

Local excision vs. radical surgery in treating rectal nets considering the biology of neuroendocrine tumors (NETs)

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Introduction. Local excision (LE) is performed for rectal neuroendocrine tumors (NETs) <1 cm in size, whereas radical surgery (RS) is performed for larger tumors. The lack of data and limited number of studies support such approaches. Thus, we determined oncological outcomes after primary tumor resection in patients with rectal NETs and identified other factors of NETs that could influence oncological outcomes.

Material and methods. We retrospectively examined patients with I–III stage rectal NETs who underwent different surgical approaches, including LE or RS, in Severance Hospital, Korea between 2006 and 2017. The association between surgery extent, tumor size (TS), depth of invasion and biological factors of NETs was examined. Oncological outcomes were analyzed.

Results. Local excision (LE) and radical surgery (RS) were performed in 64 and 23 patients, respectively. Patients who underwent RS were more likely to have larger TS; deeper invasion; higher grade, mitotic index, Ki-67; more lymph node metastasis (LNMTs); and a higher lymphovascular invasion rate ($p < 0.001$). Most patients with TS < 1.0 cm underwent LE had better DFS and OS. Primary TS > 10 mm was an independent predictor of invasion ($p = 0.001$) whereas depth of invasion was an independent predictor of LN metastases ($p = 0.003$). In the multivariate analysis, only invasion was an independent factor associated with poor DFS and OS ($p = 0.023$ and 0.015 , respectively).

Conclusions. Local excision could be an effective method to use in treating rectal NETs in the early stage of the disease, and depth of invasion was an important factor influencing oncological outcomes. Our findings need to be confirmed in future prospective and randomized studies.

Key words: rectal neuroendocrine tumor, local excision, radical surgery, invasion, tumor size

Introduction

Rectal neuroendocrine tumors (NETs) are rare tumors accounting for approximately 2% of all rectal tumors. However, rectal NETs are the second most frequent tumors among all gastrointestinal tract NETs and account for 20%; they have showed the highest recent increase in incidence [1, 2]. The prognosis for rectal NETs is favorable, with a 5-year survival rate of approximately 90% [3–5]. The current National Comprehensive Cancer Network (NCCN) and European Neuroendocrine Tumor Society (ENETS) guidelines advise providing aggressive

surgical treatments for rectal NETs >2 cm in size [6, 7]. However, these size-based surgical approaches are controversial because only limited studies on these approaches are available [8–10]. Common surgical methods, including low anterior resection or APR, are used to excise rectal NETs >2 cm in size [6, 11, 12].

Endoscopic approaches, including endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), enable resection of rectal NETs with small sizes (<10 mm) and are recommended by the ENETS 2016 guidelines [7]. However, these endoscopic methods have a high rate of positive resec-

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tion margins (approximately 24%–46%) according to some modern studies [13, 14]. Lee et al. revealed 17% positive resection margins after EMR among patients with tumors 15 mm in diameter [15]. Studies demonstrated a significant improvement with approximately 96% complete resections when ESR was used instead of EMR [16–18]. Transanal minimally invasive surgery (TAMIS) or transanal endoscopic microsurgery (TEM) enable safe resection of rectal NETs with negative margins, although the size is >2 cm [19–20].

Some studies have suggested that the size of rectal NETs is one of the most important factors in prognosis. According to their results, positive LN metastasis significantly increase with the size of the tumor and was observed from 40 to 80% of patients with tumor size >2 cm [21–25].

In contrast, a recent assessment of the SEER database showed that LN metastasis occurred in only 11.7%, and distant metastases occurred in only 12% of tumors >2 cm [26]. According to other modern data, there are no significant differences in oncological outcomes among patients with rectal NETs of different sizes (<2 or >4 cm) who underwent local excision or standard surgical approaches with disease-free LN status [26]. Moreover, there was a paradoxical contradictory report of outcomes after local excision versus radical surgery. The 10-year overall survival (OS) rates for T2 rectal NETs after local excision or radical surgery were 79.8% and 63.2% and those for T3/4 were 82.3% and 28.3%, respectively ($p < 0.01$). In addition, Ki-67 >3% and lymphatic or venous invasion were strong predictors in multivariate analysis [27].

It is worth indicating that compared with local excision approaches, low anterior resection of the rectum or abdominoperineal resection significantly compromises the quality of life (QOL) of patients. It also can be hypothesized that the biological features of NETs appear to play a more important role than the size of NETs. For example, NET features, including high Ki-67 index, high grade and mitotic index, and lymphovascular invasion are more crucial when the surgical approach is chosen and their presence results in varying prognosis [26, 28]. However, the nature and biology of rectal NETs needs to be considered in further studies because of their increasing incidence and the promising results of local excision with no evidence of LN metastasis. The new data might prove the effectiveness of local excision with the same oncological outcomes as radical surgery but with better QOL for patients.

Thus, this study aimed to determine oncological outcomes depending on the extent of primary tumor resection in patients with I–III stage rectal NETs in addition to identifying other factors associated with NET biology and aggressiveness that can influence oncological outcomes.

Materials and methods

In this single-center, retrospective, nonrandomized study, patients with I–III stage rectal NETs who underwent different surgical treatments, including local excision or radical opera-

tion, in Severance Hospital, Yonsei University Health System, Seoul, Korea between 2006 and 2017, were examined. Data were collected from the electronic medical record database of Severance Hospital. The clinicopathological characteristics, such as patients' age at diagnosis, gender, year of diagnosis, type of operation, stage, grade, differentiation, distance from AV, mitotic index, Ki-67, CD56, synaptophysin, chromogranin status, depth of invasion, and last follow-up status (alive/dead), were obtained from the database. Type of operation was defined as radical surgery, which included low anterior resection, abdominoperineal resection and intersphincter resection performed via the open or laparoscopic/robot approach; local excision was performed by TAMIS or transanal excision. All types of operations were included for retrospective analysis based on inclusion and exclusion criteria.

Based on the inclusion and exclusion criteria, patients were categorized depending on the surgical approach and clinicopathologic characteristics. The inclusion criteria were as follows: localization – rectum; stage I, II and III (AJCC TNM 7th ed.); tumor size ranging from 1 to 50 mm; tumor distance within 15 cm from the anal verge; type of operation (local excision versus radical surgery); patient's age between 19 and 80 years and the availability of histopathological and radiologic data. The exclusion criteria were as follows: stage IV (AJCC TNM 7th ed.), patient's age <19 or >80 years, treatment for previous cancer besides rectal NETs; follow-up loss; or incomplete clinical/histopathological/radiologic data.

The primary endpoints of this study were long-term survival outcomes of patients with rectal NETs after surgical treatment using two different approaches, namely radical surgery or TAMIS. Different factors associated with tumor biology and aggressiveness were also investigated regardless of the surgical approaches. OS was calculated from the date of surgery to the date of death. Disease-free survival (DFS) was calculated from the date of surgery to the date of recurrence.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, version 23 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as frequencies (%), whereas continuous variables were presented as means, with their range or standard deviation. The means of continuous variables were compared using an independent sample t-test. Categorical variables were compared using the Pearson test. OS and DFS were estimated using the Kaplan-Meier method and were compared using a log-rank test. A multivariate Cox proportional hazards model with stepwise method was used to identify statistically significant independent prognostic factors for OS and DFS. In logistic regression analysis, p values <0.05 were used to define statistical significance of variables influencing DFS. A receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value of the tumor size. The variance inflation factor (VIF) method was used to detect

whether multicollinearity was presented among the independent variables (VIF >3 indicated the existent correlation among investigated variables).

Results

Overall, 1046 patients with rectal NETs underwent different treatments. An endoscopic approach was performed in 928

patients (365, cold polypectomy and 563, EMR or ESD), local excision in 72, and radical surgery in 46. Among those, based on the study aim and eligibility criteria, we further analyzed only the clinical data of 64 patients who underwent local excision and the 23 patients who underwent radical surgery. The characteristics of both groups of patients are summarized in table I.

Table I. Patients' characteristics

Variables	Radical surgery	Local excision	p
no. of patients	23	64	
age, mean ± SD (years)	52.3 ± 11.3	49.7 ± 12.1	0.420
age (years)			0.198
≤65	18 (78.3%)	57 (89.1%)	
>65	5 (21.7%)	7 (10.9%)	
gender			0.323
male	17 (73.9%)	24 (37.5%)	
female	6 (26.1%)	40 (62.5%)	
^aprimary tumor size (mm)			<0.001
≤10.2	8 (34.8%)	54 (84.4%)	
>10.2	15 (65.2%)	10 (15.6%)	
^bprimary tumor size (mm)			<0.001
≤16.5	12 (52.2%)	62 (96.9%)	
>16.5	11 (47.8%)	2 (3.1%)	
distance from AV, mean ± SD (cm)	7.7 ± 3.3	6.2 ± 2.6	0.038
differentiation			0.116
well	20 (87.0%)	62 (96.8%)	
moderate	3 (13.0%)	2 (3.1%)	
invasion			<0.001
mucosa + submucosa	8 (34.8%)	60 (93.8%)	
muscularis propria + pericolic tissue	15 (65.2%)	4 (6.3%)	
grade			<0.001
G1	12 (52.2%)	59 (92.2%)	
≥G2	11 (47.8%)	5 (7.8%)	
HPF			<0.001
≤2/10	14 (60.9%)	61 (95.3%)	
>2/10	9 (39.1%)	3 (4.7%)	
TNM stage			<0.001
I, IIA, IIB	13 (56.5%)	64 (100.0%)	
IIIA, IIIB	10 (43.5%)	0	
T status			<0.001
T1, T2	11 (47.8%)	62 (96.9%)	
T3, T4	12 (52.2%)	2 (3.1%)	
N status			<0.001
N0	13 (56.5%)	64 (100.0%)	
N1	10 (43.5%)	0	
Ki-67			0.004
≤2%	15 (65.2%)	58 (90.6%)	
>2%	8 (34.8%)	6 (9.4%)	
PNIV			0.055
positive	3 (13.0%)	1 (1.6%)	
negative	20 (87.0%)	63 (98.4%)	
LVIN			<0.001
positive	9 (39.1%)	1 (1.6%)	
negative	14 (60.9%)	63 (98.4%)	
CD56			0.044
positive	21 (91.3%)	45 (70.3%)	
negative	2 (8.7%)	19 (29.7%)	

Variables	Radical surgery	Local excision	p
synaptophysin			0.218
positive	21 (91.3%)	50 (78.1%)	
negative	2 (8.7%)	14 (21.9%)	
chromogranin			0.457
positive	4 (17.4%)	16 (25.0%)	
negative	19 (82.6%)	48 (75.0%)	

SD – standard deviation; AV – anal verge; HPF – high power field; TNM – tumor-node-metastasis; PNIV – peri-neural invasion; LVIN – lympho-vascular invasion

^a cutoff based on mean value

^b cutoff based on ROC curve

Patients' age, gender, differentiation of NET and some tumors markers according to immunohistochemical analysis (synaptophysin and chromogranin) were not significantly different between the two groups (all $p > 0.05$). Patients in the radical surgery group were more likely to have larger primary tumors (65.2% vs. 15.6%, $p < 0.001$), deeper invasion (65.2% vs. 7.8%, $p < 0.001$), higher grade (39.1% vs. 7.8%, $p < 0.001$), higher mitotic index and Ki-67 (2/10 HPFs: 39% vs. 4.7%; Ki-67 >2%: 30.4% vs. 9.4%, $p < 0.001$), T stage and LN metastasis (T3/4: 52.2% vs. 3.1%; N1: 43.5% vs. 0%, $p < 0.001$) and a higher lymphovascular invasion rate (39.1% vs. 1.6%, $p < 0.001$) than those in the local excision group. A vast majority of patients with tumors <1.0 cm underwent local excision (54/64, 84.4%), whereas those with tumors ≥ 2 cm underwent radical surgery (15/23, 65.2%). Recurrence was observed in five (21.7%) and three (4.7%) patients in radical surgery and local excision groups, respectively ($p = 0.055$).

Typically, the tumor size is one of the most important factors that predict outcomes and subsequently the surgical approach. According to the literature, tumor size >2 cm seems to be a cutoff for local excision, whereas a size between 1 and 2 cm remains controversial. We attempted to identify which primary tumor size would be applicable in our analysis. We used a ROC curve analysis to determine the optimal cutoff value of the tumor size that could influence oncological outcomes. The optimal cutoff value was 16.5 mm (sensitivity, 80%; and specificity, 90.2%) with an area under the curve of 0.877 (95% confidence interval [CI]: 0.764–0.990, $p = 0.005$). However, only two (3.1%) patients in the local excision group had a tumor size >16.5 mm compared with 11 patients (47.8%) in the radical surgery group (< 0.001), resulting in inconsistency. To identify the comparable primary tumor size for analysis in both groups, we used the descriptive method to determine the mean tumor size in all 87 patients. We found that a mean size of 10.2 mm was more homogenous between the two groups. Thus, 15 and 10 patients in the radical surgery and local excision groups, respectively, had a primary tumor size >10.2 mm. A tumor size of 10 mm has been previously reported as a cutoff for local excision. Considering that, the primary tumor size of 10.2 mm was chosen for subsequent analysis of oncological outcomes in our study.

Factors associated with DFS

DFS rates were better in the local excision group than in the radical surgery. The cumulative 1-, 3-, and 5-year DFS rates of patients were 82.6%, 72.9% and 68%, respectively in the radical surgery group; 96.9%, 96.9%, and 94.4%, respectively in the local excision group ($p < 0.05$) (table III). Factors associated with an increased risk of recurrence included the type of surgical treatment (radical surgery vs. local excision), the primary tumor size >10 mm, poorer differentiation of primary tumor, invasion, grade >1, mitotic index (>1/10 HPFs), N positivity, perineural and lymphovascular invasions and Ki-67 >2% according to the univariate analysis ($p < 0.05$).

In contrast, in the multivariate analysis only deep invasion (HR, 17.385; 95% CI 3.684–82.052; $p < 0.001$) was independently associated with an increased risk of tumor recurrence and influenced DFS (HR, 8.374; 95% CI 1.342–52.248; $p = 0.023$). Table II provides details on the clinicopathologic factors associated with DFS.

Factors associated with OS

The cumulative 1-, 3-, and 5-year OS rates of patients were 95.7%, 90.6% and 84.6%, respectively, in the radical surgery group and 100% in all the years in the local excision group (tab. III). Factors associated with poor OS included primary tumor size >10 mm and tumor invasion depth ($p < 0.05$). In the multivariate analysis, depth of invasion (mucosa/submucosa vs. muscularis propria/pericolonic tissue) was independently associated with poor OS (HR, 15.333; 95% CI, 1.710–137.447; $p = 0.015$) (tab. II).

DFS and OS were different between the two groups ($p = 0.001$). The 1-, 3-, and 5-year DFS and OS were longer in the local excision group than in the radical surgery group (tab. III).

Influence of the depth of invasion on 1-, 3-, and 5-year OS and DFS

Depth of invasion was an independent factor associated with higher recurrence rate and poor OS; thus, we analyzed the cumulative 1-, 3-, and 5-year DFS and OS with respect to this factor. We found that the cumulative 1-, 3-, and 5- DFS and OS rates were shorter in patients with deep invasion (muscularis propria and pericolonic tissue) than in those with superficial invasion (mucosa and submucosa) – regardless of the surgical approaches (tab. III; figs. 1 and 2). As shown in table III and

Table II. Univariate and multivariate analyses for disease-free survival (DFS) and overall survival (OS) of patients with rectal NETs after local excision of the rectum or rectum resection

Variables	Disease-free survival				Overall survival			
	Univariate analysis		^a Multivariate analysis		Univariate analysis		^a Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	P
groups	0.138 (0.036–0.534)	0.004	1.823 (0.086–3.167)	0.551	0.006 (0.001–20.571)	0.216		
age (years)	3.367 (0.867–13.077)	0.08			2.557 (0.266–24.612)	0.416		
gender	1.168 (0.302–4.519)	0.822			1.449 (0.240–8.754)	0.686		
primary tumor size (mm)	11.790 (2.496–55.686)	0.002	3.291 (0.491–22.043)	0.468	12.453 (1.387–111.771)	0.024	4.468 (0.358–55.707)	0.245
distance from AV (cm)	1.889 (0.532–6.701)	0.325			1.927 (0.321–11.562)	0.473		
differentiation	5.421 (1.145–25.675)	0.033	2.618 (0.492–13.943)	0.408	4.477 (0.464–43.247)	0.195		
invasion	17.385 (3.684–82.052)	<0.001	8.374 (1.342–52.248)	0.023	15.333 (1.710–137.447)	0.015	15.333 (1.710–137.447)	0.015
grade	5.181 (1.494–17.966)	0.01	0.156 (0.003–7.929)	0.89	2.782 (0.463–16.701)	0.263		
HPF	4.518 (1.274–16.019)	0.02	3.419 (0.147–79.551)	0.98	3.233 (0.535–19.529)	0.201		
N status	14.731 (4.131–52.529)	<0.001	4.021 (0.896–18.037)	0.069	4973.5 (0.001–7.825E)	0.518		
Ki-67	4.144 (1.165–14.747)	0.028	0.931 (0.197–5.200)	0.759	1.422 (0.159–12.727)	0.753		
CD56	1.355 (0.288–6.390)	0.701			32.824 (0.006–183676)	0.428		
synaptophysin	0.541 (0.140–2.095)	0.374			28.549 (0.002–381675)	0.489		
chromogranin	0.376 (0.048–2.966)	0.353			0.033 (0.001–327.922)	0.468		

HR – hazard ratio; CI – confidence interval; AV – anal verge; HPF – high power field

^aCox proportional hazards models adjusted for groups (local excision [reference], radical surgery), age (≤ 65 [reference], >65), gender (male [reference], female), primary tumor size (<10 [reference], ≥ 10), distance from AV (≤ 6 [reference], >6), differentiation (well [reference], moderate), invasion (mucosa + submucosa [reference], muscularis propria + pericolic tissue), grade (G1 [reference], G2), HPF ($\leq 2/10$ [reference], $>2/10$), N status (N0 [reference], N1), Ki-67 ($\leq 2\%$ [reference], $>2\%$), CD56 (negative [reference], positive), synaptophysin (negative [reference], positive), chromogranin (negative [reference], positive).

Table III. Proportion of disease-free survival and overall survival of patients with rectal neuroendocrine tumors in radical surgery and local excision groups, depending on the depth of invasion of rectal neuroendocrine tumors in both groups over 1, 3, and 5 years ($p = 0.001$)

Time		Groups		Depth of invasion	
		Radical surgery	Local excision	Mucosa/submucosa	Muscularis/pericolic tissue
1 year	disease free survival	82.6%	96.9%	98.5%	78.9%
	overall survival	95.7%	100%	100%	94.4%
3 years	disease-free survival	72.9%	–	97.1%	72.9%
	overall survival	90.6%	–	100%	87.7%
5 years	disease-free survival	68%	94.4%	97.1%	53.1%
	overall survival	84.6%	100%	100%	87.7%

figures 1 and 2, patients with rectal NETs having invasion to the mucosa and submucosa had better 1-, 3- and 5-year DFS and OS rates than those with invasion to the muscularis propria and pericolic tissue in both the groups ($p = 0.001$).

Factors associated with invasion and LN metastasis

Regarding survival and recurrence rates, we identified factors associated with invasion that corresponded to poor DFS and OS.

We also investigated additional factors influencing DFS, such as LN positivity. We used logistic regression analysis to identify associated factors and compare potential factors. We included primary tumor size, grade, differentiation of primary tumor, T status, mitotic activity, synaptophysin, chromogranin, N status and invasion.

Factors predicting invasion

We analyzed factors that could predict the depth of invasion of the primary tumor. As shown in table IV, the mitotic index (HPF)

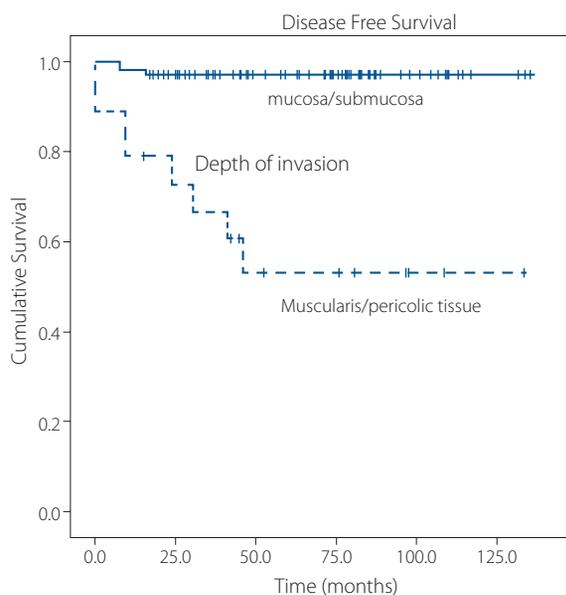


Figure 1. Disease-free survival (DFS) of patients with rectal neuroendocrine tumors (NETs) with two depths of invasion ($p < 0.001$)

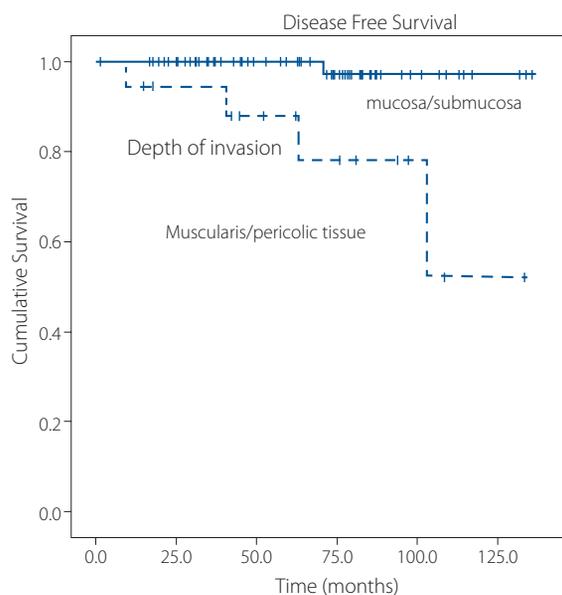


Figure 2. Overall survival (OS) of patients with rectal neuroendocrine tumors (NETs) with two depths of invasion ($p = 0.001$)

Table IV. Logistic regression analysis of factors predictive for invasion

Variables	Groups		p	Logistic regression analysis		
	Radical surgery	Local excision		Odds ratio	95% confidence interval	p
primary tumor size (>11 mm)	15 (65.2%)	10 (15.6%)	<0.001	38.515	4.343–341.594	0.001
high power field ($\geq 2/10$)	9 (39.1%)	3 (4.7%)	<0.001	55.560	4.711–655.309	0.001
grade ($\geq G2$)	11 (47.8%)	5 (7.8%)	<0.001			a_
N (+)	10 (43.5%)	0	<0.001	7.570	0.871–65.766	0.066
Ki-67 (>2%)	8 (34.8%)	6 (9.4%)	0.001			a_
CD56 (+)	21 (91.3%)	45 (70.3%)	0.802			
synaptophysin (+)	21 (91.3%)	50 (78.1%)	0.735			
chromogranin (+)	4 (17.4%)	16 (25.0%)	0.697			
differentiation (moderate)	3 (13.0%)	2 (3.1%)	0.011			b_

^aInsignificant and not presented

^bExcluded by the variance inflation factor (VIF)

associated with NET biology was predictive of the depth of invasion in the univariate analysis and remained an independent predictor in the multivariate analysis (odds ratio [OR], 55.560; 95% CI, 4.711–655.309; $p = 0.001$). Primary tumor size >10 mm was also an independent predictor of invasion according to the univariate and multivariate analyses (OR, 38.515; 95% CI, 4.343–341.594; $p = 0.001$).

Factors predicting LN positivity

We used the same model to investigate factors that could predict LN metastasis in the multivariate analysis. We found that only invasion of the primary tumor remained an independent predictor of LN positivity (OR 14.893 CI 2.532–87.587, $p = 0.003$) in the multivariate analysis.

Discussion

According to modern data, an increasing number of patients visit hospitals with small rectal NETs because of the efficient screening program. Thus, the proportion of tumors of ≤ 10 mm in size with maximum invasion to the submucosa (T1) has increased over time, accounting for 45–65% of patients in recent years. This makes the local treatment of rectal NETs with good oncological outcomes feasible in many cases [1, 4, 26, 27]. In our study, we failed to include a large number of cases that were treated with local excision and radical surgery because most cases had small tumors (<10 mm) and were treated with EMR/ESD or cold polypectomy. Nonetheless, we included a small proportion of patients with tumors >10 mm in size who received bigger surgical treatments such as local excision or

radical surgery. We analyzed the effectiveness of local excision compared with radical surgery and also challenged the main idea based on NCCN and ENETS guidelines regarding the size of primary tumors that should be considered as the most important factor when treatment is planned.

We found that the groups were quite heterogeneous for analysis. Patients in the local excision group had better DFS and OS than those in the radical surgery group. However, that was because the early stage of the disease was mostly found among patients in the group with LE. The radical surgery group included patients with larger primary tumor size, LN+, higher grade and deeper invasion. However, it is worth indicating that regardless of more aggressive NETs in patients in the radical surgery group, radical surgery could not improve the oncological outcomes.

We also investigated other factors that could influence oncological outcomes. Factors such as mitotic index, Ki-67, grade, N+, PNIV and LVIV were insignificant and did not influence DFS and OS according to the results of univariate and multivariate analysis. However, invasion appeared to be an independent factor influencing the DFS and OS of patients with rectal NETs. Patients with rectal NETs who had invasion beyond the submucosa layer had a poorer 1-, 3-, and 5-year DFS and OS compared with those having superficial invasion. Based on these results, we attempted to identify factors that influenced invasion. We found that tumor size >10 mm, mitotic index >2 and LN+ were independent predictors of the depth of invasion and thus influenced the recurrence rate and survival of patients. In contrast, we also revealed that the depth of invasion (beyond the submucosa) was an independent predictor of LN positivity, which predicted poor oncological outcomes in many previous studies. We suggest that the depth of invasion of primary NETs is the most important factor that should be considered when treatment strategies are planned. Our study also reviewed modern data found in much larger studies and discovered that where the size of the primary tumor or a more radical treatment failed to be independent factors of DFS and OS.

However, our study does have significant limitations such as its small sample size, selection bias owing to retrospective non-randomized data and group heterogeneity. We believe that more comparative prospective randomized studies with a larger number of cases are needed to corroborate our findings and investigate other prognostic factors of rectal NETs that can determine treatment strategies.

Conclusion

In summary, our findings demonstrated that local excision could be effective in treating rectal NETs in the early stage. They revealed that the depth of invasion was an important factor in influencing oncological outcomes. Nonetheless, our findings need to be confirmed in more prospective and randomized studies with a larger number of cases and more homogeneous data.

Conflict of interest: none declared

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