Endoscopic mucosal resection of large rectal adenomas in the era of centralization: Results of a multicenter collaboration

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on behalf of the TREND study group

Abstract

Background and objective: Endoscopic mucosal resection (EMR) of large rectal adenomas is largely being centralized. We assessed the safety and effectiveness of EMR in the rectum in a collaboration of 15 Dutch hospitals.

Methods: Prospective, observational study of patients with rectal adenomas >3 cm, resected by piecemeal EMR. Endoscopic treatment of adenoma remnants at 3 months was considered part of the intervention strategy. Outcomes included recurrence after 6, 12 and 24 months and morbidity.

Results: Sixty-four patients (50% male, age 69 ± 11 , 96% ASA 1/2) presented with 65 adenomas (diameter 46 ± 17 mm, distance ab ano 4.5 cm (IQR 1–8), 6% recurrent lesion). Sixty-two procedures (97%) were technically successful. Histopathology revealed invasive carcinoma in three patients (5%), who were excluded from effectiveness analyses. At 3 months' follow-up, 10 patients showed adenoma remnants. Recurrence was diagnosed in 16 patients during follow-up (recurrence rate 25%). Fifteen of 64 patients (23%) experienced 17 postprocedural complications.

Conclusion: In a multicenter collaboration, EMR was feasible in 97% of patients. Recurrence and postprocedural morbidity rates were 25% and 23%. Our results demonstrate the outcomes of EMR in the absence of tertiary referral centers.

Keywords

Rectum, adenoma, endoscopic mucosal resection, recurrence, morbidity

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Introduction

Early endoscopic detection and removal of colorectal adenomas reduces the incidence of colorectal cancer.¹ It has recently been shown that colonoscopic polypectomy also significantly reduces colorectal cancer associated mortality as compared to the general population.² Colorectal cancer screening programs, which are currently broadly implemented, will facilitate the detection of cancers in a curable stage, but will also diagnose more adenomas. This increased adenoma detection demands expansion of treatment capacities and optimization of treatment strategies to facilitate cost-effective care.

Endoscopic treatment of colonic adenomas may prevent surgical interventions such as segmental resection or hemicolectomy and their associated complications. However, large colonic adenomas demand treatments

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beyond simple loop polypectomy or single-piece endoscopic mucosal resection. The most common endoscopic resection technique for large adenomas is piecemeal endoscopic mucosal resection (EMR). In a systematic review of 20 studies on EMR of large (>2 cm) colorectal adenomas, we have previously described an early recurrence rate (after a single attempt) of 11.2%; in fact, these lesions are residual adenomas rather than recurrences. When permitting re-treatment of these adenoma remnants within 6 months, the late recurrence rate was 1.5% and complication rate 3.8%.³ The majority of the studies included in this review consisted of retrospective case series from specialized centers and might not reflect daily practice.

Piecemeal adenoma resection is associated with high rates of residual adenoma at follow-up.⁴ Two recently published prospective studies on piecemeal EMR of colorectal adenomas, published by endoscopists with extensive experience and high case-volumes, report residual adenoma rates of 20–38%. However, late recurrence was eventually diagnosed in less than 5% of patients.^{5,6} In many countries, EMR is considered a complex endoscopic procedure and is mostly being centralized to guard its effectiveness and safety.⁷ In the Netherlands, tertiary referral centers are developing but most patients are still treated by general endoscopists with low case-volumes of these large lesions.

With regards to large rectal adenomas, it is still debated whether endoscopic or surgical resection is the preferable treatment method. An ongoing prospective randomized trial by a multicenter collaboration of dedicated endoscopists and surgeons (TREND-study) compares the cost-effectiveness of EMR and transanal endoscopic microsurgery (TEM) for the resection of large (>3 cm) rectal adenomas.⁸ Whereas the results of TEM have been extensively reported in previous literature, data on EMR in the rectum alone seem absent, with the exception of one single-center prospective study of 62 patients, reporting a local recurrence rate of 8% within a median follow-up of 14 months and a postprocedural bleeding rate of 8%.⁹ Additional prospective data on EMR in the rectum are important to assess the outcomes of EMR in the absence of expert centers with high case-volumes, especially while the results of the TREND study are awaited until the fall of 2015. Therefore, we aimed to assess the outcomes, including safety and effectiveness, of EMR of large adenomas located in the rectum only, performed in a dedicated multicenter setting.

Methods

Patients

Patients who were eligible for inclusion in the TREND study, but refused randomization because of a distinct

preference for endoscopic treatment between January 2009 and August 2011 were included. Patients were eligible if they presented with non-pedunculated rectal adenomas larger than 3 cm, of which the distal border was situated within 15 cm from the dentate line. Adenoma size was estimated endoscopically using an open biopsy forceps or resection snare. Patients were excluded if there was any suspicion of submucosal invasion during diagnostic workup, if patients were medically unfit for surgery or if either EMR or TEM was considered non-feasible by the gastroenterologist or surgeon. Inclusion and exclusion criteria for the TREND-study are extensively described elsewhere.⁸ If patients fulfilled criteria but refused randomization in the TREND-study and requested endoscopic treatment, informed consent was asked for prospective follow-up in the current study. The Institutional Review Boards (IRB) of all participating hospitals reviewed and approved the TREND-study protocol as well as the current study protocol.

Participating centers and endoscopists

Patients could be enrolled in one of 18 Dutch and Belgian hospitals also involved in the TREND-study. All participating hospitals were referral centers for interventional endoscopy in their geographical region. To strive for a centralization effect, we co-opted a single gastroenterologist per hospital to perform all study procedures. As the extent of EMR experience varied among participating endoscopists, an expert panel reviewed video-recorded cases for quality assurance purposes prior to study involvement. A consensus meeting was held prior to the start of the study to agree on EMR equipment and technique.

Interventions

Split-dose bowel preparation was used, but not otherwise standardized. Anticoagulant therapy was typically discontinued three days prior to the procedure; single agent antiplatelet therapy such as acetyl-salicylic acid was continued. EMR was performed as described by Karita and Hurlstone.^{9,10} At the discretion of the endoscopist, conscious or deep sedation could be administered with midazolam, fentanyl or propofol. Diagnostic gastroscopes (such as GIF-H180 or GIF-HQ180, Olympus, Tokyo, Japan) were preferably used for the procedure because of their flexibility. After proper endoscopic visualization of the adenoma, it was lifted submucosally using a solution of saline 0.9%, 1 mL methylene blue, and 1:10,000 units adrenaline. Adenoma margins were not routinely marked with mucosal cautery. The lesions were removed by sequential inject and resect EMR technique.

The adenoma was resected in a piecemeal fashion by alternated use of standard large (30 mm, Boston Scientific, Natick, Massachusetts, USA), barbed (20 mm, Olympus, Tokyo, Japan) and standard small (13 mm, Boston Scientific, Natick, Massachusetts, USA) snares and electro-coagulation (endocut, ERBE Elektromedizin GmbH, Vienna, Austria). Snare resection was continued until the lesion was macroscopically entirely removed and the blue colored submucosa was visualized. Thereafter, the borders of the mucosal defect and potential remnants within the resection crater were treated with argon plasma coagulation (APC) to enhance adenoma clearance. Visible vessels in the EMR defect that were not bleeding were not treated prophylactically. Polypectomy sites were not closed with clips. Tattoos were not routinely placed at the polypectomy site in the rectum. Patients were discharged after the procedure in accordance with current practice.

Histopathological evaluation

All pieces that were resected by EMR were processed in a standard fashion by the pathologist. As evaluation of the resection margins is impossible in piecemeal resection specimens, only the basal margins, lesion type, and degree of dysplasia were assessed. When submucosally invasive carcinoma was diagnosed in the resection specimen, the necessity of additional treatment was discussed in a multidisciplinary team, and the patient was excluded from further analyses in the current study.

Follow-up and outcome parameters

All patients underwent repeat endoscopy at 3 months. Endoscopic treatment of remnants at 3 months was considered part of the initial intervention strategy. Surveillance endoscopies were scheduled at 6, 12, and 24 months after EMR. In all endoscopies following EMR, biopsies of presumed adenomatous tissue were taken to confirm the presence of neoplasia by histology. All remnants and recurrences were treated endoscopically if feasible. If the scar appeared normal without the presence of adenomatous tissue, random biopsies were taken from the center of the scar and its edges. The primary outcome was recurrence of neoplasia, defined as the presence of histologically proven neoplastic tissue in either visible recurrent lesions or in random biopsies at 6, 12, or 24 months' follow-up.

Secondary outcomes were postprocedural complication rates, including complications associated with additional endoscopic treatment of adenoma remnants at 3 months' follow-up. All patients who had consented to follow-up by telephone, in addition to solely

endoscopic follow-up, were contacted by a research nurse on the first postprocedural day as well as 2 weeks and 3, 6, 12, and 24 months after the procedure for inquiry into possible adverse events other than those already reported in patients' medical correspondence during follow-up. The correlation of each event to the intervention strategy was classified according to likelihood (unlikely, possibly, probably or definitely related, respectively).

Statistical analysis

Results for continuous variables were summarized using mean (standard deviation (SD)) or median (interquartile range (IQR)) for skewed data. Frequencies (%) were used to summarize categorical variables. By univariable logistic regression analyses, possible predictors of recurrence and complications were identified. All predictors identified by a P-value of <0.1 were candidate variables for inclusion in a multivariable model. Multiple regression with backward stepwise Wald variable selection, in which a P-value of <0.05 was considered statistically significant was then used to identify independent predictors of the outcomes. Calculations were made in SPSS statistics package for Windows (International Business Machines Corp., Armonk, NY, USA), version 19.0.

Results

Patients and lesions

A total of 64 patients who were eligible for the TREND study between January 2009 and August 2011 denied randomization because of a distinct preference for endoscopic treatment, but all agreed on being followed in the current study protocol. They underwent treatment and surveillance in one of 15 Dutch hospitals (three academic, 12 general). Participating endoscopists had a mean annual case volume of 2.6 ± 2.1 (range 0.3–7.7) rectal adenomas ≥ 3 cm, assuming that all cases were registered in the TREND study or current study. Eleven patients (17%) were treated in academic hospitals; the remaining 53 were treated in general hospitals. In these 64 patients, 65 large rectal adenomas (mean diameter 46 ± 17 mm) were diagnosed; one patient had two adenomas. Patient and adenoma characteristics are summarized in Table 1. The mucosal aspect (Kudo pit pattern) of the resected adenoma was only described in 12% of lesions.

EMR procedures

The majority of EMRs were performed under conscious sedation, mostly consisting of midazolam and/or fentanyl. Two patients were treated under

Table 1. Patient and lesion characteristics

Patient characteristics (<i>n</i> = 64)	
Male sex (%)	32 (50)
Mean age $\pm$ SD	69 $\pm$ 11
ASA classification (%) (2 missing)	
1	26 (41)
2	31 (48)
3	5 (8)
Lesion characteristics (<i>n</i> = 65)	
Mean maximum diameter (mm) $\pm$ SD	46 $\pm$ 17
Median distance ab ano (cm) (IQR)	4.5 (1–8)
Mean % of rectal circumference covered $\pm$ SD	39 $\pm$ 13
Paris classification (%)	
Is	37 (57)
Ila	15 (23)
Is + Ila	12 (18)
Unknown	1 (2)
Recurrent or remnant lesion (%)	4 (6)
Prior treatment	
Endoscopic mucosal resection	4
Transanal endoscopic microsurgery	0
Conventional transanal excision	0
Median time (months) since prior treatment (IQR)	3.5 (2.4–161.1)

deep sedation administered with propofol and three patients were not sedated. The patient with two adenomas had both lesions treated in a single session.

EMR was technically successful in 62 of 64 patients (97%), although a perforation demanded a staged procedure in one patient. The two remaining patients were referred for TEM because of procedure intolerance and insufficient lifting of the submucosal plane respectively. These patients were excluded from follow-up analysis as EMR had failed. APC was administered after snare resection in only 55 patients (89%) even though the protocol prescribed it to be applied in all patients. After treatment, 54 resections (87%) were considered endoscopically complete. Following EMR, patients were discharged from the hospital after a median of 0 days (IQR 0–0.25, range 0–16). One patient was hospitalized for 16 days. She required perioperative heparin because of a mechanic aortic valve implant. The procedure was complicated by two hemorrhagic events, which required re-endoscopy without transfusion.

Intraprocedural complications

Other than the abovementioned perforation, no other intraprocedural complications occurred (complication rate 2%). The perforation was closed using endoclips

and EMR could be completed uneventfully four weeks later.

Histopathology

In both patients who underwent TEM after EMR failure, the resection specimen contained villous adenoma with high-grade dysplasia. Histopathological evaluation of the 63 adenomas (in 62 patients) resected by EMR revealed adenoma in 60 cases (95%); dysplasia was low-grade in 34 cases, high-grade in 25 patients, and was not specified in one patient. In three patients (5%), the lesion appeared to be a submucosally invasive adenocarcinoma. Two patients underwent subsequent total mesorectal excision (TME) after neo-adjuvant therapy. Both TME specimens showed no tumor remnant. The third patient chose not to undergo additional therapy because of her old age and significant cardiovascular comorbidity. After 24 months' follow-up, all three patients were alive and did not show signs of local recurrence or distant metastasis. These patients were excluded from further analysis in the current study.

Follow-up

Total median follow-up of the 59 patients who had undergone EMR of a histopathologically confirmed rectal adenoma was 24 months (IQR 18–25). Fifty-three patients (90%) underwent a per-protocol repeat sigmoidoscopy after 3 months. Remnant adenomatous tissue was found in 10/53 patients (19%). Two remnants were diagnosed by random biopsies of normally appearing scars. One patient was referred for TEM because biopsies of the remnant lesion had shown intramucosal carcinoma with possible submucosal invasion. Eventually, the TEM specimen only contained high-grade dysplasia. EMR was considered to have failed in this patient, who was excluded from further effectiveness analyses. Recurrence was diagnosed in five patients at 6 months, nine patients at 12 months, and two patients at 24 months' follow-up (overall recurrence rate 25%). Again, two recurrences were diagnosed by random biopsies. Table 2 summarizes the follow-up of all patients with remnants and recurrences. Univariable regression analyses did not reveal any associations between recurrence and tumor size, distance from the anus, prior attempt of resection, use of APC, macroscopically complete character of the resection as judged by the endoscopist after the procedure, or the presence of remnant adenomatous tissue at 3 months' follow-up (Table 3).

Postprocedural complications

Fifteen of 64 patients in whom EMR was attempted (23%) had at least one postprocedural complication

Table 2. Summary of the follow-up of all patients with remnant and/or recurrences

FU 3 m (53 patients)				FU 6 m (43 patients)			FU 12 m (49 patients)			FU 24 m (49 patients)		
Patient	Outcome	Visible lesion/ random Bx	Treatment	Outcome	Visible lesion/ random Bx	Treatment	Outcome	Visible lesion/ random Bx	Treatment	Outcome	Visible lesion/ random Bx	Treatment
1	Remnant	Visible	TEM	Lost to FU (EMR failure)			Lost to FU (EMR failure)			Lost to FU (EMR failure)		
2	Remnant	Visible	Biopsy	No recurrence	-	-	No recurrence	-	-	No recurrence	-	-
3	Remnant	Random Bx	-	No recurrence	-	-	No recurrence	-	-	No recurrence	-	-
4	Remnant	Visible	Biopsy + APC	No recurrence	-	-	No recurrence	-	-	No recurrence	-	-
5	Remnant	Visible	APC	No recurrence	-	-	No recurrence	-	-	No recurrence	-	-
6	Remnant	Visible	None	No recurrence	-	-	No recurrence	-	-	No recurrence	-	-
7	Remnant	Visible	APC	No recurrence	-	-	No recurrence	-	-	Recurrence	Visible	APC
8	Remnant	Visible	Biopsy + APC	No recurrence	-	-	Recurrence	Visible	Biopsy + APC	No recurrence	-	-
9	Remnant	Random Bx	-	No recurrence	-	-	Lost to FU			Lost to FU		
10	Remnant	Visible	Biopsy	No endoscopy	-	-	Recurrence	Visible	Biopsy	No endoscopy	-	-
11	No remnant	-	-	Recurrence	Visible	EMR + APC	No recurrence	-	-	No recurrence	-	-
12	No remnant	-	-	Recurrence	Visible	Biopsy + APC	No recurrence	-	-	No recurrence	-	-
13	No remnant	-	-	Recurrence	Visible	Biopsy + APC	No recurrence	-	-	No recurrence	-	-
14	No remnant	-	-	Recurrence	Visible	Biopsy	No recurrence	-	-	No recurrence	-	-
15	No remnant	-	-	Recurrence	Visible	EMR + APC	Recurrence	Random Bx	-	No recurrence	-	-
16	No remnant	-	-	No recurrence	-	-	Recurrence	Random Bx	-	No recurrence	-	-
17	No remnant	-	-	No recurrence	-	-	Recurrence	Visible	Biopsy	No recurrence	-	-
18	No remnant	-	-	No recurrence	-	-	Recurrence	Visible	Biopsy	No recurrence	-	-
19	No remnant	-	-	No recurrence	-	-	Recurrence	Visible	APC	Recurrence	Visible	Biopsy
20	No remnant	-	-	No endoscopy	-	-	Recurrence	Visible	EMR + APC	No recurrence	-	-
21	No remnant	-	-	No endoscopy	-	-	Recurrence	Visible	APC	Recurrence	Visible	Biopsy
22	No remnant	-	-	No endoscopy	-	-	Recurrence	Visible	EMR + APC	Recurrence	Visible	Biopsy
23	No endoscopy	-	-	No recurrence	-	-	No recurrence	-	-	Recurrence	Visible	Biopsy + APC

Table 3. Univariable analysis of possible predictors of recurrence, with odds ratios (OR), 95% confidence intervals (95% CI) and p-values

	OR	95% CI	p
Tumor size (per cm)	1.35	.83–2.98	.230
Distance of distal adenoma margin to anus (per cm)	.99	.88–1.14	.982
Prior attempt of adenoma resection	3.23	.41–25.26	.264
APC used during EMR procedure	2.21	.24–20.03	.481
Resection judged macroscopically incomplete by endoscopist	3.64	.78–16.93	.100
Remnant adenoma at 3 months	1.25	.27–5.68	.776

Table 4. Multivariable analysis of possible predictors of complications, with odds ratios (OR), 95% confidence intervals (95% CI) and p-values

	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Tumor size (per cm)	1.19	.74–1.93	.469			
Distance of distal adenoma margin to anus (per cm)	.93	.81–1.08	.377			
ASA classification (vs. 1)	6.00	1.15–31.23	.019	6.00	1.15–31.23	.019
2	36.00	2.46–527.06		36.00	2.46–527.06	
3						
Use of anticoagulant medication	7.24	1.91–27.38	.004	2.50	.49–12.89	.273
Prior attempt of adenoma resection	1.08	.10–11.26	.951			

ASA: American Society of Anaesthesiologists.

that was probably or definitely related to the EMR procedure. The total number of complications was 17; 14 patients encountered one event and one patient encountered three events. The most common complication was hemorrhage (n = 13). Seven patients in whom hemorrhage occurred were on anticoagulant or antiplatelet therapy. Less frequent complications included postprocedural abdominal pain (n = 2), rectal stenosis (n = 1), and atrial fibrillation that occurred during bowel preparation (n = 1). Eight patients underwent endoscopic inspection or treatment for postprocedural hemorrhage. One case of hemorrhage was surgically sutured after three attempts of endoscopic therapy using adrenaline, gold probe coagulation and APC. The patient with rectal stenosis required surgical stenoplasty.

Multivariable regression analysis identified ASA classification as the only independent predictor of postprocedural complications. No significant associations were found between complications and tumor size, distance from the anus, or prior attempt of resection. The use of anticoagulant medication was significantly associated with complications in univariable analyses, but could not be identified as an independent

predictor of complications in multivariable analyses (Table 4).

Discussion

This multicenter prospective study provides a faithful reflection of current daily practice in the Netherlands, although the potential bias of including only patients who refused participation in a randomized trial should be considered. EMR of large rectal adenomas was technically successful in 97% of patients. Subsequent endoscopic follow-up and treatment of adenoma remnants was feasible in 98% of patients. The recurrence and complication rates in our study compare unfavorably with prior published data on large colonic EMRs. In a recent, prospective study, colleagues Moss and Bourke have demonstrated the feasibility of piecemeal EMR in colorectal adenomas, reporting very high case-volumes and demonstrating elaborate expertise in a multicenter collaboration. Their results (early recurrence rate 20.4%; morbidity 7.7%) have established a sound standard for future endoscopists pursuing similar proficiency.⁶ In the Netherlands, EMR was slowly implemented from the early 2000s onwards. When our

current study started in 2009, the participating endoscopists from 15, largely non-academic hospitals were gradually acquiring a tertiary referral setting in their geographical region. However, the low number of included patients in our study reflects their low case-volumes compared to those of the few expert centers dominating the current EMR literature. Although our endoscopists were considered as experienced, some of them may have still been early in their learning curve when the study was commenced. Due to the small numbers in our study, a comparison of patients treated in academic and non-academic hospitals could not be made.

According to a recent study by Buchner et al., who reported the results of colorectal EMR in a single endoscopist tertiary referral setting, independent predictors of recurrence and complications were larger polyp size and piecemeal character of the resection.⁵ In our study, tumor size did not independently predict recurrence or complications. This may be explained by our inclusion criteria; the relatively large size of all included adenomas (mean diameter 46 mm) demanded all resections to be performed in a piecemeal fashion. Whether non-adherence to the study protocol with regards to the use of APC has influenced recurrence rates, remains questionable; previous studies have shown contradictory results with regards to the effect of APC on adenoma recurrence.^{6,13}

We have shown that remnant or recurrent adenomatous tissue may present as dysplasia in random biopsies of an apparently healed mucosectomy scar. This may be explained by the fact that chromoendoscopy or virtual chromoendoscopy-like narrow band imaging were not routinely used for the detection of diminutive dysplastic lesions located at the scar. Moreover, we have detected recurrences in patients at 6, 12, and 24 months after EMR, following a prior negative surveillance endoscopy. In these cases, the adenomatous tissue might well have been missed during the prior endoscopy due to insufficient imaging, poor bowel preparation or localization behind a fold. Strict surveillance with high quality endoscopes is essential in the follow-up of these patients, and random biopsies should be considered in the absence of visible recurrent lesions.

Nevertheless, the rather high recurrence rate may be clinically overcome by the overall success rate of the total intervention strategy including endoscopic surveillance and concurrent treatment of recurrence. Fourteen of our patients, in whom a remnant or recurrent adenoma was treated endoscopically, were free of recurrence at subsequent surveillance endoscopies. All recurrences were benign and no invasive cancers were detected during follow-up endoscopies.

The diagnostic workup of large rectal adenomas remains challenging. In our study cohort, three

adenomas appeared to be submucosally invasive carcinomas. Polyp morphology and mucosal aspect may indicate a risk of submucosal invasion. Moss and Bourke identified the Paris 0-IIa+c classification as a risk factor, especially in combination with nongranular surface morphology.⁴ Although none of the included lesions in our study was classified as IIa+c, the mucosal aspect (Kudo pit pattern) of the resected adenoma was not routinely assessed and not described in 88% of lesions. This may reflect the unfamiliarity of all-round endoscopists with dedicated classification systems such as the Kudo pit pattern. Standard biopsies of large lesions will not be able to rule out invasive growth and may even cause submucosal fibrosis, thereby compromising submucosal lifting during the following therapeutic procedure. Endoscopic pattern recognition should be trained among colonoscopists, especially those who resect advanced adenomas.

With our study, we gained a clearer understanding of what is achievable when proven expert centers are scarce and dedicated gastroenterologists with lower case-volumes treat these patients. By involving a single endoscopist per hospital and organizing consensus meetings, we aimed to approach centralization and uniform treatment protocols. However, our recurrence and complication rates emphasize the importance of training and centralization. This was also suggested by suboptimal diagnostic workup and possibly missed remnants and recurrences during follow-up. Perhaps, analogous to many surgical procedures, highly complex endoscopic procedures should become subject to formal training programs, strict volume standards and quality monitoring.

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Conflict of interest

None declared.

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