# Endoscopic mucosal resection of colorectal polyps: results, adverse events and two-year outcome

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## Abstract

***Background and study aims:*** **Endoscopic mucosal resection (EMR) is the first-line treatment for large sessile and flat colorectal polyps in Western centres, however recurrence after EMR continues to be a challenge. The aim of this study is to assess efficacy, safety and recurrence rate of EMR in a tertiary centre and to identify risk factors for recurrence at first surveillance endoscopy (SE1).**

***Patients and methods:*** **We performed a retrospective study of 165 sessile and flat colorectal lesions ≥15 mm, treated by EMR between 2017-2019. We used multivariate logistic regression to identify independent risk factors for recurrence at SE1.**

***Results:*** **EMR was performed for 165 colorectal polyps in 142 patients with technical success in 158 cases (95,2%). SE1 data for 117 of 135 eligible cases (86,7%) showed recurrent adenoma in 19 cases (16,2%) after a median time of 6,2 months (IQR 5-9,9). This was primarily treated endoscopically (78,9%). Independent risk factors for recurrence at SE1 were lesion size ≥40 mm (OR 4,03; p=0,018) and presence of high-grade dysplasia (HGD) (OR 3,89; p=0,034). Early adverse event occurred in 4 patients (2,4%), with 3 bleeding complications and one perforation. Twelve patients (7,2%) presented with delayed bleeding of which 3 required transfusion, with radiological intervention in one case. All other complications were managed either conservatively (n=8) or endoscopically (n=5).**

***Conclusions:*** **EMR is a safe and effective treatment for large sessile and flat colorectal lesions with low recurrence rates. Lesion size ≥40 mm and presence of HGD were identified as risk factors for early recurrence, highlighting the importance of compliance to follow-up in these cases.** (Acta gastroenterol. belg., **2022,** 85, **47-55**).

**Keywords:** EMR, polypectomy, colorectal, recurrence.

## Introduction

Colorectal cancer (CRC) represents a large portion of the global cancer burden. It is the third most common cancer worldwide, ranking second in terms of cancer-related death. Overall, it accounts for about 1 in 10 cancer cases and deaths (1). Preventive cancer screening has been widely implemented and allows for early detection and removal of precursor lesions to CRC, thus reducing its incidence (2,3). In the past, large sessile and flat colorectal polyps were often too challenging for safe and complete endoscopic removal, making surgery the first-line treatment in these cases. When confined to the mucosa, these lesions may be removable using endoscopic mucosal resection (EMR). In the last decade, EMR has emerged as a safe and effective endoscopic treatment for large sessile and flat colorectal polyps, in order to prevent more invasive surgery and its associated morbidity, mortality and cost (4). This technique involves the submucosal injection of a lifting fluid to create a cushion, as to safely close a snare around (a portion of) the lesion to remove it, leaving the rest of the bowel wall intact. However, it is important to understand the indications and limitations of EMR. Recurrence after EMR of large lesions has been a point of contention during the emergence of this technique, delaying its introduction into general endoscopic practice (5). This has made the identification of risk factors for recurrence a priority in research regarding EMR.

A large prospective multicentre study of 1095 cases by *MOSS et al.* as part of the ongoing Australian Colonic EMR (ACE) study previously reported a successful EMR rate of 91,3% (6). Furthermore, this study indicated that a clear early surveillance endoscopy (SE1) at 3-6 months resulted in 96% of these cases staying clear at the next SE. Importantly, whilst occurring in 16,0% of cases at SE1, recurrence proved to be endoscopically treatable in the vast majority (94,5%), highlighting both the prognostic and therapeutic utility of a good follow-up program. Risk factors for recurrence identified in the ACE study include piecemeal resection, lesion size ≥ 40 mm, intraprocedural bleeding and presence of high-grade dysplasia (HGD) in the resection specimen (6,7,8).

The aim of this study was to quantify procedure success, adverse events and recurrence rate after EMR in a tertiary referral centre. We also sought to identify risk factors for recurrence after successful EMR of large sessile and flat colorectal polyps.

## Methods

### *Ethical consideration*

This study was approved by the Ethics Committee Research University Hospitals Leuven (S52432). The database containing patient information was anonymized with a decryption file stored on a separate device. This study did not receive any funding.

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*Study design*

In this retrospective study, data was collected from 167 consecutive patients referred for EMR of 193 polyps in University Hospitals Leuven between October 1, 2017 and October 1, 2019. Polyps meeting inclusion criteria were located in the colon, non-pedunculated and ≥ 15 mm in size. Patients with any of the following conditions were excluded from the study: active colorectal malignancy or history of colorectal cancer within 2 years of the procedure, inflammatory bowel disease or genetic conditions such as familial adenomatous polyposis and Lynch Syndrome. One hundred and forty-three patients, corresponding with 166 polyps, remained after application of inclusion and exclusion criteria. A database with the clinical, endoscopic and histological data was constructed based on electronic medical records and endoscopic imaging, when available.

*Outcome measures*

The primary outcome measures of this study were procedure success and the rate of polyp recurrence during first follow-up colonoscopy. The secondary endpoints were to identify risk factors associated with polyp recurrence and the rate of adverse events after EMR.

*Procedure*s

All patients received PEG-based bowel preparation. In accordance with current guidelines, anticoagulants were discontinued before the procedure and patients with a high thrombotic risk received bridging therapy with LMWH. Antiplatelet therapy was either discontinued completely or continued solely with aspirin in the presence of a high thrombotic risk (9). All procedures were performed under sedation (midazolam + pethidine or propofol). We started with a complete inspection of the bowel with white light, followed by appraisal of the individual polyps' appearance. Polyps with a high suspicion of submucosal invasion were biopsied and referred for surgery after histological analysis. The diameter of the individual lesions was visually determined before resection by an experienced endoscopist, and polyps were resected using the lift and snare method. First, a solution was injected, consisting of a mixture of saline, indigocarmine or methylene blue in order to facilitate identification of the lesion margins during resection. Dilute adrenaline (1:100 000) was sometimes added to the lifting fluid to decrease bleeding during the procedure (10). Consequently, a submucosal cushion was created in order to safely remove a portion of mucosa without perforation of the bowel (11). Using a snare, the adenomatous tissue was resected until complete excision, either en bloc or in piecemeal, depending upon size and lifting type. When necessary, added measures to achieve haemostasis or prophylactic measures for bleeding were applied before the procedure was terminated. Prophylactic clip closure of the mucosal defect was not employed. Technical success was defined as complete absence of polyp tissue after careful inspection of the post-EMR defect and margin, as recommended in the ESGE clinical guidelines (12). Patients were observed in the day clinic and were generally discharged on the evening of the procedure. All endoscopic procedures were performed or supervised by experienced gastroenterologists.

*Adverse events*

We defined adverse event as any complication related to the EMR procedure, such as bleeding or perforation, that prolonged hospitalization or resulted in unplanned readmission within 30 days of discharge, transfusion requirement or death. An early adverse event was defined as any complication associated with the EMR occurring on the day of the procedure, whereas late complications were defined as those occurring beyond this time period.

*Follow-up*

Patient follow-up was planned either in UZ Leuven or by the experienced referring endoscopist, based on histological findings, co-morbidity and age. For these reasons some patients did not undergo a follow-up colonoscopy before the end of the study. During follow-up, the EMR scar was evaluated using white-light and narrow-band imaging to identify recurrence (13). We defined recurrence as visible presence of adenomatous tissue at the EMR site during surveillance endoscopy. When in doubt, biopsies of the EMR scar were taken to confirm the absence of histological recurrence. If present and possible, recurrence was treated immediately using either polypectomy or with a re-EMR, depending on size and morphology of the lesion. Otherwise, the lesion was biopsied to determine further course of action. Detailed reports of the executed follow-up were requested for patients who did not undergo follow-up in our tertiary centre. Recurrence rates were assessed until October 2020.

*Statistical analysis*

Statistical analysis was conducted using SPSS (Statistical Package for the Social Sciences 26; SPSS Inc, Chicago, Ill, USA). Descriptive statistics are reported using median and interquartile range (IQR) for continuous variables with a skewed distribution. Categoric variables are expressed as frequencies accompanied by the proportions of non-missing cases. Univariate analysis was performed using the chi-square test or Fisher's exact test for comparison of categorical data. Variables that rendered a P value < 0,1 in this analysis were selected as independent predictors for a multivariate analysis, using binomial logistic regression to identify endoscopic and clinical risk factors for

recurrence at SE1. All P values were two-tailed and P values < .05 were regarded as statistically significant.

## Results

### *Clinicopathological and endoscopic characteristics*

A total of 143 consecutive patients were referred for EMR of 166 polyps between October 1, 2017 and October 1, 2019 in UZ Leuven and were included in this retrospective study. Baseline clinicopathological characteristics and endoscopic findings at the time of EMR are presented in Table 1. Median patient age was 68 years (IQR 62-74, range 39-87 years). The male-to-female ratio was 1,04. Polyps were most commonly located in the caecum (28,3%) and the majority measured 20-29 mm (40,4%) with a median polyp size of 25 mm (IQR 20-35). Polyp inclusion, procedure success and follow-up are represented in Figure 2. EMR was not attempted in one case due to high suspicion of submucosal invasion based on endoscopic appearance. This patient was referred for surgery. Resection was attempted for the remaining 165 polyps (Figure 1), of which 7 (4,2%) were subsequently referred for surgery. In 2 cases due

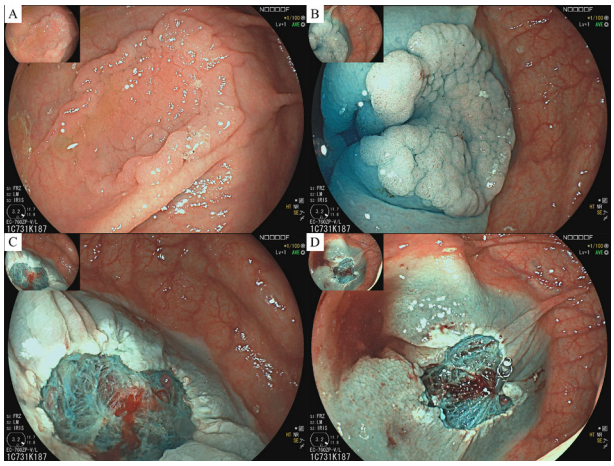


Figure 1. — Piecemeal EMR of a caecal polyp. (A) Flat caecal polyp, IIa measuring 40 mm before lifting. (B) Complete lifting after submucosal injection using indigo carmine dye. (C) Resection ulcer after piecemeal EMR. Oozing and visible vessel are apparent in the ulcer floor, persisting after soft coagulation. (D) Endoscopic haemostasis using one hemoclip.

to non-lifting after submucosal injection and in 5 cases because complete resection was not technically possible. EMR characteristics are presented in Table 2. Complete resection was successfully achieved in the remaining 158 cases (95,2%).

### *Recurrence at SE1*

Among the 158 successful cases, 141 were eligible for follow-up (Figure 2) and SE1 data was available in 117 (83,0%). Follow-up was not yet due in 6 cases (4,3%) and due but still unavailable at the time of the study in

Table 1. — **Baseline characteristics of patients and polyps**

| Characteristic | Number of patients (n = 143) Number of polyps (n = 166) |
|---|---|
| Age, years | |
| Median (IQR) | 68 (62-74) |
| Range | 39-87 |
| Male, n (%) | 73 (51,0%) |
| Antithrombotic drugs, n (%) | |
| Anticoagulant drugs | 29 (20,3%) |
| Antiplatelet drugs | 25 (17,5%) |
| Anesthesia, n (%) | |
| Sedation | 113 (80,1%) |
| General anesthesia | 28 (19,9%) |
| Polyp size, mm | |
| Median (IQR) | 25 (20-35) |
| Range | 15-70 |
| Polyp location, n (%) | |
| Caecum | 42 (28,3%) |
| Ascending colon | 37 (22,3%) |
| Hepatic flexure and transverse colon | 25 (15,0%) |
| Splenic flexure and descending colon | 15 (9,0%) |
| Sigmoid colon | 22 (13,3%) |
| Rectum | 25 (15,1%) |
| Morphology, n (%) | |
| Granular | 83 (50,0%) |
| Nongranular | 77 (46,4%) |
| Mixed | 6 (3,6%) |
| Paris classification, n (%) | |
| 0-IIa | 70 (42,2%) |
| 0-Is | 14 (8,4%) |
| 0-IIa-Is | 40 (24,1%) |
| 0-IIa-IIb | 8 (4,8%) |
| 0-IIa-IIc | 15 (9,0%) |
| 0-IIb | 7 (4,2%) |
| Other | 11 (6,7%) |
| Kudo classification, n (%) | |
| Kudo I & II | 30 (18,1%) |
| Kudo IIIs & IIIL | 58 (34,9%) |
| Kudo III-IV | 35 (21,1%) |
| Kudo IV | 21 (12,7%) |
| Kudo V | 5 (3,0%) |
| Mixed | 6 (3,6%) |
| Unable to classify | 11 (6,6%) |
| Histology, n (%) | |
| Tubular adenoma | 71 (42,8%) |
| Tubulovillous adenoma | 46 (27,7%) |
| Sessile serrated polyp | 29 (17,5%) |
| Mixed polyp histology | 9 (5,4%) |
| Adenocarcinoma | 6 (3,6%) |
| Other | 3 (1,8%) |

18 cases (12,8%). The median follow-up period after EMR was 6,2 months (IQR 5,0-9,9 months). Recurrent adenomatous tissue was detected in 19 cases (16,2%, confirmed with biopsy in 14 cases), with possibility for immediate endoscopic resection in 15 cases (polypectomy: n = 7; EMR: n = 6; biopsy avulsion: n = 2). Three patients underwent surgery because endoscopic treatment was deemed technically impossible due to

Table 2. — **EMR characteristics**

| Characteristic | Number of cases (n = 165) |
|---|---|
| EMR technique | |
| Piecemeal | 104 (88,9%) |
| En bloc | 13 (11,1%) |
| Lifting type | |
| Complete | 158 (95,8%) |
| Incomplete | 5 (3,0%) |
| Non-lifting | 2 (1,2%) |
| Additional ablation | |
| Yes | 20 (12,7%) |
| No | 138 (87,3%) |
| Early adverse event, n (%) | |
| Bleeding | 3 (1,8%) |
| Perforation | 1 (0,6%) |
| Late adverse event, n (%) | |
| Bleeding | 12 (7,3%) |

*Risk factors for early recurrence*

Results of univariate and multivariate analyses of independent risk factors and the numbers for each variable are respectively presented in Table 3 and Table 4. Univariate analysis showed that lesion size ≥ 40 mm (p = 0,006) and ≥ 30 mm (p = 0,021), occurrence of delayed bleeding (p = 0,037) and presence of HGD (p = 0,017) were found to be significantly associated with polyp recurrence at SE1. In a multivariate logistic regression analysis, lesion size ≥ 40 mm (p = 0,018) and presence of HGD (0,034) remained independent risk factors associated with polyp recurrence at SE1. This data suggests that polyps ≥ 40 mm and polyps with HGD were respectively 4,03 (95% CI 1,27-12,76) and 3,89 times (95% CI 1,67-13,15) times more likely to exhibit recurrence. The significant association between recurrence and polyp size ≥ 30 mm or delayed bleeding was not carried over in the multivariate analysis.

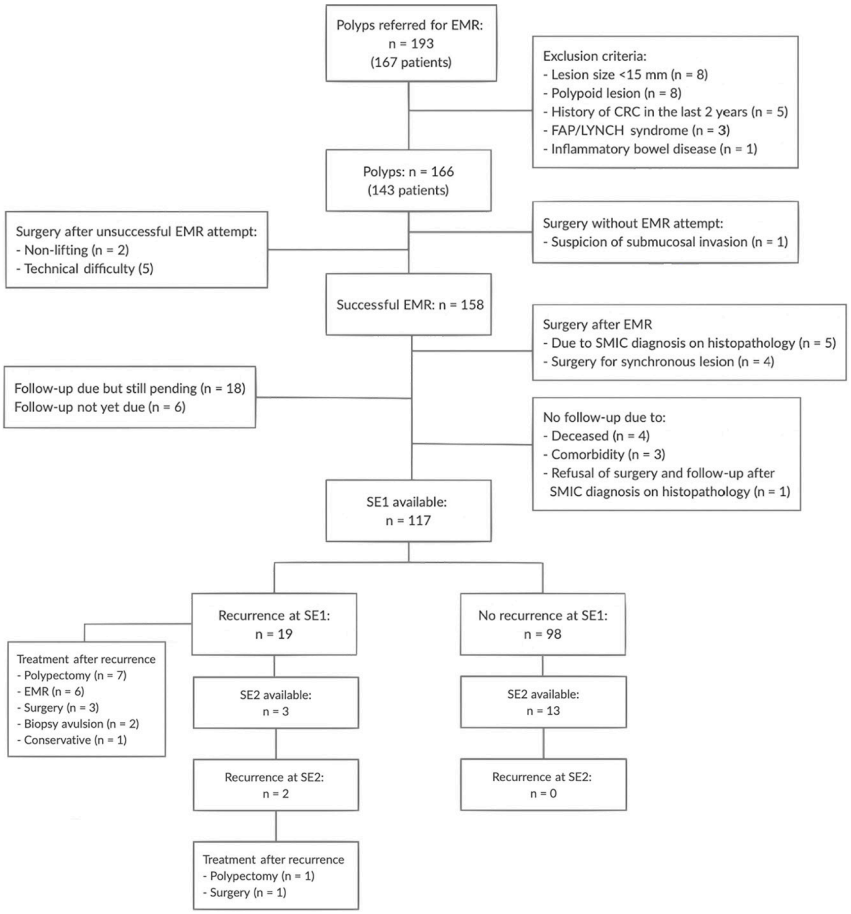


Figure 2. — Flowchart of patient and lesion selection. Lesions referred for surgery were excluded from the analysis. Surveillance endoscopy 1 (SE1) and 2 (SE2) were not available for all included lesions. Abbreviations: EMR: endoscopic mucosal resection; CRC: colorectal carcinoma; FAP: Familial Adenomatous Polyposis; SMIC: submucosal invasive cancer; SE1: first surveillance endoscopy; SE2: second surveillance endoscopy.

underlying fibrosis and instable position. The remaining patient elected a conservative approach due to age and co-morbidity. Of the 117 cases for which SE1 was available, the EMR site remained free of recurrence in 98 (83,8%).

Table 3. — **Univariate analysis of risk factors for recurrence at SE1**

| | Recurrence at SE1 | | |
|---|---|---|---|
| Variable | No n = 98 | Yes n = 19 | P value |
| Age, years, median (IQR) | 68,0 (9,9) | 68,0 (7,3) | 0,336 |
| Gender, n (%) | | | |
| Male | 50 (79,4%) | 13 (20,6%) | 0,211 |
| Female | 48 (88,9%) | 6 (11,1%) | 0,459 |
| Antithrombotic drugs, n (%) | | | |
| Anticoagulant drugs | 20 (87,0%) | 3 (13,0%) | |
| Antiplatelet drugs | 17 (77,3%) | 5 (22,7%) | |
| Polyp size, n (%) | | | |
| < 40 mm | 85 (88,5%) | 11 (11,5%) | **0,006** |
| ≥ 40 mm | 13 (61,9%) | 8 (38,1%) | |
| < 30 mm | 61 (91,0%) | 6 (9,0%) | **0,021** |
| ≥ 30 mm | 37 (74,0%) | 13 (26,0%) | |
| < 20 mm | 17 (89,5%) | 2 (10,5%) | 0,735 |
| ≥ 20 mm | 81 (82,7%) | 17 (17,3%) | 0,176 |
| Polyp location, n (%) | | | |
| Left side of colon | 34 (91,9%) | 3 (8,1%) | |
| Right side of colon * | 64 (80,0%) | 16 (20,0%) | 1,000 |
| Morphology, n (%) | | | |
| Granular | 52 (83,9%) | 10 (16,1%) | |
| Nongranular | 42 (82,4%) | 9 (17,6%) | |
| Mixed | 4 (100%) | 0 (0%) | 0,203 |
| Paris classification, n (%) | | | |
| 0-IIa | 44 (84,6%) | 8 (15,4%) | |
| 0-Is | 7 (100%) | 0 (0%) | |
| 0-IIa-Is | 20 (71,4%) | 8 (28,6%) | |
| Other | 26 (89,7%) | 3 (10,3%) | 0,521 |
| Kudo classification, n (%) | | | |
| Kudo I & II | 21 (87,5%) | 3 (12,5%) | |
| Kudo IIIs & IIIL | 30 (81,1%) | 7 (18,9%) | |
| Kudo III-IV | 26 (83,9%) | 5 (16,1%) | |
| Kudo IV | 13 (86,7%) | 2 (13,3%) | |
| Kudo V | 0 (0%) | 1 (100%) | |
| Other | 1 (100%) | 0 (0%) | 0,984 |
| Histology, n (%) | | | |
| Tubular adenoma | 42 (85,7%) | 9 (14,3%) | |
| Tubulovillous adenoma | 29 (82,6%) | 6 (17,4%) | |
| Sessile serrated adenoma/polyp | 20 (87,0%) | 3 (13,0%) | |
| Mixed | 7 (87,5%) | 1 (12,5%) | **0,017** |
| Grade of dysplasia | | | |
| Low grade of dysplasia | 88 (87,1%) | 13 (12,9%) | |
| High grade of dysplasia | 9 (60,0%) | 6 (40,0%) | 1,000 |
| Early adverse event, n (%) | | | |
| Yes | 4 (100%) | 0 (0%) | |
| No | 94 (83,2%) | 19 (16,8%) | **0,037** |
| Delayed bleeding, n (%) | | | |
| Yes | 5 (55,6%) | 4 (44,4%) | |
| No | 93 (86,1%) | 15 (13,9%) | 1,000 |
| EMR technique, n (%) | | | |
| Piecemeal | 87 (83,7%) | 17 (16,3%) | |
| En bloc | 11 (84,6%) | 2 (15,4%) | 0,513 |
| Lifting type, n (%) | | | |
| Complete | 95 (84,0%) | 18 (16,0%) | |
| Incomplete | 3 (75,0%) | 1 (25,0%) | 1,000 |
| Additional ablation, n (%) | | | |
| Yes | 13 (86,7%) | 2 (13,3%) | |
| No | 85 (83,3%) | 17 (16,7%) | |

Proportions are reported as proportions of non-missing data. * Including hepatic flexure, transverse colon and splenic flexure.

Table 4. — **Multivariate analysis of risk factors for recurrence at SE1**

| Variable | OR | 95% CI | P value |
|---|---|---|---|
| Lesion size ≥ 40 mm | 4,03 | 1,27-12,76 | **0,018** |
| Lesion size ≥ 30 mm | 2,916 | 0,97-8,76 | 0,057 |
| Delayed bleeding | 3,45 | 0,72-16,46 | 0,121 |
| High grade of dysplasia | 3,89 | 1,11-13,60 | **0,034** |

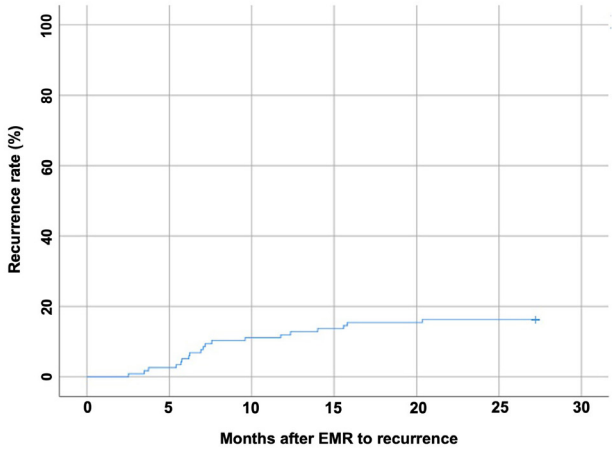


Figure 3. — Kaplan-Meier plot of recurrence during follow-up. The overall recurrence rate after successful EMR was 16,2%.

*Recurrence at SE2*

Of the 117 cases with available and clear SE1, SE2 was performed in 13 cases and still unavailable in 85. All these cases remained free of adenoma. Three patients underwent SE2 following endoscopic management of recurrence at SE1 and exhibited sustained recurrence in 2 cases. One case was immediately endoscopically treated with polypectomy. The remaining recurrence was referred for surgery. This keeps the overall recurrence rate during the study at 16,2% (Figure 3) and brings the surgical referral rate after successful EMR to 9,7%. The median SE2 follow-up period after EMR was 14,5 months (IQR 11,8-18,3 months).

*Adverse events*

For a total of 165 EMR's, we identified early adverse event in 4 cases (2,4%) and late adverse event in 12 cases (7,3%). Four patients died during follow-up. None of these deaths was procedure-related or attributable to CRC.

Early complications occurred in 4 cases (2,4%; bleeding: n = 3, perforation: n = 1) and were treated conservatively or by endoscopy. In 3 cases these adverse events resulted in extension of hospital stay by 1 night for observation or further treatment (conservative: n = 1, endoscopic hemoclip application: n = 2). One patient spent 2 additional nights in the hospital due to recurrence of RBPA after failure to achieve complete haemostasis during EMR. In this case a relook colonoscopy resulted in a conservative approach for the remaining oozing bleeding at the EMR site.

In total, 12 (7,3%) patients presented with delayed bleeding. Median time to readmission was 7,5 days after EMR (IQR 1-11,5 days) with a median length of stay of 2 days (IQR 1-8,5 days). All patients underwent a relook colonoscopy and if needed, delayed bleeding was treated endoscopically to achieve haemostasis. Of the 12 cases, 9 were handled either conservatively (n = 6) or in case of persistent oozing with coagulation (n = 2) or submucosal adrenalin injection and clipping (n = 1). The remaining 3 cases required immediate transfusion with packed cells (PC) due to haemodynamic instability. In 2 of these cases, additional endoscopic therapy during relook colonoscopy consisted of either clipping or application of hemospray with submucosal adrenalin injection. The third patient remained haemodynamically unstable despite resuscitative efforts with intravenous fluid replacement, PC and FFP. Urgent interventional radiology evaluation revealed active arterial bleeding from a branch of the ileocolic artery, which was successfully embolised under general anesthesia with sustained resolution of symptoms within 24 hours.

No adverse events were recorded after endoscopic treatment of recurrence during SE1 and SE2.

## Discussion

Endoscopic mucosal resection is the current first-line treatment for large sessile and flat colorectal lesions without suspicion of submucosal invasion. We retrospectively studied the outcome, adverse event and recurrence rates of two years of EMR in a tertiary centre. The results of our study show that high technical success rates can be achieved with few complications, consisting predominantly of delayed bleeding. Recurrence at SE1 occurred in 16,2% and was largely endoscopically treatable, underlining the importance of follow-up. Polyp size ≥ 40 mm and presence of HGD in the EMR resection specimen were identified as independent risk factors for local recurrence.

The current literature on colorectal EMR reflects our high technical success rate. One recent large Australian prospective study by *TATE et al.* reported a 97,6% successful resection rate in over 1600 large colorectal lesions (14). Reasons for unsuccessful EMR have been well documented in previous studies. Difficult access and submucosal fibrosis with poor lesion lifting are reported as the most frequent reasons for incomplete resection.[6] Consequently, biopsy should not be performed before attempting EMR as it may interfere with complete resection due to submucosal fibrosis and subsequent poor lifting (15). In Western centres, these lesions often warrant a surgical approach. Still, the overwhelming majority of large sessile and flat colorectal polyps remain non-invasive and endoscopically resectable, reinforcing the important role of EMR in general endoscopic practice (16).

Delayed bleeding is the most common adverse event described after EMR of large colorectal lesions (17). We encountered this adverse event in 7,2% of cases in our series. This is comparable to a number of studies, with reported rates ranging around 6-7% (18,19,20,21). Post-EMR hemorrhage often results in a short additional hospital readmission, but is in itself rarely serious and mostly either conservatively or endoscopically manageable. As such, transfusion, angiographic or surgical management are infrequently required. Nonetheless, EMR should only be performed by skilled endoscopists with proficiency in endoscopic haemostasis techniques, most commonly coagulation and clipping. Routine prophylactic clip closure after EMR is currently not recommended. A number of recent studies, however, suggest that the use of mechanical prophylaxis (e.g. clip closure) in the presence of certain risk factors, such as proximal location and large mucosal defect sizes may reduce the incidence of delayed bleeding after EMR (22,23). Further guidelines may address what the most suitable defects are for prophylactic closure. Perforation after EMR was exceedingly rare in our study, occurring in but one person. Described in around 1-2% of cases after EMR, it is also predominantly endoscopically treated by clipping the defect in the post-resection ulcer to attain closure (20,21,24). Hence, the morbidity associated with these complications remains low and acceptable. We accordingly find EMR to be a safe resection method for large colorectal lesions.

In the present study we found a recurrence rate of approximately 16% at SE1, consistent with the findings of several other groups (6,14,20,21). A recent systematic review reported a mean recurrence risk of 15% (95% CI 12-19%) after EMR (8). In a large prospective study of 1000 lesions, *MOSS et al.* demonstrated that while present in 16% of their cases, the majority of recurrences are small and easily endoscopically treatable (6). Our high endoscopic treatment rate confirms that in most cases recurrence does not constitute a significant barrier to a second chance at minimally invasive eradication.

Data on long term follow-up is too limited at this time to draw firm conclusions regarding late recurrence in our centre. However, as stated by *BELDERBOS et al.* nearly 90% of recurrences are detected during first follow-up (8). Our limited data seems to support this, as none of the 13 patients with clear SE1 exhibited late recurrence. The remaining percentage of recurrences will nonetheless arise after a normal previous colonoscopy. Therefore, a normal SE1 is reassuring, but this finding certainly does not negate the need for further follow-up. Furthermore, we observed sustained recurrence after endoscopic treatment of recurrence at SE1 in 2 of the 3 available cases. This finding demonstrates the difficulty of a repeat endoscopic resection at the site of a previous EMR. This is not surprising when, as stated above, we consider the effect of a simple biopsy on EMR difficulty. In these situations, the role of endoscopic submucosal dissection (ESD) may be considered.

A number of risk factors for recurrence have previously been identified, among them lesion size ≥ 40 mm, presence of HGD and piecemeal resection (6,20,25). Our results confirmed lesion size ≥ 40 mm and HGD as risk factors. As maintained by *TATE et al.*, a probable explanation for these risk factors may be the higher potential for residual tissue between snare placements in larger lesions, and the increased potential for propagation of remaining adenomatous tissue in the presence of HGD (25). Polyp size ≥ 30 mm was not significantly associated with a higher recurrence rate, though a trend was observed, further illustrating the strength of lesion size as a risk factor. We did not confirm piecemeal resection as a risk factor for recurrence, however our study proved insufficiently powered to appreciate this association, as most polyps in our study were removed in piecemeal. In addition, the number of lesions above 40 mm in size was also limited. Importantly, the relevance of this risk factor has been called into question by multiple authors, citing overall low recurrence rates and evidence of predominantly small recurrences amenable to endoscopic treatment. This finding is reinforced by our high endoscopic treatment rate (79%) during SE1. We therefore believe that even when en-bloc resection proves impractical, piecemeal EMR by a trained endoscopist remains a preferred treatment for large colorectal lesions. Albeit under the strict condition that resected lesions, especially those exhibiting one or more risk factors for recurrence, be included in a structured surveillance program to adequately detect and resect any recurrent polyp.

Indeed, our findings reassert the importance of a structured follow-up program after EMR. Still, compliance with follow-up colonoscopies remains a substantial issue, even in tertiary centres. After EMR and histopathology, patients and their general practitioner receive a report with an endoscopist-recommended follow-up interval. Yet, when actively pursuing follow-up reports, we found that approximately 13% of cases had not yet undergone a colonoscopy past the recommended interval. General practitioners were contacted and instructed to refer their patients for further follow-up. This phenomenon is ubiquitous in the EMR literature. In a large study with more than 1500 patients eligible for follow-up, *TATE et al.* reported that 11% failed to schedule or appear for SE1 after EMR (14). Consequently, increased efforts to improve adherence to follow-up certainly seem necessary. Preliminary results of a quality improvement project by *WERLANG et al.* suggest that a reminder system significantly increases follow-up compliance after EMR (26). Additionally, patients should be educated about the risk of interval CRC and the importance of adherence to follow-up in its prevention and early detection.

Though the majority of non-polypoid colorectal lesions can be removed in a curative manner through EMR, it is worth mentioning that ESD is a viable alternative, with higher en bloc resection rates and

lower local recurrence rates (27, 28). Certainly when we consider lesions exhibiting signs of potential submucosal invasion, en bloc resection is preferred in order to assess the resection margins through histopathology. This technique, however, is more time-consuming and technically challenging. In centers where ESD expertise is readily available and en bloc resection is preferred, patients may directly be scheduled for ESD.

This study is subject to several inherent limitations. Although patients were prospectively enrolled, data were retrospectively collected and analyzed and therefore vulnerable to the weaknesses of a retrospective analysis. Second, all procedures were performed or supervised by endoscopists with extensive EMR experience in a tertiary referral centre. Our results may therefore not be completely generalized. Moreover, although most recurrences are detectable within 6 months, longer follow-up is needed to make conclusive statements about long-term recurrence and clinically relevant parameters such as long-term surgical reference rate. Furthermore, due to a small number of recurrences, our study may not have been sufficiently powered to detect any additional risk factors.

In conclusion, this study demonstrates that in a tertiary centre, EMR is safe and effective in the treatment of large sessile and flat colorectal lesions. Delayed bleeding remains the most common adverse event but can easily be managed upon readmission. Recurrence, however infrequent, is largely endoscopically treatable during follow-up, highlighting the importance of a structured follow-up program. Lesion size $\geq$ 40 mm and presence of HGD in the resection specimen are risk factors for recurrence at SE1. Their presence should be considered when planning SE in order to emphasize the value of strict adherence to follow-up. Future studies with longer surveillance will provide more information regarding long-term outcome in our centre.

## Conflict of interest statement

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

## References


1. BRAY F., FERLAY J., SOERJOMATARAM I., SIEGEL R. L., TORRE L. A., JEMAL A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 2018, **68**: 394-424.
2. WINAWER S. J., ZAUBER A. G., HO M. N., O'BRIEN M. J., GOTTLIEB L. S., STERNBERG S. S. *et al.* Prevention of Colorectal Cancer by Colonoscopic Polypectomy. *New England Journal of Medicine*, 1993, **329**: 1977-1981.
3. ZAUBER A. G., WINAWER S. J., O'BRIEN M. J., LANSDORP-VOGELAAR I., VAN BALLEGOOIJEN M., HANKEY B. F. *et al.* Colonoscopic Polypectomy and Long-Term Prevention of Colorectal-Cancer Deaths. *New England Journal of Medicine*, 2012, **366**: 687-696.
4. WORLAND T., CRONIN O., HARRISON B., ALEXANDER L., DING N., TING A. Clinical and financial impacts of introducing an endoscopic mucosal resection service for treatment of patients with large colonic polyps into a regional tertiary hospital. *Endoscopy International Open*, 2019, **07**: E1386-E1392.
5. KHASHAB M., EID E., RUSCHE M., & REX D. K. Incidence and predictors of "late" recurrences after endoscopic piecemeal resection of large sessile adenomas. *Gastrointestinal Endoscopy*, 2009, **70**: 344-349.
6. MOSS A., WILLIAMS S. J., HOURIGAN L. F., BROWN G., TAM W., SINGH R. *et al.* Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: Results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut*, 2015, **64**: 57-65.
7. MOSS A., BOURKE M. J., WILLIAMS S. J., HOURIGAN L. F., BROWN G., TAM W. Endoscopic Mucosal Resection Outcomes and Prediction of Submucosal Cancer From Advanced Colonic Mucosal Neoplasia. *Gastroenterology*, 2011, **140**: 1909-1918.
8. BELDERBOS T., LEENDERS M., MOONS L., SIERSEMA P. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. *Endoscopy*, 2014, **46**: 388-402.
9. VEITCH A. M., VANBIERVLIET G., GERSHLICK A. H., BOUSTIERE C., BAGLIN T. P., SMITH L.-A. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. *Gut*, 2016, **65**: 374-389.
10. HSIEH Y. H., LIN H. J., TSENG G. Y., PERNG C. L., LI A. F., CHANG F. Y. *et al.* Is submucosal epinephrine injection necessary before polypectomy? A prospective, comparative study. *Hepato-Gastroenterology*, 2001, **48**: 1379-1382.
11. HWANG J. H., KONDA V., ABU DAYYEH B. K., CHAUHAN S. S., ENESTVEDT B. K., FUJII-LAU L. L. *et al.* Endoscopic mucosal resection. *Gastrointestinal Endoscopy*, 2015, **82**: 215-226.
12. FERLITSCH M., MOSS A., HASSAN C., BHANDARI P., DUMONCEAU J.-M., PASPATIS G. *et al.* Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy*, 2017, **49**: 270-297.
13. BISSCHOPS R., EAST J. E., HASSAN C., HAZEWINKEL Y., KAMIŃSKI M. F., NEUMANN H. *et al.* Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2019. *Endoscopy*, 2019, **51**: 1155-1179.
14. TATE D. J., DESOMER L., AWADIE H., GOODRICK K., HOURIGAN L., SINGH R. *et al.* EMR of laterally spreading lesions around or involving the appendiceal orifice: technique, risk factors for failure, and outcomes of a tertiary referral cohort (with video). *Gastrointestinal Endoscopy*, 2018, **87**: 1279-1288.
15. HAN K. S., SOHN D. K., CHOI D. H., HONG C. W., CHANG H. J., LIM S.-B. *et al.* Prolongation of the period between biopsy and EMR can influence the nonlifting sign in endoscopically resectable colorectal cancers. *Gastrointestinal Endoscopy*, 2008, **67**: 97-102.
16. BOGIE R., VELDMAN M., SNIJDERS L., WINKENS B., KALTENBACH T., MASCLEE A. *et al.* Endoscopic subtypes of colorectal laterally spreading tumors (LSTs) and the risk of submucosal invasion: a meta-analysis. *Endoscopy*, 2018, **50**: 263-282.
17. VAN DER STAR S., MOONS L. M. G., TER BORG F., VAN BERGEIJK J. D., GEESING J. M. J., GROEN J. N. *et al.* Management of delayed bleeding after endoscopic mucosal resection of large colorectal polyps: a retrospective multi-center cohort study. *Endoscopy International Open*, 2020, **08**: E1052-E1060.
18. BURGESS N. G., WILLIAMS S. J., HOURIGAN L. F., BROWN G. J., ZANATI S. A., SINGH R. *et al.* A Management Algorithm Based on Delayed Bleeding After Wide-Field Endoscopic Mucosal Resection of Large Colonic Lesions. *Clinical Gastroenterology and Hepatology*, 2014, **12**: 1525-1533.
19. BURGESS N. G., METZ A. J., WILLIAMS S. J., SINGH R., TAM W., HOURIGAN L. F., *et al.* Risk Factors for Intraprocedural and Clinically Significant Delayed Bleeding After Wide-field Endoscopic Mucosal Resection of Large Colonic Lesions. *Clinical Gastroenterology and Hepatology*, 2014, **12**: 651-661.
20. PELLISE M., BURGESS N. G., TUTTICCI N., HOURIGAN L. F., ZANATI S. A., BROWN G. J. *et al.* Endoscopic mucosal resection for large serrated lesions in comparison with adenomas: A prospective multicentre study of 2000 lesions. *Gut*, 2017, **66**: 644-653.
21. HASSAN C., REPICI A., SHARMA P., CORREALE L., ZULLO A., BRETTHAUER M. *et al.* Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. *Gut*, 2016, **65**: 806-820.
22. YANG T., WU Y., LEE P., CHANG C., LU H., CHEN Y. *et al.* Prophylactic clipping after endoscopic mucosal resection of large nonpedunculated colorectal lesions: A meta-analysis. *Journal of Gastroenterology and Hepatology*, 2021, Advance online publication. doi: 10.1111/jgh.15472

23. AYOUB F., WESTERVELD D. R., FORDE J. J., FORSMARK C. E., DRAGANOV P. V, YANG D. Effect of prophylactic clip placement following endoscopic mucosal resection of large colorectal lesions on delayed polypectomy bleeding: A meta-analysis. *World Journal of Gastroenterology*, 2019, **25**(18): 2251-2263.
24. SWAN M. P., BOURKE M. J., MOSS A., WILLIAMS S. J., HOPPER A., METZ A. The target sign: an endoscopic marker for the resection of the muscularis propria and potential perforation during colonic endoscopic mucosal resection. *Gastrointestinal Endoscopy*, 2011, **73**: 79-85.
25. TATE D. J., DESOMER L., KLEIN A., BROWN G., HOURIGAN L. F., LEE E. Y. T. *et al.* Adenoma recurrence after piecemeal colonic EMR is predictable: the Sydney EMR recurrence tool. *Gastrointestinal Endoscopy*, 2017, **85**: 647-656.
26. WERLANG M., KANDEL P., AHN I., BINGHAM R., BRAHMBHATT B., RAIMONDO M. *et al.* Improving Surveillance Follow-up Rates After Colonoscopy Endoscopic Mucosal Resection: A Quality Improvement Project. *American Journal of Gastroenterology*, 2017, **112**: S622-S624
27. WANG J., ZHANG X.-H., GE J., YANG C.-M., LIU J.-Y., ZHAO S.-L. Endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal tumors: a meta-analysis. *World Journal of Gastroenterology*, 2014, **20**(25): 8282-8287.
28. TAJIKA M., NIWA Y., BHATIA V., KONDO S., TANAKA T., MIZUNO N. *et al*. Comparison of endoscopic submucosal dissection and endoscopic mucosal resection for large colorectal tumors. *European Journal of Gastroenterology & Hepatology*, 2011, **23**(11), 1042-1049.