

Multivariable analysis for complete resection rate of 10-20 mm non-metastatic rectal neuroendocrine tumors: a retrospective clinical study

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ABSTRACT

Background: This retrospective study aimed to identify key factors affecting the rate of complete resection for non-metastatic rectal neuroendocrine tumors (NETs) using both transanal local excision (TLE) and endoscopic submucosal dissection (ESD).

Methods: Records in the past 10 years were retrieved, for a total of 95 patients diagnosed with nonmetastatic rectal NETs sized between 10-20 mm. Treatment outcomes were first compared between TLE and ESD to identify significantly associated factors. Monofactor analysis was then performed between complete and local resections to identify risk factors, which were then subjected to a multivariable analysis to identify independent risk factors.

Results: Treatment outcomes between TLE and ESD were significantly associated with depth of invasion (P=0.039) and complete/local resection (P=0.048). By monofactor analysis between complete and local resections, depth of invasion, tumor size, tumor stage and endoscopic manifestation were identified to be risk factors (P=0.014, 0.003, 0.002 and 0.028, respectively). In subsequent multivariable analysis, depth of invasion and tumor size were independent risk factors, with odds ratio of 18.838 and 37.223, and 95% confidence interval of 1.242-285.800 and 2.839-488.078, respectively.

Conclusion: Depth of invasion and tumor size were independent risk factors that significantly affect the complete resection rate of 10-20 mm non-metastatic rectal NETs.

Keywords: Rectal neuroendocrine tumors · Multivariable analysis · Transanal local excision · Endoscopic submucosal dissectionscriptome · Metastasis

Introduction

Neuroendocrine tumors (NETs) is a type of

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gastrointestinal NETs in the rectum, which constitutes over 30% of all gastrointestinal NET diagnosis and ranks the most frequent only after small bowel NETs (1). The incidence rate of rectal NETs has risen by nearly 10 times in the past 3 decades (2). This sharp increase is thought to be a result of elevated awareness of the disease development, as well as improved preventive screening for colorectal cancer, because significant fraction of renal

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neoplasms are of low grade/stage at diagnosis (3, 4). It's estimated that at the time of diagnosis, approximately 80% of rectal NETs are less than 10 mm in diameter, with no indication of invasion or metastasis (5). According to European Neuroendocrine Tumor Society (ENETS) guidelines, medium sized rectal NETs (10-20 mm) are considered to have low risk of metastasis, for which adequate local resection is appropriate (6, 7).

Conventional polypectomy has been used to treat rectal NETs, but its efficacy is less than ideal for tumors with submucosal invasion (8, 9), therefore novel improved techniques, including endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), are developed (2). EMR is advantageous over conventional polypectomy because submucosal injection produces a peduncle to lift the rectal NET away from the muscularis propria thereby enabling simple resection with snare cautery (1). Similar to EMR, tumors are also lifted out of the muscularis propria layer through submucosal injection in ESD, which has been consistently suggested to yield higher rate of complete resection than EMR (10, 11). However, compared to EMR, ESD is associated with increased incidence of complications and adverse events, including bowel perforation and delayed bleeding postprocedure (2).

In this retrospective study, we retrieved records in the past 10 years, including a total of 95 patients diagnosed with non-metastatic rectal NETs sized between 10-20 mm. Risk factors affecting the rate of complete resection for non-metastatic rectal NETs between transanal local excision (TLE) and ESD were analyzed and hereby reported.

Materials and Methods Ethical statements

The current retrospective study was approved by the Ethical Committee of the Affiliated Suqian Hospital of Xuzhou Medical University and the Affiliated Jiangning Hospital of Nanjing Medical University. All patients provided written consent forms, and their records were used anonymously.

Inclusion and exclusion criteria

Patients with records that met these inclusion criteria were included: 1) being diagnosed of rectal NET with a size between 10-20 mm; 2) with clear endoscopic images and complete post-operation pathology and immunohistochemistry results; 3) with complete baseline characteristics including magnetic resonance imaging (MRI), computerized tomography (CT) and hematology results; 4) without local or distant metastasis; 5) received either TLE or ESD surgical treatments; 6) with tumor stage classification using post-operation tissue sample based on the 2010 World Health Organization (WHO) classification (12). Patient records were excluded if they were: 1) with non-rectal NETs or mixed adenoneuroendocrine carcinoma; 2) with rectal NETs smaller than 10 mm or larger than 20 mm.

Patients

Records of a total of 95 patients with rectal NETs, who were admitted in the Affiliated Suqian Hospital of Xuzhou Medical University and the Affiliated Jiangning Hospital of Nanjing Medical University between January 2008 and April 2019, were eventually eligible for the current study. These 95 patients included 59 males and 36 females, aged from 29 to 58 years with a median age of 49.

Statistical analysis

SPSS 17 software was used for statistical analysis. First, chi square test was used to compare enumeration and categorical data, while Student t test was used to compare quantitative data. Significant factors were then subjected to monofactor analysis to identify risk factors differentiating between complete and local resections. Risk factors with P < 0.05 were further subjected to multivariate logistic regression analysis, to calculate odds ratio (OR) with 95% confidence interval (CI). P < 0.05 indicates statistical significance.

Results

Patient characteristics are listed in Table 1. In the total of 95 eligible patients analyzed in the current study, 59 were males and 36 were females, and their median age was 49 years old. By endoscopic examination of their rectal NETs, 39 patients presented as wide-base polyp and 56 as protrusive mass. Pre-operation trans-rectal ultrasound indicated that 47 cases had mucosal invasion and the other 48 cases had tumor invasion into the submucosa. Median distance of the NETs to anal verge was 6.5 cm, ranged from 3-15 cm. 51 patients underwent TLE while the other 44 were treated by ESD. Median tumor size of all patients was 11.5 cm, with the range 10-20 cm (by inclusion criteria). Based on WHO classification, 87 patients were in G1 stage, while 8 were in G2, and no G3 patient. Among all 95 patients, 75 cases continued with endoscopic follow-up, with a median follow-up length of 37.1 months, ranged from 3.5-113.0 months.

Next, treatment outcomes were first compared between TLE and ESD to identify significantly associated factors (**Table 2**). Among 51 TLE cases, 43 were complete resection (84.3%), while only 24 cases were complete resection in 44 ESD procedures (54.5%), with statistically significant difference (P=0.048). Depth of invasion was another significant factor between TLE and ESD (P=0.039).

Monofactor analysis was then performed between complete and local resections to identify risk factors (**Table 3**). Depth of invasion (P=0.014), tumor size (P=0.003), tumor stage (P=0.002) and endoscopic manifestation (P=0.028) were found to be significant risk factors distinguishing complete resection and local resection.

The abovementioned four single risk factors were then

Table 1. Clinical characteristics of patients.

Factors	Data			
Gender (male/female)	59/36			
Age, year [median (range)]	49 (29-58)			
Endoscopic manifestation				
Sessile polyp	39			
Protrusive mass	56			
Depth of invasion				
Mucosa	47			
Submucosa	48			
Distance to anal verge, cm [median (range)]	6.5 (3-15)			
Treatment				
TLE	51			
ESD	44			
Tumor size, mm [median (range)]	11.5 (10-20)			
Tumor stage				
G1	87			
G2	8			
Cases of follow-up, n (%)	75 (78.94%)			
Length of follow-up, months [median (range)]	37.1 (3.5-113.0)			

subjected to multivariate logistic regression analysis, among which only depth of invasion and tumor size were calculated to be independent risk factors (**Table 4**). The OR for depth of invasion was 18.838 with 95% CI of 1.242-285.800, while the OR of tumor size was 37.223 with 95% CI of 2.839-488.078.

Discussion

Surgical strategy for rectal NETs

NETs are a type of well-differentiated epithelial neoplasm, with the main characteristic of predominant neuroendocrine differentiation. According to the 2010 WHO classification, NETs can be categorized into G1 (mitotic count < 2 per 10 high-power fields and/or Ki67 index < 3%) and G2 (mitotic count 2-20/10 high-power fields and/or Ki67 index 3-20%) stages.(6, 12) Due to low atypia and proliferation of tumor cells, rectal NETs generally present good prognosis with 5-year overall survival of 88.3 (13), with complete resection being the only guaranteed curative option (14). However, for most well-differentiated NETs of small size (< 10 mm), local resection is considered more appropriate because radical surgery carries a higher risk to benefit ratio. The metastatic risk of rectal NETs smaller than 10 mm, which can be completed resected, was considered to be only 3-9.8%,(9) whereas metastatic risk of rectal NETs between 10-20 mm was as high as 10-15% (15). Consistent with the above reported metastasis rates, a very recent analysis has also concluded that, there is no survival benefit to radical resection of 10-20 mm, nonmetastatic rectal NETs (16). Moreover, endoscopic/local resection was also controversial due to the lack of a consistent recognition of its efficacy (17). In comparing complete vs local resections, as well as TLE vs ESD, data in our study suggested that, although ESD is a safer surgical approach, it carries certain post-operation complications especially bleeding and perforation. Despite of these complications, the outcome of ESD is not impacted by the distance of tumor to anal verge, suggesting potential clinical benefits in cases of NETs with long distance. On the other hand, we have observed that pre-operation trans-rectal ultrasound for depth of invasion also affected the surgical outcome between complete and local resections, indicating that local resection yielded better efficacy. Therefore, local resection is the preferred surgical approach for rectal NETs between 10-20 mm, when permitted by distance of tumor to anal verge. Of note, 75 patients were re-visited endoscopic examination after surgery, putting the effective follow-up rate of our study as high as 78.94%, and no recurrence was observed.

Factors contributing to degree of resection for rectal NETs

Since surgical strategies for rectal NETs are mainly determined based on tumor size and stage, accurately assessing the size and invasion depth of the tumor by trans-rectal ultrasound is of critical importance before surgery (18). Currently there has been no clear recommendation for the best endoscopic resection strategy, but recent studies have suggested that, complete tumor resection with clear surgical margin is difficult to achieve by traditional rectal endoscopic polypectomy, especially when the tumor is sessile or arises from the deep portion of the epithelial glands penetrating the mucosa into the submucosa (19). Clinical limitations still exist even though constantly improving surgical techniques have greatly

Table 2.	Treatment	outcomes	between	TLE and ESD.
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Factors	TLE (n=51)	ESD (n=44)	P value	
Age, year [median (range)]	48 (30-58)	50 (29-57)	0.445	
Gender (male/female)	19/32	40/4	0.250	
Degree of resection				
Complete	43	24	0.048	
Local	8	20		
Endoscopic manifestation				
Sessile polyp	19	20	0.356	
Protrusive mass	31	25		
Depth of invasion				
Mucosa	35	12	0.039	
Submucosa	16	32		
Distance to anal verge, cm [median (range)]	6.7 (3-9)	10.1 (8-15)	0.128	
Tumor size, mm [median (range)]	15.6 (10-20)	11.9 (10-19)	0.582	
Tumor stage				
G1	47	40	0.963	
G2	4	4		
Post-operation complications				
Bledding	8	8 4		
Perforation	0	4	0.996	

TLE: transanal local excision; ESD: endoscopic submucosal dissection.

Table 2. Treatment outcomes b	between TLE and ESD.
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Factors	Complete (n=67)	Local (n=28)	P value	
Treatment				
TLE	43	8	0.112	
ESD	24	20		
Gender (male/female)	31/36	28/0	0.999	
Age, year [median (range)]	49 (29-58)	50 (36-57)	0.919	
Depth of invasion				
Mucosa	47	0	0.014	
Submucosa	20	28		
Distance to anal verge, cm [median (range)]	9 (3-15)	7 (5-10)	0.471	
Tumor size, mm [median (range)]	13 (10-19)	19 (12-20)	0.003	
Tumor stage				
G1	59	28	0.002	
G2	8	0		
Endoscopic manifestation				
Wide-base polyp	35	4	0.028	
Protrusive mass	32	24		
Post-operation complications				
Bleeding	8	4		
Perforation	0	4	0.866	
None	59	20		

TLE: transanal local excision; ESD: endoscopic submucosal dissection.

Table 4. Multivariable analysis.

	В	SE	Wald	DF	Sig.	OR	95% CI of OR
Depth of invasion	2.936	1.387	4.477	1	0.034	18.838	1.242-285.800
Tumor size	3.617	1.313	7.588	1	0.006	37.223	2.839-488.078

B: B coefficient; SE: standard error; Wald: Wald chi-square test; DF: degrees of freedom; OR: odds ratio; CI: confidence interval.

increased the complete resection rate by EMR and ESD. In our present study, complete resection rate was 84.3% (43/51) for TLE and 54.5% (24/44) for ESD, respectively, and is significantly correlated with tumor size and invasion depth. Nevertheless, full-thickness excision is still a first surgical option for complete removal of rectal NETs (20, 21). in which the broadened operative field by carbon dioxide insufflations allows accurate determination of margins and the possibility of suturing. In addition, full-thickness excision greatly reduces complications such as bleeding and perforation, the latter of which could be repaired without conversion to a transabdominal approach. The 8 cases of bleeding after TLE healed spontaneously without perforation following conservative treatment. On the contrary, 4 cases of perforation occurred during ESD as a result of an effort to preserve intact samples, all of which were repaired immediately during surgery. In the actual surgeries reported here, distance of tumor to anal verge also hindered operation and consequently impacted complete resection rate, although no statistically significant correlation was observed, likely due to small sample size.

Moreover, besides tumor size (no less than 10 mm), lymphovascular invasion, muscularis invasion and mitotic count, all of which were correlated with recurrence and metastasis of rectal NETs (22, 23), histologically complete resection is also key factor in preventing recurrence and metastasis. In line with this, for rectal NETs between 10-20 mm, National Comprehensive Cancer Network has recommended rectal endoscopic follow-up at 6 and 12 months after surgery (24).

Lymph node dissection for rectal NETs

According to the European Neuroendocrine Tumor Society Consensus Guidelines, rectal NETs are considered to be indolent, and complications are only observed in a small proportion of patients. However, recent study has pointed out that, despite a relatively indolent behavior, approximately 5% of rectal NETs smaller than 10 mm are indeed malignant and can metastasize locally (25).

A retrospective study in epidemiology has found that, rectal tumors 11-19 mm in size are more frequent of lymph node involvement than smaller ones (26). Patients receiving radical excision general have higher tumor stage and/or grade, and their tumors may have invaded into the muscularis propria, which is independently correlated with lymphatic metastasis (15). Although the 5-year overall survival rate of rectal NETs is close to 85%, that with local metastasis is sharply reduced to 50%, which is further decreased merely 20% in cases with distant metastasis (27). In the present study, no lymph node involvement was detected in either TLE or ESD. Based on

pre-operation trans-rectal ultrasound scan, tumor invasion was restricted to mucosa and submucosa. Therefore, even in the case of incomplete resection, a localized colectomy is still appropriate for rectal NETs smaller than 20 mm with submucosal invasion (28).

Conclusion

Both TLE and ESD are appropriate therapies to treat rectal NETs between 10-20 mm. Tumor size and invasion depth are independent risk factors associated with rate of complete resection. Cautions should be taken when treating these tumors with malignant potential in clinic, and it is critical to follow systematic diagnosis and management in latest guidelines,(29) in order to choose the therapy with the highest benefit-to-risk ratio for patients.

Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

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