Full-thickness resection of neuroendocrine tumors in the rectum

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ABSTRACT

Background Rectal neuroendocrine tumors (NETs) are subepithelial tumors with potential for malignancy. Depending on tumor characteristics, endoscopic or surgical resection is recommended. However, the optimal endoscopic approach is not defined. This is the first larger study evaluating endoscopic full-thickness resection (EFTR) of rectal NETs.

Methods For resection, the full-thickness resection device (FTRD) was used. A registry was created as part of post-market clinical follow-up. All cases of rectal NETs in the registry were analyzed retrospectively.

Results 31 German centers entered data of 501 FTRD procedures and 40 cases of rectal NETs were identified. The median lesion size was 8 mm. All lesions could be resected using FTRD. The median procedure time was 18.5 minutes. Resection was macroscopically and histologically complete in all cases. Full-thickness resection was achieved in 95 %. No major adverse events occurred. Endoscopic follow-up showed no evidence of residual or recurrent tumor.

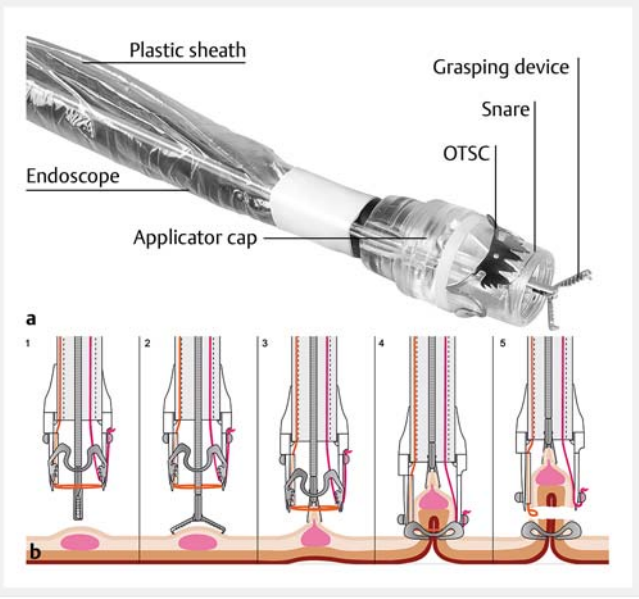
Conclusion EFTR is safe and effective for resection of smaller rectal NETs. Prospective comparative trials are needed to define the role of EFTR of rectal NETs.

Introduction

Rectal neuroendocrine tumors (NETs) are subepithelial tumors with potential for malignancy. Prevalence is low but has increased over past decades [1]. Depending on tumor size and histological characteristics, endoscopic or surgical resection is recommended. However, the optimal endoscopic approach is still being discussed and is currently not clearly defined. Conventional endoscopic mucosal resection (EMR) is fast and safe but often incomplete [2], as tumors arise from deeper layers than the mucosa. Endoscopic submucosal dissection (ESD) allows for high rates of complete en bloc resection [3] but is associated with higher complication rates [4]. Clip-assisted endoscopic full-thickness resection (EFTR) has been shown to be feasible, effective, and safe for smaller colorectal subepithelial tumors [5], including tumors infiltrating the muscularis propria. The aim of this study was to further evaluate the feasibility, efficacy, and safety of EFTR of rectal NETs.

Methods

For endoscopic resection, the full-thickness resection device (FTRD; Ovesco Endoscopy, Tübingen, Germany), which allows clip-assisted EFTR, was used (▶ **Fig. 1**, ▶ **Fig. 2**) [5–7]. Ovesco



▶ **Fig. 1** Full-thickness resection. **a** The full-thickness resection device (FTRD). **b** Resection using the FTRD: 1 = The lesion is identified. 2 = The lesion is grasped. 3 = The lesion is pulled into the applicator cap; a duplication of the rectal wall is created. 4 = The over-the-scope clip (OTSC) is deployed. 5 = The lesion is resected. Source: Ovesco Endoscopy AG.

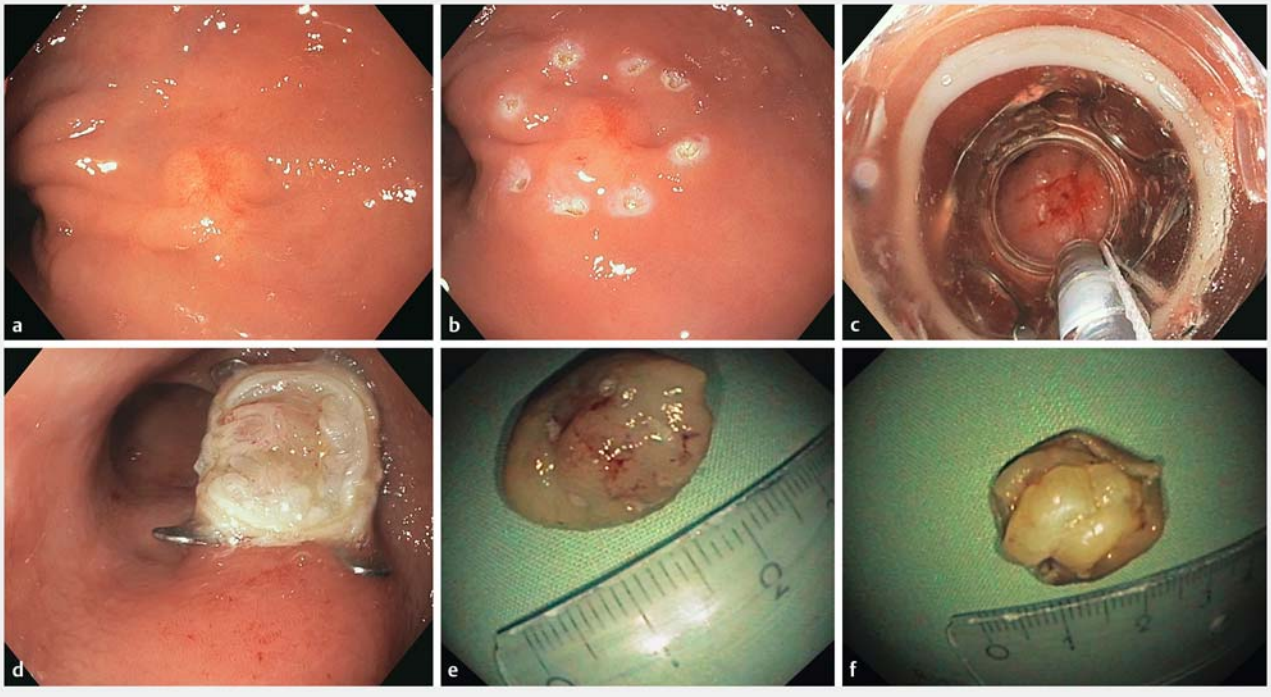
Endoscopy initiated post-market clinical follow-up to further evaluate FTRD functionality, efficacy, and safety.

An online database (FTRD registry) was created comprising 31 German endoscopy centers. All centers were invited to submit pseudonymized data of all performed FTRD resections. The following items were recorded: patient characteristics, indication for EFTR, date of intervention, lesion characteristics, histology before EFTR, endoscopic or surgical pretreatment, procedure time, size of resection specimen, technical success (macroscopic complete resection), adverse events and management, histology, full-thickness resection (visibility of all layers of the colonic wall including serosa), R0 resection, follow-up data.

The registry was searched for all cases of rectal NETs and data were analyzed retrospectively. If necessary, centers were contacted to obtain additional or missing information.

Results

Between September 2015 and May 2017, 31 German centers entered data from 501 FTRD procedures into the registry. A total of 16 centers (tertiary referral centers and community hospitals) contributed 40 cases of rectal NETs. Before resection all rectal NET were evaluated using endoscopic ultrasound. For lesions > 10 mm, advanced imaging was available to exclude risk factors.



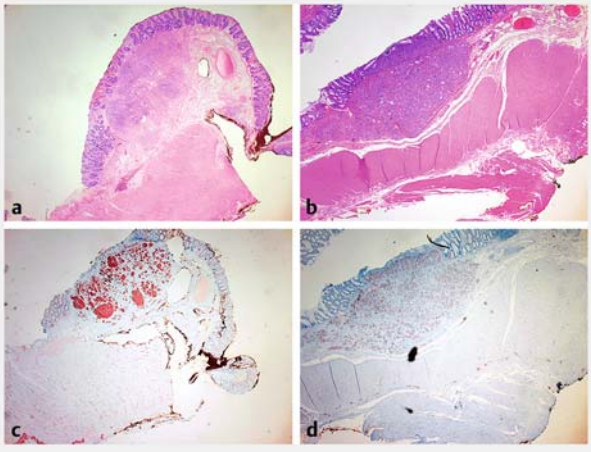
▶ **Fig. 2** Resection using the full-thickness resection device. 1 = The lesion is identified. 2 = The lesion is marked by coagulation. 3 = The lesion is grasped. 4 = Typical resection site after endoscopic full-thickness resection. 5 and 6 = Full-thickness resection specimen and complete resection (macroscopic).

A total of 21 female (52.5 %) and 19 male (47.5 %) patients with a median age of 57 years (range 28 – 81 years) were included in the study. Median lesion size was 8 mm (range 3 – 25 mm, standard deviation 4.43 mm), and lesions were < 10 mm in 67.5 % (27/40), 10 – 20 mm in 30.0 % (12/40), and > 20 mm in 2.5 % (1/40). Lesions were located in the middle (24 /40), lower (13/40), and upper (3/40) rectum. Overall, 15.0 % (6/40) were recurrent NETs and had been pretreated with EMR (4/6; 66.7 %) or multiple forceps biopsies (2/6; 33.3 %).

All lesions could be reached and resected using FTRD. The median procedure time was 18.5 minutes (range 7 – 60 minutes). Resection was macroscopically and histologically complete in all cases (▶ **Fig. 3**). Full-thickness resection was achieved in 95.0 % (38/40). Histology after EFTR showed low grade NETs (G1) without lymphovascular infiltration (L0, V0), and without other risk factors in 70.0 % (28/40). In 30.0 % (12/40) histology revealed granulation tissue or scarring.

No major adverse events occurred. Procedure-related minor adverse events were observed in 12.5 % (5/40). In four cases, minor periprocedural bleeding was observed and was managed endoscopically (coagulation and/or injection). In one case, the FTRD snare ruptured after clip application. This procedure was completed using a conventional resection snare, which resulted in a longer procedure time (60 minutes). Other adverse events were not observed.

Endoscopic follow-up was available in 80.0 % (32/40) and performed 12 weeks (median, range 1 – 49 weeks) after EFTR. Eight patients were lost to follow-up (five patients did not show up, three patients refused). In 71.9 % (23/32), the over-the-scope clip (OTSC) had spontaneously detached, and in 28.1 % (9/32) the OTSC was still in situ. No macroscopic evidence of residual or recurrent lesion was found.



▶ **Fig. 3** Histology. Example of two rectal neuroendocrine tumors after full-thickness and R0 resection. **a,b** Hematoxylin and eosin. **c, d** Synaptophysin.

Discussion

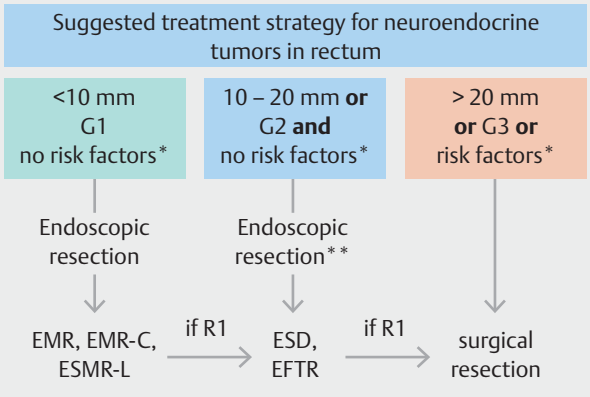
This is the first larger study (n = 40) of EFTR of rectal NETs using FTRD. The median lesion size was 8 mm (range 3 – 25 mm). All lesions could be resected successfully and the median procedure time was short (18.5 minutes). No major complications occurred. Endoscopic follow-up showed no signs of residual or recurrent lesions, and OTSCs detached spontaneously in 72 %, which is comparable to a recent larger study [5]. In one case, rupture of the FTRD snare after clip application occurred and was handled by subsequent use of a conventional snare. In the meantime, the FTRD snare was revised by the company as several cases of dysfunctional FTRD snares had been reported [5, 8]. Since then, to our knowledge, no further reports of FTRD snare rupture have occurred.

Rectal NETs are rare and are usually detected incidentally. However, prevalence of rectal NETs is increasing [1] and tumors bear malignant potential in about a quarter of cases. In consequence, depending on tumor size and risk factors (grading, mitotic index, Ki-67 index, invasion of muscularis propria, lymphovascular infiltration), endoscopic or surgical resection is necessary. Rectal NETs ≤ 10 mm are usually low grade (G1, Ki-67 index ≤ 2 %, and ≤ 2 mitoses/10 high power fields) with low (2 %) metastatic potential [1]. Current international guidelines recommend endoscopic resection for rectal NETs ≤ 10 mm without risk factors (G1, no lymphovascular infiltration, no invasion of the muscularis propria). For high grade rectal NETs (G3, Ki-67 index > 20 % or ≥ 20 mitoses/10 high power fields) or tumors > 20 mm in size or tumors with risk factors, surgical resection is recommended. Intermediate grade rectal NETs (G2, Ki-67 index 3 % – 20 % or 2 – 20 mitoses/10 high power fields) or lesions 10 – 20 mm in size can be managed endoscopically but the decision to use endoscopic resection should be made on an individual patient basis depending on risk factors, age, and comorbidities.

In this study, all rectal NETs were G1 without risk factors. Overall, 67.5 % were < 10 mm, 30 % were 10 – 20 mm, and one lesion was 25 mm (patient refused surgery). In all, 15 % were recurrent NETs and had been pretreated with EMR (66 %) or multiple forceps biopsies (33 %). In all cases, EFTR allowed for complete (R0) resection and accurate risk stratification.

In 30 %, histology showed a completely resected scar or granulation tissue (indication for EFTR was Rx or macroscopic suspicion of local recurrent NET).

Remarkably, clear recommendations for the type of endoscopic resection for rectal NETs are lacking, as prospective comparative studies between different resection techniques are scarce. The main objective of any technique is completeness (R0) and thus cure. In addition, the other pivotal question is the cost – benefit ratio of the resection technique at hand. EMR is fast and safe but often incomplete [2]. A recent study (n = 277) showed histological complete resection of rectal NETs (median size 5 mm) after EMR in only 72 % – 74 % [9]. ESD allows for precise resection with high rates (90 % – 100 %) of complete en bloc and R0 resection, and excellent diagnostic yield [3]; however, it is associated with higher complication rates and longer procedure times [4]. A meta-analysis by Zhong et al.



▶ **Fig. 4** Suggested treatment strategy for rectal neuroendocrine tumors.

showed higher R0 rates for ESD compared with EMR, but comparable rates of adverse events [10]. Modified EMR (mEMR) techniques, such as cap-assisted EMR (EMR-C), allow for endoscopic submucosal resection (ESMR). Deeper resection can be achieved with a ligation device after application of an elastic band (ESMR-L). Recent studies implicate superiority of mEMR over EMR regarding R0 resection for rectal NETs ≤ 10 mm. Remarkably, R0 rates (89.5 % – 94.1 %) were similar between mEMR and ESD [11, 12]. In contrast, a recent meta-analysis showed that mEMR (with suction) is superior to ESD for small rectal NETs (≤ 10 mm) in terms of histological complete resection and procedure time [13].

To date, no larger series have reported successful EFTR of rectal NETs with secondary or primary defect closure [6, 14, 15]. Our study is the first larger study of EFTR of rectal NETs.

The high R0/full-thickness resection rates in our study demonstrate that precise resection of small rectal tumors is possible with FTRD, even if the technique was reported to be more difficult and associated with lower full-thickness resection rates in the rectum (reduced mobility) compared with the colon [5, 6]. Given the short procedure time, low complication rate, and simplicity of the technique, EFTR with FTRD may be preferable to EMR/ESD for small rectal NETs.

Resection with FTRD is associated with a risk of bleeding, postpolypectomy syndrome, and perforation. FTRD-specific adverse events include stenosis, adhesion or damage of extraluminal structures (e. g. neurovascular bundle) after tissue incorporation/clip application, and the potential to affect the success of subsequent surgical resection if necessary. However, endoscopic clip removal is possible and, to date, no published reports have demonstrated a negative impact of FTRD resection on subsequent surgical resection.

Summing up our data and the available evidence, we suggest a size dependent treatment strategy for rectal NET (▶ **Fig. 4**). Lesions of 10 – 20 mm should be resected by FTRD/ESD, whereas smaller lesions should be resected by less invasive and less costly techniques. For larger tumors, surgery should be conducted. Of course, prospective comparative trials are needed to prove this concept and better define the role of EFTR.

Several limitations of our study need to be taken into account. Due to the rarity of rectal NETs, the patient numbers were small and a retrospective design was adopted in order to obtain adequate patient numbers. Hence, it was possible to include 40 cases of rectal NETs. Follow-up time was short (median 12 weeks). Centers with different endoscopic expertise were included (high proportion of community hospitals). However, high technical success and low complication rates show that the technique is feasible and safe even in smaller centers.

In summary, we demonstrated that EFTR with FTRD is a fast, safe, and effective option for rectal NETs < 20 mm without risk factors. We propose a size-dependent treatment strategy for rectal NETs. Owing to its safety and simplicity, EFTR with FTRD might be considered as an alternative to ESD for small tumors. However, prospective comparative trials are needed to better define the role of EFTR for rectal NETs.

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Competing interests

Drs. Schmidt and Caca have received lecture fees for FTRD training courses from Ovesco Endoscopy.

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