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Laparoscopic versus open surgery for rectal neuroendocrine tumors: a multicenter real-world study

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Abstract

Background Owing to the lack of evidence-based medical studies with large sample sizes, the surgical approach for the radical resection of rectal neuroendocrine tumors remains controversial.

Methods We retrospectively collected the medical records of patients with rectal neuroendocrine tumors who underwent radical resection at 17 large tertiary care hospitals in China between January 1, 2010, and April 30, 2022. All patients were divided into laparoscopic and open surgery groups. After propensity score matching to reduce confounders, the postoperative and oncologic outcomes were compared between the groups.

Results We enrolled 174 patients with rectal neuroendocrine tumors who underwent radical surgery. After random matching, 124 patients were included in the comparison (62, laparoscopic surgery group; 62, open surgery group). The laparoscopic surgery group had fewer complications (14.5% vs. 35.5%, $P = 0.007$) and superior relapse-free survival ($P = 0.048$). Subgroup analysis revealed that the laparoscopic surgery group had fewer complications (10.9% vs. 34.7%, $P = 0.004$), shorter postoperative hospital stays (9.56 ± 5.21 days vs. 12.31 ± 8.61 days, $P = 0.049$) and superior relapse-free survival ($P = 0.025$) in the rectal neuroendocrine tumors ≤ 4 cm subgroup.

Conclusions Laparoscopic surgery was associated with improved postoperative outcomes and oncologic prognosis for patients with rectal neuroendocrine tumors ≤ 4 cm; it can serve as a safe and feasible option for radical surgery of rectal neuroendocrine tumors.

Keywords Neuroendocrine tumors, Laparoscopic surgery, Open surgery, Prognosis, Rectum

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Background

Neuroendocrine neoplasms (NENs) are rare neoplasms that arise from embryonic neuroendocrine cells and are characterized by the presence of neuroendocrine markers. These neoplasms can occur in various organs throughout the body, with the rectum being a common site of incidence (1.04 per 100,000 people) [1, 2]. Based on the Ki-67 index and mitotic count, rectal NENs (RNENs) can be stratified into rectal neuroendocrine tumors (RNETs), rectal neuroendocrine carcinoma (RNEC), and rectal mixed neuroendocrine and non-neuroendocrine neoplasms (RMiNENs), which exhibit substantial heterogeneity. Tumor grade is a major predictor of metastasis and prognosis in RNENs [3, 4].

Currently, the National Comprehensive Cancer Network (NCCN), European Neuroendocrine Tumor Society (ENETS), and Chinese Society of Clinical Oncology (CSCO) guidelines recommend radical resection for RNETs with risk factors (e.g., tumor size > 2 cm, T stage > T1, and lymph node metastasis), RNEC, and RMiNEN [5–7]. Laparoscopic techniques have been widely used in the treatment of RNETs [8, 9]. However, the outcomes of laparoscopic surgery for RNETs have been scarcely described owing to their rarity and the even rarer indications for radical surgery. Additionally, laparoscopic surgery lacks tactile sensation and poses the risk of tumor rupture and iatrogenic dissemination. However, comparisons with open surgery are lacking; thus, the surgical options for RNETs remain to be determined.

In this study, we collected diagnostic and treatment data from 17 large tertiary care hospitals in China over a 13-year period to evaluate the efficacy of laparoscopic and open surgery through a subgroup analysis of tumor size.

Materials and methods

Patients and data collection

This study retrospectively reviewed the data of patients diagnosed with RNETs at 17 large-scale medical centers in China between January 1, 2010, and April 30, 2022. Demographic, clinicopathological, treatment, and outcome data were extracted from the electronic medical records of each hospital by surveyors with expertise in NENs using standardized data collection templates. The inclusion criteria were as follows: (1) confirmation of neuroendocrine tumors by pathology; (2) primary rectal neuroendocrine tumors; (3) surgical treatment. The exclusion criteria were as follows: (1) comorbidities with other malignancies; (2) incomplete clinical data or follow-up information; (3) distant metastasis; (4) local resection. In total, 174 of 1,459 patients were enrolled in the study. The procedure used to identify eligible study participants is shown in Fig. 1.

Criteria

Tumor size was determined based on the longest tumor diameter, as recorded in the pathological reports. Tumor site was divided into low (≤7 cm), median (7–12 cm), and

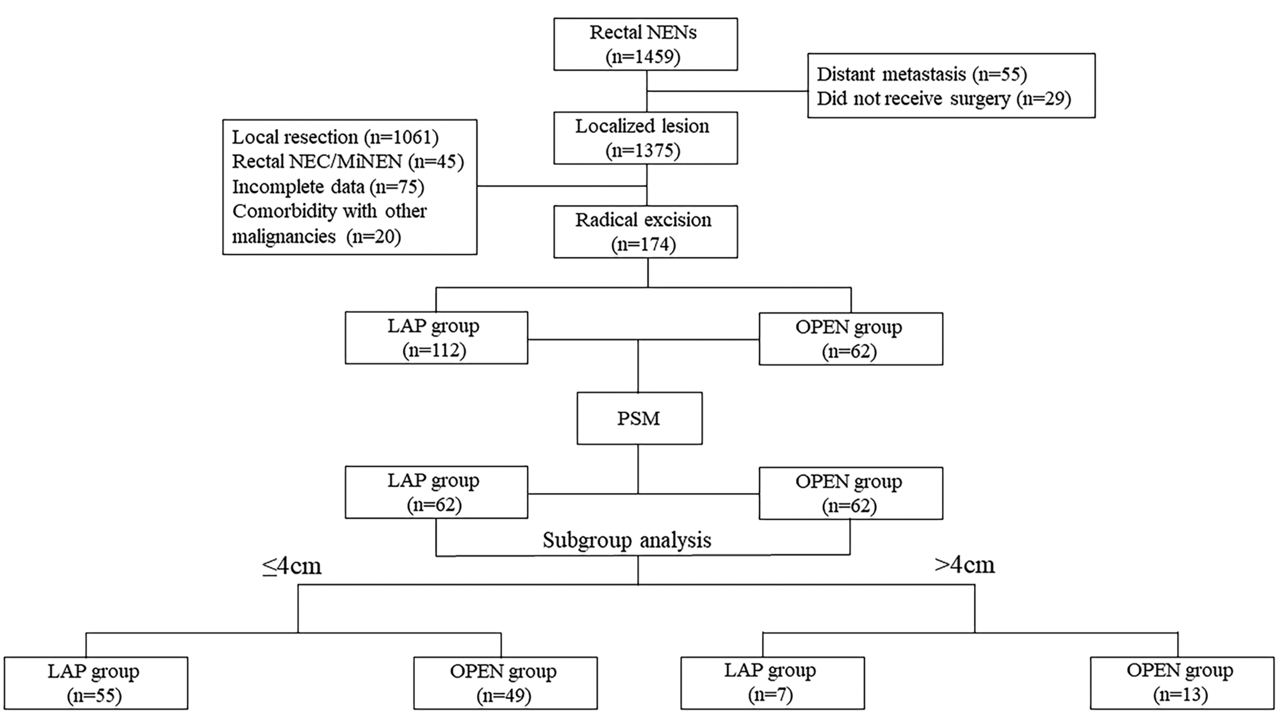

Fig. 1 Patient selection flowchart

high RNETs (12–15 cm), according to the distance from the lower edge of the tumor to the anal verge. Tumor stage was classified according to the American Joint Committee on Cancer (AJCC) cancer staging manual, whereas tumor grade was classified based on the WHO 2019 classification. The mitotic count was expressed as the number of mitotic cells in ten high-power fields from hematoxylin and eosin-stained slides examined under a microscope. The Ki-67 index was calculated as the percentage of cells labeled using immunohistochemistry. Complications within 30 days after surgery were recorded and graded according to the Clavien-Dindo classification. Patients with tumor size > 2 cm, T stage > T1, tumor grade G3, lymph node metastasis, or neurovascular invasion were recommended to undergo radical resection. Patients with T stage ≥ T2, lymph node metastasis, neurovascular invasion, or tumor size > 2 cm were considered to have a high risk for recurrence; a multidisciplinary team was involved in formulating adjuvant therapy plans for these patients. Somatostatin analog therapy was recommended for somatostatin receptor-positive patients.

Follow-up

Relapse-free survival (RFS) was calculated from the date of intervention to that of recurrence. Follow-up was conducted via telephone and out- or inpatient means. Patients who underwent complete resection were followed up every 6 months for the first 5 years and annually thereafter. The final follow-up was conducted in July 2022. Follow-up examinations included routine blood tests, chromogranin A tests, chest computed tomography (CT), and whole-abdominal and pelvic contrast-enhanced CT or magnetic resonance imaging (MRI). Positron-emission tomography (PET)-CT was performed if recurrence or metastasis was suspected. Loss to follow-up was defined as failure to contact patients or their family members.

Statistical analysis

Normally distributed quantitative data were presented as means ± standard deviations and were compared using the independent-sample t test; non-normally distributed quantitative data were presented as medians with interquartile ranges and were compared using the Mann−Whitney U test. Categorical data were expressed as numbers and percentages, and were analyzed using either the chi-square test or Fisher's exact test. RFS was analyzed using the Kaplan-Meier method, wherein variables were compared using the log-rank test in univariate analysis and Cox proportional hazard regression in multivariable analysis. Propensity score matching was employed to minimize the influence of confounding factors; propensity score matching (PSM) was employed [10]. The propensity score was calculated according to the preoperative data available regarding sex, age, tumor size, tumor site, and neoadjuvant therapy. The nearest neighbor matching algorithm was used to match patients based on the logic of the propensity score. A standard deviation < 10% was considered acceptable for assessing the matching covariate balance [11]; the distribution of propensity scores in both matched and unmatched groups was assessed using dot plots (Supplemental Fig. 1).

Statistical analyses were performed using R software (version 4.0.0). The optimal cut-off value for continuous variables was determined using the X-tile software. Variables with $P < 0.10$ in the univariate analysis were included in the multivariate analysis. $P < 0.05$ was considered statistically significant.

Results

Demographic data and clinicopathological characteristics

This study included 174 patients who underwent radical surgery for localized RNETs. Among them, 112 (64.4%) were males and 62 (35.6%) were females. The median patient age was 56 years (range: 26–83 years). The median tumor size was 2.0 cm, ranging from 0.1 to 7.5 cm. The tumor grade was categorized as G1 in 95 (54.6%) patients, G2 in 52 (29.9%), and G3 in 27 (15.5%). According to the TNM staging, 52 (29.9%) patients were classified as T1, 50 (28.7%) as T2, 56 (32.2%) as T3, and 16 (9.2%) as T4. Lymph node metastasis was clinically positive in 88 (50.6%) patients based on histopathology results. Sixty (34.5%) patients received adjuvant therapy. The demographic and clinicopathological characteristics of the patients are summarized in Table 1.

Before PSM, 112 (64.4%) patients underwent laparoscopic surgery, while 62 (35.6%) underwent open surgery. No significant differences were observed between the groups in terms of sex ($P = 0.976$), age ($P = 0.976$), tumor site ($P = 0.144$), neoadjuvant therapy ($P = 0.139$), or adjuvant therapy ($P = 0.383$); however, the tumor size in the laparoscopic surgery (LAP) group was significantly lower than that in the open surgery (OPEN) group ($P = 0.041$). No significant differences were observed after matching. The clinicopathological characteristics of the two groups before and after matching are shown in Table 1.

Surgical outcomes

The operation time and postoperative hospital stay were comparable between the LAP and OPEN groups (Before PSM: 176.63 ± 56.56 min vs. 172.08 ± 86.52 min, $P = 0.676$; 10.41 ± 5.56 days vs. 12.32 ± 7.78 days, $P = 0.062$. After PSM: 174.45 ± 60.82 min vs. 172.08 ± 86.52 min, $P = 0.860$; 10.11 ± 5.55 days vs. 12.32 ± 7.78 days, $P = 0.071$). Moreover, the proportion of patients in the LAP group who underwent stoma creation and total mesorectal

Table 1 Comparison of demographic and clinicopathological characteristics before and after propensity score matching

Clinicopathological characteristics	Overall population (*n* = 174)	Before PSM[d]			After PSM		
		LAP[e] group (*n* = 112)	OPEN[f] group (*n* = 62)	*P* value	LAP group (*n* = 62)	OPEN group (*n* = 62)	*P* value
Baseline characteristics							
Gender, n (%)				0.976			0.704
Female	62 (35.6%)	40 (35.7%)	22 (35.5%)		20 (32.3%)	22 (35.5%)	
Male	112 (64.4%)	72 (64.3%)	40 (64.5%)		42 (67.7%)	40 (64.5%)	
Age, n (%), year				0.976			0.579
≤60	112 (64.4%)	72 (64.3%)	40 (64.5%)		37 (59.7%)	40 (64.5%)	
>60	62 (35.6%)	40 (35.7%)	22 (35.5%)		25 (40.3%)	22 (35.5%)	
Tumor size, n (%), cm				**0.041**			0.143
≤4	150 (86.2%)	101 (90.2%)	49 (79.0%)		55 (88.7%)	49 (79.0%)	
>4	24 (13.8%)	11 (9.8%)	13 (21.0%)		7 (11.3%)	13 (21.0%)	
Tumor site, n (%)				0.144			0.713
Low	98 (56.3%)	57 (50.9%)	41 (66.1%)		38 (61.3%)	41 (66.1%)	
Medium	52 (29.9%)	37 (33.0%)	15 (24.2%)		19 (30.6%)	15 (24.2%)	
High	24 (13.8%)	18 (16.1%)	6 (9.7%)		5 (8.1%)	6 (9.7%)	
Tumor grade, n (%)				0.155			0.192
G1	95 (54.6%)	60 (53.6%)	35 (56.5%)		30 (48.4%)	35 (56.5%)	
G2	52 (29.9%)	38 (33.9%)	14 (22.6%)		23 (37.1%)	14 (22.6%)	
G3	27 (15.5%)	14 (12.5%)	13 (21.0%)		9 (14.5%)	13 (21.0%)	
Lymph node metastasis, n (%)				0.074			0.716
Negative	86 (49.4%)	61 (54.5%)	25 (40.3%)		27 (43.5%)	25 (40.3%)	
Positive	88 (50.6%)	51 (45.5%)	37 (59.7%)		35 (56.5%)	37 (59.7%)	
Neoadjuvant, n (%)				0.139			1.000
No	158 (90.8%)	99 (88.4%)	59 (95.2%)		59 (95.2%)	59 (95.2%)	
Yes	16 (9.2%)	13 (11.6%)	3 (4.8%)		3 (4.8%)	3 (4.8%)	
Adjuvant, n (%)				0.383			0.710
No	114 (65.5%)	76 (67.9%)	38 (61.3%)		40 (64.5%)	38 (61.3%)	
Yes	60 (34.5%)	36 (32.1%)	24 (38.7%)		22 (35.5%)	24 (38.7%)	
Surgical outcomes							
Resection margin, n (%)				**0.049**			0.133
R0	170 (97.7%)	111 (99.1%)	59 (95.2%)		61 (98.4%)	59 (95.2%)	
R1	3 (1.7%)	0 (0.0%)	3 (4.8%)		0 (0.0%)	3 (4.8%)	
R2	1 (0.6%)	1 (0.9%)	0 (0.0%)		1 (1.6%)	0 (0.0%)	
Resection procedure				0.180			0.549
With TME[a]	118 (67.8%)	72 (64.3%)	46 (74.2%)		43 (69.4%)	46 (74.2%)	
With PME[b]	56 (32.2%)	40 (35.7%)	16 (25.8%)		19 (30.6%)	16 (25.8%)	
Stoma creation				0.582			0.854
No	99 (56.9%)	62 (55.4%)	37 (59.7%)		38 (61.3%)	37 (59.7%)	
Yes	75 (43.1%)	50 (44.6%)	25 (40.3%)		24 (38.7%)	25 (40.3%)	
Operation time, mean ± SD[c], min	175.01 ± 68.53	176.63 ± 56.56	172.08 ± 86.52	0.676	174.45 ± 60.82	172.08 ± 86.52	0.860
Complication, n (%)				**0.001**			**0.007**
No	137 (78.7%)	97 (86.6%)	40 (64.5%)		53 (85.5%)	40 (64.5%)	
Yes	37 (21.3%)	15 (13.4%)	22 (35.5%)		9 (14.5%)	22 (35.5%)	
Complication type							
Incision complication	8 (4.6%)	2 (1.8%)	6 (9.7%)	**0.045**	1 (1.6%)	6 (9.7%)	0.114
Anastomotic leakage	6 (3.4%)	2 (1.8%)	4 (6.5%)	0.188	1 (1.6%)	4 (6.5%)	0.365
Ileus	4 (2.3%)	2 (1.8%)	2 (3.2%)	0.617	1 (1.6%)	2 (3.2%)	1.000
Urinary retention	3 (1.7%)	2 (1.8%)	1 (1.6%)	1.000	2 (3.2%)	1 (1.6%)	1.000
Pneumonia	4 (2.3%)	2 (1.8%)	2 (3.2%)	0.617	1 (1.6%)	2 (3.2%)	1.000
Pelvic abscess	1 (0.6%)	0 (0.0%)	1 (1.6%)	0.356	0 (0.0%)	1 (1.6%)	1.000
Arrhythmias	4 (2.3%)	2 (1.8%)	2 (3.2%)	0.617	1 (1.6%)	2 (3.2%)	1.000
Pleural effusion	3 (1.7%)	1 (0.9%)	2 (3.2%)	0.289	0 (0.0%)	2 (3.2%)	0.496

Table 1 (continued)

Clinicopathological characteristics	Overall population (*n* = 174)	Before PSM[d]			After PSM		
		LAP[e] group (*n* = 112)	OPEN[f] group (*n* = 62)	*P* value	LAP group (*n* = 62)	OPEN group (*n* = 62)	*P* value
Gastric paralysis	4 (2.3%)	2 (1.8%)	2 (3.2%)	0.617	2 (3.2%)	2 (3.2%)	1.000
Postoperative hospital stay, mean ± SD, days	11.09 ± 6.48	10.41 ± 5.56	12.32 ± 7.78	0.062	10.11 ± 5.55	12.32 ± 7.78	0.071

[a]TME = total mesorectal excision. [b]PME = partial mesorectal excision.[c]SD = standard deviation. [d]PSM = propensity score matching. [e]LAP = laparoscopic surgery. [f]OPEN = open surgery

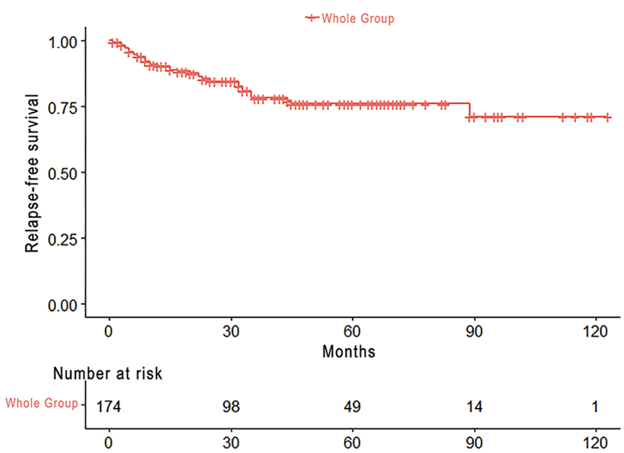

Fig. 2 Relapse-free survival curve of the entire cohort of 174 rectal neuroendocrine tumors patients

excision (TME) was similar to that in the OPEN group (Before PSM: 44.6% vs. 40.3%, $P=0.582$; 64.3% vs. 74.2%, $P=0.180$; After PSM: 38.7% vs. 40.3%, $P=0.854$; 69.4% vs. 74.2%, $P=0.549$). Before PSM, the R0 resection rate was higher in the LAP group than in the OPEN group (99.1% vs. 95.2%; $P=0.049$). Moreover, the LAP group had a lower incidence of postoperative complications as compared to the OPEN group (13.4% vs. 35.5%, $P=0.001$). After PSM, there was no significant difference in the R0 resection rate between the two groups (98.4% vs. 95.2%, $P=0.133$). However, the LAP group had a significantly lower postoperative complication rate than the OPEN group (14.5% vs. 35.5%, $P=0.007$). The surgical outcomes of the two groups before and after matching are shown in Table 1.

Oncologic outcomes

The study had a median follow-up period of 34 months (range: 1-123). The 1-, 3-, and 5-year RFS for RNETs patients who underwent radical surgery were 90.3%, 78.1%, and 76.0%, respectively (Fig. 2). The optimal cut-off value for tumor size to predict RFS was determined to be 4.0 cm for the two subgroups, and 2.0 and 4.0 cm for the three subgroups. Multivariate analysis revealed that tumor grade (G2: hazard ratio [HR], 3.263; 95% CI: 1.369–7.652, $P=0.012$; G3: HR, 4.036. 95% CI: 1.102–9.632, $P=0.009$), lymph node metastasis (Positive: HR, 2.896; 95% CI: 1.135–6.320, $P=0.030$), and surgery type (OPEN: HR, 2.362; 95% CI: 1.069–5.324, $P=0.040$) were independent risk factors for RFS. The log-rank test and Cox proportional hazards regression analysis of RFS are shown in Table 2.

Before PSM, the 1-, 3-, and 5-year RFS were 93.6%, 83.2%, and 81.4% in the LAP group, and 84.3%, 69.8%, and 67.4% in the OPEN group, respectively. The difference was statistically significant ($P=0.045$). After PSM, the 1-, 3-, and 5-year RFS were 95.2%, 85.3%, and 85.3% in the LAP group, and 84.3%, 69.8%, and 67.4% in the OPEN group, respectively. The difference was also statistically significant ($P=0.048$). Survival curves according to surgical type before and after PSM are shown in Fig. 3A and B.

Subgroup analysis

Tumor size was strongly correlated with surgical resection difficulty; thus, we performed a subgroup analysis based on this factor. In the aforementioned prognostic analysis, we found that the optimal cut-off value of the tumor size for predicting RFS was 4.0 cm. In the RNETs ≤ 4 cm subgroup, there were 49 patients in the LAP group and 55 in the OPEN group; in the RNETs > 4 cm subgroup, there were 13 patients in the LAP group and seven in the OPEN group. No significant differences were observed in their baseline characteristics.

There were no significant differences in the R0 resection rate or operation time in either the RNETs ≤ 4 cm (100.0% vs. 95.9%, $P=0.220$; 175.29 ± 63.16 min vs. 170.63 ± 92.01 min, $P=0.762$) or the RNETs > 4 cm subgroups (85.7% vs. 92.3%, $P=0.299$; 167.86 ± 40.50 min vs. 177.54 ± 64.41 min, $P=0.724$). Meanwhile, the proportion of patients in the LAP group who underwent stoma creation and TME was similar to those in the OPEN group, in either the RNETs ≤ 4 cm (38.2% vs. 36.7%, $P=0.879$; 67.3% vs. 73.5%, $P=0.490$) or the RNETs > 4 cm subgroups (42.9% vs. 53.8%, $P=1.000$; 71.4% vs. 84.6%, $P=0.587$). The LAP group had a lower incidence of postoperative complications than the OPEN group in the RNETs ≤ 4 cm subgroup (10.9% vs. 34.7%, $P=0.004$), while no significant difference was observed in the RNETs > 4 cm subgroup (42.9% vs. 38.5%, $P=1.000$). Similarly, the postoperative hospital stay in the LAP group was significantly shorter than that in the OPEN group in the RNETs ≤ 4 cm subgroup (9.56 ± 5.21 days vs. 12.31 ± 8.61 days, $P=0.049$),

Table 2 Univariate and multivariate relapse-free survival analysis

Clinicopathological factors	Univariate analysis			Multivariable analysis		
	HR[c]	**95% CI**[d]	***P* value**	**HR**	**95% CI**	***P* value**
Gender (Male/Female)	1.082	0.538–2.178	0.825			
Age (>65/≤65)	0.635	0.315–1.279	0.204			
Tumor site			0.508			
Low	-	-	-			
Medium	0.638	0.298–1.370	0.249			
High	0.792	0.297–2.115	0.642			
Tumor size, cm			0.235			
≤2	-	-	-			
2～4	1.827	0.853–3.912	0.121			
>4	2.018	0.658–6.192	0.220			
Tumor grade			**0.029**			**0.012**
G1	-	-	-	-	-	-
G2	3.006	1.200-7.532	**0.019**	3.263	1.369–7.652	**0.012**
G3	3.111	1.309–7.390	**0.010**	4.036	1.102–9.632	**0.009**
Lymph node metastasis (Positive/Negative)	4.526	1.526–8.563	**0.009**	2.896	1.135–6.320	**0.030**
Surgery (OPEN[a] /LAP[b])	2.050	1.015–4.140	**0.045**	2.362	1.069–5.324	**0.040**
Neoadjuvant (Yes /No)	0.981	0.301–3.194	0.974			
Adjuvant (Yes /No)	3.335	1.602–6.943	**0.001**	1.356	0.862–12.369	0.103

[a]OPEN = open surgery. [b]LAP = laparoscopic surgery. [c]HR = hazard ratio. [d]CI = confidence interval

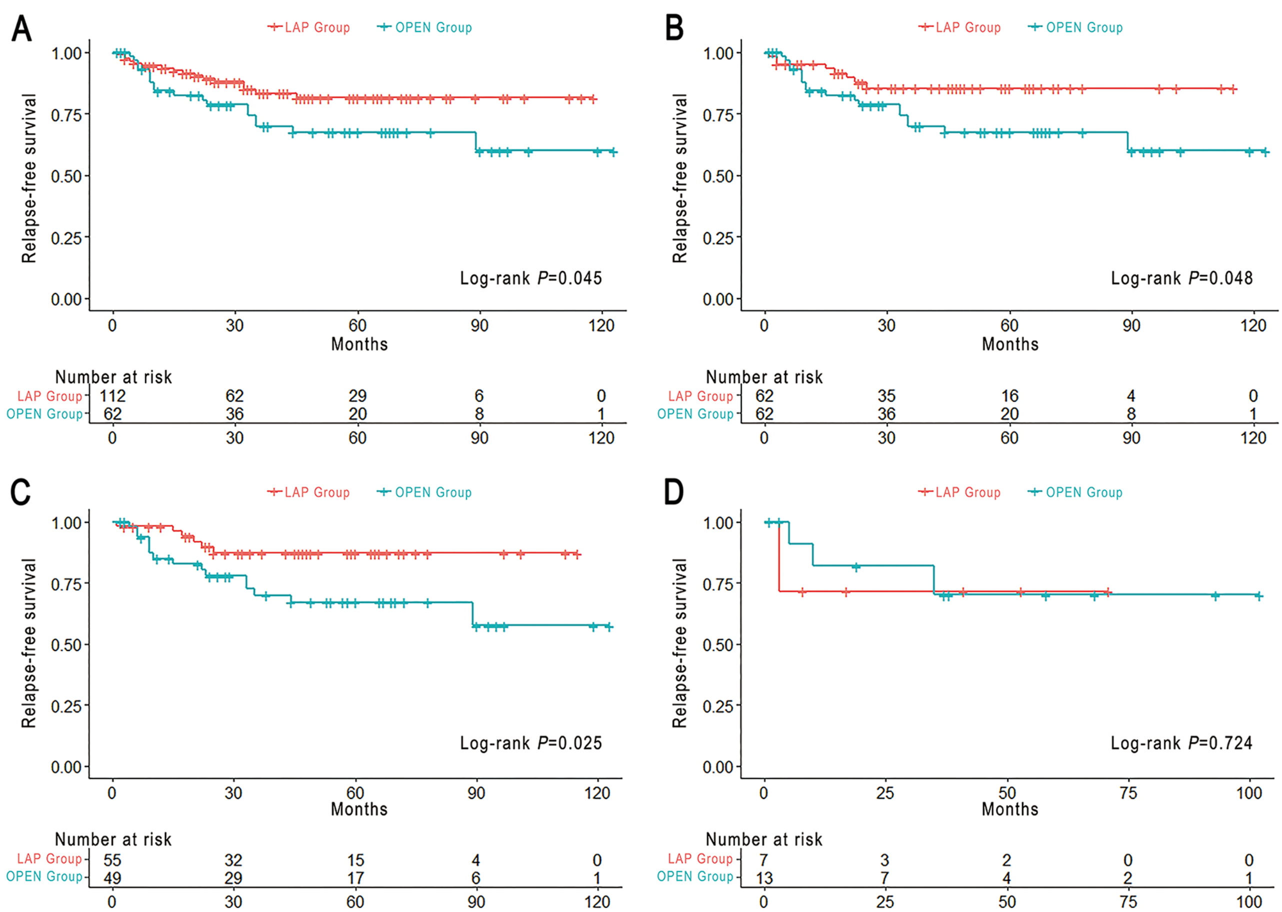

Fig. 3 Comparison of relapse-free survival between the laparoscopic surgery group and open surgery group: (**A**) Before propensity score matching; (**B**) After propensity score matching; (**C**) ≤ 4 cm subgroup after propensity score matching; (**D**) > 4 cm subgroup after propensity score matching

while no significant difference was observed in the RNETs > 4 cm subgroup (14.43 ± 6.60 days vs. 12.38 ± 3.33 days, $P = 0.465$). The clinicopathological characteristics and surgical outcomes of the subgroups are shown in Table 3.

The RFS of the LAP group was superior to that of the OPEN group in the RNETs ≤ 4 cm subgroup ($P = 0.025$), whereas no significant difference was found in the RNETs > 4 cm subgroup ($P = 0.724$). Survival curves according to the surgical type are shown in Fig. 3C and D.

Discussion

Radical resection, including low anterior and abdominoperineal resection, is the primary treatment for localized RNETs. However, while radical resection achieves more complete tumor dissection and improves patient survival, it may also result in poor functional outcomes as compared to local excision [12–16]. Therefore, the choice between local excision and radical resection is crucial in managing patients with RNETs.

In this study, the preoperative imaging results served as important references for selecting surgical methods for patients with RNETs. By effectively communicating with the patients and their families, we determined the optimal surgical approach after carefully assessing the tumor size, tumor grade, T stage, and lymph node metastasis status. For RNETs, we recommend radical resection for patients with tumor size > 2 cm, T stage > T1, tumor grade G3, lymph node metastasis, or neurovascular invasion. Radical resection has been suggested in patients with RNEC and RMANEC. These indications for radical resection are similar to those outlined in the CSCO guidelines for RNENs [5].

Laparoscopic surgery has become the standard treatment for digestive tract tumors. Several retrospective case-control studies and randomized controlled trials have demonstrated that laparoscopic surgery has a long-term prognosis not inferior to that of open surgery, as well as having the advantages of less trauma and rapid postoperative recovery [17–20]. However, evidence comparing laparoscopic and open surgery for RNETs remains scarce, owing to their rarity and even rarer indications for radical surgery. Therefore, we designed and implemented a multicenter study to compare the postoperative and oncological outcomes between laparoscopic and open surgery for RNETs. To the best of our knowledge, this is the largest study of RNETs in patients who underwent radical resection.

RNETs are located in the pelvic cavity, with complex adjacent organs and a narrow surgical space, thus making precise localization and safe resection difficult. Laparoscopic surgery can effectively reduce traction injury to the surrounding organs by directly reaching the lesion site with extended surgical instruments. Image reproduction is achieved through the endoscope and monitor, which makes it possible for surgeons to observe the surgical field more intuitively, thus assisting in safe tumor resection. Studies have shown that laparoscopic surgery for NENs in the stomach and small bowel yields short-term outcomes comparable to those of open surgery [21, 22]. In this study, we found that laparoscopic surgery for RNETs resulted in a lower incidence of complications and a higher rate of R0 resection than open surgery. To improve the credibility of our retrospective data analysis, we performed PSM between the groups to balance the covariates and confounders. After PSM, we found a lower incidence of postoperative complications in the LAP group, with no significant differences in the R0 resection rate, operation time, or postoperative hospital stay. These results demonstrate that laparoscopic surgery may offer better surgical outcomes for RNETs owing to its minimally invasive nature.

Although laparoscopic surgery lacks tactile sensation, which poses a risk for tumor rupture and iatrogenic dissemination, studies have shown satisfactory long-term prognosis in laparoscopic resection of RNETs, with a 3-year overall survival rate of 97.8% [8, 9]. However, comparisons between laparoscopic and open surgeries, in terms of oncological outcomes for RNETs, remain lacking. In our study, we used PSM to minimize the influence of confounding factors. The results suggested that laparoscopic surgery was associated with a better RFS than open surgery before and after PSM. In conclusion, laparoscopic surgery is a safe and feasible option for radical surgery in patients with RNETs.

Tumor size is associated with difficulty in surgical resection during the treatment of digestive tract tumors; a larger tumor size often indicates a more complicated surgical procedure, thus increasing the risk for intraoperative complications. To assess the impact of tumor size on short- and long-term outcomes, we performed a subgroup analysis of patients with RNETs after PSM using a cutoff value of 4 cm. Among patients with RNETs ≤ 4 cm, those in the laparoscopic group had fewer complications, shorter postoperative hospital stays, and superior RFS as compared with those in the open group. Among patients with RNETs > 4 cm, the short- and long-term outcomes did not significantly differ between the laparoscopic and open groups. Similarly, previous studies at our medical center have shown that in rectal gastrointestinal stromal tumors, laparoscopic surgery was associated with superior RFS and fewer complications only in patients with ≤5-cm tumors, whereas these advantages were lost in those with > 5 cm [23]. These results suggest that laparoscopic surgery has advantages related to tumor size in the management of rectal neoplasms.

This study had several limitations. First, although we used PSM to reduce potential bias and performed a

Table 3 Comparison of demographic and clinicopathological characteristics in subgroup analysis of tumor size after propensity score matching

Clinicopathological characteristics	≤ 4 cm			> 4 cm		
	LAP[d] group (n = 55)	OPEN[e] group (n = 49)	P value	LAP group (n = 7)	OPEN group (n = 13)	P value
Baseline characteristics						
Gender, n (%)			0.849			1.000
Female	17 (30.9%)	16 (32.7%)		3 (42.9%)	6 (46.2%)	
Male	38 (69.1%)	33 (67.3%)		4 (57.1%)	7 (53.8%)	
Age, n (%), year			0.557			1.000
≤60	34 (61.8%)	33 (67.3%)		3 (42.9%)	7 (53.8%)	
>60	21 (38.2%)	16 (32.7%)		4 (57.1%)	6 (46.2%)	
Tumor site, n (%)			0.952			0.386
Low	35 (63.6%)	32 (65.3%)		3 (42.9%)	9 (69.2%)	
Medium	16 (29.1%)	13 (26.5%)		3 (42.9%)	2 (15.4%)	
High	4 (7.3%)	4 (8.2%)		1 (14.3%)	2 (15.4%)	
Tumor grade, n (%)			0.155			0.828
G1	29 (52.7%)	34 (69.4%)		1 (14.3%)	1 (7.7%)	
G2	22 (40.0%)	11 (22.4%)		1 (14.3%)	3 (23.1%)	
G3	4 (7.3%)	4 (8.2%)		5 (71.4%)	9 (69.2%)	
Lymph node metastasis, n (%)			0.585			0.197
Negative	24 (43.6%)	24 (49.0%)		3 (42.9%)	1 (7.7%)	
Positive	31 (56.4%)	25 (51.0%)		4 (57.1%)	12 (92.3%)	
Neoadjuvant, n (%)			1.000			1.000
No	52 (94.5%)	47 (95.9%)		7 (100.0%)	12 (92.3%)	
Yes	3 (5.5%)	2 (4.1%)		0 (0.0%)	1 (7.7%)	
Adjuvant, n (%)			0.668			1.000
No	37 (67.3%)	31 (63.3%)		3 (42.9%)	7 (53.8%)	
Yes	18 (32.7%)	18 (36.7%)		4 (57.1%)	6 (46.2%)	
Surgical outcomes						
Resection margin, n (%)			0.220			0.299
R0	55 (100.0%)	47 (95.9%)		6 (85.7%)	12 (92.3%)	
R1	0 (0.0%)	2 (4.1%)		0 (0.0%)	1 (7.7%)	
R2	0 (0.0%)	0 (0.0%)		1 (14.3%)	0 (0.0%)	
Resection procedure			0.490			0.587
With TME[a]	37 (67.3%)	36 (73.5%)		5 (71.4%)	11 (84.6%)	
With PME[b]	18 (32.7%)	13 (26.5%)		2 (28.6%)	2 (15.4%)	
Stoma creation			0.879			1.000
No	34 (61.8%)	31 (63.3%)		4 (57.1%)	6 (46.2%)	
Yes	21 (38.2%)	18 (36.7%)		3 (42.9%)	7 (53.8%)	
Operation time, mean ± SD[c], min	175.29 ± 63.16	170.63 ± 92.01	0.762	167.86 ± 40.50	177.54 ± 64.41	0.724
Complication, n (%)			**0.004**			1.000
No	49 (89.1%)	32 (65.3%)		4 (57.1%)	8 (61.5%)	
Yes	6 (10.9%)	17 (34.7%)		3 (42.9%)	5 (38.5%)	
Complication type						
Incision complication	0 (0.0%)	5 (10.2%)	**0.021**	1 (0.0%)	1 (7.7%)	1.000
Anastomotic leakage	0 (0.0%)	2 (4.1%)	0.220	1 (14.3%)	2 (15.4%)	1.000
Ileus	1 (1.8%)	1 (2.0%)	1.000	0 (0.0%)	1 (7.7%)	1.000
Urinary retention	1 (1.8%)	1 (2.0%)	1.000	1 (14.3%)	0 (0.0%)	0.350
Pneumonia	1 (1.8%)	2 (4.1%)	0.600	0 (0.0%)	0 (0.0%)	-
Pelvic abscess	1 (1.8%)	1 (2.0%)	1.000	0 (0.0%)	0 (0.0%)	-
Arrhythmias	1 (1.8%)	1 (2.0%)	1.000	0 (0.0%)	1 (7.7%)	1.000
Pleural effusion	0 (0.0%)	2 (4.1%)	0.220	0 (0.0%)	0 (0.0%)	-
Gastric paralysis	1 (1.8%)	2 (4.1%)	0.600	0 (0.0%)	0 (0.0%)	-
Postoperative hospital stay, mean ± SD, days	9.56 ± 5.21	12.31 ± 8.61	**0.049**	14.43 ± 6.60	12.38 ± 3.33	0.465

[a]TME = total mesorectal excision. [b]PME = partial mesorectal excision.[c]SD = standard deviation. [d]LAP = laparoscopic surgery. [e]OPEN = open surgery

subgroup analysis to investigate the impact of the surgical approach on patient outcomes, the retrospective nature of the study affected its statistical power and clinical value. In addition, RNETs are slow-growing tumors [24]; a longer follow-up period is required for a comprehensive clinical evaluation of patient status. Furthermore, the number of cases in the RNETs>4 cm subgroup was too low to draw definitive conclusions. However, to the best of our knowledge, this is currently the largest study to compare laparoscopic with open surgery for RNETs, and thus may provide valuable guidance for their treatment. We look forward to a subsequent large prospective multicenter study to provide more reliable medical evidence for choosing a radical surgical approach for RNETs.

Conclusion

In summary, laparoscopic surgery is a safe and feasible option for radical resection of localized RNETs. For patients with RNETs≤4 cm, laparoscopic surgery was associated with a superior RFS, a reduced rate of complications, and shorter postoperative hospital stays. For patients with RNETs>4 cm, laparoscopic surgery has oncological and surgical outcomes similar to those of open surgery.

Abbreviations

AJCC	American Joint Committee on Cancer
CSCO	Chinese Society of Clinical Oncology
CT	Computed tomography
ENETS	European Neuroendocrine Tumor Society
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NENs	Neuroendocrine neoplasms
PET	Positron-emission tomography
PSM	Propensity score matching
RFS	Relapse-free survival
RMANEC	Rectal mixed adenoneuroendocrine carcinoma
RNEC	Rectal neuroendocrine carcinoma
RNENs	Rectal neuroendocrine neoplasms
RNETs	Rectal neuroendocrine tumors
TME	Total mesorectal excision

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

Weizhong Jiang and Kaixiong Tao had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.Concept and design: Chengguo Li, Weizhong Jiang, Kaixiong Tao.Acquisition, analysis, or interpretation of data: Xinyu Zeng, Chengguo Li, Minhao Yu, Rui Zhang, Guole Lin, Maojun Di, Hongxue Wu, Yueming Sun, Zhiguo Xiong, Congqing Jiang, Bin Yu, Shengning Zhou, Yong Li, Xiaofeng Liao, Lijian Xia, Wei Zhang.Drafting of the manuscript: Xinyu Zeng, Chengguo Li.Critical revision of the manuscript for important intellectual content: Minhao Yu, Rui Zhang, Guole Lin, Maojun Di, Hongxue Wu, Yueming Sun, Zhiguo Xiong, Congqing Jiang, Bin Yu, Shengning Zhou, Yong Li, Xiaofeng Liao, Lijian Xia, Wei Zhang, Weizhong Jiang, Kaixiong Tao.Statistical analysis: Minhao Yu, Rui Zhang, Guole Lin, Maojun Di, Hongxue Wu, Yueming Sun.Administrative, technical, or material support: Zhiguo Xiong, Congqing Jiang, Bin Yu, Shengning Zhou, Yong Li, Xiaofeng Liao, Lijian Xia, Wei Zhang, Weizhong Jiang, Kaixiong Tao.Supervision: Weizhong Jiang, Kaixiong Tao.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study conformed to the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Approval Number: [2022]0433). At the last follow-up, we informed the patients about the study in detail and obtained signed informed consent. For patients who died at the time of the study, we contacted their immediate family members, explained the study in detail, and obtained signed informed consent forms.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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References

1. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335–42.https://doi.org/10.1001/jamaoncol.2017.0589<PMID: 28448665>
2. Cives M, Strosberg JR. Gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin. 2018;68(6):471–87.https://doi.org/10.3322/caac.21493<PMID: 30295930>
3. Ramage JK, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012;61(1):6–32. https://doi.org/10.1136/gutjnl-2011-300831<PMID: 22052063>
4. Anthony LB, Strosberg JR, Klimstra DS, 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. 10.1097/MPA.0b013e3181ec1261> <pmid: 20664474=></pmid:>. https://doi.org/10.1097/MPA.0b013e3181ec1261<PMID: 20664474>
5. Li YW, He YP, Liu FQ, et al. Grade G2 rectal neuroendocrine tumor is much more invasive compared with G1 tumor. Front Oncol. 2021;11:646536.https://doi.org/10.3389/fonc.2021.646536<PMID: 33777809>
6. Ramage JK, De Herder WW, Delle Fave G, et al. ENETS Consensus guidelines Update for Colorectal Neuroendocrine neoplasms. Neuroendocrinology. 2016;103(2):139–43.https://doi.org/10.1159/000443166<PMID: 26730835>
7. Shah MH, Goldner WS, Benson AB, et al. Neuroendocrine and adrenal tumors, Version 2.2021, NCCN Clinical Practice guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(7):839–68.https://doi.org/10.6004/jnccn.2021.0032<PMID: 34340212>
8. Takatsu Y, Fukunaga Y, Nagasaki T, et al. Short- and long-term outcomes of laparoscopic total mesenteric excision for neuroendocrine tumors of the rectum. Dis Colon Rectum. 2017;60(3):284–9.https://doi.org/10.1097/DCR.0000000000000745<PMID: 28177990>
9. Inoue T, Nakagawa T, Nakamura S, et al. Laparoscopic surgery after endoscopic resection for rectal cancer and neuroendocrine tumors. Surg Endosc. 2015;29(6):1506–11.https://doi.org/10.1007/s00464-014-3832-z<PMID: 25277475>
10. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998;17(19):2265–81. 3.0.co;2-b>.https://doi.org/10.1002/(sici)1097-0258(19981015)17:19<2265::aid-sim918>3.0.co;2-b><PMID: 9802183>
11. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083–107.https://doi.org/10.1002/sim.3697<PMID: 19757444>
12. Caulfield H, Hyman NH. Anastomotic leak after low anterior resection: a spectrum of clinical entities. JAMA Surg. 2013;148(2):177–82.https://doi.org/10.1001/jamasurgery.2013.413<PMID: 23426596>
13. Phillips BR, Harris LJ, Maxwell PJ, Isenberg GA, Goldstein SD. Anastomotic leak rate after low anterior resection for rectal cancer after chemoradiation therapy. Am Surg. 2010;76(8):869–71. [J].<PMID: 20726419>
14. Bryant CL, Lunniss PJ, Knowles CH, Thaha MA, Chan CL. Anterior resection syndrome. Lancet Oncol. 2012;13(9):e403–8.https://doi.org/10.1016/S1470-2045(12)70236-X<PMID: 22935240>
15. Pucciani F. A review on functional results of sphincter-saving surgery for rectal cancer: the anterior resection syndrome. Updates Surg. 2013;65(4):257–63.https://doi.org/10.1007/s13304-013-0220-5<PMID: 23754496>
16. Emmertsen KJ, Laurberg S. Bowel dysfunction after treatment for rectal cancer. Acta Oncol. 2008;47(6):994–1003.https://doi.org/10.1080/02841860802195251<PMID: 18607875>
17. de Mestier L, Lorenzo D, Fine C et al. Endoscopic, transanal, laparoscopic, and transabdominal management of rectal neuroendocrine tumors. Best Pract Res Clin Endocrinol Metab. 2019;33(5):101293. 10.1016/j.beem.2019.101293> < PMID: 31326374>https://doi.org/10.1016/j.beem.2019.101293<PMID: 31326374>
18. Li K, Liu Y, Han J, Gui J, Zhang X. The genetic alterations of rectal neuroendocrine tumor and indications for therapy and prognosis: a systematic review. Endocr J. 2023;70(2):197–205.https://doi.org/10.1507/endocrj.EJ22-0262<PMID: 36403965>
19. Gallo C, Rossi RE, Cavalcoli F, et al. Rectal neuroendocrine tumors: current advances in management, treatment, and surveillance. World J Gastroenterol. 2022;28(11):1123–38. 10.3748/wjg.v28.i11.1123> <pmid: 35431507=></pmid:>.https://doi.org/10.3748/wjg.v28.i11.1123<PMID: 35431507>
20. Sekiguchi M, Matsuda T, Saito Y. Treatment strategy and post-treatment management of colorectal neuroendocrine tumor. DEN Open. 2023;4(1):e254.https://doi.org/10.1002/deo2.254<PMID: 37313123>
21. Zhao YJ, Zhuang LP, Liu YY et al. Comparative study of laparoscopic versus open radical gastrectomy in advanced gastric neuroendocrine carcinoma: Analysis from a high-volume institution. Asian J Surg. 2020;43(3):488–496.https://doi.org/10.1016/j.asjsur.2019.07.017<PMID: 31405628>
22. Kaçmaz E, van Eeden S, Koppes JCC, et al. Value of Laparoscopy for Resection of Small-Bowel Neuroendocrine neoplasms Including Central Mesenteric Lymphadenectomy. Dis Colon Rectum. 2021;64(10):1240–8.https://doi.org/10.1016/j.asjsur.2019.07.017<PMID: 31405628>
23. Jia J, Wang M, Lin G, et al. Laparoscopic Versus Open surgery for rectal gastrointestinal stromal tumor: a Multicenter Propensity score-matched analysis. Dis Colon Rectum. 2022;65(4):519–28.https://doi.org/10.1097/DCR.0000000000002014<PMID: 34759244>
24. Nam SJ, Kim BC, Chang HJ, Jeon HH, Kim J, Kim SY. Risk factors for Lymph Node Metastasis and oncologic outcomes in small rectal neuroendocrine tumors with Lymphovascular Invasion. Gut Liver. 2022;16(2):228–35. https://doi.org/10.5009/gnl20364<PMID: 34552040>

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