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Application of Modified Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection in Treating Rectal Neuroendocrine Tumors and Prognostic Analysis

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Abstract: *Objective:* To analyze the application value of modified endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) in rectal neuroendocrine tumors, with a view to providing new clinical options for the early diagnosis and treatment of patients with such tumors, and thus improving their prognosis. *Methods:* Seventy-two patients with rectal neuroendocrine tumors who underwent surgical treatment in a hospital between October 2023 and September 2024 were selected and divided into a control group and an observation group using the mean score method, each with 36 cases. In the control group, traditional foreign body forceps combined with laparoscopic resection were performed, and in the observation group, modified EMR and ESD were performed as needed. The mass resection rate, histologically intact resection rate, postoperative serum vascular endothelial growth factors (VEGFA, VEGFB, VEGFC levels) in the postoperative period of 7d, and indicators of the rate of related complications of the two groups of patients were compared. *Results:* The mass resection rate of 91.67% and histological complete resection rate of 94.44% in the observation group were significantly higher than those of 72.22% and 66.67% in the control group; the VEGFA, VEGFB, and VEGFC levels of the observation group were 82.08 ± 7.94 ng/ml, 168.89 ± 16.53 ng/ml, and 121.07 ± 10.75 ng/ml, respectively, in the postoperative period of 7 d after surgery; the levels were significantly higher than those of the control group: 68.39 ± 6.82 ng/ml, 141.06 ± 14.12 ng/ml, and 98.45 ± 9.87 ng/ml, respectively, and the difference was statistically significant ($P < 0.05$); the patients in the observation group had a lower rate of surgical complications than those in the control group (2.78% vs 8.33%), the difference was not statistically significant ($P > 0.05$). *Conclusion:* Modified EMR and ESD in rectal neuroendocrine tumors are effective, not only can it effectively improve the rate of mass resection and histological integrity of the resection rate, but it can also further improve the level of serum vascular endothelial growth factor (VEGFA, VEGFB, VEGFC); thus, it is recommended to be promoted for use in clinical practice.

Keywords: Modified endoscopic mucosal resection; Endoscopic submucosal dissection; Rectal neuroendocrine tumor

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1. Introduction

Rectal neuroendocrine tumors (R-NETs) are rare tumors originating from the endocrine cells of the intestinal mucosa, accounting for 1–2% of all rectal tumors [1]. With the popularization of endoscopic techniques and the improvement of pathological diagnosis in recent years, the detection rate of R-NETs has been on the rise year by year. According to the World Health Organization (WHO) classification, the prognosis of R-NETs is closely related to tumor size, infiltration depth, histological grading (G1/G2/G3), and lymph node metastasis [2]. Among them, G1/G2 grade tumors with a diameter of ≤ 1 cm and confined to the mucosa or submucosa usually have a good prognosis, and the 5-year survival rate after complete resection can reach more than 95%; while those with tumors > 2 cm or with myxoid infiltration and lymph node metastasis have a significantly increased risk of recurrence. Therefore, accurate early diagnosis and minimally invasive treatment are crucial for improving patient prognosis [3]. Clinically, endoscopic resection is recommended for R-NETs ≤ 1 cm in diameter, while > 2 cm or high-grade tumors require radical surgery (e.g., total rectal mesentery resection). However, the treatment strategy for tumors between 1 and 2 cm remains controversial. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are increasingly used as minimally invasive techniques in the treatment of R-NETs [4]. EMR is easy to perform and has a short operation time, but there are problems such as insufficient resection depth and a high rate of positive margins. ESD can achieve whole resection and improve the R0 resection rate, but it is technically difficult and has a higher risk of perforation. Currently, studies on the selection of indications, differences in efficacy, and long-term prognosis of the two procedures in R-NETs are still limited, especially the optimal management of 1–2 cm tumors for which no consensus has been reached [5]. The aim of this study was to systematically analyze the efficacy of modified EMR versus ESD in the treatment of R-NETs, with a view to providing an evidence-based basis for clinical decision-making.

2. Information and methodology

2.1. General information

Seventy-two patients with rectal neuroendocrine tumors who underwent surgical treatment in a hospital during the period from October 2023 to September 2024 were selected and divided into a control group and an observation group, each with 36 cases, using the mean score method. The general data of patients in the two groups are shown in **Table 1**.

Inclusion criteria: (1) Histopathologically confirmed diagnosis of rectal neuroendocrine tumor (grade G1/G2), in accordance with the WHO 2019 classification criteria; (2) Tumor confined to the mucosa or submucosa (stage T1) without lymph node or distant metastasis, as assessed by imaging; (3) Treated with modified EMR or ESD, and with complete clinical data (including preoperative evaluation, surgical records, and postoperative follow-up data); (4) Postoperative follow-up ≥ 12 months, with regular endoscopic and imaging review records; (5) All patients signed an informed consent form.

Exclusion criteria: (1) Pathological grade of G3 (neuroendocrine carcinoma) or tumor infiltrating the muscularis propria and above (T2–T4) with lymph node/distant metastasis (M1); (2) Previous rectal surgery, radiotherapy or systemic anti-tumor therapy (e.g. chemotherapy, targeted therapy); (3) Intraoperative finding of tumor unable to be completely resected, or intermediate open surgery; (4) Presence of severe cardiac, pulmonary, hepatic, renal functional Insufficiency, unable to tolerate endoscopic surgery; (5) Loss of postoperative visits or incomplete key clinical data (e.g. pathological results, imaging reports).

Table 1. Comparison of the general information of patients in the two groups

Groups	Gender		Age (mean ± SD, years)	Carcinoid diameter [*n* (%)]		Distance from anal dentate line (mean ± SD, cm)
	Male	Female		< 7 mm	≥ 7 mm	
Control group (*n* = 36)	21	15	50.02 ± 4.34	24 (66.67)	12 (33.33)	6.34 ± 1.48
Observation group (*n* = 36)	23	13	49.77 ± 5.28	26 (72.22)	10 (27.78)	6.31 ± 1.52
χ^2/t	0.2338		0.2195	0.2618		0.0848
P	0.6287		0.8269	0.6089		0.9326

SD: Standard deviation

2.2. Methodology

The control group implemented a traditional foreign body clamp combined with loopers resection. Preoperative conventional colonoscopy was performed to clarify the location and scope of the lesion, and then the lesion was fully elevated by submucosal injection of saline (containing epinephrine and indigo carmine), and the proximal mucosa of the lesion was clamped with a foreign body forceps and lifted upward to fully expose the base of the lesion. Subsequently, a high-frequency electrical coiler was placed, and the coiler was tightened at the base of the lesion, and electroresection was performed using the ENDOCUT mode (effect 3, power 40 W). After excision, the wound was inspected, and active bleeding points were stopped using hot biopsy forceps or metal clips. The excision specimen was fixed using filter paper and sent for pathological examination to assess the horizontal and vertical cutting edges. Postoperatively, patients were required to fast for 24 hours and were closely monitored for complications such as delayed hemorrhage or perforation.

The observation group underwent modified EMR and ESD as needed. (1) Endoscopic clear cap-assisted submucosal resection (EMR-C): Endoscopic multi-point injection of a melphalan-saline mixture around the lesion using a mucosal injection needle was performed until the lesion was fully elevated. Subsequently, a transparent cap was installed at the anterior endoscopic end, and the pre-set loopers were embedded in the inner groove of the transparent cap, and the elevated lesion was completely sucked into the transparent cap by negative pressure suction, and the loopers were slowly tightened to ensure complete ligation. A high-frequency electric knife (ENDOCUT mode) was used for resection, and the resection area included the tumor and the surrounding 0.5 cm of normal mucosal tissue. The wound was hemostatized by electrocoagulation and closed with additional titanium clips if necessary. The completely resected specimen was immediately fixed in 10% formalin solution and sent for pathological examination to assess the completeness of the resection. (2) Endoscopic submucosal dissection: Electrocoagulation marking was performed at 0.5 cm from the edge of the lesion using a Dual knife, followed by multi-point injections of a melphalan-saline mixture at the base of the lesion to fully elevate the submucosa. The Dual knife was used to circumferentially incise the mucosal layer along the marking point to reach the submucosal layer, and then the submucosal layer was delicately peeled off, with adequate hemostasis maintained to ensure a clear field of vision, and supplemental submucosal injections were given to maintain the lifting effect when necessary. Care was taken to maintain the integrity of the lesion during dissection until the lesion was completely detached from the muscularis propria. Thorough electrocoagulation was performed to stop hemorrhage, and hemostatic clips were used where appropriate to expose larger vessels. The specimen of complete stripping was fixed in 10% formalin solution immediately after endoscopic removal and sent for pathological examination to assess the horizontal and vertical cutting edges.

2.3. Observation indicators

(1) Surgical indicators: Statistical analysis of the rate of whole mass resection, histological complete resection rate, and the rate of related complications in the two groups of patients; (2) Vascular endothelial growth factor (VEGF) levels: 7d after surgery, patients' venous blood was collected and centrifuged to separate the serum, and then the serum was extracted using the enzyme-linked immunosorbent assay (ELISA) to measure VEGFA, VEGFB, and VEGFC levels.

2.4. Statistical methods

SPSS 21.0 statistical software was used to process the data, and the measurement information was expressed as mean ± SD with *t*-test, and the count information was expressed as percentage (%) with χ^2 test, and the difference was considered statistically significant with $P < 0.05$.

3. Results

The whole mass resection rate and histologically complete resection rate of patients in the observation group were higher than those in the control group, and the VEGFA, VEGFB, and VEGFC levels were significantly higher than those in the control group at 7d postoperatively, and the difference was statistically significant ($P < 0.05$); there was no statistical significance in the comparison of the related complication rates between the two groups ($P > 0.05$), as shown in **Table 2**.

Table 2. Comparison of clinical outcomes between the two groups of patients

Groups	Whole mass removed [*n* (%)]	Histologically complete resection [*n* (%)]	Serum vascular endothelial growth factor (VEGF) levels at 7d postoperatively (mean ± SD, ng/ml)			Complication rate [*n* (%)]
			VEGFA	VEGFB	VEGFC	
Control group ($n = 36$)	26 (72.22)	24 (66.67)	68.39 ± 6.82	141.06 ± 14.12	98.45 ± 9.87	3 (8.33)
Observation group ($n = 36$)	33 (91.67)	34 (94.44)	82.08 ± 7.94	168.89 ± 16.53	121.07 ± 10.75	1 (2.78)
χ^2/t	4.5997	8.8670	7.8476	7.6809	9.2998	0.2647
P	0.0320	0.0029	< 0.001	< 0.001	< 0.001	0.6069

4. Discussion

Rectal neuroendocrine tumors (R-NETs) are a group of low-grade malignant tumors originating from the endocrine cells of the intestinal mucosa, and their biological behaviors are closely related to tumor size, depth of infiltration, and histological grading. Surgical resection is the treatment of choice for G1/G2 grade tumors ≤ 2 cm in diameter that are confined to the mucosa or submucosa, with the core goals of achieving R0 resection (negative margins) and reducing the risk of local recurrence, while preserving anal function as much as possible [6]. Conventional foreign body forceps combined with loopers resection is a commonly used endoscopic treatment technique, whereby the lesion is lifted using a foreign body forceps after submucosal injection, and then resected electrically with a loopers [7]. However, there are significant limitations of this procedure: (1) a high rate of segmental resection, which can easily lead to positive margins and increase the risk of residual tumor; (2)

insufficient depth of resection, which makes it difficult to ensure complete resection of the submucosal layer, especially for slightly larger (1–2 cm) or slightly deeper infiltrating tumors [8]; (3) restricted intraoperative field of view and less precise operation, which may increase the risk of hemorrhage or perforation; and (4) postoperative pathology assessment is difficult, affecting subsequent treatment decisions [9,10]. Therefore, for R-NETs requiring high-precision resection, the efficacy and safety of this procedure are inadequate. Modified endoscopic mucosal resection (EMR-C) can improve the whole resection rate and ensure sufficient resection extent (0.5 cm of normal mucosa outside the tumor) through transparent cap-assisted negative pressure suction, while ESD achieves the whole resection of the lesion through layer-by-layer submucosal dissection, which is especially suitable for larger or complexly located tumors. Both can provide more complete pathological specimens, which is conducive to accurately assessing the status of the margins, and are less invasive with faster recovery, which is an important advancement in the minimally invasive treatment of R-NETs.

The results of this study showed that the whole mass resection rate of 91.67% and the histological complete resection rate of 94.44% in patients of the observation group were significantly higher than those of the control group, which were 72.22% and 66.67% respectively; and the serum VEGFA level in patients of the observation group in the 7d postoperative period was 82.08 ± 7.94 ng/ml, VEGFB level was 168.89 ± 16.53 ng/ml, and VEGFC level was 121.07 ± 10.75 ng/ml, which were significantly higher than those of 68.39 ± 6.82 ng/ml, 141.06 ± 14.12 ng/ml, and 98.45 ± 9.87 ng/ml in the control group, and the difference was statistically significant ($P < 0.05$), suggesting that endoscopic clear-cap assisted mucosal resection (EMR-C) and ESD can obtain more complete tumor clearance, significantly improve the quality of treatment for R-NETs, and reduce the risk of recurrence.

5. Conclusion

In conclusion, modified EMR with ESD is a highly effective minimally invasive procedure for the treatment of rectal neuroendocrine tumors, which can significantly improve the whole resection rate and pathological integrity with good safety. Appropriate surgical modalities should be selected according to tumor characteristics in clinical practice to achieve the best prognosis.

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Disclosure statement

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