Annals of Internal Medicine ORIGINAL RESEARCH

Endoscopic En Bloc Versus Piecemeal Resection of Large Nonpedunculated Colonic Adenomas

A Randomized Comparative Trial

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Background: Endoscopic resection of adenomas prevents colorectal cancer, but the optimal technique for larger lesions is controversial. Piecemeal endoscopic mucosal resection (EMR) has a low adverse event (AE) rate but a variable recurrence rate necessitating early follow-up. Endoscopic submucosal dissection (ESD) can reduce recurrence but may increase AEs.

Objective: To compare ESD and EMR for large colonic adenomas.

Design: Participant-masked, parallel-group, superiority, randomized controlled trial. (ClinicalTrials.gov: NCT03962868)

Setting: Multicenter study involving 6 French referral centers from November 2019 to February 2021.

Participants: Patients with large (≥25 mm) benign colonic lesions referred for resection.

Intervention: The patients were randomly assigned by computer 1:1 (stratification by lesion location and center) to ESD or EMR.

Measurements: The primary end point was 6-month local recurrence (neoplastic tissue on endoscopic assessment and scar biopsy). The secondary end points were technical failure, en bloc R0 resection, and cumulative AEs.

Results: In total, 360 patients were randomly assigned to ESD (n = 178) or EMR (n = 182). In the primary analysis set (n = 318 lesions in 318 patients), recurrence occurred after 1 of 161 ESDs (0.6%) and 8 of 157 EMRs (5.1%) (relative risk, 0.12 [95% CI, 0.01 to 0.96]). No recurrence occurred in R0-resected cases (90%) after ESD. The AEs occurred more often after ESD than EMR (35.6% vs. 24.5%, respectively; relative risk, 1.4 [CI, 1.0 to 2.0]).

Limitation: Procedures were performed under general anesthesia during hospitalization in accordance with the French health system.

Conclusion: Compared with EMR, ESD reduces the 6-month recurrence rate, obviating the need for systematic early follow-up colonoscopy at the cost of more AEs.

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The incidence of colorectal cancer (CRC) can be reduced by screening (1–3), which not only detects early stages of CRC but also facilitates identification and removal of early and preneoplastic lesions. In the West, flat large adenomas are commonly removed piecemeal by endoscopic mucosal resection (EMR) using electrocautery snares. However, EMR is associated with a substantial rate of recurrent–residual adenoma at the first follow-up colonoscopy (4–6), most likely because of incomplete resection. This might partially explain the worse prognosis in patients with larger and more advanced adenomas (7–9), especially when adherence to follow-up colonoscopy is suboptimal (10). Thus, early follow-up colonoscopy must be systematically performed after EMR of larger adenomas, increasing cost and patient discomfort.

Reducing recurrence was one of the motivations underlying the development of techniques beyond EMR to finally allow en bloc resection of the neoplasm. Endoscopic submucosal dissection (ESD) was developed in Japan to increase oncologic safety in suspicious or malignant lesions but it may also be instrumental in reducing recurrence. Studies from Japan have shown that ESD facilitates en bloc resection in more than 95% of cases with very low recurrence rates (11, 12); however, it is also more technically complex and has a higher rate of adverse events (AEs). Therefore, its use is commonly limited to experts. No randomized trials have yet compared the outcomes of EMR and ESD. Current evidence is therefore based on meta-analyses of case series of variable quality (13, 14).

See also:

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Web-Only
Supplement

We conducted a randomized controlled trial of these 2 techniques for larger benign colonic neoplasms with the main study aim of reducing recurrence rates and the need for immediate follow-up. The study design was not meant to address oncologic issues because suspected or known types of cancer were not included in this trial.

METHODS

Study Design

The RESECT-COLON trial was a participant-masked, parallel-group, superiority, randomized controlled trial in 6 French centers (5 university hospitals and 1 private hospital). The full protocol is available in the Supplement Protocol (available at Annals.org). All adult patients referred between September 2019 and February 2021 for resection of large flat colonic lesions, called laterally spreading tumors (LSTs), were assessed for eligibility. Written informed consent was obtained from each patient at the screening visit after evaluating the inclusion and exclusion criteria based on the index colonoscopy report from the referring institutions. The study followed the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement (15), and the trial was approved by the institutional review board of each participating center.

Inclusion and Exclusion Criteria

The *eligibility criteria* were checked during the screening visit: LST with a nonpedunculated–flat shape, size of more than 25 mm, location in the colon (>15 cm from the anal verge), and indication for endoscopic treatment (no endoscopic features suspicious of deep submucosal invasion). The *exclusion criteria* are listed in Supplement Text 1 (available at Annals.org). The primary exclusion criteria were checked during the screening visit, and the secondary exclusion criteria were checked during the study colonoscopy with resection.

In addition, a *postrandomization exclusion criterion* was added for patients treated by surgery before the primary end point analysis (for complications, failure, or poor prognostic histologic criteria) because they could not be evaluated for the primary end point of local recurrence. These patients were followed up until the end of the study for the secondary end point analysis.

Randomization and Masking

Randomization was done after the operator had confirmed the eligibility criteria. Randomization was centralized, conducted over a secured internet connection, done using blocks of mixed size, and stratified according to center and lesion location (right colon, transverse colon, or left colon). The patients were blinded and the pathologists were not informed about the treatment, but the physicians who performed the initial and follow-up procedures were not blinded (Supplement Text 2, available at Annals.org).

Study Procedures

The study procedures are detailed in Supplement Text 2 and Figure 1.

Therapeutic colonoscopy was performed under general anesthesia with intubation. A high-resolution video endoscope with virtual chromoendoscopy was used to predict the histologic diagnosis using validated classifications.

Polyp characteristics were defined using the LST classification (16) and Paris classification (17), and lesion size was measured using an open polypectomy snare.

The choice of endoscope, injection fluid, and device (ESD knife or polypectomy snare) was at the physician's discretion. Thirteen physicians, all experienced in both procedures, performed the procedures (Supplement Table 1, available at Annals.org). In case of technical failure, crossover to the other technique was allowed; however, this was counted as a failure, even if it led to complete resection. Clip closure of the resection site after both techniques was at the physician's discretion.

Endoresection Techniques

Both procedures were performed after lesion elevation by submucosal fluid injection: ESD consisted of en bloc resection by dissecting around and underneath the lesion (18) and EMR consisted of resection in several pieces using a polypectomy snare (19). After resection of all macroscopically visible adenoma tissue by EMR, snare-tip thermal ablation of the margin was performed to reduce the recurrence rate (20, 21).

Follow-up

Patients were hospitalized the night after the procedure for clinical monitoring. A consultation was done at 1 month postoperatively to inform the patients of the histopathological results and to check for AEs. At 6 months, control colonoscopy was performed to check for residual–recurrent adenoma with same-session endoscopic treatment of any detected recurrences.

The primary and secondary end point data were independently monitored by a monitoring board at each participating center.

Histologic Assessment

En bloc specimens from ESD were pinned on cork, and specimens from EMR were pinned and/or placed in formaldehyde solution. Parallel cross-sectional slices of 2- to 3-mm thickness along the longest axis of the specimen were obtained. Histopathologic definitions are detailed in Supplement Text 3 (available at Annals.org).

Outcomes

The primary end point was neoplastic local recurrence at the first follow-up colonoscopy at 6 months. Biopsy of the scar was mandatory. Recurrence was defined as a positive mandatory biopsy or a recurrence specimen obtained through resection, regardless of the macroscopic appearance on endoscopy.

The secondary end points were technical failure of EMR/ESD, the R0 resection rate, and cumulative procedural AEs at 30 days. The AEs were graded according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2A standard (22) and the lexicon for endoscopic AEs (23). Definitions of the secondary end points and the method of evaluation of AEs are available in **Supplement Text 4** and **5** (available at Annals.org).

We defined baseline resection histologic outcomes (that is, very low-risk resection, low-risk resection, local-risk resection, high-risk resections) according to the updated European Society of Gastrointestinal Endoscopy (ESGE) guidelines (**Supplement Text 3**) (24).

The histologic results and risk factors for recurrence were compared as a post hoc analysis.

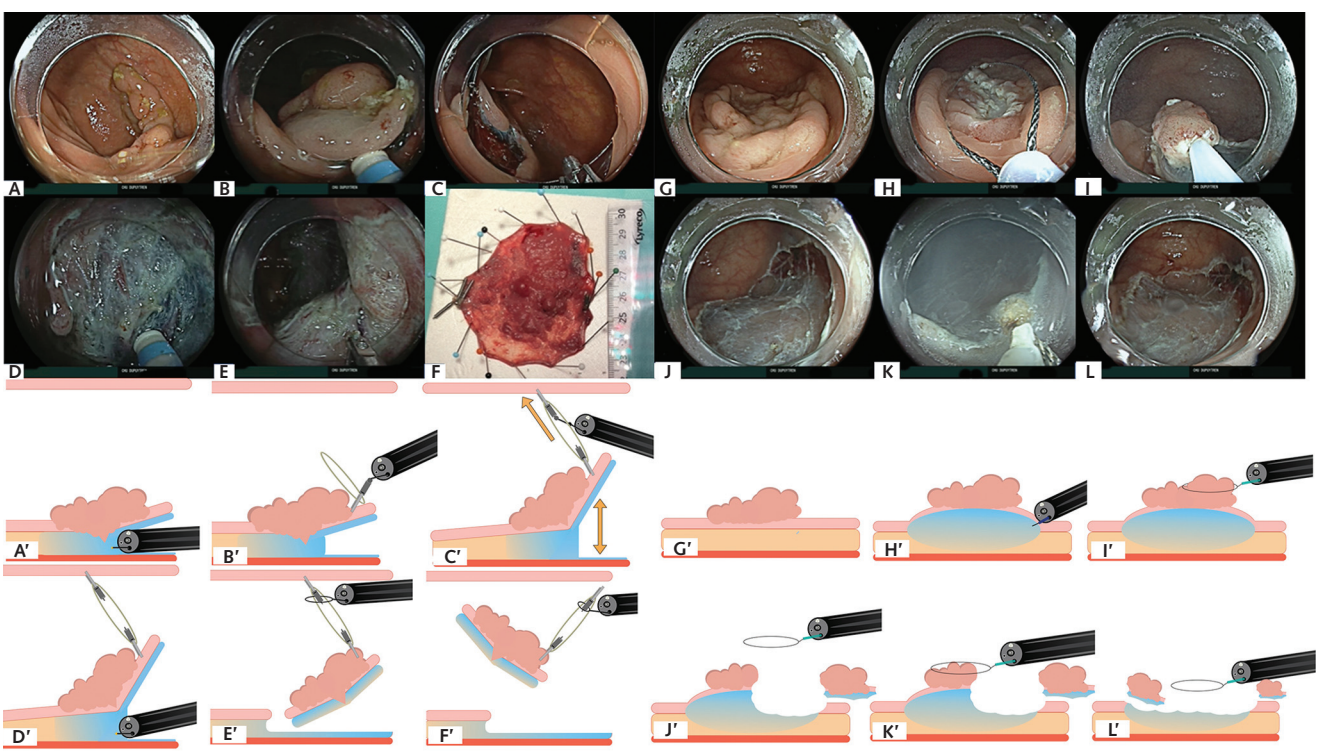
Statistical Analysis

With the type I error of 5% and power of 90%, the 6-month expected recurrence rate was assumed to be 10% in the EMR group (4) and 2% in the ESD group (12). Without continuity correction, at least 150 patients were determined to be required in each group (total of 300 patients) (nQuery Advisor v.7.0; Statistical Solutions). Based on an estimated unevaluable patient rate of 10%, we enrolled 330 patients. After the initial few cases, the sample size was adjusted through a protocol amendment. This adjustment was made to account for the anticipated 10% cancer rate that would necessitate surgery. The purpose of increasing the sample size by this 10% was to ensure that the primary outcome, which focused on local recurrence, would not include case patients who had already undergone surgery.

The primary analysis set included all randomly assigned patients excluding those who met the secondary exclusion criteria and those who could not be evaluated for the primary end point (**Figure 2**). The per-protocol population further excluded patients in whom the procedure had failed or those who had undergone the procedure despite a secondary exclusion criterion. The secondary analysis (secondary outcomes and AEs) was done on the intention-to-treat population corresponding to all included and randomly assigned patients who benefited from the procedures (no secondary exclusion criteria) (**Figure 2**).

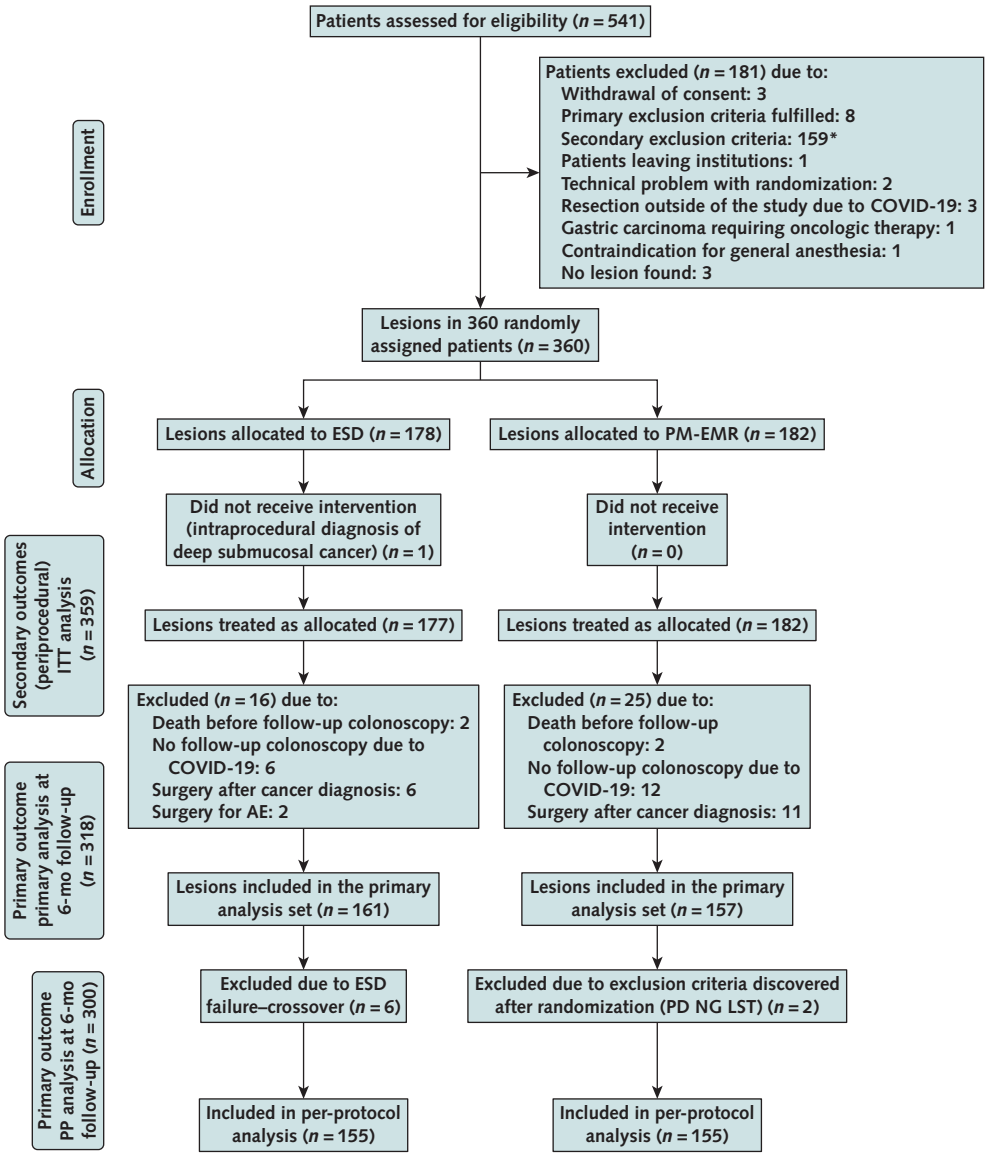
For descriptive statistics, binary and categorical variables are reported as frequencies and percentages and continuous variables as medians and IQRs. For primary analyses, the risk difference, relative risk (RR), and their 2-sided 95% CIs were estimated using the exact method. A sensitivity analysis was done by imputing data for patients who had bowel surgery after endoscopy as best and worst cases. For the secondary analyses, the RR when applicable and 2-sided 95% CIs of the effect sizes using the exact method were estimated. The comparability of the 2 groups in the primary analysis

Figure 1. Examples of both procedures.



A–F. Steps of the endoscopic submucosal dissection (ESD) procedure. G–L. Steps of the endoscopic mucosal resection (EMR) procedure. A′–F′. Schematic steps of the ESD procedure with traction applied with clips and rubber bands. G′–L′. Schematic steps of the EMR procedure.

Figure 2. Flowchart of the study.



AE = adverse event; ESD = endoscopic submucosal dissection; ITT = intention-to-treat; PD NG LST = pseudodepressed nongranular laterally spreading tumor; PM-EMR = piecemeal endoscopic mucosal resection with thermal ablation of the margins.
* For reasons, see the Supplement.

set was checked before the analysis (Supplement Table 2). Statistical analysis was done using SAS Enterprise Guide v.7.1 (SAS Institute).

Role of the Funding Source

This funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Patients and Lesions

Between September 2019 and February 2021, 541 patients from 6 centers were included (Figure 2; Supplement Figure, available at Annals.org). After application of the exclusion criteria, 360 lesions in 360 patients were randomized: 178 to the active group (ESD) and 182 to the control group (EMR). After 1 secondary exclusion due to clearly visible cancer contraindicating endoscopic resection (discovered immediately after randomization), 359 lesions in 359 patients were included in the intention-to-treat analysis (Supplement Table 3).

After further excluding 41 patients (4 unrelated deaths before the primary end point, 19 postresection surgeries, and 18 cancellations of the 6-month colonoscopy because of the COVID-19 pandemic), 318 lesions in 318 patients were included in the primary

analysis set (Table 1; more details in Supplement Table 2). Two patients in the EMR group were randomly assigned and treated by EMR despite a secondary exclusion criterion (nongranular pseudodepressed LST); they were kept in the primary analysis set but not in the per-protocol analysis because this was not a contraindication to endoscopic resection but a protocol violation. The demographic and baseline characteristics were balanced between the 2 groups (Table 1; Supplement Tables 2 and 3, available at Annals.org).

Technical Details

In the EMR group, thermal margin ablation was performed in 180 patients (98.9%). In 61 EMR procedures (33.5%), fewer fragments than the number of cut fragments were retrieved, and more were retrieved in 28 procedures (15.4%) (Table 2; Supplement Table 4, available at Annals.org). In the ESD group, double-clip traction with a rubber band was used in 167 patients (94.3%). Ninety resection sites (50.8%) and 101 resection sites (55.5%) were completely closed using clips in the ESD and EMR groups, respectively.

The median duration of the resection procedure (from initial injection to the last cut of fiber or piece) and anesthesia were 14.5 minutes (IQR, 10 to 25 minutes; 95% CI, 12.1 to 15.9 minutes) and 66 minutes (IQR, 52 to 84 minutes; CI, 62.0 to 70.0 minutes) in the EMR group and 47 minutes (IQR, 30 to 71 minutes; CI, 40.8 to 53.2 minutes) and 104 minutes (IQR, 75 to 133 minutes; CI, 95.2 to 112.7 minutes) in the ESD group, respectively.

Primary Outcome

The results of the main outcome are shown in Table 3. The median time to the first follow-up colonoscopy was 6.5 months (IQR, 6.0 to 7.6 months). Recurrence occurred in 1 of 161 patients (0.6% [CI, 0.0% to 3.4%]) in the ESD group and 8 of 157 patients (5.1% [CI, 2.2% to 9.8%]) in the EMR group (RR, 0.12 [CI, 0.01 to 0.96]) in the primary analysis set (see Supplement Tables 5 and 6 [available at Annals.org] for details of the recurrence cases and rates). In the per-protocol analysis, the RR for recurrence was 0.12 (CI, 0.02 to 0.98). By sensitivity analysis, the RR for recurrence is estimated between 0.12 (CI, 0.02 to 0.98) (best cases) and 0.47 (CI, 0.22 to 1.01) (worst cases) (Table 3).

In the ESD group, no recurrence occurred after R0 resection. In the EMR group, no risk factors for recurrence were identified in univariate analysis (Supplement Table 7, available at Annals.org).

Secondary Outcomes

Technical Success

The en bloc resection rates were higher in the ESD group (171 [96.6%] vs. 19 [10.4%]). The technical failure rate did not differ between the 2 groups and was managed by rescue endoscopic treatment during the same session ($n = 6$ [3.4%] EMR in the ESD group and $n = 3$ [1.6%] ESD [use of an ESD knife] in the EMR group; RR, 2.06 [CI, 0.52 to 8.10]). No patient in either group needed surgery for technical resection failure, but 2 patients in the ESD group needed surgery for complications. Details on resection are shown in Supplement Table 4, and examples of both procedures are shown in Figure 1.

Table 1. Characteristics of Patients and Lesions Included in the Primary Analysis Set for Assessment of Primary Outcome*

Primary Set Analysis	All Patients ($n = 318$)†	
	ESD ($n = 161$)	EMR ($n = 157$)
Patient characteristics		
Height, *cm*	169 (162–175)	168 (160–173)
Missing value	1 (0.6)	0 (0)
Weight, *kg*	74.5 (65.0–83.5)	74 (61.5–85)
Missing value	1 (0.6)	1 (0.6)
BMI, kg/m^2	26 (22.8–29)	25.6 (23.2–29)
Missing value	1 (0.6)	1 (0.6)
Age, *y*	69 (61–74)	71 (62–75)
Female sex	63 (39.1)	75 (47.7)
ASA‡		
I	37 (22.9)	39 (24.8)
II	90 (55.9)	83 (52.8)
III	34 (21.1)	31 (19.7)
IV	0 (0)	4 (2.5)
Antiplatelets agents	28 (17.4)	27 (17.2)
Anticoagulants	15 (9.3)	20 (12.7)
Lesion characteristics		
Lesion size, *mm*	40 (35–50)	35 (30–50)
Location		
Left colon	36 (22.4)	35 (23)
Right colon	125 (77.6)	122 (77)
SMSA score§		
Missing data	0 (0)	1 (0.6)
II	1 (0.6)	0 (0)
III	21 (13)	41 (26.1)
IV	139 (86.3)	115 (73.2)
Type of lesion on endoscopy		
Granular homogeneous LST	51 (31.7)	46 (29.3)
Granular mixed-type LST	55 (34.2)	56 (35.7)
Flat nongranular LST	37 (23)	29 (18.5)
Pseudodepressed nongranular LST	0 (0)	2 (1.3)
Sessile serrated lesion	13 (8)	15 (9.6)
Protruding lesion	5 (3.1)	9 (5.7)
Paris classification of lesions by endoscopy‖		
Missing data	0 (0)	1 (0.6)
0-Ip	2 (1.2)	2 (1.3)
0-Is	75 (46.6)	73 (46.5)
0-IIa	137 (85)	133 (84.7)
0-IIc	4 (2.5)	8 (5.1)
0-III	0 (0)	0 (0)

ASA = American Society of Anesthesiologists; BMI = body mass index; EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; LST = laterally spreading tumor; SMSA score = size, morphology, site, access score.
* Data for the ITT analysis (see Supplement Table 3).
† Data are *n* (%) or median (IQR).
‡ For ASA, I = healthy patient, II = mild systemic disease, III = severe systemic disease, and IV = severe systemic disease that is a constant threat to life.
§ For the SMSA score, II = 6 to 9 points, III = 9 to 12 points, and IV = >12 points.
‖ For the Paris classification, 0-Ip = pedunculated lesion, 0-Is = sessile lesion, 0-IIa = slightly elevated lesion, 0-IIc = superficial shallow-depressed lesion, and 0-III = excavated lesion.

Table 2. Histopathologic Data of Resection Specimens in Both Groups

Histopathologic Outcomes	ESD*	EMR*
	(*n* = 177)	(*n* = 182)
Specimens retrieved after resection		
Missing data	0	1
Congruence between endoscopy-pathology†	NA	92 (50.8) (43.3–58.3)
No congruence between endoscopy-pathology†	NA	89 (49.2) (41.7–56.7)
	(*n* = 177)	(*n* = 182)
Pathologic analysis		
Sessile serrated lesions	12 (6.8) (3.5–11.5)	13 (7.1) (3.9–10.9)
LGD	52 (29.4) (22.8–36.7)	71 (39.0) (31.9–46.5)
HGD, including so-called intramucosal cancer	100 (56.5) (48.8–63.9)	89 (48.9) (41.4–56.4)
Superficial submucosal cancer, ≤1000 μm	6 (3.4) (1.2–7.2)	2 (1.1) (0.1–3.9)
Deep submucosal cancer, >1000 μm	7 (4.0) (1.6–8.0)	7 (3.8) (1.6–7.8)
	(*n* = 13)	(*n* = 9)
Pathologic criteria in submucosal cancer		
At least 1 poor prognostic factor	6 (46.2) (19.2–74.8)	4 (44.4) (13.7–78.8)
High-grade budding	5 (38.5) (13.9–68.4)	3 (33.3) (7.5–70.1)
Lymphovascular infiltration	2 (15.4) (0.6–1.3)	2 (22.2) (2.8–60.0)
Poor differentiation (G3)	2 (15.4) (1.9–45.4)	0 (0.0) (-)
Free deep margin (R0 basal)	12 (92.3) (64.0–99.8)	1 (11.1) (0.3–48.2)

EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; HGD = high-grade dysplasia; LGD = low-grade dysplasia; NA = not applicable.
* Data are *n* (%) (95% CI).
† With regard to number of specimens, exclusively applies to piecemeal EMR.

Immediate Histologic Outcome

Very low-risk or low-risk resection was achieved in 160 of 177 patients (90.4%) in the ESD group and 11 of 182 patients (6.0%) in the EMR group (RR, 14.22 [CI, 8.22 to 24.61] and RR, 14.96 [CI, 8.42 to 26.57]). In the ESD group, 10 procedures (5.6%) were R1 resection (adenoma or low-risk T1 cancer) and 7 (4.0%) were high-risk (noncurative) resections (T1 cancer with poor prognostic criteria). In the EMR group, 164 procedures (90.1%) were local-risk resections and 7 (3.9%) were high-risk resections. Regarding unexpected submucosal cancer diagnoses, details of the histopathological analyses are presented in Table 2 and details of the cases with cancer are presented in Supplement Table 8 (available at Annals.org).

Surgery After Endoscopic Resection

Details of all patients treated by surgery after the procedure are shown in Supplement Table 9 (available at Annals.org). Eight patients in the ESD group were treated by surgery (2 for complications and 6 for submucosal cancer with poor prognostic features). Eleven patients in the EMR group had surgery decided by the tumor board because of histologic criteria.

Adverse Events

The rate of procedure-related AEs was 35.7% in the ESD group and 24.7% in the EMR group (RR, 1.4 [CI, 1.0 to 2.0]) (Table 4). Intraprocedural perforation (5.7% vs. 2.2%; RR, 2.6 [CI, 0.8 to 8.0]) and delayed bleeding (7.9% vs. 5.5%; RR, 1.4 [CI, 0.7 to 3.2]) were more frequent in the ESD than EMR group but without statistical significance. Postpolypectomy syndrome was more frequent in the ESD than EMR group (11.9% vs. 5.5%, respectively; RR, 2.16 [CI, 1.05 to 4.45]).

Of the 2 operations for AEs in the ESD group (none in the EMR group), 1 was performed for delayed perforation confirmed by computed tomography and surgical exploration; the second was performed for severe postpolypectomy syndrome on clinical grounds, although computed tomography and pathologic findings were normal. The complete safety analysis is shown in Supplement Table 10 (available at Annals.org).

Beyond the similar usual hospital stay in both groups regardless of AEs (median, 2 days; IQR, 1 to 2 days in each group), 76 patients with AEs in the ESD group stayed a total of 202 days (including 65 days for a single patient with debatable surgery secondary to postpolypectomy syndrome), whereas 65 patients with AEs in the EMR group stayed for a total of 130 days (Supplement Table 11, available at Annals.org).

DISCUSSION

The main finding in our study is that for large colonic adenomas, ESD significantly reduced the risk for local recurrence compared with EMR. More widely available than ESD on a global scale, EMR was associated with a higher recurrence rate; however, it was still relatively low (5%), most likely because of the addition of margin coagulation after EMR (20). Moreover, it was associated with a significantly lower overall rate of AEs than was ESD. This points toward broader applicability of the EMR technique; however, EMR requires systematic early follow-up colonoscopy. No variables related

to either polyps or the EMR procedure are available to predict recurrence. Recurrences were mostly small with benign histology. However, endoscopic treatment of recurrence is an additional challenge and requires substantial skills using various techniques and additional follow-up (25), and these recurrences can be invasive cancer (26). As with ESD, for which expertise is needed to reduce the rate of AEs, expertise is needed in EMR to reproduce low recurrence rates (27, 28). On the other hand, as in previous studies (11, 26, 29), patients who had complete en bloc resection (90%) achieved a 0% recurrence rate with ESD. This allowed patients to skip early follow-up colonoscopies, which are costly and stressful for the patient and lead to repeated bowel preparations, work absences, and lowered productivity (30). Imperfect adherence, with a missed follow-up rate of up to 20%, has been reported and could be worrisome when a patient is at risk for recurrence (25).

The potential advantage of ESD over EMR to reduce recurrence and follow-up colonoscopies must be balanced against a higher rate of adverse events. Intraprocedural perforations were more frequent in the ESD group (10 vs. 4) but were managed endoscopically. The AEs, mostly postpolypectomy syndrome, were more frequent after ESD; they led to 2 emergency surgeries in the ESD group and were otherwise managed conservatively. Clinical surveillance led to prolongation of hospitalization in both groups, with more days overall in the ESD group, related to a single patient. Generalizing these findings beyond expert centers and across different countries may be challenging because the results of both procedures can vary. The same is true for the learning curve and skill set required, which have been insufficiently studied with variable results (31–33). Nevertheless, it is likely that with the substantial skills required for both techniques in large adenomas (ESD perhaps more than EMR), performance of these procedures in expert centers should be recommended, in line with European guidelines (34). This issue is relevant because up to 20% of large benign colorectal lesions are still directly referred for surgery (35) without endoscopic evaluation by an expert team, despite the increased morbidity (36) and mortality and low cost-effectiveness.

The oncologic aspect of our study, although not included in the predefined outcomes, must also be discussed. The inclusion criteria (benign lesions) explain the low rate of unexpected submucosal cancer (6%) and similar secondary surgery rates for histology in both groups. These risk criteria are currently being expanded, and deeper submucosal infiltration may be considered low risk in the future (37). If such infiltration can be completely (R0) endoscopically resected, ESD will be expected to be superior. High-grade dysplasia and superficial submucosal cancer were more frequent in the ESD group. A loss of information due to fragmented resection could explain this. Indeed, in 34% of cases, the number of recovered fragments was lower than the number of cut fragments. Furthermore, en bloc (ESD) specimens allow for better histologic assessment.

The strengths of our study were its rigorous design, blinding of patients, case inclusion before therapeutic colonoscopy without excluding cases for potential technical difficulties in resection for either technique, and performance of up-to-date resection techniques. Moreover, the results align with those obtained in ESD expert centers in Japan (38) or EMR standards in

Table 3. Study End Points

Study Outcomes	ESD, *n* (%) [95% CI]	EMR, *n* (%) [95% CI]	RR (95% CI)	RD (95% CI)
Primary study outcome, recurrence at first follow-up				
	(*n* = 161)	**(*n* = 157)**		
Primary analysis set	1 (0.6) [0.0 to 3.4]	8 (5.1) [2.2 to 9.8]	0.12 (0.01 to 0.96)	−0.04 (−0.08 to −0.01)
	(*n* = 169)	**(*n* = 168)**		
Sensitivity analysis				
Worst cases	9 (5.3) [2.5 to 9.9]	19 (11.3) [6.9 to 17.1]	0.47 (0.22 to 1.01)	−0.06 (−0.12 to −0.00)
Best cases	1 (0.6) [0.0 to 3.2]	8 (4.8) [2.1 to 9.2]	0.12 (0.02 to 0.98)	−0.04 (−0.08 to −0.01)
	(*n* = 155)	**(*n* = 155)**		
Per-protocol analysis	1 (0.6) [0.0 to 3.5]	8 (5.2) [2.5 to 9.9]	0.12 (0.02 to 0.98)	−0.04 (−0.08 to −0.01)
Secondary outcomes				
	(*n* = 177)	**(*n* = 182)**		
ITT analysis				
R0 resection	166 (93.8)	12 (6.6)	14.22 (8.22 to 24.61)	–
Failure of procedure	6 (3.4)	3 (1.6)	2.06 (0.52 to 8.10)	–
Periprocedural perforation	10 (5.6)	4 (2.2)	2.57 (0.82 to 8.04)	–
Clinically significant postprocedural bleeding	14 (7.9)	10 (5.5)	1.44 (0.66 to 3.15)	–
Postprocedural perforation	1 (0.6)	0 (0.0)	–	–
Postpolypectomy syndrome	21 (11.8)	10 (5.5)	2.16 (1.05 to 4.45)	–
Surgery for complications	2 (1.1)	0 (0)	-	–

EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; ITT = intention-to-treat; RD = risk difference; RR = relative risk.

Table 4. Adverse Events

AEs	All Cases (*n* = 359), *n* (%)	ESD (*n* = 177), *n* (%)	EMR (*n* = 182), *n* (%)	RR (95% CI)
Patients with at least 1 AE*				
AEs overall	141 (39.3)	76 (42.9)	65 (35.7)	1.2 (0.9–1.6)
AEs related to the procedure	108 (30.1)	63 (35.6)	45 (24.7)	1.4 (1.0–2.0)
Grading of AEs				
I: Mild	118 (32.9)	64 (36.2)	54 (29.7)	1.2 (0.9–1.6)
II: Moderate	34 (9.5)	20 (11.3)	14 (7.7)	1.5 (0.8–2.8)
III: Severe	3 (0.8)	3 (1.7)	0	–
IV: Fatal	0	0	0	–
Types-grades of AEs				
Intraprocedural perforation	14 (3.9)	10 (5.7)	4 (2.2)	2.6 (0.8–8.0)
Postprocedural perforation	1 (0.3)	1 (0.6)	0	–
Postprocedural bleeding	24 (6.7)	14 (7.9)	10 (5.5)	1.4 (0.7–3.2)
Postpolypectomy syndrome	31 (8.6)	21 (11.9)	10 (5.5)	2.2 (1.0–4.5)
Postprocedural management of AEs				
Surgery	2 (0.6)	2 (1.1)	0	–
Repeated endoscopy	7 (2.0)	3 (1.7)	4 (2.2)	1.5 (0.2–18.8)
ICU stay†	2 (0.6)	2 (1.1)	0	–
Total nights in hospitalization, *n*	232	202	130	–

AE = adverse event; EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; ICU = intensive care unit; RR = relative risk.
* Patients with ≥2 AEs for the same AE are counted only once for that AE. Total may not reach 100% as it represents the number of patients and not the number of events and patients can be counted several times according to events.
† Two cases in the ESD group spent 1 and 26 days, respectively, in the ICU after surgery.

Australia (20), eliminating any expertise imbalances between the techniques.

Our study also had some limitations. The exclusion of rectal lesions may be one, but we focused on colonic lesions because of their different biology, the possibly higher rate of (unexpected) submucosal types of cancer (39), and perceived lower technical challenges for rectal ESD. A randomized trial of rectal lesions is currently under way (40). Inclusion of both adenomas and sessile serrated lesions can be debated as well; it is believed that sessile serrated lesions are easier to resect and can even be handled by cold snare resection (41). However, because we focused on decreasing the recurrence rate after resection of large benign lesions and avoiding early control colonoscopy, we did not exclude these lesions.

Furthermore, there are specifics of the French health system that influence study logistics and economic comparisons. First, performance of all procedures under anesthesiologic control is mandated by French regulations, and anesthesiologists prefer intubation for complex colonic resections. No data prove an increase in safety or, in turn, an increase in complications of general anesthesia versus propofol sedation. Second, performance of therapeutic endoscopy on an inpatient or outpatient basis varies widely on a global scale because of different health care systems. In France, as in many European countries, more complex therapeutic procedures are almost always performed in an inpatient setting although recent studies from various countries have shown that even ESD can mostly be performed in an outpatient setting (42–45). We do not know whether safety issues would vary in different organizational settings using deep sedation and/or treatment as outpatients.

The absence of reimbursement of ESD in several Western countries is also an important limitation that prevents generalization of the results. However, presenting these findings within a well-designed randomized study, highlighting the advantages and limitations of each strategy, could inform reimbursement policies in these countries.

Future health economic analyses can use the data generated by our study, including details such as the procedure times, AEs and their management, and long-term follow-up results, which must be adapted to the specific health care system to be used by decision makers. Together with other trials focusing on the oncologic aspects of large polyps, our study could help establish a meaningful clinical strategy for the use of ESD and/or EMR and perhaps even a selective approach. To date, 3 cost-effectiveness analyses based on observational cohort modeling in different countries have reached different conclusions (46–48).

Patients and physicians should be aware of these study results not only to know when to choose endoscopic resection instead of surgery but also to choose the endoscopic resection strategy that best fits the patient according to the lesion, the acceptance of follow-up colonoscopy, and the available expertise at the center. Cost-effectiveness of the 2 strategies can later be analyzed from our long-term results to complement our clinical findings during long-term follow-up.

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