



Research article

Long-term outcomes of 1–2 cm rectal neuroendocrine tumors after local excision or radical resection: A population-based multicenter study

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ABSTRACT

Objectives: Studies on rectal neuroendocrine tumors (R-NETs) that are 1–2 cm in size are limited, and the optimal treatment for these tumors is not well established.

Methods: Data from patients with primary localized R-NETs 1–2 cm in size were retrospectively collected from 17 large-scale referral medical centers in China. Long-term prognosis, quality of life (QOL), and fecal incontinence were evaluated, and the effects of local excision (LE) or radical resection (RR) were elucidated using propensity score matching (PSM).

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Results: A total of 272 patients were included in this study; 233 underwent LE, and the remaining 39 underwent RR. Patients in the LE group showed lower tumor location, fewer postoperative Clavien–Dindo III–V complications, more G1 tumors, and lower tumor stage. There were no significant differences in the relapse-free survival or overall survival (OS) between the LE and RR groups after PSM. Patients in the LE group reported superior physical, role, emotional, social, and cognitive functions, global QOL, and Wexner fecal incontinence scores compared with those in the RR group (all $P < 0.050$). Eighteen (6.6%) patients had lymph node metastases. Multivariable analysis revealed that tumor location (odds ratio [OR] = 3.19, 95% confidence interval [CI] 1.04–10.07, $P = 0.010$), neutrophil-to-lymphocyte ratio (NLR) > 1.80 (OR = 4.50, 1.46–15.89, $P = 0.012$), and T3–T4 (OR = 36.31, 95% CI 7.85–208.62, $P < 0.001$) were independent risk factor for lymph node metastasis.

Conclusions: R-NETs measuring 1–2 cm generally have a favorable prognosis, and there is no difference in postoperative survival between LE and RR. For patients without lymph node metastasis, LE should be the preferred choice; however, for patients with a higher tumor location, preoperative NLR > 1.8 or T3/T4 tumors, RR should be considered.

Abbreviations

AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
CI	confidence interval
EORTC	The European Organisation for Research and Treatment of Cancer
LE	local excision
NETs	neuroendocrine tumors
NLR	neutrophil-to-lymphocyte ratio
OR	odds ratio
OS	overall survival
PLR	platelet-to-lymphocyte ratio
PSM	propensity score matching
QOL	quality of life
RFS	relapse free survival
R-NETs	rectal neuroendocrine tumors
ROC	receiver operating characteristic
RR	radical resection
SD	standard deviation

1. Introduction

Neuroendocrine tumors (NETs) derived from sensory and secretory neuroendocrine cells are the most common endocrine tumors of the gastrointestinal tract [1,2]. The rectum is the most common site for gastrointestinal NETs with an incidence of approximately 0.31–1.22 cases per 100,000 population [3,4]. Currently, complete resection is the primary treatment for rectal NETs (R-NETs) without distant metastases. Guidelines from the European Neuroendocrine Tumor Society recommend local excision (LE) with a transanal or endoscopic approach for R-NETS < 1 cm, and radical resection (RR) for rectal tumors > 2 cm [5].

For intermediate-sized tumors between 1 and 2 cm, an additional evaluation that assesses the lymph node status and depth of invasion is recommended to guide LE or RR, and the optimal surgical therapy is not well established. Currently, only a few studies have evaluated the outcomes of local versus radical surgical resection of R-NETS 1–2 cm in size [6–10]. Two studies from the National Cancer Database, one of which used propensity score matching (PSM), compared the prognosis of these two groups of R-NETS patients and found no significant differences in overall survival (OS) [9,10]. Therefore, LE has been suggested as a feasible and less morbid option for intermediate-sized R-NETS. However, the group of patients who should be considered for radical surgery is not well-defined. Moreover, the quality of life (QOL) and anal function of the patients in the two groups have not been studied.

Therefore, based on a multicenter large sample size cohort from China, we analyzed the prognosis of patients with R-NETS measuring 1–2 cm and the impact of surgery on the QOL. Our primary aim is to elucidate the prognostic features of intermediate-sized R-NETS and the secondary aim is to suggest a reasonable surgical treatment approach for these patients.

2. Materials and methods

2.1. Patient selection

The data of patients with R-NETs from 17 referral medical centers between January 1, 2010, and April 11, 2022, were collected retrospectively using standardized data collection forms. The inclusion criteria were as follows [1]: pathologically confirmed NETs [2], primary R-NETs, and [3] tumor resection. The exclusion criteria were as follows [1]: synchronous metastatic disease [2], synchronous or heterochronous malignant tumors, and [3] incomplete clinical data. A flowchart of the inclusion and exclusion of patients is shown in Fig. 1. This retrospective study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval no. 0433).

2.2. Clinicopathological data collection

Patient demographic data, including sex, age, and preoperative hematological indicators, were collected retrospectively using standardized forms, which were collected independently at each center and then aggregated. The complete blood cell count was measured within 7 days before the operation. The platelet-to-lymphocyte ratio (PLR) was defined as the ratio of platelets to lymphocytes. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. Other clinicopathological characteristics, such as tumor size, tumor location, surgical method, pathological grade, and TNM staging were also collected. The tumor size was determined via pathological evaluation. The lymph node status of the patients in the LE group was determined based on preoperative or postoperative endoscopic ultrasound or imaging examinations. According to the 2010 World Health Organization classification of digestive system tumors [11], R-NETs were graded as G1 or G2 based on the degree of differentiation and cell proliferation. The pathological TNM stage of R-NETs was re-evaluated according to the 8th Edition of TNM Classification issued by the American Joint Committee on Cancer (AJCC) [12]. Patients who underwent abdominoperineal resection, low anterior resection, or Hartmann operation were classified into the RR group [13–15], whereas patients who underwent transanal excision, transanal minimally invasive surgery, transanal endoscopic microsurgery, transsacral resection, transperineal resection, endoscopic mucosal resection, or endoscopic submucosal dissection were classified into the LE group [16,17]. Complications within 30 days after resection or excision were recorded and classified according to the Clavien–Dindo classification [18].

2.3. Follow-up and questionnaires

Follow-up was conducted independently at each medical center. Patients with R-NETs were followed-up every 3–6 months, and the last follow-up was in July 2022. Generally, endoscopy, magnetic resonance imaging, and/or computed tomography examinations were performed during follow-up. The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 [19] questionnaire and Wexner fecal incontinence scale [20] were administered in July 2022. The questionnaires were designed for use as an online version and the results collected online. The EORTC QLQ-C30 questionnaire is designed to assess various aspects of QOL and functioning. It consists of both multi-item and single-item measures, covering functional scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), and a global health and QOL scale. The Wexner fecal incontinence scale includes several factors such as the ability to control gas, liquid stool, and

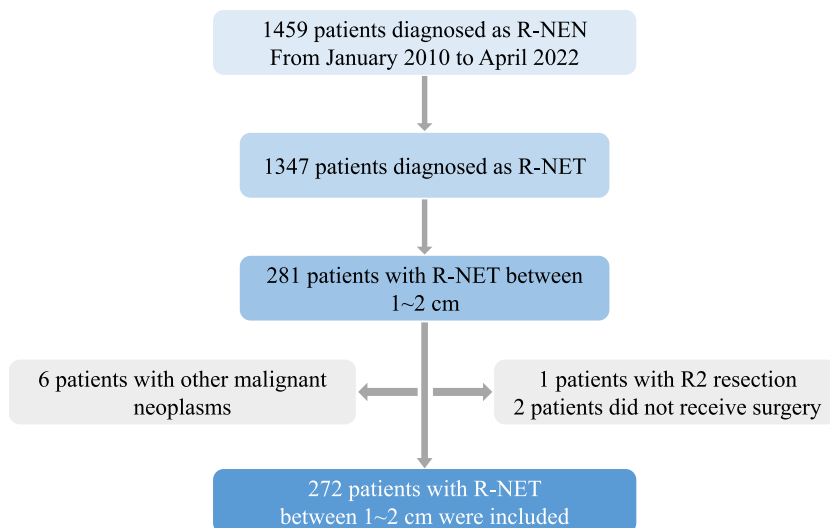


Fig. 1. Study scenario of the patients undergoing resection for R-NETs between 1 and 2 cm.

solid stool, and the overall impact on lifestyle. The questionnaire typically includes questions related to the frequency and type of incontinence episodes, use of protective measures (such as pads), and impact of incontinence on daily activities and QOL. Scores on the Wexner fecal incontinence scale range from 0 to 20 and are often divided into categories representing mild, moderate, and severe incontinence based on the total score. The primary endpoints of this study were relapse free survival (RFS) and OS. RFS was defined as the time from excision or resection to relapse in patients with recurrence or to death or last follow-up in patients with no recurrence. OS was defined as the time from surgery to all-cause mortality or last follow-up.

2.4. Statistical analysis

All statistical analyses were performed using SPSS 25.0 version (IBM, Armonk, NY, USA). Normally distributed continuous variables are presented as the mean \pm standard deviation (SD) and compared using the Student's *t*-test. Non-normally distributed continuous variables are represented by a median with an interquartile range and compared using the Mann–Whitney *U* test. The optimal cutoff values for PLR, NLR, and alkaline phosphatase (ALP) were determined using the receiver operating characteristic (ROC) curve method. To reduce the baseline difference between the LE and RR groups and increase comparability, nearest-neighbor PSM analysis was conducted using R 4.0.0. The matching ratio was 2:1 and the caliper value was set to 0.02. The 'nearest' method was chosen in the PSM analysis. The Kaplan–Meier method and log-rank test were used to calculate the cumulative survival rate and perform univariate survival analysis. The Cox proportional hazards regression model was used for the multivariate survival analysis. A logistic regression model was used to analyze risk factors for lymph node metastasis. A two-tailed *P* value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical and pathological characters of the whole group

Based on the inclusion and exclusion criteria, 272 patients with primary R-NETs measuring 1–2 cm were identified. As shown in Table 1, there were 119 women (43.8%) and 153 men (56.2%). The median patient age was 54 years (range: 26–79 years). None of the patients had clinical symptoms related to hormone levels. The mean tumor size was 1.6 ± 0.3 cm (mean \pm SD) and the distance

Table 1
Demographic characteristics of all the patients included in this study.

	[ALL] N = 272	Local excision N = 233	Radical resection N = 39	<i>P</i>
Gender ^a				0.022
Female	119 (43.8%)	109 (46.8%)	10 (25.6%)	
Male	153 (56.2%)	124 (53.2%)	29 (74.4%)	
Age (year) ^b	52.8 (12.6)	52.4 (12.4)	55.1 (13.4)	0.244
Distance from the anus (cm) ^b	6.2 (2.6)	6.0 (2.4)	7.6 (3.2)	0.004
Clavin-Dindo III-IV complications ^c				0.020
No	270 (99.3%)	233 (100.0%)	37 (94.9%)	
Yes	2 (0.7%)	0 (0.0%)	2 (5.1%)	
Size (cm) ^b	1.6 (0.3)	1.6 (0.3)	1.7 (0.3)	0.213
Pathological grade ^a				<0.001
G1	222 (81.6%)	204 (87.6%)	18 (46.2%)	
G2	50 (18.4%)	29 (12.4%)	21 (53.8%)	
T stage ^c				<0.001
T1	247 (90.8%)	225 (96.6%)	22 (56.4%)	
T2	16 (5.9%)	8 (3.4%)	8 (20.5%)	
T3	8 (2.9%)	0 (0.0%)	8 (20.5%)	
T4	1 (0.4%)	0 (0.0%)	1 (2.6%)	
Lymph node metastasis ^c				–
No	254 (93.4%)	233 (100%)	21 (53.8%)	
Yes	18 (6.6%)	0	18 (46.2%)	
TNM stage ^c				<0.001
I	241 (88.6%)	225 (96.6%)	16 (41.0%)	
II	12 (4.4%)	8 (3.4%)	4 (10.3%)	
III	19 (7.0%)	0 (0.0%)	19 (48.7%)	
Neurovascular invasion ^c				0.001
No	258 (94.9%)	226 (97.0%)	32 (82.1%)	
Yes	14 (5.1%)	7 (3.0%)	7 (17.9%)	
Adjuvant therapy ^c				<0.001
No	261 (96.0%)	230 (98.7%)	31 (79.5%)	
Yes	11 (4.0%)	3 (1.3%)	8 (20.5%)	

^a Data are expressed in the form of number (percentage) and are test using a chi-square test.

^b Data are shown as mean (standard deviation) and test with student's *t*-test.

^c Data are shown as number (percentage) and test with Fisher exact probability test.

between the inferior margin of the tumor and anal verge was 6.2 ± 0.3 cm. In total, 233 patients underwent LE, of whom 124 underwent endoscopic resection and 109 underwent surgical LE. The remaining 39 patients underwent RR, 10 of whom underwent RR after endoscopic resection. No peri-operative deaths occurred.

Regarding pathological grade, 222 cases (81.6%) were classified as G1 and 50 cases (18.4%) were classified as G2. According to the AJCC staging, 247 cases (90.8%) had T1, 16 (5.9%) had T2, 8 (2.9%) had T3, and 1 (0.4%) had T4. Eighteen (6.6%) patients had lymph node metastases. Seven patients each in the LE and RR groups had lymphatic or vascular invasion. Eleven patients (4.0%) received adjuvant treatment after surgery, of whom four were treated with somatostatin analogs, five with etoposide plus cisplatin chemotherapy, one with oxaliplatin plus capecitabine, and one with capecitabine plus temozolomide.

As shown in Table 1, the LE group showed a greater number of female patients (46.8% vs. 25.6%, $P = 0.022$), higher tumor location (7.6 ± 3.2 vs. 6.0 ± 2.4 cm, $P = 0.004$) and fewer Clavien–Dindo III–V postoperative complications (0 vs. 5.1%, $P = 0.020$). In addition, patients in the LE group mainly had G1 (87.6% vs. 46.2%, $P < 0.001$) and T1 (96.6% vs. 56.4%, $P < 0.001$) tumors. Lymphatic or vascular invasion (3.0% vs. 17.9%, $P = 0.001$) was less common, and the proportion of patients receiving adjuvant therapy (1.3% vs. 20.5%, $P < 0.001$) was also lower.

3.2. Oncologic outcomes

In total, 245 patients (90.1%) were followed up, with a median follow-up time of 36 (range 2–123) months. During follow-up, nine patients experienced recurrence, of which five were in the LE group and four were in the RR group. The pattern of recurrence was distant metastasis in seven patients (77.8%) and local recurrence in two patients (22.2%). The sites of distant metastases were the liver in six patients (85.7%) and the bone in one patient (14.3%). Ten patients had died at the final follow-up: eight (80.0%) due to recurrence and two (20.0%) due to other causes. The 1-, 3-, and 5-year RFS rates of the entire patient group were 98.0%, 96.1%, and 94.0%, respectively, while the OS rates were 99.1%, 95.3%, and 93.5%, respectively. For the LE group, the 1- and 3-year RFS rates of the entire patient group were 98.7% and 97.1%, respectively, while the OS rates were 99.5% and 98.8%, respectively. For the RR group, the 1- and 3-year RFS rates of the entire patient group were 91.2% and 72.9%, respectively, while the OS rates were 93.7% and 70.3%, respectively. In the Kaplan–Meier analysis, patients in the LE group showed superior RFS (Fig. 2A) than those in the RR group ($P = 0.049$), whereas there was no significant difference in OS ($P = 0.420$) (Fig. 2B).

To balance the baseline differences between the LE and RR groups and increase comparability, PSM analysis was conducted, and variables that significantly differed between the LE and RR groups or might influence patient survival, including sex, tumor location, pathological grade, T stage, lymph node metastasis, neurovascular invasion, postoperative complications, and adjuvant treatment were employed. After matching, 35 patients with local resection and 18 patients in the RR group were enrolled (Table 2). As shown in Fig. 3, no significant differences were observed in the RFS ($P = 0.840$, Fig. 3A) or OS ($P = 0.840$, Fig. 3B) between the LE and RR groups after matching.

3.3. Quality of life and fecal incontinence score

A total of 130 patients completed the EORTC QLQ-C30 and Wexner fecal incontinence score questionnaires, of whom 105 underwent LE and 25 were in the RR group. In the entire group, the median time from surgery to completion of the questionnaire was 32 months. Within 24 months after surgery, patients in the LE group show superior physical function (shown as mean \pm SD) (98.5 ± 4.3 vs. 84.1 ± 19.1 , $P < 0.001$), role function (98.4 ± 6.2 vs. 70.8 ± 34.2 , $P < 0.001$), emotional function (98.4 ± 5.0 vs. 85.4 ± 18.2 , $P < 0.001$), social function (94.8 ± 10.1 vs. 68.8 ± 36.1 , $P < 0.001$), cognitive function (97.2 ± 7.3 vs. 72.9 ± 34.4 , $P < 0.001$) and global QOL (93.7 ± 10.5 vs. 81.3 ± 18.2 , $P = 0.010$) than those in the RR group. After 24 months, the LE group still showed superior physical function (96.8 ± 8.4 vs. 78.8 ± 17.4 , $P < 0.001$), role function (97.6 ± 10.3 vs. 66.7 ± 36.3 , $P < 0.001$), emotional function (96.1 ± 8.8 vs. 82.8 ± 14.9 , $P < 0.001$), social function (96.0 ± 12.2 vs. 61.8 ± 32.1 , $P < 0.001$), cognitive function (93.9 ± 14.8 vs. $64.6 \pm$

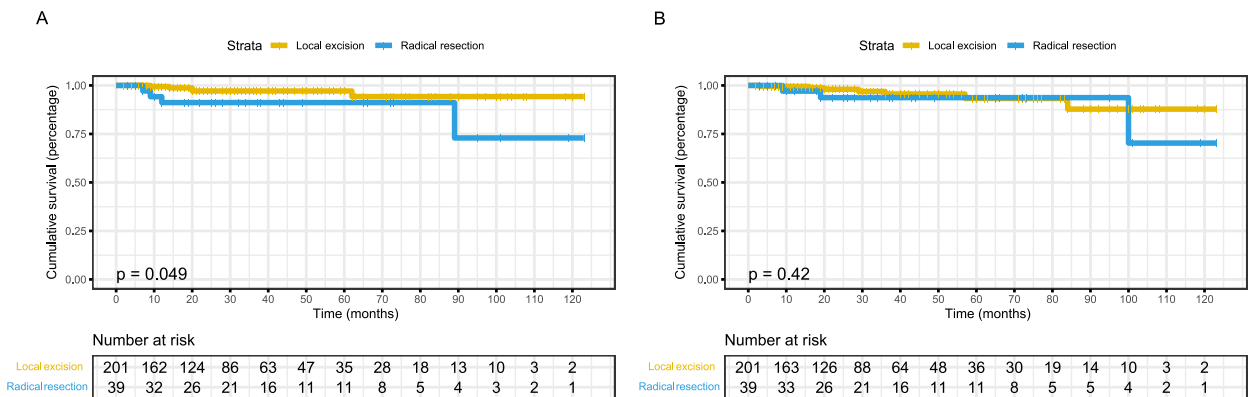


Fig. 2. Kaplan-Meier analyses of 1–2 cm R-NETs undergoing local excision or radical resection before PSM. A. Showing the result of relapse free survival (RFS). B. Showing the result of overall survival (OS).

Table 2
Demographic characteristics of patients after PSM.

	[ALL] N = 53	Local excision N = 35	Radical resection N = 18	P
Gender ^a				0.210
Female	21 (39.6%)	18 (51.4%)	6 (33.3%)	
Male	32 (60.4%)	17 (48.6%)	12 (66.7%)	
Age (year) ^b	56.0 (12.6)	56.6 (11.4)	54.8 (14.9)	0.668
Distance from the anus (cm) ^a				1
≤7	25 (47.2%)	17 (48.6%)	8 (44.4%)	
>7	28 (52.8%)	18 (51.4%)	10 (55.6%)	
Distance from the anus (cm) ^b	7.2 (2.8)	6.8 (2.5)	7.9 (3.2)	0.197
Clavin-dindo III-IV complications (No)	53 (100.0%)	35 (100.0%)	18 (100.0%)	.
Size (cm) ^b	1.6 (0.3)	1.6 (0.3)	1.6 (0.3)	0.647
Pathological grade ^a				1
G1	36 (67.9%)	24 (68.6%)	12 (66.7%)	
G2	17 (32.1%)	11 (31.4%)	6 (33.3%)	
T stage ^c				1
T1	46 (86.8%)	30 (85.7%)	16 (88.9%)	
T2	7 (13.2%)	5 (14.3%)	2 (11.1%)	
Lymph node metastasis (No)	53 (100.0%)	35 (100.0%)	18 (100.0%)	–
TNM stage ^c				1
I	46 (86.8%)	30 (85.7%)	16 (88.9%)	
II	7 (13.2%)	5 (14.3%)	2 (11.1%)	
Neurovascular invasion (No)	53 (100.0%)	35 (100.0%)	18 (100.0%)	–
Adjuvant therapy ^c				1
No	48 (90.6%)	32 (91.4%)	16 (88.9%)	
Yes	5 (9.4%)	3 (8.6%)	2 (11.1%)	

PSM: Propensity score matching.

^a Data are expressed in the form of number (percentage) and are test using a chi-square test.

^b Data are shown as mean (standard deviation) and test with student's *t*-test.

^c Data are shown as number (percentage) and test with Fisher exact probability test.

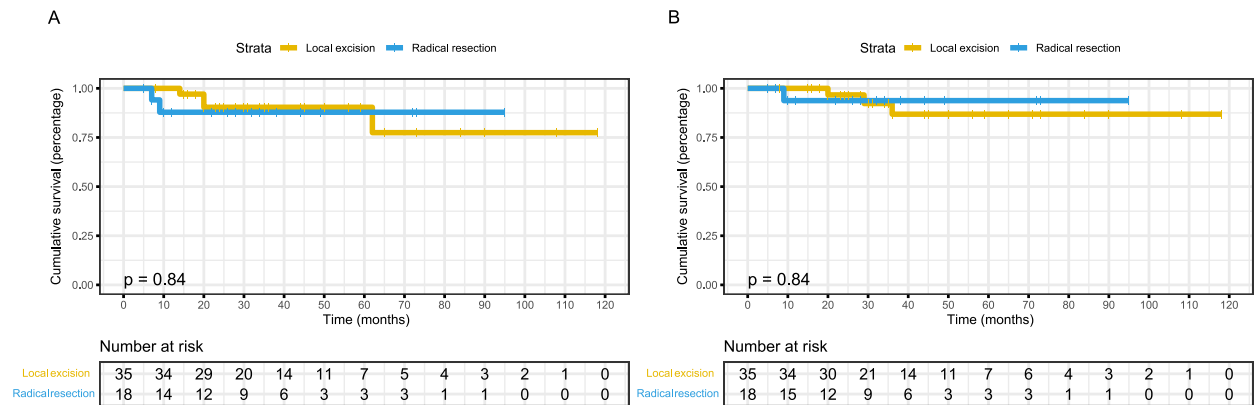


Fig. 3. Kaplan-Meier analyses of 1–2 cm R-NETs undergoing local excision or radical resection after propensity score matching. A. Showing the result of relapse free survival (RFS). B. Showing the result of overall survival (OS).

26.9, $P < 0.001$) and Global QOL (89.7 ± 16.8 vs. 66.2 ± 22.1 , $P < 0.001$). The Wexner incontinence score of the RR group was significantly higher than the LE group both within (≥ 2 points, 50.0% vs. 4.8%, $P = 0.004$) or after (≥ 2 points, 64.7% vs. 11.1%, $P < 0.001$) 24 months postoperatively (Table 3).

3.4. Risk factors for lymph node metastasis

To analyze the risk factors for lymph node metastasis of R-NETs 1–2 cm in size, several preoperative hematological factors were included. The mean values of PLR, NLR, and ALP in the entire cohort were 123 ± 69 , 2.01 ± 1.83 , and 75 ± 24 (mean \pm SD) respectively. According to the ROC analysis, the optimal cutoff values of PLR, NLR, and ALP for recurrence were 95, 1.80, and 78, respectively. Univariate analysis showed that tumor location, NLR, T stage, pathological grade, and neurovascular invasion were associated with an increased risk of lymph node metastasis. To better guide clinical treatment, only indicators available before surgery were included in the multivariate analysis, including tumor location, preoperative NLR, and T stage. Multivariable analysis (forward

Table 3
EORTC QLQ-C30 and Wexner fecal incontinence scale evaluation of 1~2 cm R-NETs patients with local excision or radical resection.

	Within 24 months post-surgery				After 24 months post-surgery		
	[ALL]	Local excision	Radical resection	P	Local excision	Radical resection	P
	N = 130	N = 42	N = 8		N = 63	N = 17	
Physical function ^a	94.3 (12.0)	98.5 (4.3)	84.1 (19.1)	<0.001	96.8 (8.4)	78.8 (17.4)	<0.001
Role function ^a	92.2 (20.8)	98.4 (6.2)	70.8 (34.2)	<0.001	97.6 (10.3)	66.7 (36.3)	<0.001
Emotional function ^a	94.5 (11.0)	98.4 (5.0)	85.4 (18.2)	<0.001	96.1 (8.8)	82.8 (14.9)	<0.001
Social function ^a	89.5 (21.5)	94.8 (10.1)	68.8 (36.1)	<0.001	96.0 (12.2)	61.8 (32.1)	<0.001
Cognitive function ^a	89.9 (20.1)	97.2 (7.3)	72.9 (34.4)	<0.001	93.9 (14.8)	64.7 (26.9)	<0.001
Global QOL ^a	87.4 (18.1)	93.7 (10.5)	81.3 (18.2)	0.010	89.7 (16.8)	66.2 (22.1)	<0.001
Wenex points ^b				0.004			<0.001
<2	106 (81.5%)	40 (95.2)	4 (50.0)		56 (88.9)	6 (35.3)	
≥2	24 (18.5%)	2 (4.8)	4 (50.0)		7 (11.1)	11 (64.7)	
Wenex points ^a	1.5 (3.6)	0.29 (1.274)	4.75 (6.112)	<0.001	0.9 (3.1)	5.4 (4.6)	<0.001

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Global QOL: global quality of life.

^a These data were test with Mann-Whitney *U* test.

^b Using Fisher exact probability test.

stepwise likelihood ratio method) showed that tumor location (odds ratio [OR] = 3.19, 95% confidence interval [CI] 1.04–10.07, *P* = 0.010), NLR >1.80 (OR = 4.50, 95% CI 1.46–15.89, *P* = 0.012), and T3–T4 (OR = 36.31, 95% CI 7.85–208.62, *P* < 0.001) were independent risk factors for lymph node metastasis (Table 4).

4. Discussion

R-NETs are a rare subset, composing only 1–2% of all rectal tumors [21,22]. Most R-NETs are small, with diameters <1 cm, whereas R-NETs between 1 and 2 cm are relatively rare. In this population-based analysis, we captured all diagnosed R-NETs documented in 17 medical centers in China over a 12-year period and sought to characterize the clinicopathologic features and correlate local management and outcomes. Consistent with previous studies, our study found that the majority of patients were male, and most of the R-NETs 1–2 cm in size were located in the lower rectum [23,24]. The pathological grade was mostly G1 and lymph node metastases were rare. R-NETs are less aggressive and have a more favorable prognosis. Our results demonstrated that the 5-year RFS and OS rates were 94.0% and 93.5%, respectively, comparable to previously reported rates of 88.0–91.5% in large-scale studies on NETs [3,25].

Curative resection is the primary treatment option for local or locoregional R-NETs. Few studies have assessed the impact of LE or RR on the short- and long-term outcomes of R-NETs measuring 1–2 cm. Adam et al. retrospectively analyzed 321 patients with 1–2 cm R-NETs in the National Cancer Database [9]. They reported a higher incidence of complications and longer postoperative hospital stay in the RR group, with no difference in OS between the LE and RR groups [9]. In this study, we found that the OS of the two groups was similar; however, the RFS of the RR group was slightly worse than that of the LE group. Considering the higher tumor grade and incidence of lymph node metastasis in the RR group, which may bias the results, PSM analysis was conducted to increase the comparability between the two groups of patients. PSM is a statistical method commonly used to reduce selection bias in observational studies. With the application of PSM, we can further balance the LE and RR groups and draw stronger conclusions about the influence of treatment. After PSM, we found no significant differences in the RFS or OS between the two groups.

RR is more traumatic because of the greater extent of resection and the possibility of intraoperative damage to muscle or nerve function. Therefore, we compared QOL and stool function between the two groups of patients. The EORTC QLQ-C30 scale is widely

Table 4
Univariate and multivariate analysis of the risk factors associated with lymph node metastasis in patients with R-NETs between 1 and 2 cm.

	Univariate ^a			Multivariate ^b		
	OR	95% CI	P	OR	95% CI	P
Age (>60)	1.49	0.56–3.99	0.430			
Size (>1.6 cm)	2.16	0.81–5.75	0.120			
Distance from the anus (>7.0 cm)	2.98	1.13–7.85	0.030	3.19	1.04–10.07	0.041
PLR (>95)	2.89	0.81–10.24	0.100			
NLR (>1.80)	3.77	1.37–10.39	0.010	4.50	1.46–15.89	0.012
ALP (>78)	1.14	0.43–2.97	0.800			
T stage (3–4)	41.83	9.32–187.87	<0.001	36.31	7.85–208.62	<0.001
Pathological grade (G2)	21.19	6.61–68	<0.001			
Neurovascular invasion	15.37	4.6–51.39	<0.001			

OR: odd ratio. CI: confidence interval. PLR: Platelet-to-Lymphocyte Ratio. NLR: Neutrophil-to-Lymphocyte Ratio. ALP: Alkaline Phosphatase.

^a Univariate analysis was performed with Log-Rank test.

^b Multivariate analysis was performed with Cox's proportional hazards regression model.

used to assess the QOL of patients with cancer [26,27]. To the best of our knowledge, this is the first study involving the QOL and anal function in patients with R-NETs measuring 1–2 cm. We found that patients in the LE group had higher physical, role, emotional, social, and cognitive function, and global QOL scores than those in the RR group, suggesting that patients in the LE group may have a better QOL. For anal function, we used the Wexner incontinence score, which has a score of 0 for no incontinence and 20 for complete incontinence [20]. In this study, we demonstrated that the patients in the RR group had significantly higher Wexner scores than those in the LE group. These results suggest that patients in the RR group may have a poorer QOL and anal function than those in the LE group. Therefore, LE is the preferred treatment choice for patients without lymph node metastases.

To better guide clinical treatment, we further analyzed the risk factors for lymph node metastasis in patients with R-NETs measuring 1–2 cm. For better clinical relevance, clinicopathological factors, including several preoperative hematological factors, were included. We found that tumors with a distance of >7 cm from the lower edge to the anus were prone to lymph node metastasis. This result may be related to different lymphatic drainage pathways above and below the peritoneal reflection. The NLR is an inflammatory marker that has been demonstrated to be closely related to the prognosis of many types of tumors [28,29]. A pooled analysis of the RADIANT-3 and RADIANT-4 studies revealed that NLR is a robust prognostic marker for NETs and could be used to identify patients who may benefit the most from targeted therapies [30]. In this study, we demonstrated that patients with $\text{NLR} > 1.8$ have a higher risk of lymph node metastasis. Therefore, patients with a high NLR should be aware of the risk of lymph node metastasis and relevant examinations should be refined. In addition, we found that T3/T4 tumors were independent risk factors for lymph node metastasis, which is consistent with the results of previous studies. These results can assist in patient risk stratification and guide clinical decision-making. Considering that the LE and RR groups showed no significant difference in prognosis but the LE group had superior QOL and anal function, LE should be preferred for patients with R-NETs 1–2 cm in size. However, for patients with a higher tumor location, $\text{NLR} > 1.8$, or T3/4 tumors, more examinations are needed, and RR should be considered.

This study has some limitations. First, this was a retrospective study with an unavoidable selection bias, which may have weakened the conclusion; therefore, the conclusion of the study needs to be validated by prospective clinical trials. Second, the analysis of QOL and anal function in this study was a cross-sectional survey that did not include the preoperative baseline situation or continuity analysis of postoperative time. Therefore, to better understand the impact of surgical methods on patients' QOL and anal function, longitudinal long-term follow-ups at different time points after surgery are required. Third, the lymph node status in the LE group was determined by endoscopic ultrasound or imaging examination, which do not have 100% sensitivity. In addition, the inherent limitations of statistical methods, including the Kaplan–Meier method, log-rank test, and Cox regression model, may also weaken the conclusions. Nevertheless, as this was a multicenter study with a large sample size, the results are valuable and can provide a reference for the management of R-NETs measuring between 1 and 2 cm.

5. Conclusion

R-NETs that are 1–2 cm in size are generally indolent and have a favorable prognosis. There was no significant difference in the long-term prognosis between the LE and RR groups, but the QOL and fecal incontinence in the LE group were better than those in the RR group. Therefore, for patients with R-NETs 1–2 cm in size without metastasis, LE should be the preferred choice. For patients with tumors located above the peritoneal reflection, patients with preoperative $\text{NLR} > 1.8$, or T3/T4 tumors, the risk of lymph node metastasis should be taken into account, and RR should be considered.

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Ethical approval

Our study was conducted in accordance with the guidelines set forth by the Declaration of Helsinki and was approved by the Institutional Review Board of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval no. 0433). Given the retrospective study design and analysis of clinical data, the requirement for written consent was formally waived by the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology Ethics Committee.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Chengguo Li: Investigation, Formal analysis, Data curation. **Minhao Yu:** Investigation, Formal analysis, Data curation. **Weizhen Liu:** Supervision, Software, Conceptualization. **Wei Zhang:** Software, Resources, Data curation. **Weizhong Jiang:** Visualization, Validation, Supervision, Data curation. **Peng Zhang:** Funding acquisition, Data curation, Conceptualization. **Xinyu Zeng:** Software, Methodology. **Maojun Di:** Data curation. **Xiaofeng Liao:** Data curation. **Yongbin Zheng:** Methodology, Data curation. **Zhiguo Xiong:** Methodology, Investigation, Data curation. **Lijian Xia:** Validation, Resources, Data curation. **Yueming Sun:** Validation, Supervision.

Rui Zhang: Software, Resources. **Ming Zhong:** Validation, Resources. **Guole Lin:** Writing – original draft, Visualization, Supervision. **Rong Lin:** Writing – review & editing, Writing – original draft, Conceptualization. **Kaixiong Tao:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e28335>.

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