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Endoscopic full-thickness resection of duodenal lesions—a retrospective analysis of 20 FTRD cases

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Abstract

Background: Endoscopic resections in the duodenum harbor a significant risk of complications. The full-thickness resection device (FTRD) has shown favorable results concerning efficacy and safety in the resection of colorectal lesions. Data of its use in the duodenum are limited to a single, small case series ($n = 4$).

Methods: Data of all consecutive patients scheduled for endoscopic full-thickness resection (EFTR) of duodenal lesions by FTRD in our institution were collected and analyzed retrospectively. Primary endpoint was technical success.

Results: Between March 2014 and June 2017 EFTR of a duodenal lesion was planned in a total of 20 patients. Overall technical success was 17/20 (85.0%). Indication for EFTR was: adenomas ($n = 13$, seven treatment naïve, six pretreated), subepithelial tumors ($n = 5$) and T1 adenocarcinoma ($n = 1$). The FTRD could be advanced to the lesion in 19/20 cases (95.0%). R0-resection rate was 12/19 (63.2%). During follow-up after 3 and 12 months there were two recurrent adenomas that were successfully re-resected by FTRD. Minor bleedings occurred at the first postinterventional day in 3/19 (15.8%). There were no major bleedings and perforations.

Conclusion: This study confirmed the feasibility of duodenal EFTR and indicates good efficacy and safety. Larger studies are needed to further investigate this novel technique.

Keywords

Endoscopic full-thickness resection, FTRD, duodenum, duodenal adenoma, subepithelial tumor

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Key summary

1. Established knowledge on this subject:
- Endoscopic full-thickness resection of adenomas and subepithelial tumors using the full-thickness resection device (FTRD) has been reported to be effective and safe in the colorectum.
- The feasibility of endoscopic full-thickness resection of duodenal lesions with FTRD has been shown in a small case series ($n = 4$).

2. Significant findings of this study:
- The FTRD indicates good technical efficacy and safety for resection of duodenal non-ampullary adenomas and subepithelial tumors.
- The FTRD offers the possibility of re-resections at the same site (e.g. in case of an incomplete resection or recurrence).
- Endoscopic full-thickness resection may be considered especially in pretreated or "difficult" lesions (such as non-lifting adenomas).

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Introduction

Duodenal adenomas develop spontaneously or are associated with hereditary polyposis syndromes such as familial adenomatous polyposis (FAP) or *MUTYH*-associated polyposis. Similar to colorectal adenomas they may undergo malignant transformation according to the adenoma carcinoma sequence model. Studies have shown progression to duodenal adenocarcinoma in about 5% of all cases.[1,2] Therefore, resection of the duodenal adenoma is mandatory. The excision of duodenal subepithelial tumors may be necessary in case of symptoms (e.g. bleeding) or suspected malignancy, such as gastrointestinal (GI) stromal tumors (GISTs) or neuroendocrine tumors (NETs).

Surgical resection of duodenal lesions is associated with a higher morbidity compared to less-invasive endoscopic techniques. Endoscopic mucosal resection (EMR) of duodenal lesions is effective, but harbors relevant complication rates such as bleeding and perforation.[3–7] Endoscopic full-thickness resection (EFTR) using the full-thickness resection device (FTRD®, Ovesco Endoscopy AG, Tuebingen, Germany) has been reported to be effective and safe in the colorectum.[8–10] The feasibility of EFTR of duodenal lesions with the FTRD has been reported in a small case series.[11] We present a larger retrospective study investigating the safety and efficacy of FTRD application in the duodenum.

Methods

The margins of duodenal lesions were marked with a high-frequency (HF) probe. Balloon dilatation (20 mm) of the upper esophageal sphincter and the pylorus was performed in all cases to facilitate advancing of the FTRD. After pulling the duodenal lesion into the cap with a grasper or a tissue anchor (OTSC® Anchor, Ovesco Endoscopy AG), the FTRD clip was deployed and the lesion immediately resected with the preloaded snare. The resected specimen was retrieved for histopathological analysis (Figures 1 and 2). The FTRD has been Conformité Européenne marked for utilization in the colorectum. For a more detailed technical description of the FTRD, we refer to a previous publication by our group.[12]

A single-shot antibiotic prophylaxis with ceftriaxone or ciprofloxacin was administered immediately prior to or during the intervention. Second-look endoscopy was scheduled 24–72 hours after resection. Endoscopic follow-up (including biopsies) was performed after 3 and 12 months. After approval by our institutional review board (IRB approval number 2017-0628, ethics committee of Regionale Kliniken Holding (RKH), June 28, 2017), data were collected and analyzed retrospectively. Written informed consent was obtained from all patients. This study conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

The primary endpoint was technical success, defined as reaching the target lesion with the FTRD, correct application of the FTRD clip underneath the lesion and immediate resection with the integrated snare. Secondary endpoints were clinical success (defined as technical success + absence of lesion recurrence at the latest available follow-up), R0 resection rate, adverse events and evidence of residual/recurrent lesions detected in follow-up endoscopies. Major bleeding

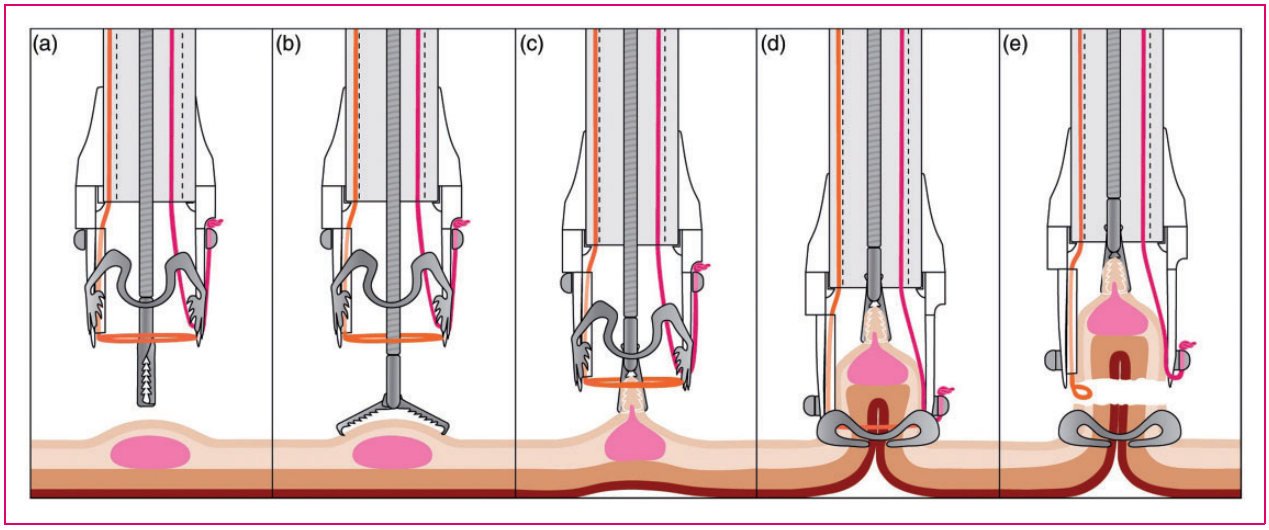

Figure 1. Schematic illustration of the full-thickness resection device procedure. ((a), (b)) A grasping forceps is advanced through the working channel of the endoscope. (c) The target lesion is grasped and pulled into the cap. (d) The OTSC is deployed and creates a full-thickness plication of the gastrointestinal wall. (e) The pseudopolyp is resected above the OTSC with the preloaded snare. (Courtesy of Ovesco Endoscopy AG, Tuebingen, Germany, with permission.)

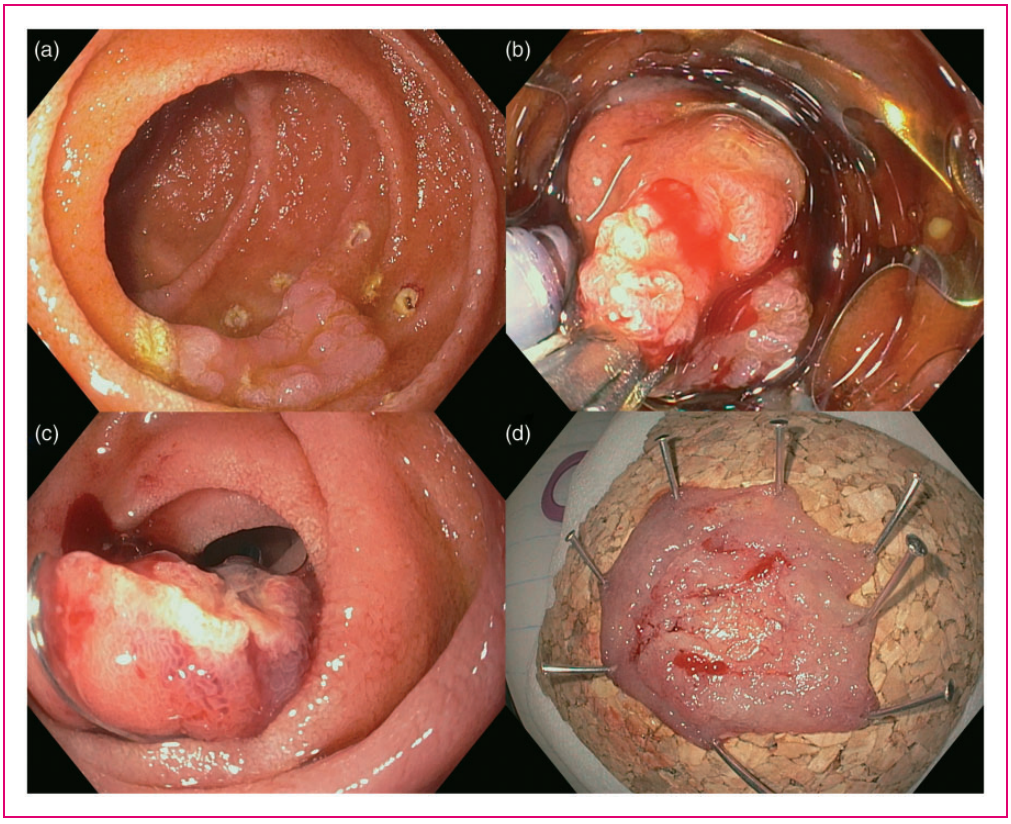

Figure 2. Endoscopic full-thickness resection of a duodenal adenoma. (a) The margins of the duodenal adenoma were marked with a high-frequency probe. (b) The adenoma is pulled into the cap using a tissue anchor (OTSC Anchor, Ovesco Endoscopy AG). (c) Resection site with OTSC securing wall patency. (d) Resected specimen. Histology showed R0-resected tubular adenoma with high-grade dysplasia.

was defined as a bleeding episode requiring blood transfusion or surgery.

Results

Between March 2014 and June 2017 a total of 20 patients (13 male, 7 female) were scheduled for EFTR of a duodenal lesion. Technical success was achieved in 17/20 cases (85.0%).

In one case advancing the FTRD through the pylorus was not possible despite balloon dilatation. Indication for EFTR was: duodenal adenomas ($n = 13$, seven treatment naïve, six non-lifting adenomas unsuccessfully pretreated by EMR), subepithelial tumors ($n = 5$) and T1 adenocarcinoma ($n = 1$). Localization and tumor sizes are shown in Table 1. Mean patient age was 68 years (range 35–82 years). Mean procedure time was 61 minutes (range 25–130 minutes).

In two cases the FTRD clip was deployed correctly, but the integrated snare could not be closed because of device dysfunction. Both lesions were then resected with a standard snare above the FTRD clip after extraction of the device. In both cases there was no macroscopic evidence of residual adenoma. However, R0 resection could not be confirmed in both cases. In the first case a R1-resected NET in the duodenal bulb was resected by two-thirds gastrectomy with

Table 1. Description of duodenal lesions.

Indication	
Duodenal adenoma, *n*	13
Treatment naïve, *n*	7
Non-lifting sign, *n*	6
Subepithelial tumor, *n*	5
T1 adenocarcinoma, *n*	1
Lesion localization	
Duodenal bulb, *n*	4
Descending part of the duodenum, *n*	13
Horizontal part of the duodenum, *n*	2
Lesion sizes	
Mean diameter of all lesions (range), mm	17 (5–35)
Diameter of adenomas, mean (range), mm	19 (5–35)
Diameter of subepithelial tumors, mean (range), mm	12 (8–15)
Diameter of adenocarcinoma, mm	15

Roux-Y anastomosis three months later. In the second case (tubulovillous adenoma with high-grade dysplasia) there was no macroscopic or histological evidence of residual adenoma at the three-month follow-up. However, eight months after intervention recurrence of a tubulovillous adenoma with high-grade dysplasia was detected. Re-resection with the FTRD was successful (R0), with no evidence of residual lesion three months later.

R0 resection could be confirmed in 12/19 cases (63.2%). Minor bleeding occurred in 3/19 cases (15.8%) on the first postinterventional day. Hemostasis was endoscopically achieved by thermal coagulation, application of hemoclips and injection of diluted suprarenine in all cases. There was no major bleeding. There were no perforations. In the subgroup of non-lifting adenomas ($n = 6$) full-thickness resection was technically successful in all cases. In four of those cases R0 resection could be confirmed.

Mean follow-up was nine months (range 3–32). At the three-month follow-up endoscopy there was no evidence of residual or recurrent lesion in 17/18 cases (94.4%), resulting in a clinical success rate of 80.0%. In one case (initially R1-resected adenoma) residual tubulovillous adenoma with high-grade intraepithelial neoplasia was detected and successfully resected by FTRD. There was no three-month follow-up endoscopy of the patient with the two-thirds gastrectomy. At the three-month follow-up the FTRD clip was still in situ in 12/18 cases (66.7%). The clip was removed using a bipolar cutting device (remOVE system™, Ovesco Endoscopy AG) prior to taking biopsies in 10 cases. Biopsies from adjacent tissue were taken in two cases.

One-year follow-up was obtained from 10 patients. Residual adenoma was detected in a patient with an incompletely resected tubulovillous adenoma (one of the cases with snare dysfunction, as mentioned above). In all other cases there was no evidence of recurrence macroscopically and histologically. In one case there was no one-year follow-up endoscopy scheduled because histology showed an R0-resected inflammatory fibroid polyp. Two patients were lost to follow-up after three-month endoscopy (initially R0-resected adenoma). In five cases one-year follow-up is still pending. Outcome and adverse events are summarized in Table 2. A detailed list of RX/R1 cases is provided in Table 3.

Table 2. Outcome and adverse events.

Outcome	
Technical success (= reaching the lesion, application of FTRD-clip and resection with integrated snare)	17/20 (85.0%)
Target lesion reached with FTRD	19/20 (95.0%)
Macroscopic complete resection	17/19 (89.5%)
Microscopic complete resection (R0 resection)	12/19 (63.2%)
Clinical success (= technical success + absence of recurrent lesion at latest follow-up)	16/20 (80.0%)
Follow-up endoscopy	
Residual/recurrent lesion after 3 months	1/18 (5.6%)
Residual/recurrent lesion after 12 months	1/10 (10.0%)
Adverse events	
Minor bleeding (all at day 1 after intervention)	3/19 (15.8%)
Major bleeding	0/19 (0%)
Perforation	0/19 (0%)

FTRD: full-thickness resection device.

Table 3. Overview of RX and R1 cases ($n = 7$).

Histology	Follow-up/Outcome	Initial resection status
Tubular adenoma (low-grade dysplasia)	No recurrence after 3 and 12 months	RX
Tubular adenoma (high-grade dysplasia)	No recurrence after 3 and 12 months	RX
Neuroendocrine tumor	Resected by two-thirds gastrectomy with Roux-Y-anastomosis	R1
Tubulovillous adenoma (high-grade dysplasia)	Recurrent adenoma after eight months, successful repeat FTRD (R0), no sign of recurrence after further three months	R1
Tubular adenoma (low-grade dysplasia)	No recurrence after 3 and 12 months	RX
Tubular adenoma (low-grade dysplasia)	No recurrence after 3 months, 12-month follow-up is pending	RX
Tubular adenoma (high-grade dysplasia)	Recurrent adenoma after three months, successful repeat FTRD (R0), further follow-up is pending	R1

FTRD: full-thickness resection device.

Discussion

Owing to its unique anatomic features, endoscopic resection in the duodenum harbors a high risk of adverse events. On the other hand, surgical therapy of duodenal lesions often results in extensive resection and is associated with significant morbidity. This retrospective pilot study reports our experience of EFTR in the duodenum with the FTRD in 20 consecutive patients.

The duodenum is less flexible than other GI parts because of its retroperitoneal fixation, thus making endoscopic advancement to target lesions more difficult (especially if they are located at the superior or inferior duodenal flexure). The risk of bleeding is higher and hemostatic management may be impaired because the duodenum receives blood from two arterial sources forming an anastomotic loop (the celiac trunk and superior mesenteric artery). Additionally, the duodenal wall is thin and prone to perforation during endoscopic interventions. Despite those local risk factors, endoscopic resection of duodenal lesions is associated with a significant lower morbidity than surgical resection.[13]

EMR is the current standard technique for treatment of duodenal non-ampullary adenomas. Complete resection rates are considerably high (87%–96%), and in duodenal adenomas smaller than 30 mm en bloc resection is reported in 87%.[3–5] However, adverse events are frequent. Bleeding was reported in 9%–24.5% of cases.[3,4,6,7] Most bleedings occur during the intervention but there are also delayed bleedings in up to 12%.[6] The perforation rate in studies is in the range of 0.6%–5.0%.[3,6,7]

Endoscopic submucosal dissection (ESD) is not recommended for resection of duodenal lesions since the perforation rate may be as high as 35%.[6,14,15]

EFTR of duodenal lesions may be an alternative to the techniques mentioned above. Recent prospective data from the WALL-RESECT study demonstrated that EFTR of "difficult" colorectal adenomas and subepithelial tumors is effective and safe using the FTRD.[10] Feasibility of EFTR in duodenal lesions with the FTRD has been reported in a small case series.[11]

In our study, resection was technically successful in 85% of cases. Technical problems concerning the integrated snare occurred in two cases. In one case the snare could not be closed; in the second case the snare slipped off the tissue. Since it was possible to properly place the FTRD clip, the lesions could be resected with a standard snare. Both cases happened before October 2015 (case numbers 6 and 7). Similar problems with closing the snare were observed using the FTRD in the colorectum in 13 of 181 cases.[10] In the meantime, the snare mechanism has been modified by the manufacturer. Subsequently, no major problems with the snare have been reported (neither in the duodenal nor in the colorectal indication). Therefore, the technical success of duodenal EFTR may increase in future studies. Moreover, accessing duodenal lesions should be easier using a modified device with a smaller outer diameter, which will be available in the near future.

The overall confirmed R0-resection rate was 63.2%. In the subgroup of duodenal adenomas, R0 resection was achieved in 53.8%. This rate is substantially lower than the complete resection rates reported for EMR of duodenal adenomas. It is important to stress that our study included six duodenal adenomas that had been unsuccessfully pretreated by EMR because of a non-lifting sign and five treatment-naïve duodenal adenomas with a diameter of ≥ 20 mm. Thus, the proportion of "difficult" lesions was considerably high. Full-thickness resection was technically successful in all non-lifting cases; in four cases R0 resection could be confirmed. This emphasizes the role of FTRD resection in difficult lesions. Additionally, adenoma recurrence in follow-up endoscopies was lower than expected by the low R0-resection rate in this case series (cumulative recurrence in only two cases), implying that several resections must have been complete although histologically classified as "RX" (Table 3). This results in a good clinical success rate of 80.0%. In case of a residual or recurrent lesion, full-thickness resection by FTRD can be repeated, as demonstrated in two cases within this study. Endoscopic re-treatment may therefore obviate the need for surgical resection in those cases.

In the subgroup of subepithelial tumors complete resection rate was 80.0% (4/5). In one case of a NET, surgical resection was necessary because the defective snare mechanism resulted in an incomplete resection. As mentioned above such a defect should be less frequent in the future. Three out of five resected subepithelial tumors had malignant potential (well-differentiated NET). FTRD may be a valuable tool for diagnostic as well as therapeutic resections in those cases. Further studies are needed for this specific indication.

The bleeding rate of 15.8% was within the range of complication rates of EMR studies. Major bleeding did not occur (no need for surgery or blood transfusion). All bleeding occurred at the resection site and on the first postinterventional day. Hemostasis could be achieved by standard endoscopic procedures in all cases. We did not observe any perforations or other major adverse events in our study. Possible procedure-specific complications include local ulceration next to the clip, luminal obstruction and accidental clipping of extraluminal structures. In case of such complications removal of the FTRD clip is indicated. Acute and delayed perforation are also possible severe

adverse events. Since data on FTRD application in the duodenum are limited to a small number of cases, the real frequency of such complications cannot be assessed in this series and needs to be investigated in larger studies.

Compared to available data from FTRD clips in the colorectum,[10] the rate of spontaneous dislodgement of FTRD clips from the duodenal wall was lower within the three-month-interval in this cases series (33.3% vs. 68.8% in the WALL-RESECT study). Whether this might indicate a stronger fixation of FTRD clips to the duodenal wall compared to the colonic wall may not be deduced from this case series.

There are several limitations of FTRD use in the upper GI tract. Advancing the FTRD into the duodenum usually is impaired by its outer diameter of 21 mm, especially when passing the upper esophageal sphincter and the pylorus. In this study balloon dilatation of those anatomic sites was performed prior to the introduction of the device. Nevertheless, the FTRD could not be advanced through the pylorus in one case. While advancing the FTRD through the upper GI tract no complications occurred. Currently a modified FTRD with a lower outer diameter for use in the duodenum is being developed. Thanks to further modifications to the cap it will still be possible to incorporate a similar volume of tissue into the cap as with the colorectal FTRD.

Furthermore, it is important to emphasize that ampullary duodenal lesions cannot be resected by FTRD because of the risk of accidentally clipping the bile duct. Before EFTR of a duodenal lesion it is mandatory to localize and inspect the papilla and ensure a minimum distance of 20 mm between the papilla and the lesion to be resected (recommendation based on the experience of our group, no analytical data available). Moreover, the cap size of the FTRD limits the maximum size of lesions to be resected. Within the colorectum lesions up to 30 mm in diameter have been reported to be resectable with an acceptable resection success.[10] Within this study duodenal adenomas up to 35 mm in diameter could be resected, but the number of cases is too low for a sufficient analysis of suitable adenoma sizes. From our experience we recommend a maximum size of 25 mm for full-thickness resection of duodenal adenomas, since the duodenum is less flexible than the colorectum.

Further limitations of this analysis are its monocentric and retrospective design and the lack of a control group. A multicenter, randomized, controlled study investigating the use of a modified FTRD in comparison to EMR for resection of duodenal non-ampullary adenomas is in preparation.

In conclusion, this is the largest case series investigating resection of duodenal lesions with the FTRD. This study confirms the feasibility of duodenal EFTR and indicates good technical efficacy and safety. A randomized, controlled trial comparing EFTR with EMR may clarify the role of this novel technique for treatment of duodenal lesions.

Declaration of conflicting interests

A. Schmidt and K. Caca and received lecture fees from Ovesco Endoscopy AG. M. Bauder has nothing to declare.

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Ethics approval

This study was approved by the institutional review board (IRB approval number 2017-0628, ethics committee of Regionale Kliniken Holding (RKH), June 28, 2017) and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Informed consent

Written informed consent was obtained from all patients.

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