up for ≥ 10 years died as a result of rNETs. Follow-up may be deemed acceptable for specific cases, such as those involving older patients with underlying conditions. These findings offer valuable perspectives regarding management strategies for rNETs after endoscopic treatment.

Abbreviations

cEMR	Conventional endoscopic mucosal resection
CR	Curative resection
CT	Computed tomography
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
EVG	Elastica van Gieson
GI-NET	Gastrointestinal neuroendocrine tumor
HE	Hematoxylin and eosin
LVI	Lymphovascular invasion
mEMR	Modified endoscopic mucosal resection
OS	Overall survival
rNET	Rectal neuroendocrine tumor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03736-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements

We thank Editage (www.editage.jp) for editing the English language.

Author contributions

Yasuyo Hayashi, HO and EI drafted the manuscript. Yasuyo Hayashi, HO, YM, YT, and Yoshitaka Hata were involved in the conceptualization and design of the study. YHayashi, MK, Seiichiro Sakisaka, KH, SF, SI, DY, ST, MT, HK, and Shinichi Somada collected the data. YO supervised this article. All the authors were involved in the analysis and revision of the manuscript. All the authors have read and approved the final manuscript.

Funding

This study was not supported by any sponsor or funder.

Data availability

The data generated or analyzed during this study were used solely for the purposes of this research and are not publicly available. Requests for access to the data can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by Institutional Review Board (IRB) for Clinical Research of Kyushu University Medical Institutions (approval no. 2020 – 722; approval date: April 3, 2021). Additionally, the ethics committee of each participating hospital approved the study protocol (as indicated by each hospital's IRB and affiliated institution). Because of the retrospective nature of this study, it was difficult to obtain individual consent; therefore, information about this study was made public on the website (https://www.intmed3.med.kyushu-u.ac.jp/research/) and consent was waived by the Ethics Committee. This study was conducted in accordance with the Declaration of Helsinki. Each hospital's IRB and affiliated institution: Kyushu University Medical Institutions: Ethics Committee: Institutional Review Board for Clinical Research. Affiliated Organization: Kyushu University Medical Institutions. Aso Iizuka Hospital: Ethics Committee: Institutional Review Board, Aso Iizuka Hospital. Affiliated Organization: Aso Iizuka Hospital. Saiseikai Fukuoka General Hospital: Ethics Committee: Research Ethics Committee of Saiseikai Fukuoka General hospital. Affiliated Organization: Saiseikai Fukuoka General Hospital. Harasanshin Hospital: Ethics Committee: Harasanshin Hospital Clinical Research Review Board. Affiliated Organization: Harasanshin Hospital. Kitakyushu Municipal Medical Center: Ethics Committee: Kitakyushu City Hospital Organization Institutional Review Board. Affiliated Organization: Kitakyushu City Hospital Organization. Kyushu Rosai Hospital: Ethics Committee: Kyushu Rosai Hospital Institutional Review Board. Affiliated Organization: Japan Organization of Occupational Health and Safety. National Hospital Organization Kyushu Medical Center: Ethics Committee: Kyushu Medical Center Ethics Committee. Affiliated Organization: National Hospital Organization (NHO) Kyushu Medical Center. Fukuoka City Hospital: Ethics Committee: Fukuoka City Hospital Institutional Review Board. Affiliated Organization: Fukuoka City Hospital. National Hospital Organization Fukuokahigashi Medical Center: Ethics Committee: Ethical Committee of Fukuokahigashi Medical Center. Affiliated Organization: NHO Fukuokahigashi Medical Center. Social Insurance Nakabaru Hospital: Ethics Committee: Social Insurance Nakabaru Hospital Ethics Review Committee. Affiliated Organization: Social Insurance Nakabaru Hospital. National Hospital Organization Beppu Medical Center: Ethics Committee: Ethical Committee of Beppu Medical Center. Affiliated Organization: NHO Beppu Medical Center.

Competing interests

The authors declare no competing interests.

Consent for publication

Not applicable.

Author details

[1]Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Higashi-Ku, Fukuoka, Japan

[2]Department of Gastroenterology, Aso Iizuka Hospital, Iizuka, Japan
[3]Department of Internal Medicine, Saiseikai Fukuoka General Hospital, Fukuoka, Japan
[4]Department of Gastroenterology, Harasanshin Hospital, Hakata-Ku, Fukuoka, Japan
[5]Department of Gastroenterology, Kitakyushu Municipal Medical Center, Kokurakita-Ku, Kitakyushu, Japan
[6]Department of Gastroenterology, Kyushu Rosai Hospital, Kitakyushu, Fukuoka, Japan
[7]Department of Gastroenterology, National Hospital Organization Kyushu Medical Center, Chuo-Ku, Fukuoka, Japan
[8]Department of Gastroenterology, Fukuoka City Hospital, Hakata-Ku, Fukuoka, Japan
[9]Department of Gastroenterology and Hepatology, NHO Fukuokahigashi Medical Center, Koga, Japan
[10]Sasaki Hospital, Kitakyushu, Fukuoka, Japan
[11]Department of Gastroenterology, National Hospital Organization Beppu Medical Center, Beppu, Oita, Japan

Received: 29 October 2024 / Accepted: 26 February 2025
Published online: 11 March 2025

References

1. Klöppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. Ann N Y Acad Sci. 2004;1014(1):13–27.
2. Soga J. Early-stage carcinoids of the Gastrointestinal tract: an analysis of 1914 reported cases. Cancer. 2005;103(8):1587–95.
3. Fujishiro M. Perspective on the practical indications of endoscopic submucosal dissection of Gastrointestinal neoplasms. World J Gastroenterol. 2008;14(27):4289–95.
4. Jernman J, Välimäki MJ, Louhimo J, Haglund C, Arola J. The novel WHO 2010 classification for Gastrointestinal neuroendocrine tumours correlates well with the metastatic potential of rectal neuroendocrine tumours. Neuroendocrinology. 2012;95(4):317–24.
5. Frilling A, Akerström G, Falconi M, Pavel M, Ramos J, Kidd M, et al. Neuroendocrine tumor disease: an evolving landscape. Endocr Relat Cancer. 2012;19(5):R163–85.
6. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after carcinoid: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the united States. J Clin Oncol. 2008;26(18):3063–72.
7. Cives M, Strosberg JR. Gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin. 2018;68(6):471–87.
8. Ito T, Sasano H, Tanaka M, Osamura RY, Sasaki I, Kimura W, et al. Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. J Gastroenterol. 2010;45(2):234–43.
9. Scherübl H. Rectal carcinoids are on the Rise: early detection by screening endoscopy. Endoscopy. 2009;41(2):162–5.
10. Caplin M, Sundin A, Nillson O, Baum RP, Klose KJ, Kelestimur F, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. Neuroendocrinology. 2012;95(2):88–97.
11. Ito T, Masui T, Komoto I, Doi R, Osamura RY, Sakurai A, et al. JNETS clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms: diagnosis, treatment, and follow-up: a synopsis. J Gastroenterol. 2021;56(11):1033–44.
12. Konishi T, Watanabe T, Kishimoto J, Kotake K, Muto T, Nagawa H, et al. Prognosis and risk factors of metastasis in colorectal carcinoids: results of a nationwide registry over 15 years. Gut. 2007;56(6):863–8.
13. Shields CJ, Tiret E, Winter DC, International Rectal Carcinoid Study Group. Carcinoid tumors of the rectum: a multi-institutional international collaboration. Ann Surg. 2010;252(5):750–5.
14. Kasuga A, Chino A, Uragami N, Kishihara T, Igarashi M, Fujita R, et al. Treatment strategy for rectal carcinoids: a clinicopathological analysis of 229 cases at a single cancer institution. J Gastroenterol Hepatol. 2012;27:1801–7.
15. Maione F, Chini A, Milone M, Gennarelli N, Manigrasso M, Maione R, et al. Diagnosis and management of rectal neuroendocrine tumors (NETs). Diagnostics (Basel). 2021;11(5):771.
16. Park CH, Cheon JH, Kim JO, Shin JE, Jang BI, Shin SJ, et al. Criteria for decision making after endoscopic resection of well-differentiated rectal carcinoids with regard to potential lymphatic spread. Endoscopy. 2011;43(9):790–5.
17. Ramage JK, De Herder WW, Delle Fave G, Ferolla P, Ferone D, Ito T, et al. ENETS consensus guidelines update for colorectal neuroendocrine neoplasms. Neuroendocrinology. 2016;103(2):139–43.
18. Anthony LB, Strosberg JR, Klimstra DS, Maples WJ, O'Dorisio TM, Warner RR, et al. The NANETS consensus guidelines for the diagnosis and management of Gastrointestinal neuroendocrine tumors (NETS): well-differentiated Nets of the distal colon and rectum. Pancreas. 2010;39(6):767–74.
19. Park J, Cheon JH. Multidimensional approach for perianal Crohn's disease. BMC Gastroenterol. 2022;22(1):103.
20. Nakade Y, Fukui A, Ono Y, Sugihara T, Kamada N, Okamoto R, et al. Clinical effectiveness of biologics in treatment-naïve elderly patients with ulcerative colitis: A multicenter retrospective study. BMC Gastroenterol. 2023;23(1):183.
21. Fahy BN, Tang LH, Klimstra D, Wong WD, Guillem JG, Paty PB, et al. Carcinoid of the rectum risk stratification (CaRRs): a strategy for preoperative outcome assessment. Ann Surg Oncol. 2007;14(2):396–404.
22. Kim GU, Kim KJ, Hong SM, Yu ES, Yang DH, Jung KW, et al. Clinical outcomes of rectal neuroendocrine tumors ≤ 10 mm following endoscopic resection. Endoscopy. 2013;45(12):1018–23.
23. Nakamura K, Osada M, Goto A, Iwasa T, Takahashi S, Takizawa N, et al. Short- and long-term outcomes of endoscopic resection of rectal neuroendocrine tumours: analyses according to the WHO 2010 classification. Scand J Gastroenterol. 2016;51(4):448–55.
24. Sekiguchi M, Sekine S, Sakamoto T, Otake Y, Nakajima T, Matsuda T, et al. Excellent prognosis following endoscopic resection of patients with rectal neuroendocrine tumors despite the frequent presence of lymphovascular invasion. J Gastroenterol. 2015;50(12):1184–9.
25. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76(2):182–8.
26. Toriyama K, Yamamura T, Nakamura M, Maeda K, Sawada T, Mizutani Y, et al. An evaluation of resectability among endoscopic treatment methods for rectal neuroendocrine tumors < 10 mm. Arab J Gastroenterol. 2021;22(2):104–10.
27. Kim KM, Eo SJ, Shim SG, Choi JH, Min BH, Lee JH, et al. Treatment outcomes according to endoscopic treatment modalities for rectal carcinoid tumors. Clin Res Hepatol Gastroenterol. 2013;37(3):275–82.
28. Zhou X, Xie H, Xie L, Li J, Cao W, Fu W. Endoscopic resection therapies for rectal neuroendocrine tumors: A systematic review and meta-analysis. J Gastroenterol Hepatol. 2014;29(2):259–68.
29. Hong SM, Baek DH. Endoscopic treatment for rectal neuroendocrine tumor: which method is better? Clin Endosc. 2022;55(4):496–506.
30. Kitagawa Y, Ikebe D, Hara T, Kato K, Komatsu T, Kondo F, et al. Enhanced detection of lymphovascular invasion in small rectal neuroendocrine tumors using D2-40 and elastica Van Gieson immunohistochemical analysis. Cancer Med. 2016;5(11):3121–7.
31. Becker AL, Gonzalez Y, Bass JA, Lemke LA, Trujillo H, Shah S, et al. Artificial intelligence and endoscopy: A systematic review of the literature and roadmap for advanced AI solutions in the clinical setting. BMC Gastroenterol. 2023;23(1):272.
32. de Mestier L, Lorenzo D, Fine C, Cros J, Hentic O, Walter T, et al. Endoscopic, Transanal, laparoscopic, and transabdominal management of rectal neuroendocrine tumors. Best Pract Res Clin Endocrinol Metab. 2019;33(5):101293.
33. Emoto S, Kawai K, Nozawa H, Sasaki K, Murono K, Yokoyama Y, et al. Prediction of lymph node metastasis of well-differentiated rectal neuroendocrine tumours using multiple diagnostic modalities. Colorectal Dis. 2023;25(7):1414–22.
34. Sekiguchi M, Hotta K, Takeuchi Y, Tanaka S, Yamamoto H, Shinmura K, et al. Characteristics of colorectal neuroendocrine tumors in patients prospectively enrolled in a Japanese multicenter study: a first report from the C-NET STUDY. J Gastroenterol. 2022;57(8):547–58.
35. Rinke A, Ambrosini V, Dromain C, Garcia-Carbonero R, Haji A, Koumarianou A, et al. European neuroendocrine tumor society (ENETS) 2023 guidance paper for colorectal neuroendocrine tumours. J Neuroendocrinol. 2023;35(6):e13309.

Publisher's note