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Retrospective Cohort Study

Multicenter evaluation of recurrence in endoscopic submucosal dissection and endoscopic mucosal resection in the colon: a Western perspective

Recurrence in endoscopic resection: Western perspective

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Abstract

BACKGROUND

Background: While colon EMR is an effective technique, removal of larger polyps often requires piecemeal resection, which can increase recurrence rates. ESD in the colon offers the ability for *en bloc* resection and is well-described in Asia, but there are limited studies comparing ESD *vs* EMR in the West.

AIM

Aim: We sought to evaluate different techniques in endoscopic resection of large polyps in the colon and to identify factors for recurrence.

METHODS

Methods: The study is a retrospective comparison of ESD, EMR and knife-assisted endoscopic resection performed at Stanford University Medical Center and Veterans Affairs Palo Alto Health Care System between 2016 and 2020. Knife-assisted endoscopic resection was defined as use of electrosurgical knife to facilitate snare resection, such as for circumferential incision. Patients ≥18 years of age undergoing colonoscopy with removal of polyp(s) ≥20mm were included. The primary outcome was recurrence on follow-up.

RESULTS

Results: A total of 376 patients and 428 polyps were included. Mean polyp size was greatest in the ESD group (35.8mm), followed by knife-assisted endoscopic resection (33.3mm) and EMR (30.5mm) [$p<0.001$]. ESD achieved highest *en bloc*resection (90.4%) followed by knife-assisted endoscopic resection (31.1%) and EMR (20.2%) [$p<0.001$]. A total of 287 polyps had follow-up (67.1%). On follow-up analysis, recurrence rate was lowest in knife-assisted endoscopic resection (0.0%) and ESD (1.3%) and highest in EMR (12.9%) [$p=0.0017$]. *En bloc* polyp resection had significantly lower rate of recurrence (1.9%) compared to non-*en bloc* (12.0%, $p=0.003$). On multivariate analysis, ESD (in

comparison to EMR) adjusted for polyp size was found to significantly reduce risk of recurrence (adjusted hazard ratio 0.06 (95%CI: 0.01-0.57, *p*-value 0.014).

CONCLUSION

Conclusion: In our study, EMR had significantly higher recurrence compared to ESD and knife-assisted endoscopic resection. We found factors including resection by ESD, *en bloc* removal, and use of circumferential incision were associated with significantly decreased recurrence. While further studies are needed, we have demonstrated the efficacy of ESD in a Western population.

Key Words: Endoscopic mucosal resection; endoscopic submucosal dissection; recurrence; colonoscopy; polypectomy

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Core Tip: Endoscopic submucosal dissection is an effective and safe technique. Compared to endoscopic mucosal resection, we find that endoscopic submucosal dissection as well as knife-assisted endoscopic resection to achieve higher en bloc resection, circumferential incision, R0 resection as well as lower recurrence rate. While further studies are needed, we have demonstrated the efficacy of ESD in a Western population.

INTRODUCTION

Large non-pedunculated colorectal polyps (LNPCPs) are currently removed primarily through endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).[1] ESD has been slowly adopted in the United States, limited in large part due to lack of experts, long training required and significantly increased time for resection

compared to EMR.[2] As a result, there is limited data for Western experience in ESD. In the largest prospective multicenter study to date in North America, Draganov *et al* identified 399 cases of ESD in the colorectum, identifying an *en bloc* resection rate of 87.2%, and recurrence rate of 2.7% (8 of 296).[3] With the growing experience in North America in performing endoscopic submucosal dissection, there is increased attention to performance outcomes of ESD compared to EMR. In this study, we seek to evaluate our experience of ESD compared to EMR at two tertiary centers in California.

MATERIALS AND METHODS

Study cohort

We performed a retrospective study evaluating endoscopic resection performed of polyps ≥20mm at two centers (Stanford University Medical Center and Veterans Affairs Palo Alto Health Care System) by two practitioners (JHH and SF), between January 1, 2016, and December 31, 2020. Inclusion criteria included adults age ≥ 18 who presented for colonoscopy with endoscopic removal of polyp ≥20mm in size. Exclusion criteria included age <18 and pregnancy.

Definitions for endoscopic resection

Endoscopic resection was categorized as EMR, knife-assisted endoscopic resection and ESD. EMR was defined by hot or cold snare resection of the polyp with or without submucosal injection. Knife-assisted endoscopic resection was defined as use of electrosurgical knife to facilitate snare resection, such as for circumferential incision and minimal submucosal dissection with an ESD knife. ESD was defined as use of electrosurgical knife for circumferential incision and submucosal dissection with the intention of performing a complete *en bloc* resection using the knife (**Figure 1**).[4] *En bloc* resection was defined as removal of the polyp in its entirety in one singular piece. Determination of each technique is up to the discretion of the endoscopist. Knife-assisted endoscopic resection was performed when the endoscopist determined at the initial submucosal injection step that full ESD would be too dangerous, typically due to

fibrosis or poor scope stability, but that there was a clinical benefit to utilizing an ESD knife to perform selected parts of the procedure.

Endoscopy was performed using high-definition video endoscopes (e.g. PCF-H190DL; GIF-1TH190). A transparent cap was attached to the tip of the endoscope for each procedure. Each polyp was carefully examined under both white light and narrow band imaging (NBI)[5] and evaluated to predict histopathological diagnosis and invasion depth. Polyps were characterized by Paris classification[6] as well as by Japan NBI Expert Team (JNET).[7,8] Submucosal injection was performed using hydroxyethyl starch with dye, saline with dye, ORISE™ gel (Boston Scientific), Eleview™ liquid composition (Aries Pharmaceuticals), or EverLift™ (GI Supply). Lesion marking, mucosal incision, and submucosal dissection were performed using an DualKnife (Olympus), FlushKnife (Fujinon), Hybrid Knife (ERBE) or ProKnife (Boston Scientific) with an electrosurgical generator (ERBE Elektromedizin, Tübingen, Germany). In select cases, the resection site was closed with hemostatic clips, X-Tac (Apollo Endosurgery), or OverStitch (Apollo Endosurgery). Resected specimens were pinned on cork or foam board for better pathologic analysis. The specimens were fixed with formalin.[1]

The size of the polyp was determined by using the snare as reference, or if the polyp was removed *en bloc*, was measured against a ruler when it was retrieved from the colon.

Data collection

All procedures performed by SF (Stanford and Veterans Affairs Palo Alto Health Care System) and JHH (Stanford) between January 1, 2016 and December 31, 2020 were reviewed. Data collected included patient demographics (age, sex, race/ethnicity), sedation, bowel preparation, polyp size, location, Paris and JNET classification, history of prior resection, method of resection, *en bloc* removal of polyp, and pathology of the polyp. Bowel preparation was characterized as adequate or inadequate. 30-day complications recorded included bleeding with or without intervention, perforation,

small bowel obstruction, abdominal pain, as well as complications unrelated to procedure. Follow-up endoscopic evaluation was measured for presence or absence of recurrence. Follow-up was reviewed up to December 31, 2022. Recurrence was defined as evidence of polyp in the area of the prior resection. During follow-up endoscopy, careful examination was performed in the area of the resection, with both white light and narrow band imaging, to evaluate for recurrence. When there was suspicion for recurrence, resection or biopsies were performed of the area. The primary outcome was recurrence on follow-up. Secondary outcomes included *en bloc* resection and complication rates

Specimen histology

Specimen from knife-assisted endoscopic resection and ESD were spread and pinned onto cork or Styrofoam boards immediately following endoscopic resection. The specimens were fixed in 10% buffered formalin, paraffin-embedded, and cut into 2-mm-thick slices, prior to evaluation by a pathologist.

Statistical analysis

All analyses were performed with p-value <0.05 considered significant. All tests were 2-tailed. Chi-squared (χ^2) test was performed to compare the frequencies of categorical outcomes and student's t-test was performed to evaluate averages of normally distributed continuous variables. Cox regression analysis was performed to estimate unadjusted and adjusted hazard ratios (HR and aHR) relating potential confounders such as resection technique, age, sex, race, polyp location, prior resection attempt, polyp size, with polyp recurrence.

Ethics Statement

This study was performed under the approval of the Institutional Review Board at Stanford University, Stanford, California, USA

RESULTS

Patient demographics

There were 376 patients included in the study, 122 of whom received ESD, 44 received knife-assisted endoscopic resection and 216 received EMR. A total of 38 patients had more than one ≥20mm polyp removed. There was similar distribution in age, sex, race/ethnicity across the three categories of procedures (**Table 1**). Patients undergoing ESD had a higher likelihood of receiving the procedure under general anesthesia or monitored anesthesia care (85.2%) compared to knife-assisted endoscopic resection (70.5%) and EMR (57.4%).

Polyp resection, overall

A total of 428 polyps underwent endoscopic resection, with 258 by EMR and 125 by ESD (**Supplemental Table 1**). Polyps removed by ESD (35.8mm) were larger compared to by knife-assisted endoscopic resection (33.3mm), which was larger than by EMR (30.5mm) [p<0.001]. ESD achieved the highest *en bloc* resection (90.4%) followed by knife-assisted endoscopic resection (31.1%) and EMR (20.2%) [p<0.001]. There was no significant difference in proportion of polyps that had history of prior resection attempt in the three resection techniques. Non-neoplastic polyps were removed more frequently in EMR (5.8%) compared to ESD (0.0%), while cancer was removed more frequently with ESD (13.6%) compared to EMR (3.5%).

Polyp resection, follow-up

EMR (69.0%) and knife-assisted endoscopic resection (71.1%) had greater proportion of patients that underwent follow-up compared to in the ESD group (61.6%), though this was not statistically significant [p=0.266]. On evaluation of polyps that received follow-up evaluation (**Table 2**), ESD had highest rate of *en bloc* resection (89.6%) followed by knife-assisted endoscopic resection (25.0%), followed by EMR (15.2%) [p<0.001]. A higher proportion (44.2%) of polyps undergoing ESD were identified in the rectum compared to knife-assisted endoscopic resection and EMR, while a higher percentage of polyps were removed in the right colon by knife-assisted endoscopic resection or EMR. A higher proportion (74.0%) removed by ESD were identified as Paris classification Is, compared to 56.3% for knife-assisted endoscopic resection and 36.0% for EMR. EMR had the longest mean follow-up (516.2 days) compared to ESD (456.8) and knife-

assisted endoscopic resection (365.0), though this was not statistically significant [p=0.061]. ESD (74.0%) and knife-assisted endoscopic resection (18.8%) had higher R0 resection compared to EMR (4.5%) [p<0.001]. There was no recurrence in the knife-assisted endoscopic removal group (0/30). Recurrence rate was lowest in knife-assisted endoscopic resection (0.0%), followed by ESD (1.3%), and highest in EMR (12.9%) [p=0.002].

In categorizing polyps by presence of recurrence (**Table 3**), there was overall a low proportion of polyps with recurrence (8.4%). Polyps with recurrence had greater mean average size (37.4 *vs* 32.7mm, p=0.202), though this was not statistically significant. Polyps with recurrence more often had non en bloc resection (91.7 *vs* 61.2%, p=0.003). Polyps with recurrence more often did not undergo circumferential incision (95.8 *vs* 62.7%, p=0.001). Of note, polyps removed with circumferential incision had higher proportion of *en bloc* removal (76.8 *vs* 14.9%, p<0.0001). Recurrence polyps had a higher proportion of polyps that had prior attempt at removal (17.6 *vs* 5.3%), though this was not statistically significant (p=0.154). There was no significant difference in pathology or mean follow-up between the two groups. Compared to no recurrence, polyps with recurrence had higher proportion of R1 (91.7 *vs* 67.7%) and lower proportion of R0 (4.2 *vs* 26.6%) [p=0.041].

Procedural complications

Overall, there was a low patient complication rate (25 patients [6.6%]), with similar proportion of complication (6.5-6.8%) among the three procedures (**Table 4**). There were 3 cases of perforation (two ESD and one knife-assisted endoscopic resection). One patient received knife-assisted endoscopic resection of a >50mm polyp in cecum involving the ileocecal valve. There was only partial lifting of the lesion with submucosal injection. Dense fibrosis was encountered, and as such the remainder of the resection was performed by piecemeal EMR. Following the procedure, the patient had abdominal pain, and was found to have pneumoperitoneum. The patient underwent exploratory laparotomy with resection of the terminal ileum and proximal colon.

Pathology returned as tubular adenoma with focal high-grade dysplasia. In the second case, the patient had a fungating partially obstructing 50mm mass in ascending colon. Following ESD, five hemostatic clips placed to close the wound. The patient had worsening abdominal pain following the procedure, and perforation was seen on computed tomography, leading to hemicolectomy. Pathology was consistent with tubulovillous adenoma. In the third case, a 30mm fungating non-obstructing mass was found in the cecum, encasing the appendiceal orifice. A 40 mm specimen was resected *en bloc*. A single small perforation (<2 mm) occurred, which was closed with a single clip followed by full mucosal closure with an Endoloop and clips. The patient recovered uneventfully.

Predictors of recurrence

On univariate Cox regression, age, sex, race and polyp location were not significant risk factors. Relative to EMR, ESD was found to decrease risk of recurrence (HR 0.12 [95%CI: 0.02-0.92], p=0.041). Completion of circumferential incision, *en bloc* resection as well as R0 resection were found to significantly reduce risk of recurrence [**Table 5**]. On multivariable Cox regression adjusted for polyp size and type of resection (ESD *vs* EMR), ESD significantly reduced risk of recurrence (adjusted hazard ratio 0.06 (95%CI: 0.01-0.57, p-value 0.014) [**Table 6**]. In this analysis, we did not include *en bloc* resection, R0 resection, and presence of circumferential incision as these are factors closely tied with performance of ESD. When evaluating EMR compared to knife-assisted endoscopic resection combined with ESD, on multivariate analysis ESD and knife-assisted endoscopic resection also demonstrated significant decrease in risk of recurrence (aHR 0.05 [95%CI: 0.01-0.45], p=0.008) [**Supplemental Table 3**]. Knife-assisted endoscopic resection was unable to evaluated independently of ESD as there were no cases of recurrence.

DISCUSSION

The development of advanced polypectomy techniques has allowed patients to avoid colorectal surgeries. While ESD is frequently performed in Asia, it is not commonly

performed elsewhere including in the West. However, there are several compelling arguments for performance of ESD over EMR in large (≥20mm) polyps. In a recent meta-analysis, Lim *et al* found that ESD of polyps ≥20mm was associated to higher *en bloc* resection (relative risk [RR] 1.9, 95%CI: 1.4-2.7; $p<0.001$) and lower recurrence (RR 0.19, 95%CI: 0.09-0.43; $p<0.001$) compared to EMR.[9] Given the benefits of ESD, this has culminated in a multicenter randomized controlled trial based in France led by Jacques *et al* which found ESD to be superior to EMR in *en bloc* resection as well as decreased recurrence.[10] Given advantages seen with ESD, we performed the first North American study comparing ESD to EMR.

In our retrospective comparison of ESD, EMR and knife-assisted endoscopic resection, ESD was able to achieve the highest *en bloc* resection, followed by knife-assisted endoscopic resection; EMR had the lowest *en bloc* resection rate. Recurrence rate was lowest in the ESD (1.3%) and knife-assisted endoscopic resection group (0.0%), and highest in the EMR group (12.9%). On multivariate regression, we found that performance of ESD (in comparison to EMR) significantly decreased recurrence. Increased polyp size significantly increased risk of recurrence. We were able to achieve *en bloc* resection rate of 90.4% with ESD. This is comparable to work by Gupta *et al*, in which overall *en bloc* resection rate was 73.1%, and the rate for the second half of their study was 84.6%. Similarly, our study had ESD recurrence rate of 1.3%, slightly lower than the 4.3% (n = 2) by Gupta *et al*[1] Overall, there was low risk of complication across the three procedures. Under appropriate training, we feel the three procedures to be safe techniques.

While operational proficiency is related to study outcome, in this study we try to evaluate the specific factors that lead to success in reducing polyp recurrence. Specifically, we look at factors such as *en bloc* resection and performance of circumferential incision. Circumferential incision was found to be associated with decreased recurrence. In one evaluation of ESD compared to hybrid ESD (circumferential mucosal incision followed by snare resection), hybrid ESD trended towards lower *en bloc* resection rate and complete resection rate compared to ESD,

though this did not reach statistical significance. However, importantly, on surveillance of hybrid ESD by the Korean specialist (n = 21) and US novice practitioner (n = 9), there was no recurrence in either group.[4] While this study was limited by overall low numbers, it provided early suggestion that circumferential incision alone may help improve the outcomes of polyp resection compared to EMR. A major advantage of knife-assisted endoscopic resection over ESD is the relative technical simplicity; in particular, circumferential incision is a relatively safe technique that in our experience is easily taught to trainees with sufficient experience in routine colonoscopy. Over time, with increased experience and proficiency performing ESD, we expect that many endoscopists will choose ESD over knife-assisted endoscopic resection to maximize *en bloc* and R0 resection, but our data highlights the generally excellent long-term results of the knife-assisted technique.

While there is justifiable concern about the risk of perforation with ESD, and the 3 cases of perforation in this series were all in the ESD/knife-assisted endoscopic resection group rather than EMR, it is notable that the perforations occurred in very challenging cases where EMR was deemed not feasible, and surgery was the only other viable option. For large lesions involving greater than half the circumference of the lumen, the Japan Gastroenterological Endoscopy Society does not recommend piecemeal EMR, but rather ESD and consideration for surgery if ESD is not endoscopically feasible.[8]

There were several limitations for our study. First, retrospective data from only two endoscopists were used. However, given the lack of ESD experts in the country, having 125 cases of ESD is relatively robust. In addition, while more EMR cases could have been achieved by including other endoscopists at the two hospitals included, this would potentially introduce more bias with variation in technique and approach to EMR as well as skill with polypectomy. Another concern is the limited follow-up (67.1%). A lot of the patients were referred for endoscopic removal but received follow-up with the referring provider. Despite reaching out to community providers, we only received limited response. Further, the retrospective nature of EMR and ESD studies introduce selection bias in the determination of which polyp to undergo EMR, ESD, or

knife-assisted endoscopic resection. A randomized clinical trial would be ideal but is logistically challenging given the overall low frequency of these procedures.

CONCLUSION

In this multicenter study evaluating ESD, knife-assisted endoscopic resection and EMR, ESD and knife-assisted endoscopic resection were able to achieve higher rates of *en bloc* resection and was able to achieve significantly lower risk of recurrence compared to EMR. Given the results of this study, ESD and knife-assisted endoscopic resection should be strongly considered when possible for polyps ≥20mm to improve *en bloc* and curative resection and decrease risk of recurrence.

ARTICLE HIGHLIGHTS

Research background

Adoption of endoscopic submucosal dissection has been slow in the United States, largely related to lack of experts, long training required and significant time for procedure compared to endoscopic mucosal resection.

Research motivation

In this study, we seek to evaluate our experience of endoscopic submucosal dissection compared to endoscopic mucosal resection in California.

Research objectives

We evaluate endoscopic submucosal dissection, knife-assisted endoscopic resection as well as endoscopic mucosal resection to identify factors for recurrence.

Research methods

This was a retrospective comparison performed at two tertiary centers within California between 2016 and 2020. Adult patients that received colonoscopy with endoscopic

removal of a polyp at least 20mm in size were included. Primary outcome of interest was recurrence on follow-up.

Research results

ESD achieved highest en bloc resection followed by knife-assisted endoscopic resection and EMR. On follow-up, recurrence rate was lowest in knife-assisted endoscopic resection (0.0%) and ESD (1.3%), while EMR had the highest recurrence rate (12.9%, P = 0.0017).

Research conclusions

In our study, we found that EMR had significantly higher recurrence compared to ESD or knife-assisted endoscopic resection.

Research perspectives

We have demonstrated efficacy of ESD in a Western population.

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PRIMARY SOURCES

1	Mike Wei, Andrew A. Li, Andrew Ofosu, Joo Ha Hwang, Shai Friedland. "MULTICENTER EVALUATION OF LOCAL RECURRENCE IN ENDOSCOPIC SUBMUCOSAL DISSECTION AND ENDOSCOPIC MUCOSAL RESECTION: A WESTERN PERSPECTIVE", Gastrointestinal Endoscopy, 2022 Crossref	99 words — 3%
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