

Long-Term Outcomes after the Complete Resection of Rectal Neuroendocrine Tumors: A Multicenter Cohort Study

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Background/Aims: Although rectal neuroendocrine tumors (NETs) ≤ 1 cm in size are generally considered low-risk tumors that are suitable for endoscopic resection, the long-term outcomes after histologically complete resection remain unknown.

Methods: We conducted a multicenter retrospective cohort study of patients with rectal NETs who underwent complete endoscopic resection (endoscopic mucosal resection or endoscopic submucosal dissection) between January 2014 and December 2019. A total of 860 patients with ≥ 6 months of follow-up were included. Recurrence-free survival and its associated risk factors were analyzed using Kaplan-Meier and Cox proportional hazards models.

Results: Among 860 patients, the mean age was 47.7 years, and 57.9% of the patients were male. The overall recurrence rate was 1.4% ($n=12$). Univariate and multivariate analyses identified histological grade 2 (hazard ratio [HR], 19.13; 95% confidence interval [CI], 3.51 to 104.22) and mitotic count 2–20/10 high-power field (HPF) (HR, 20.88; 95% CI, 1.61 to 270.19) as independent predictors of recurrence, while $>20/10$ HPF (HR, 7.93; 95% CI, 0.90 to 69.87) showed a marginal association. The pathological tumor size, resection method, endoscopic ultrasonography findings, and Charlson Comorbidity Index were not associated with recurrence. The 5-year and 9-year recurrence-free survival rates were 98.4% and 84.7%, respectively. Supplementary analysis excluding patients with missing data confirmed consistent findings.

Conclusions: Although recurrence is rare after the complete resection of rectal NETs ≤ 1 cm in size, patients with grade 2 tumors or a mitotic count $\geq 2/10$ HPF are at increased risk. Risk-adapted follow-up based on histological features should be considered. (*Gut Liver*, 2026;20:275-282)

Key Words: Rectal neoplasms; Neuroendocrine tumors; Endoscopic mucosal resection; Endoscopic submucosal dissection; Recurrence

INTRODUCTION

Rectal neuroendocrine tumors (NETs) are rare malignancies with an indolent course, and their incidence has been increasing, likely due to improved diagnostic techniques and broader adoption of updated classification systems.¹⁻⁵ Previous literature has suggested that rectal NETs

measuring ≤ 1 cm are good candidates for endoscopic resection.^{6,7}

Endoscopic resection has demonstrated excellent long-term outcomes for small rectal NETs.⁸ Studies using various endoscopic techniques have reported high *en bloc* resection rates ranging from 96.7% to 100%, with histologically complete resection rates between 72% and 87.1%.⁹⁻¹²

According to current guidelines, including those from the National Comprehensive Cancer Network and the European Neuroendocrine Tumor Society, surveillance may be discontinued following curative resection of grade 1–2 rectal NETs smaller than 1 cm.^{13–15} Most previous studies have shown that endoscopic resection of sub-centimeter rectal NETs is a safe and effective approach, with low recurrence rates. These findings support the efficacy of endoscopic management and suggest favorable prognosis even in cases of incomplete resection.¹⁶ Additionally, prior investigations have examined indications for endoscopic therapy, treatment methods, salvage strategies for incomplete resections, and risk factors for recurrence and *de novo* tumor development.^{3,17}

However, long-term outcomes in patients with histologically confirmed complete resection have not been thoroughly investigated. Although rectal NETs are generally considered indolent tumors, in clinical practice, discontinuation of surveillance following complete endoscopic resection is uncommon. This is particularly relevant in countries such as Korea, where access to endoscopy and imaging is readily available, and there is ongoing debate over whether to adhere strictly to Western guidelines recommending cessation of follow-up. In practice, continued surveillance using computed tomography is often employed, raising concerns about cumulative radiation exposure.¹⁸

Therefore, the aim of this study is to evaluate the long-term outcomes of patients with histologically complete resection of rectal NETs, specifically focusing on the absence of local recurrence or distant metastasis. Additionally, we aimed to assess prognostic differences through subgroup analyses based on tumor grade and mitotic index to determine whether the current guideline recommendations are applicable in real-world clinical settings.

MATERIALS AND METHODS

1. Study design and patient selection

This multicenter retrospective cohort study included patients diagnosed with rectal NETs who underwent endoscopic resection—either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)—between January 1, 2014, and December 31, 2019. Ten tertiary referral centers participated in the study. Among the 1,297 patients initially screened, 1,163 had histologically confirmed complete resection. After excluding patients with lymphovascular invasion ($n=30$), perineural invasion ($n=1$), histologically incomplete resection ($n=103$), follow-up loss or follow-up duration <6 months ($n=291$), and death during follow-up ($n=12$), 860 patients were included in the final analysis. The study cohort selection process is illustrated in Fig. 1. The study was approved by the participating institutions, including the Samsung Medical Center Institutional Review Board (IRB number 2024-07-056; EUMC 2025-05-026, CHOSUN 2024-10-020, NCC2024-0261, HALLYM 2024-07-017-001, GCIRB2024-240, BPIRB 2024-07-018, KUGH 2024-09-007). The requirement for written informed consent was waived by the IRB.

2. Data collection and variable definitions

Collected variables included age, sex, resection method (EMR or ESD), endoscopic and pathological tumor size, histologic grade (grade 1 or 2), mitotic count per 10 high-power fields (HPF), depth of invasion on endoscopic ultrasonography, and Charlson Comorbidity Index (CCI). Complete resection was defined as histologically negative lateral and vertical margins. Recurrence was defined as radiologic or histopathologic evidence of either local recurrence or distant metastasis. This definition encompassed local recurrences, lymph node metastases, and metachro-

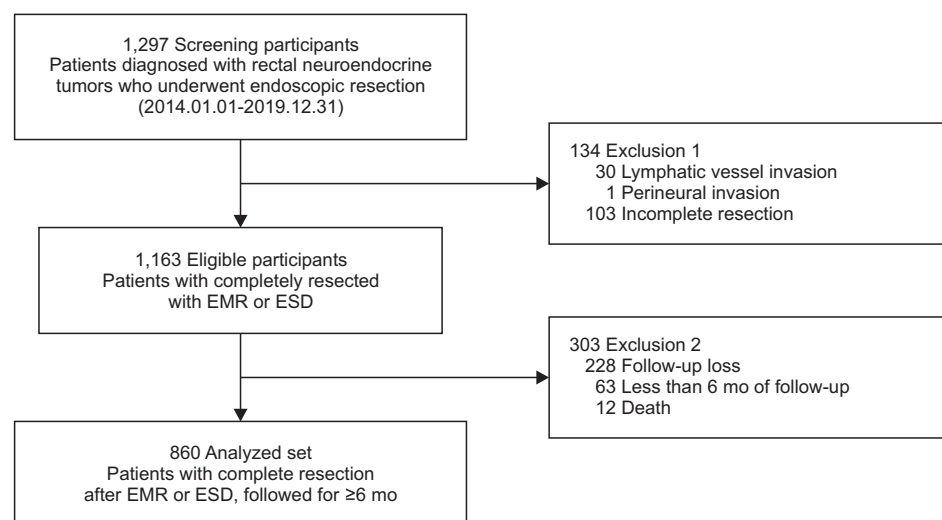


Fig. 1. Flowchart of the study population. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

nous lesions. Recurrence-free survival (RFS) was calculated from the date of resection to the date of recurrence or last follow-up.

3. Statistical analysis

Continuous variables were expressed as means with standard deviations and compared using the Wilcoxon rank sum test. Categorical variables were expressed as counts and percentages and compared using the chi-square test or Fisher exact test, as appropriate. Cox proportional hazards regression models were used to evaluate factors associated with tumor recurrence. The assumptions of proportional hazards were checked by goodness of fit test using the Schoenfeld residual. Variables included in the multivariable model were pathological tumor size and mitotic count selected by p-value <0.2 in univariable analysis. Kaplan-Meier survival analysis was performed to estimate RFS, and differences between groups were assessed using the log-rank test. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary,

NC, USA).

RESULTS

1. Baseline characteristics

Among the 860 patients included in the final analysis, the mean age was 47.7 years, and 57.9% were male. EMR and ESD were performed in 598 (69.5%) and 265 (30.8%) patients, respectively. The mean pathological tumor size was 4.69 ± 2.39 mm. Histologic grade 1 was present in 670 patients (77.9%), and grade 2 in 14 patients (1.6%). A mitotic count of <2/10 HPF was observed in 88.3% of patients. CCI score was 0 in 50.6% of patients (Table 1). The detailed distribution of CCI components is presented in Supplementary Table 1.

2. Recurrence rate and pattern

A total of 12 patients (1.4%) experienced recurrence. Recurrence patterns included recurrence in a metachronous lesion (n=8), focal mucosal recurrence (n=1), region-

Table 1. Baseline Characteristics

Variable	Total (n=860)	Non-recurred (n=848)	Recurred (n=12)	p-value
Age, yr	47.66±11.78	47.61±11.80	51.38±10.05	0.31
Male sex	498 (57.91)	488 (97.99)	10 (2.01)	0.07
EUS	304 (35.35)	301 (99.01)	3 (0.99)	0.55
EUS depth				0.57
MM	104 (34.21)	104 (100)	0	
SM	195 (64.14)	192 (98.46)	3 (1.54)	
PM	5 (1.64)	5 (100)	0	
ESD	265 (30.81)	261 (98.49)	4 (1.51)	1.00
EMR	598 (69.53)	589 (98.49)	9 (1.51)	1.00
Endoscopic size, mm	5.94±2.76	5.94±2.75	5.48±3.30	0.29
Pathologic size, mm	4.69±2.39	4.68±2.38	5.59±2.64	0.33
Grade (n=684)				<0.001
Grade 1	670 (77.91)	665 (99.25)	5 (0.75)	
Grade 2	14 (1.63)	11 (78.57)	3 (21.43)	
Mitosis (n=784)				<0.001
<2 (/10HPF)	759 (88.26)	754 (99.34)	5 (0.66)	
2–20 (/10HPF)	10 (1.16)	9 (90.00)	1 (10.00)	
>20 (/10HPF)	15 (1.74)	13 (86.67)	2 (13.33)	
Recurrence outcome				NA
None	848 (98.60)	848 (100)	0	
Focal	1 (0.12)	0	1 (100)	
Lymph node	1 (0.12)	0	1 (100)	
Metachronous	8 (0.93)	0	8 (100)	
Others	2 (0.23)	0	2 (100)	
CCI				0.30
0	435 (50.58)	431 (99.08)	4 (0.89)	
1	215 (25.00)	212 (98.60)	3 (1.40)	
≥2	210 (24.42)	205 (97.62)	5 (2.38)	

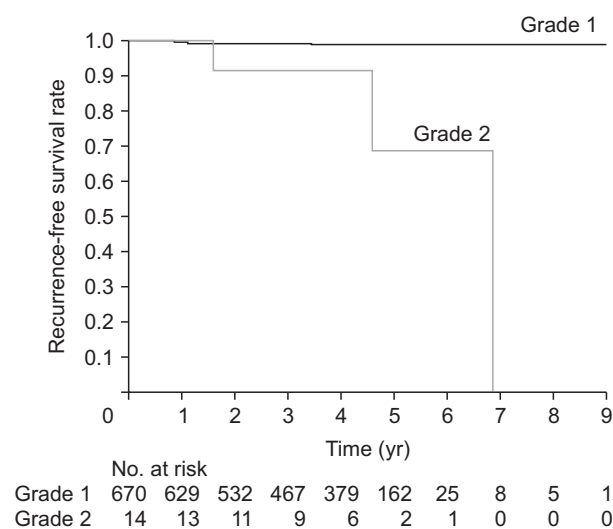
Data are presented as mean±SD or number (%).

EUS, endoscopic ultrasonography; MM, muscularis mucosae; SM, submucosal; PM, muscularis propria; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; HPF, high-power field; CCI, Charlson Comorbidity Index; NA, not available.

Table 2. Clinical Characteristics of Patients with Recurrence

Patient	Sex	Age at diagnosis, yr	EUS	ESD/EMR	Endoscopic size, mm	Pathologic size, mm	Grade (pathology)	Mitosis (/10HPF)	DOTA PET	Rectal MRI	Lesion of metastasis	Days of recurrence
1	M	54	NA	EMR	3	Missing	Missing	Missing	NA	NA	Metachronous lesion	454
2	M	33	NA	ESD	8	8	1	<2	NA	NA	Metachronous lesion	400
3	F	57	NA	EMR	3	4	Missing	<2	NA	NA	Metachronous lesion	1,269
4	M	39	NA	EMR	4	3.5	Missing	<2	NA	NA	Metachronous lesion	401
5	M	61	NA	ESD	3	4	Missing	<2	NA	NA	Metachronous lesion	2,279
6	F	50	SM	ESD	7.7	7	2	2-20	NA	NA	Lymph node	574
7	M	38	NA	EMR	3	6	1	Missing	Done	Done	Metachronous lesion	82
8	M	51	NA	EMR	3	2	1	Missing	NA	NA	Metachronous lesion	1,236
9	M	48	NA	EMR	3	3	1	<2	NA	NA	Metachronous lesion	546
10	M	61	SM	EMR	6	4	1	Missing	NA	NA	Focal	314
11	M	50	NA	EMR	13	12	2	>20	NA	NA	Lymph node & liver metastasis	1,656
12	M	67	SM	ESD	9	8	2	>20	NA	NA	Liver metastasis	2,476

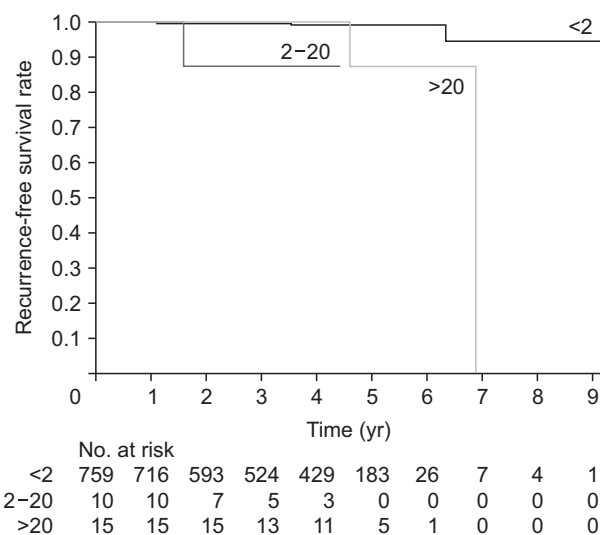
EUS, endoscopic ultrasonography; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; HPF, high-power field; DOTA PET, 68Ga-labeled DOTA-peptide positron emission tomography; MRI, magnetic resonance imaging; NA, not available; SM, submucosa.

**Fig. 2** Kaplan-Meier survival curves by tumor grade. Number at risk is shown below the X-axis at each time point.

al lymph node metastasis (n=1), and distant organ metastases (n=2). Of the 12 patients with available outcomes, nine demonstrated endoscopic recurrence, including one case of focal recurrence and eight cases of metachronous lesions. In addition, recurrence was identified radiologically in three patients as lymph node or liver metastases. The median follow-up time to recurrence was 4.2 years (range, 0.2 to 9.2 years). The 5-year RFS was 98.4% (95% confidence interval [CI], 97.0% to 99.2%), and the 9-year RFS was 84.7% (95% CI, 52.6% to 95.8%) (data not shown). Detailed clinical characteristics of the 12 patients who experienced recurrence are summarized in Table 2.

3. RFS (Kaplan-Meier analysis)

The Kaplan-Meier analysis revealed not significantly

**Fig. 3** Kaplan-Meier survival curves by mitoses per high-power field. Number at risk is shown below the X-axis at each time point.

lower RFS in patients with grade 2 tumors than grade 1 tumors (log-rank test, $p<0.01$) (Fig. 2). A stepwise decline in RFS was observed with increasing mitotic count (log-rank test, $p<0.01$) (Fig. 3).

4. Risk factors for recurrence

In the univariable analysis, grade 2 was significantly associated with an increased risk of recurrence compared to grade 1 (hazard ratio [HR], 23.60; 95% CI, 5.32 to 104.68; $p<0.001$). Recurrence risk also increased with higher mitotic counts. Pathologic tumor size, resection method (EMR/ESD), endoscopic ultrasonography-assessed invasion depth, and CCI were not significantly associated with recurrence (Table 3). In the multivariable analysis adjusted by pathological tumor size, both grade 2 (HR, 19.13; 95%

Table 3. Risk Factor Associated with Recurrence of Rectal Neuroendocrine Tumor (ver. Mitosis)

Parameter	Comparison	Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
ESD	Done vs not done	0.89 [0.27–2.99]	0.85		
EMR	Done vs not done	1.63 [0.43–6.06]	0.46		
Endoscopic size		0.91 [0.72–1.16]	0.47		
Pathologic size		1.13 [0.92–1.39]	0.23	1.12 [0.86–1.46]	0.41
Grade	2 vs 1	23.60 [5.32–104.68]	<0.001		
Mitosis			0.001		0.008
	2–20 vs <2 [/HPF]	23.65 [1.86–300.50]	0.01	20.88 [1.61–270.19]	0.02
	>20 vs <2 [/HPF]	11.19 [1.58–79.31]	0.01	7.93 [0.90–69.87]	0.07
EUS depth			0.58		
	SM vs MM	3.85 [0.04–356.15]	1.00		
	PM vs SM	5.16 [0.03–813.78]	0.93		
CCI			0.59		
	1 vs 0	1.37 [0.25–7.66]	1.00		
	2 vs 0	1.99 [0.43–9.15]	0.62		

HR, hazard ratio; CI, confidence interval; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; HPF, high-power field; EUS, endoscopic ultrasonography; SM, submucosal; MM, muscularis mucosae; PM, muscularis propria; CCI, Charlson Comorbidity Index.

CI, 3.51 to 104.22; $p < 0.001$) (Supplementary Table 2) and mitotic count 2–20 and $>20/10$ HPF (HR, 20.88; 95% CI, 1.61 to 270.19; $p = 0.02$; HR, 7.93; 95% CI, 0.90 to 69.87; $p = 0.07$) (Table 3) remained independently associated with recurrence.

5. Supplementary analysis: exclusion of missing values

In a supplementary analysis excluding cases with missing data, grade 2 and mitotic count remained consistent predictors of recurrence (Supplementary Table 3). Compared to grade 1, grade 2 was associated with a HR of 19.12 ($p < 0.001$). A mitotic count of 2–20/10 HPF and $>20/10$ HPF was associated with HRs of 20.8 ($p = 0.007$) and 7.92 ($p = 0.032$), respectively.

DISCUSSION

This multicenter retrospective cohort study evaluated the long-term outcomes of patients with rectal NETs who achieved histologically complete resection without high-risk features for metastasis. Among 860 patients included in the final analysis, the recurrence rate was low (1.4%), and both histologic grade 2 and mitotic count ≥ 2 per 10 HPF were identified as significant risk factors for recurrence. In contrast, pathologic tumor size, resection method (EMR vs ESD), endoscopic ultrasonography-assessed invasion depth, and CCI were not significantly associated with recurrence.

According to current guidelines, including those from the European Neuroendocrine Tumor Society and the Na-

tional Comprehensive Cancer Network, rectal NETs ≤ 1 cm without adverse histologic features may not require routine surveillance after complete endoscopic resection.^{15,19} However, unlike many previous studies that included heterogeneous populations with incomplete resections or shorter follow-up, our study focused exclusively on histologically completely resected cases with extended follow-up up to 9 years. This allowed us to identify high-risk subsets even after so-called “curative” resection, underscoring the need to reconsider existing surveillance strategies.

These findings also challenge the current paradigm that relies predominantly on tumor size as the primary determinant of surveillance strategy. While tumor size has been widely used to stratify risk, our study shows that histologic factors, specifically mitotic count and tumor grade offer superior prognostic value. This underscores the need for a histology-based, risk-adapted surveillance framework that can more accurately identify patients at risk of late recurrence. Such a shift in surveillance planning may be especially relevant in East Asian clinical settings where long-term endoscopic follow-up is feasible and widely accessible.

The Kaplan-Meier analysis revealed significantly lower RFS in patients with grade 2 tumors and those with higher mitotic counts. The 5-year RFS was 98.4%, and the 9-year RFS decreased to 84.7%, indicating late recurrences beyond 6 years in certain cases. This extended follow-up period, supported by our multicenter data, underscores the importance of prolonged surveillance, especially in patients with high-risk histologic features. According to the raw data analysis, the median time to recurrence was 1.3 years, with a range up to 6.9 years, emphasizing the hetero-

geneous timing of recurrence events.

Interestingly, neither pathologic tumor size nor resection method was significantly associated with recurrence. These findings may reflect the relatively homogeneous nature of the study population, which primarily consisted of small lesions, and are consistent with prior studies suggesting that histologic characteristics rather than technical factors are more predictive of long-term outcomes.^{9,20,21} Similarly, CCI was not associated with recurrence risk; most patients with recurrence had low CCI scores, as presented in Supplementary Table 1.

A supplementary analysis excluding cases with missing data confirmed the consistency of our primary findings. Grade 2 and mitotic count $\geq 2/10$ HPF remained independently associated with recurrence, with HRs of 19.13, 23.6, and 11.1 for grade 2, mitotic count 2–20, and >20 , respectively. These results reinforce the role of mitotic count as a key histopathologic determinant of prognosis in rectal NETs and support its use in individualized follow-up planning.

These findings are partly consistent with those reported by Chung *et al.* in 2020,²² who observed no extracolonic metastasis after complete endoscopic resection of small rectal NETs. However, they identified metachronous rectal NETs in 2.7% of patients during follow-up, with a significantly higher risk in those presenting with synchronous lesions at initial diagnosis (HR, 1.75; $p < 0.001$). Unlike our study, however, their work primarily emphasized endoscopic surveillance and did not advocate routine systemic imaging. In contrast, our study identified cases of liver metastasis developing during follow-up in patients with grade 2 tumors and high mitotic counts, underscoring the need for long-term imaging-based surveillance in histologically high-risk patients.

This study has several limitations. First, its retrospective design may have introduced selection and surveillance bias, as the timing and modality of follow-up assessments were not standardized across institutions. In addition, some pathology reports lacked mitotic count data, resulting in missing values that reflect an inherent limitation of retrospective studies. Second, the number of patients with grade 2 tumors or high mitotic counts was relatively small, which may have affected statistical power. Although multivariable analysis identified both mitotic count 2–20 and $>20/10$ HPF as independent predictors of recurrence, the Kaplan-Meier curve (Fig. 3) appears to show lower RFS in the 2–20 group compared to the >20 group. This discrepancy may be attributed to the small number of patients with mitotic count >20 , which limits the statistical power and may obscure the true prognostic gradient. Additionally, the wide CIs observed for some HRs (e.g., HR 19.13;

95% CI, 3.51 to 104.22) indicate a degree of statistical uncertainty that warrants cautious interpretation. Notably, two patients diagnosed in 2016 and 2018 exhibited mitotic counts exceeding 20 per 2 mm². While these tumors were classified as grade 2 under the World Health Organization 2010 criteria used in routine pathology practice at the time, they would be reclassified as grade 3 according to the current World Health Organization 2019 classification.²³ This represents a limitation of our study arising from its retrospective nature. However, at initial staging, neither patient showed evidence of distant metastasis, supporting the clinical decision for surveillance following endoscopic resection. The subsequent development of liver metastases during follow-up underscores the aggressive potential of tumors with high mitotic activity, even when initially staged as non-metastatic, and highlights the critical importance of precise histopathologic grading and long-term surveillance. Third, recurrence was often determined by radiologic findings without histologic confirmation in all cases, potentially affecting outcome classification.

Despite these limitations, this study provides robust evidence from a large, multicenter cohort regarding the long-term prognosis of completely resected rectal NETs. The findings are particularly relevant in clinical settings with broad access to endoscopy and imaging, such as Korea, and may inform future surveillance strategies. The identified risk factors remained statistically significant in all analyses, regardless of the inclusion or exclusion of cases with missing data.

Given the biological characteristics of rectal NETs,²⁴ affected patients are not confined to the elderly, and the potential risks of radiation exposure from computed tomography, particularly in younger individuals and women of reproductive age, must be carefully considered in surveillance planning.²⁵ As the underlying pathogenesis remains unclear, further genetic investigations may help elucidate potential etiologic factors and support the development of tailored management strategies.²⁶

Although grade 2 tumors were statistically associated with a higher risk of recurrence, our study also identified cases of metachronous lesions in patients with grade 1 tumors. Given that all lymph node and liver metastases occurred exclusively in grade 2 tumors with higher mitotic counts, these findings suggest that while tumor grade remains a critical factor, decisions regarding surveillance should also consider the possibility of metachronous lesions even in grade 1 tumors. Furthermore, a prior Korean case reporting delayed metastatic lymph node development following complete resection of a grade 1 tumor underscores the need for cautious long-term follow-up.^{24,27,28} Consequently, uniform cessation of surveillance in grade 1

cases may be premature. Instead, a risk-adapted and individualized approach to surveillance distinct from Western protocols should be considered for East Asian populations. Furthermore, even in patients classified as low risk (grade 1 with low mitotic activity), our findings underscore the importance of maintaining long-term follow-up given the observed instances of recurrence.

In conclusion, although the overall recurrence risk following complete resection of rectal NETs ≤ 1 cm is low, patients with grade 2 tumors or mitotic count $\geq 2/10$ HPF are at increased risk for recurrence. Given that occasional recurrences were observed even in grade 1 tumors, long-term follow-up may still be advisable in these patients. Risk-adapted surveillance strategies based on histologic factors should be considered in clinical practice.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.E.K. Data acquisition: E.R.K., E.S.J., M.J.K., S.J.K., B.K., J.S.S., J.H.K., H.S.L. Data analysis and interpretation: E.R.K., M.J.K. Drafting of the manuscript: J.E.K. Critical revision of the manuscript for important intellectual content: E.R.K., E.S.J., M.J.K., S.J.K., B.K., J.S.S., J.H.K., H.S.L., J.H.K. Statistical analysis: M.J.K. Administrative, technical, or material support; study supervision: J.E.K., J.H.K. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at <https://doi.org/10.5009/gnl250285>.

DATA AVAILABILITY STATEMENT

Data analyzed in this study are available from the corresponding author upon reasonable request.

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