OPTIMIZING ENDOSCOPIC RESECTION FOR CHALLENGING LARGE NON-PEDUNCULATED COLORECTAL POLYPS

A thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy

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The work presented in this thesis is, to the best of my knowledge, original unless otherwise specified with appropriate referencing. I hereby declare that this thesis has not been submitted to any other institution.

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Abstract

Endoscopic mucosal resection (EMR) has revolutionized the management of large (≥ 20mm) non-pedunculated colorectal polyps. However, there are still challenges in performing EMR, specifically amongst complex lesion subgroups or in the event of intra-procedural adverse events. Our aim was to assess EMR outcomes for challenging LNPCPs using data from the Australian Colonic Endoscopic Resection (ACE) study, a prospective multicenter observational cohort for the management of LNPCPs.

No difference in technical success, recurrence or adverse events were identified between LNPCPs at the anorectal junction (ARJ-LNPCPs; distal margin ≤ 20mm from the dentate line) and large non-pedunculated rectal polyps (LNPRPs), except for significant deep mural injury (S-DMI; ARJ-LNPCPs 0.0% vs. 4.5% LNPRPs; p=0.027). No recurrence was identified at first surveillance colonoscopy (SC1; 0.0% vs. 25.0%; p=0.002) amongst 30 ARJ-LNPCPs treated by EMR with margin thermal ablation (EMR-T) vs. to those that did not. Comparing a universal EMR algorithm (UEA) and a selective resection algorithm (SRA), which incorporates real-time optical evaluation to select between EMR and endoscopic submucosal dissection (ESD), significant differences in SMIC after EMR (SRA 1 (1.0%) vs. UEA 35 (12.1%); p = 0.001), and curative oncologic resection (SRA 7 (33.3%) vs. UEA 2 (5.7%); p = 0.010) were identified. No significant differences in technical success or adverse events were identified (all p > 0.137). Among LNPRPs with SMIC amenable to curative oncologic resection and which underwent ESD, 100% were cured. Significant differences in resection duration (35 minutes vs. 25 minutes; p<0.001) technical success (93.0% vs. 96.6%; p=0.026) and use of cold forceps avulsion with adjuvant snare tip soft coagulation (CAST; 46.2% vs.

7.6%; p<0.001), were identified between previously attempted LNPCPs (PA-LNPCPs) and naïve LNPCPs. After adjusting for two-stage EMR, no difference in technical success was identified (95.6% vs. 97.8%; p=0.100). No differences in adverse events or recurrence were identified. Recurrence was not identified in 65 PA-LNPCPs which underwent EMR-T at SC1 vs. 9 (18.0%; p<0.001) which did not. Significant deep mural injury (S-DMI) occurred in 101 cases (2.7%) which underwent EMR. Successful defect closure was achieved in 98 (97.0%) using a median of 4 through-the-scope clips (TTSC; IQR 3-6 TTSCs). No difference in technical success (94 (93.1%) vs. 3316 (91.7%) p = 0.62) or SC1 recurrence (12 (20.0%) vs. 363 (13.6%); p = 0.15) were identified between LNPCPs with and without S-DMI. Overall sensitivity, specificity and SMIC miss rate of real-time optical evaluation for SMIC were 67.1% (95%CI 59.2-74.2%), 95.1% (95%CI 93.9-96.1%), and 3.0% (95%CI 2.3-4.0%), respectively. Significant differences in sensitivity (90.9% vs. 52.7%), specificity (96.3% vs. 93.7%) and SMIC miss rate (0.6% vs. 5.9%) between flat and nodular LNPCPs were identified (all p < 0.027). Multiple logistic regression identified size ≥ 40mm (OR 2.0; 95%CI 1.0-3.8), rectosigmoid location (OR 2.0; 95%CI 1.1-3.7) and nodular morphology (OR 7.2; 95%CI 2.8-18.9) as predictors of missed SMIC (all p < 0.039).

Demonstrating the performance of EMR for ARJ-LNPCPs, PA-LNPCPs, EMR-related S-DMI management, real-time optical evaluation stratified by lesion morphology and the synergistic role of EMR and ESD for LNPRPs further solidifies EMR as the primary resection modality for LNPCPs.

Introduction

Large (≥ 20mm) non-pedunculated colorectal polyps (LNPCPs) are a critical health concern and a common downstream ramification of colorectal cancer screening (1-3). This is due to their increased risk of harbouring submucosal invasive cancer (SMIC) (4, 5), which in part portends to the complexity of their management and the financial burden they represent to the healthcare system (6, 7).

Endoscopic mucosal resection (EMR) is a transformative intervention in the management of LNPCPs. This is due to its comparable efficacy (8), but superior safety (9) and cost-efficiency (6, 7) compared to the morbidity, mortality and risk of permanent ostomy formation associated with colorectal surgery (10, 11). International consensus recommendations now advocate for EMR as the preferred treatment strategy for the majority of LNPCPs (12, 13).

However, challenges still remain in EMR for LNPCPs. This includes:

- **Site specific technical failure**: Modifications in high quality EMR now allow for the endoscopic removal of historically complex LNPCPs including circumferential LNPCPs (14) and those involving the ileocecal valve (15) and the appendiceal orifice (16). However, the role of EMR for LNPCPs at the anorectal junction and previously attempted LNPCPs is less well established.

- **Perforation:** Auxillary techniques and management strategies have largely mitigated technical failure (17), clinically significant post-endoscopic resection bleeding (18) and recurrence (19, 20). Although diagnostic criteria have been established for significant deep mural injury (S-DMI) (21) outcomes are not well delineated.

- **Non-curative piecemeal resection of low-risk T1 colorectal cancers:** EMR serves a definitive role for superficial submucosal invasive cancer (S-SMIC) if removed en bloc with negative histologic margins and in the absence of high-risk histologic features (22). However, due to technical limitations and the increased risk of S-DMI, piecemeal resection is commonly required therefore obscuring histologic margins and subsequently leading to surgical referral.

Endoscopic submucosal dissection (ESD) is an alternative organ-sparing minimally invasive endoscopic resection technique, which has been advocated for complex LNPCPs (23, 24); thus, questioning the role of EMR in LNPCP management. The aim of this thesis was therefore to assess the application of EMR for challenging LNPCPs, specifically: 1) LNPCPs at the anorectal junction; 2) Large non-pedunculated rectal polyps (LNPRPs) within a selective resection algorithm incorporating EMR and ESD; 3) Previously attempted LNPCPs; 4) LNPCPs with S-DMI; 5) Pre-resection real-time optical evaluation to decipher between benign and malignant LNPCPs.

The aims of this thesis will be evaluated using data from the Australian Colonic Endoscopic Resection (ACE) study, which is the world's largest prospective, multi-center observational cohort of LNPCPs. Pivotal findings and developments derived from the ACE cohort, which have subsequently been presented both nationally and internationally as well as published in internationally recognized high-impact journals include:

- Establishing the efficacy of EMR (8) including its comparative safety (9) and cost-savings to surgery (6).

- Demonstrating the benefits of carbon dioxide insufflation (25), and submucosal injection with colloidal solutions (26).

- Quantifying the frequency and identifying risk factors for recurrence (27); developing a recurrence risk stratification tool (28) and a standardized imaging protocol for detecting recurrence (29); mitigating the risk of recurrence through EMR with margin thermal ablation (EMR-T) (19, 20).

- Describing the frequency and identifying risk factors for intra-procedural bleeding and clinically significant post-resection bleeding (30); demonstrating the efficacy of STSC for the treatment of intra-procedural bleeding (31); delineating a management algorithm for clinically significant post-resection bleeding (32).

- Defining the "target sign" as an indicator of deep mural injury (33); developing a classification for deep mural injury and perforation (21).

- Identifying risk factors for SMIC (5); describing the risk of invisible or "covert" SMIC (34).

- Recognizing risk factors for dysplasia in sessile serrated lesions (SSLs) (35); describing endoscopic features of dysplasia for SSLs (36); showcasing the efficacy of cold-snare resection for large SSLs (37).

- Highlighting the effectiveness of EMR for LNPCPs which historically have solely been treated by surgery, including: peri-appendiceal LNPCPs (16), LNPCPs involving the ileocecal valve (ICV) (15), nearly/completely circumferential LNPCPs (14), as well as those with require a two-staged approach (17).

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<center>**Literature Review**</center>

Colorectal Cancer

      Colorectal cancer (CRC) is a worldwide health concern. It is the fifth most commonly diagnosed cancer and the fifth leading cause of cancer-related mortality (1). By 2030, a 60% increase in the burden of CRC is projected (2). This underscores the importance of colonoscopy in the early detection of CRC and its prevention through the removal of colorectal polyps (3, 4); as highlighted by a 53% reduction in CRC mortality amongst patients who underwent polypectomy for an adenomatous polyp in the National Polyp Study (median follow-up 15.8 years) (3).

Colorectal Polyps

      During colonoscopy, the majority of detected polyps are small (5). These polyps have a low likelihood of cancer and are readily removed by standard polypectomy techniques. Large (≥ 20mm) non-pedunculated colorectal polyps (LNPCPs), which have previously been referred to as laterally spreading lesions (LSLs), are carpet-like lesions extending along the colorectal wall. In a national colorectal cancer screening program, 11,130 LNPCPs were identified in 125,155 fecal immunochemical test positive participants (8%; 1 in every 13 participants undergoing colonoscopy) (6). They represent a complex lesion subgroup, as they have a higher risk of submucosal invasive cancer (SMIC) (7, 8). Fuccio et al. demonstrated in a systematic review and meta-analysis of 51 studies and 11,260 lesions, the risk of SMIC was 15.7% (8). Therefore, LNPCPs require a multi-disciplinary approach between interventional endoscopists who

perform minimally invasive endoscopic resection techniques and general/colorectal

surgeons.

Colorectal Surgery

Surgery is the historical standard of care for the management of LNPCPs.

However, it is associated with substantial morbidity, mortality and permanent ostomy

formation; specifically for distal rectal surgery in close proximity to the anus (9, 10). Ma

and colleagues evaluated 262,843 surgeries for non-malignant colorectal polyps with

post-operative mortality and morbidity of 0.8% (95% CI 0.7-0.9%) and 25.3% (95% CI

24.2-26.4%), respectively (9). Moreover, the length of stay in hospital was 6.3 days (SE

0.03 days) with a mean cost of hospitalization of $49,566.48 USD (SE $591.90 USD).

Peery and colleagues evaluated 1,230,458 non-malignant colorectal polyps and CRC

surgeries (10). Twenty-five percent of surgeries were for non-malignant colorectal

polyps with the incidence increasing from 5.9 per 100,000 adults to 9.4 per 100,000

adults between 2000 to 2014; thus, highlighting the potential clinical and economic

ramifications of alternative treatment strategies for a predominantly benign disease

process.

Endoscopic Mucosal Resection (EMR)

Endoscopic-mucosal resection (EMR) is an organ-sparing minimally invasive

endoscopic resection technique for the removal of LNPCPs (11). Using the working

channel of the colonoscope, a viscous colloid solution is injected into the submucosa;

thereby creating a cushion underneath the LNPCP to facilitate tissue capture and avoid

injury to the muscularis propria (MP). This is followed by placing a snare, similar to a lasso, around the polypoid tissue. The snare is then closed by an assistant, and the tissue is transected using electrocautery. The specimen is then collected and sent for histopathology review.

Endoscopic mucosal resection (EMR), can be performed in one-piece, termed en bloc; however, this is generally limited to LNPCPs ≤ 25mm. This is due to the propensity to capture the MP during snare closure, leading to significant deep mural injury (S-DMI), or perforation after tissue transection. In an analysis of 570 LNPCPs ≤ 25mm, en bloc EMR was associated with a significant increase in S-DMI (3.5% en bloc EMR vs. 1.0% piecemeal EMR; $p = 0.05$) (12). Therefore, LNPCPs are commonly removed by piecemeal EMR.

Endoscopic Submucosal Dissection (ESD)

Endoscopic submucosal dissection (ESD) is an alternative organ-sparing minimally invasive endoscopic resection technique (13). After submucosal injection, a circumferential mucosal incision is created using an electrosurgical knife followed by dissection underneath the lesion within the submucosal plane.

A major advantage of ESD is it empowers the endoscopist to better perform en bloc resection (14). However, it is more difficult to perform, requires advanced training, is more time consuming, and has a higher frequency of adverse events (14).

Large Non-Pedunculated Colorectal Polyp Management

Current North American and European consensus recommendations advocate for EMR as the primary resection modality for the majority of LNPCPs (15, 16). This is due to its proven efficacy, efficiency, safety and cost-saving compared to colorectal surgery (17-19). Site-specific technical modifications in high-quality EMR technique allow for the removal of complex LNPCP subgroups including circumferential LNPCPs (20) and those involving the ileocecal valve (21) and the appendiceal orifice (22). Moreover, auxiliary techniques and strategies have largely mitigated technical failure (23), clinically significant post-EMR bleeding (24) and recurrence (25, 26). Large non-pedunculated colorectal polyps harbouring superficial submucosal invasive cancer (S-SMIC; < 1000µm depth of invasion into the submucosa), without high-risk histologic features and removed en bloc with negative histologic margins (R0 resection) have a low risk of malignant recurrence (27). In a recent systematic review and meta-analysis of 71 studies and 5167 patients with an endoscopically treated colorectal lesion with SMIC, pooled incidence of recurrence for low risk SMIC was 0.7% (95% CI 0.4-1.2%) (28). When compared to the adverse event profile of colorectal surgery, patients with a low-risk SMIC are now recommended to undergo surveillance instead of completion surgery (27).

Although EMR has revolutionized the management of LNPCPs, challenges remain which directly question its position in an evolving selective resection algorithm incorporating piecemeal resection techniques, en bloc resection techniques, and surgery (11).

Large Non-Pedunculated Colorectal Polyps at the Anorectal Junction

Large non-pedunculated colorectal polyps at the anorectal junction (ARJ-LNPCPs) are defined as those within 20mm of the dentate line (29); which is consistent with that of the anal transition zone (30). It is occupied by the columns of Morgagni which are longitudinal mucosal folds harbouring a submucosal plexus which become the hemorrhoidal plexus. The epithelium has both columnar and squamous characteristics histologically. It is a complex location for the application of minimally invasive resection techniques due to these unique anatomical, sensory and physiologic characteristics including: 1) limited endoscopic visualization as the columns of Morgagni converge towards the anal canal; 2) the potential to elicit peri-procedural pain due to the somatic innervation of the squamous epithelium; 3) the risk of infection given the relative lack of protection by the reticuloendothelial function of the portal lymphovenous system; 4) the ability to achieve an adequate surgical resection margin and therefore select between a sphincter-sparing low anterior resection and an abdominal perineal resection with permanent ostomy formation.

Given the significant morbidity, mortality, and the heightened risk of permanent ostomy formation, distal colorectal surgery should be discouraged for ARJ-LNPCPs that are amenable to minimally invasive endoscopic resection techniques (15, 16, 31, 32). However, the optimal strategy for removing these lesions remains unknown. There is currently a lack of randomized trials comparing different resection modalities and high-quality prospective cohort studies with longterm outcomes.

En bloc resection techniques including ESD and trans-anal endoscopic surgeries (TES; transanal endoscopic microsurgery [TEM], transanal minimally invasive surgery

[TAMIS], classical transanal excision) have been advocated for ARJ-LNPCPs. This is due to their potential benefit for en bloc resection of S-SMIC (31, 32). Moreover, to reduce the risk of recurrence specifically pertaining to ESD (14). However, their universal application has been questioned due to limited retrospective data supporting their utility (33-39), the frequency of S-SMIC in LNPCPs and the modest R0 resection frequencies achieved by these modalities (8). This is further supported by a cost-effectiveness analysis demonstrating that a selective resection algorithm with EMR as the workhorse modality is the most cost-effective (40).

Endoscopic mucosal resection, with site-specific technical modifications to treat the distal resection margin, has also been evaluated for ARJ-LNPCPs (29). Short term outcomes have shown promising results. With advances in the ability to differentiate between benign and malignant LNPCPs alongside margin thermal ablation techniques to mitigate recurrence, EMR holds promise in the management of ARJ-LNPCPs.

Non-Curative Piecemeal Resection of Low-Risk Colorectal Cancers

Large non-pedunculated rectal polyps (LNPRPs) are a complex lesion subgroup, analogous to ARJ-LNPCPs. Cronin and colleagues evaluated 618 LNPRPs compared to 2787 large non-pedunculated colonic polyps (41), identifying significant differences in male sex (53.4% vs. 47.8%; $p < 0.011$), lesion size (median; 40mm IQR 30-60mm vs. 30mm IQR 25-40mm; $p < 0.001$), nodular morphology (Paris 0-IIA+IS or 0-IS morphology; 69.3% vs. 28.2%; $p < 0.001$), granularity (79.0% vs. 49.9%; $p < 0.001$), and villous histopathology (74.8% vs. 47.4%; $p < 0.001$). Notably, a significant difference

in the frequency of SMIC was identified on multivariable regression analysis (15.0% vs. 6.2%; p < 0.001; OR 1.77 95% CI 1.25-2.53).

The primary limitation of EMR is the necessity for piecemeal resection to avoid the risk of S-DMI. Due to the increased risk of SMIC in the rectum, and thus the risk of piecemeal resection of low-risk SMIC, a universal EMR approach questions the very premise of minimally invasive endoscopic resection techniques; which is the avoidance of unnecessary surgery. This highlights the potentially synergistic role of EMR and ESD by mitigating the risk of piecemeal resection of low-risk SMIC while optimizing their respective adverse event profiles. However, a mechanism for modality selection between EMR and ESD has not been delineated.

Optical evaluation, also termed optical biopsy, evaluates lesion surface microvasculature and pit pattern prior to endoscopic resection to predict: 1) LNPCP histopathology; 2) SMIC; 3) depth of submucosal invasion to stratify between S-SMIC and deep (> 1000μm) SMIC (D-SMIC) (42). This is commonly performed by carefully evaluating the lesion's surface under high-definition white-light followed by virtual chromoendoscopy such as narrow band imaging (NBI). Narrow band imaging applies a light spectrum filter, mainly correlating with bue and green light, to the endoscopist's visual field which is readily absorbed by hemoglobin and reflected by the surrounding tissue; thus, accentuating changes in the surface microvasculature. Surface microvasculature changes have been correlated with advanced histopathology with validated optical evaluation classifications including: 1) Kudo Pit Pattern [KPP] classification (43), 2) NBI International Colorectal Endoscopic [NICE] classification (44), 3) Japanese NBI Expert Team [JNET] classification (45). Within the KPP and JNET

classifications, Kudo Vi and JNET IIB optical features are associated with S-SMIC. In a

systematic review and meta-analysis of 33 studies and 31,568 lesions (46), NBI had a

pooled sensitivity of 85% (95% CI 75-91%), and specificity of 94% (95% CI 82-98%) for

SMIC and a pooled sensitivity of 77% (95% CI 68-84%) and specificity of 98% (95% CI

95-99%) for D-SMIC. However, in studies solely evaluating LNPCPs, modest optical

evaluation performance was observed (47, 48). In a multi-center prospective study by

Backes and colleagues (47), evaluating 343 LNPCPs, NBI had a sensitivity of 78.7%

(95% CI 64.3-89.3%) and specificity of 94.2% (95% CI 90.9-96.6%) for SMIC. For D-

SMIC, sensitivity and specificity were 63.3% (95% CI 43.9-80.1%) and 99.0% (95% CI

97.1-100.0%), respectively. This demonstrates the risk of missed or covert SMIC which

has been evaluated by Burgess and colleagues (48). After excluding LNPCPs with

visible or overt SMIC features based on optical evaluation, distal location, lesion size,

non-granularity and nodular morphology (Paris 0-IS or 0-IIA+IS morphology) were

associated with covert SMIC on multivariable logistic regression analysis. Importantly, a

combination of location, morphology and granularity defined a LNPCP subgroup at high-

risk (> 10%) for covert SMIC. Alongside optical features suggestive of S-SMIC, this

identifies potential candidates for ESD and provides a framework for a rectum-specific

selective resection algorithm.

Previously Attempted Large Non-Pedunculated Colorectal Polyps

Submucosal fluid expansion with colloid injectate allows for effective and safe

tissue capture and is a requisite for technical success with EMR (49). Previous attempts

at endoscopic resection, occurring in upwards of 16% of LNPCP referrals (50), leads to

scar formation and fibrosis. This can impair future attempts by EMR due to obliteration of the submucosal plane; therefore, limiting therapeutic options to advanced auxiliary techniques, alternative resection techniques or surgery (51).

Auxillary techniques for previously attempted LNPCPs (PA-LNPCPs) include: 1) ablative techniques (50), 2) avulsion techniques (52); and 3) curetting techniques (53). However, the majority of evaluations are small single-arm retrospective cohorts which focus on technique description. In a prospective cohort study of 1000 LNPCPs which underwent EMR, argon plasma coagulation (APC) was independently associated with recurrence on multivariable regression analysis (44.4% APC vs. 13.2% No APC $p < 0.001$; OR 2.42 95% CI 1.55-3.80) (50). Moreover, as ablative techniques (APC, snare-tip soft coagulation; STSC) do not allow for tissue sampling their use is now largely discouraged. In a retrospective analysis of 112 lesions requiring hot avulsion vs. 425 which did not, no difference in adverse events or recurrence were identified (all $p > 0.15$) (52); however, the frequency of recurrence was 17.5%. In the era of EMR with margin thermal ablation (EMR-T) (25, 26), the utility of hot avulsion requires re-evaluation. The EndoRotor is a thorugh-the-scope curetting device (53). However, pilot data showed suboptimal technical success (52.6% after 1 attempt; 84.1% after 2 attempts). Endoscopic submucosal dissection and endoscopic full-thickness resection (EFTR) have been evaluated for PA-LNPCPs (54, 55). However, ESD is similarly dependent on submucosal fluid expansion (54). Although EFTR has shown promising results for PA-LNPCPs, in a prospective multicenter evaluation, emergency surgery was required in 2.2% of study participants (55). Therefore, the development of effective but safe techniques for PA-LNPCPs are necessary.

There remains limited evidence concerning the overall management of PA-LNPCPs. Recently, critical advances in high-quality EMR technique have been described including: 1) cold forceps avulsion with adjuvant snare-tip soft coagulation (CAST) for non-lifting polypoid tissue (56) and 2) EMR-T. Therefore, an evaluation of EMR outcomes for PA-LNPCPs, in comparison to naïve LNPCPs (N-LNPCPs) is warranted.

Significant Deep Mural Injury

Iatrogenic perforation, secondary to electrocautery induced injury to the MP, is the most feared intra-procedural adverse event associated with EMR. Although infrequent, with estimated frequencies of < 1% (57), it is associated with significant morbidity (58); therefore, emphasizing the importance of early endoscopic recognition followed by successful defect closure.

Swan and colleagues first described endoscopic characteristics of MP injury in a prospective evaluation of 445 patients with LNPCPs (59). Intra-procedural identification of the target sign (white/grey central circular disk surrounded by blue-stained submucosal tissue on the resected specimen) occurred in 10 patients (2.2%); in all cases MP was confirmed histologically. Subsequently, Burgess and colleagues established the Sydney Deep Mural Injury Classification (57), which stratifies the degree of MP injury. Significant deep mural injury is defined as Sydney DMI classification type III (MP injury as evidenced by specimen or defect target sign), type IV (actual hole in the MP within a white cautery ring with no observed contamination) or type V (actual hole in

the MP within a white cautery ring with observed contamination) with estimated frequencies of 2.1%.

A number of endoscopic defect closure techniques have been described. This includes T-tags (60), plicators (61), and suturing devices (62). However, the 2 predominant techniques for colorectal iatrogenic perforation are through-the-scope mechanical clips (TTSC), and over-the-scope mechanical clips (OTSC). The European Society of Gastrointestinal Endoscopy currently recommends TTSC for defects < 10mm and OTSC for defects > 10mm. However, recommendations for the role of endoscopic defect closure are largely derived from small retrospective series with limited data on clinically relevant EMR-related short and long-term outcomes (63-68).

Optical Evaluation to Differentiate between Benign and Malignant Large Non-Pedunculated Colorectal Polyps

As highlighted above, the ability of real-time optical evaluation to reliability predict SMIC is critical as it informs therapeutic decisions. It enables the endoscopist to select between piecemeal resection techniques, en bloc resection techniques and surgery. However, optical evaluation for LNPCPs have only shown modest performance (47, 48). Moreover, it can be challenging to quantify the pre-test probability of SMIC based on lesion characteristics including: 1) location; 2) size; 3) morphology; 4) granularity; 5) surface microvasculature and pit pattern (42). This is further complicated by the multitude of optical evaluation classifications including KPP, NICE, and JNET amongst others (43-45); thus, limiting the universal adoption of optical evaluation amongst endoscopists performing colonoscopy and LNPCP management.

Lesion morphology is a logical stratification tool for the performance of optical evaluation. Nodularity may increase the likelihood of missing optical features of SMIC, either by hindering their identification or due to a lack of expression on the surface of the lesion. Therefore, assessing optical evaluation performance stratified by lesion morphology may identify lesion subgroups with high optical evaluation performance; thus, facilitating the selection between minimally invasive endoscopic resection techniques and surgery.

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Chapter 1: Endoscopic mucosal resection is effective for laterally spreading lesions at the anorectal junction

Summary: By comparing 100 large laterally spreading lesions at the anorectal junction (ARJ-LSL) and 313 rectal LSLs, we demonstrated that ARJ-LSLs can be effectively and safely managed with endoscopic mucosal resection (EMR); with margin thermal ablation effectively negating recurrence for this historically complex lesion subgroup. Therefore, EMR should be viewed as a first-line treatment strategy for ARJ-LSLs

Endoscopic mucosal resection is effective for laterally spreading lesions at the anorectal junction

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Conflicts of Interest

Michael J. Bourke: Research Support: Olympus Medical, Cook Medical, Boston Scientific.

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Abbreviations

ACE, Australian Colonic Endoscopic Resection

ARJ-LSL, laterally spreading lesion at the anorectal junction

ASA, American Society of Anesthesiologists

CAST, cold-avulsion with adjuvant snare-tip soft coagulation

CSPEB, clinically significant post-endoscopic mucosal resection bleeding

CSIPB, clinically significant intra-procedural bleeding

DMI, deep mural injury

D-SMIC, deep submucosal invasive cancer

EAES, European Association for Endoscopic Surgery

EMR, endoscopic mucosal resection

ESD, endoscopic submucosal dissection

IQR, interquartile range

IV, intravenous

MDT, multi-disciplinary team

NBI, narrow-band imaging

SC, surveillance colonoscopy

SD, standard deviation

SMIC, submucosal invasive cancer

S-SMIC, superficial submucosal invasive cancer

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

STSC, snare-tip soft coagulation

TAE, trans-anal excision

TAMIS, trans-anal minimally invasive surgery

TEM, trans-anal endoscopic microsurgery

TES, trans-anal endoscopic surgery

Abstract

Objective: The optimal approach for removing large laterally spreading lesions at the anorectal junction (ARJ-LSLs) is unknown. Endoscopic mucosal resection (EMR) is a definitive therapy for colorectal LSLs. It is unclear whether it is an effective modality for ARJ-LSLs.

Design: EMR outcomes for ARJ-LSLs (distal margin ≤ 20mm from the dentate line) in comparison to rectal LSLs (distal margin > 20mm from the dentate line) were evaluated within a multi-center observational cohort of LSLs ≥ 20mm. Technical success was defined as removal of all polypoid tissue during index EMR. Safety was evaluated by the frequencies of intra-procedural bleeding, delayed bleeding, deep mural injury, and delayed perforation. Long-term efficacy was evaluated by the absence of recurrence (either endoscopic or histologic) at surveillance colonoscopy (SC).

Results: Between July 2008 to August 2019, 100 ARJ-LSLs and 313 rectal LSLs underwent EMR. ARJ-LSL median size was 40mm (IQR 35 to 60mm). Median follow-up at SC4 was 54 months (IQR 33 to 83 months). Technical success was 98%. Cancer was present in 3 (3.0%). Recurrence occurred in 15.4%, 6.8%, 3.7% and 0% at SC1 to SC4, respectively. Amongst 30 ARJ-LSLs which received margin thermal ablation, no recurrence was identified at SC1 (0.0% vs. 25.0%; p=0.002). Technical success, recurrence, and adverse events were not different between groups, except for deep mural injury (ARJ-LSLs 0% vs. rectal LSLs 4.5%; p=0.027).

Conclusion: EMR is an effective technique for ARJ-LSLs and should be considered a first-line resection modality for the majority of these lesions.

Summary Box

What is already known about this subject?

While endoscopic mucosal resection, endoscopic submucosal dissection, and trans-anal endoscopic surgery are existing techniques for resecting large colorectal laterally spreading lesions at the anorectal junction, the optimal strategy is unknown.

What are the new findings?

This study demonstrates that endoscopic mucosal resection is an effective, efficient, and safe method for treating laterally spreading lesions at the anorectal junction.

How might it impact on clinical practice in the foreseeable future?

Endoscopic mucosal resection should be viewed as a first-line option for treating laterally spreading lesions at the anorectal junction.

Introduction

Large (≥ 20mm) laterally spreading lesions at the anorectal junction (ARJ-LSLs) have historically been referred to surgery due to the unique anatomical, sensory and physiological characteristics of this area. However, distal colorectal surgery carries a significant risk of morbidity, mortality and permanent ostomy formation (1). With evidence supporting the efficacy, safety and cost-effectiveness of minimally invasive resection techniques (2-5), distal colorectal surgery for early colorectal neoplasia should be discouraged.

Nevertheless, the optimal minimally invasive strategy for removing ARJ-LSLs remains unknown. This is due to a lack of randomized trials comparing different local excision modalities and a lack of long-term observational data. As the primary resection modality for the colorectum, evidence demonstrating the short-term efficacy of endoscopic mucosal resection (EMR) for treating ARJ-LSLs exists (6, 7). Modifications in EMR technique are required to successfully treat the distal resection margin. This is due to rectal fold convergence, presence of the hemorrhoidal plexus, and somatic innervation at the squamous epithelium.

Two alternative strategies, endoscopic submucosal dissection (ESD) and trans-anal endoscopic surgery (TES), are currently used to treat ARJ-LSLs. Both can perform en bloc resection of lesions ≥ 20mm. Therefore, they carry the ability to perform curative resection for superficial submucosal invasive cancer (≤ 1000 µm; S-SMIC), in the absence of other high-risk histologic features (8-10). However, the infrequency of S-SMIC in colorectal LSLs coupled with the modest R0 resection frequencies of ESD and TES directly question their universal application (11, 12). Moreover, concerning ARJ-

LSLs, there is limited retrospective data supporting the utility of these techniques (13, 14).

With major advances in optical evaluation allowing for effective SMIC risk stratification (15-17) alongside thermal ablation techniques mitigating the risk of recurrence after EMR (18), we sought to evaluate its efficacy for treating ARJ-LSLs in a retrospective analysis of a prospectively collected multi-center observational cohort.

Methods

This manuscript was created in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (19).

The Australian Colonic Endoscopic Resection Study

The Australian Colonic Endoscopic Resection (ACE) study (clinicaltrials.gov identifiers: NCT01368289; NCT02000141) is a prospectively collected, multi-center, observational cohort of consecutive patients referred for managing colorectal LSLs ≥ 20mm (July 2008 to Present). Center-specific Institutional Review Board approval is maintained at each center. Written informed consent is obtained from each patient prior to study participation.

Consecutive rectal LSLs enrolled at two sites in the ACE study between July 2008 to August 2019 were evaluated. Laterally spreading lesions at the anorectal junction were defined as those either crossing or within 20mm of the dentate line. Consistent with previous descriptions (6, 7), an anatomically and clinically relevant cut-off of ≤ 20mm was selected to define ARJ-LSLs. Anatomically, although variable, the

anal transition zone is commonly defined as the proximal 20mm above the dentate line (20). Histologically, it shares characteristics of columnar and squamous epithelium. Longitudinal mucosal folds, known as the columns of Morgagni, occupy the anal transition zone. These harbor a submucosal plexus which forms the hemorrhoidal plexus. This area is therefore clinically relevant for the management of distal colorectal lesions and the application of minimally invasive resection techniques due to: 1) impaired endoscopic visualization as the columns of Morgagni converge towards the dentate line; 2) the risk of precipitating pain given the somatic innervation of squamous epithelium in the context of obtaining a healthy margin of normal tissue during high-quality EMR; 3) the risk of bacteremia due to the relative lack of protection by the reticulo-endothelial function of the portal lympho-venous drainage system; 4) the implications of achieving an adequate surgical resection margin and thus appropriately selecting between sphincter-sparing surgery and abdominal perineal resection[21].

Technique

All endoscopic procedures were performed by one of four study investigators (accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal EMR) or a senior interventional endoscopy fellow under supervision. Endoscopic resections were performed in a standardized fashion across all centers (5). Technical innovations in EMR were adopted as the evidence to support them emerged. Anti-platelet and anti-coagulation medications were held pre-procedure, in accordance with consensus recommendations (22).

A standardized previously described inject and resect EMR technique was used at all centers (5). Currently, all colorectal EMRs are performed using high-definition Olympus 190 series variable-stiffness colonoscopes (Olympus, Tokyo, Japan). Carbon dioxide is used for insufflation (23). After lesion identification, optical evaluation under high-definition white-light and narrow-band imaging (NBI) is performed to exclude features of SMIC. In a systematic fashion, a submucosal cushion is created with injection of succinylated gelatin (24) (Gelofusine; B. Braun, Bella Vista, Australia) with 0.4% indigo carmine and 1:100,000 epinephrine. Using a microprocessor-controlled generator (ERBE VIO ENDO CUT Q, Effect 3 (ERBE, Tubingen, Germany)) snare excision is performed.

After complete resection, the defect is carefully examined to ensure no polypoid tissue remains and to assess for deep mural injury (DMI) (25). Areas of deep injury (DMI III-V) are subsequently treated by mechanical clip closure. Thermal ablation of the resection margin to mitigate the risk of recurrence is performed using snare-tip soft coagulation (STSC) (ERBE VIO SOFT COAG: 80W, Effect 4) to create a 2 to 3mm rim of ablated tissue (18). Clinically significant intra-procedural bleeding (CSIPB) is treated with coagulation forceps or mechanical hemostasis. Resection specimens are collected and evaluated by specialist gastrointestinal pathologists at their respective centers.

After completion of the procedure, patients are observed for 4 hours. If well, they are subsequently discharged on a clear fluid diet overnight. At 2 weeks, patients are contacted by an ACE study coordinator and undergo a structured telephone interview to identify peri-procedural adverse events. Intervals between subsequent colonoscopies are at the discretion of the endoscopist performing surveillance with recommended

surveillance colonoscopy (SC) intervals of 6, 12, 36, and 60 months (SC1 to SC4, respectively). During SC, patients undergo a standardized evaluation of the EMR scar (26). Biopsies are routinely performed.

Specific procedural aspects for EMR at the anorectal junction are as follows (Figures 1 and 2; Supplemental video 1) (6).

1. **Prophylactic Antibiotics:** Antibiotics (ceftriaxone 1000mg intravenous (IV) and metronidazole 500mg IV) are administered intra-procedurally given the theoretical risk of bacterial translocation. Continued antibiotic prophylaxis post-procedure is not routinely provided.

2. **Lesion Access:** A gastroscope with cap-attachment can be used to maximize maneuverability in the retroflexed position, and optimize visibility by deflecting mucosal folds at the anorectal junction, respectively.

3. **Pain management:** At the distal margin, long-acting local anesthetic (ropivacaine 0.5%; maximum dose 40mg) is added to the submucosal injectate to provide anaesthesia (4 hours) and analgesia (24 hours). Cardiac monitoring is required. Oral paracetamol every 4 - 6 hours as needed is prescribed to all patients at discharge.

4. **Resection over hemorrhoidal columns:** Anterograde tangential submucosal injection is performed to facilitate adequate submucosal expansion away from the hemorrhoidal plexus. Resection is initiated at the distal margin, with meticulous snare placement and tissue capture with a 2-3mm rim of normal tissue irregardless of proximity to the dentate line.

5. **Margin Thermal ablation:** Using identical settings and technique in the colorectum, STSC is carefully performed along the distal resection margin, being mindful of the somatic innervation of the squamous epithelium.

Data Extraction

Collected data included: 1) Patient characteristics: sex, age, American Society of Anesthesiologists (ASA) classification; 2) Lesion characteristics: size, Paris classification (27), surface topography, Kudo pit pattern (28), histopathology; 3) Procedure outcomes: technical success, peri-procedural adverse events, recurrence.

Technical success was defined as complete removal of all polypoid tissue during index EMR. Clinically significant intra-procedural bleeding was defined by oozing or spurting blood loss for ≥ 60 seconds, not responding to water jet irrigation and requiring either coagulation forceps or mechanical hemostasis (29). Clinically significant post-EMR bleeding (CSPEB) was defined as any bleeding which occurred after the procedure and required emergency room presentation, hospitalization, or re-intervention (endoscopy, angiography, surgery) (30). Deep mural injury was defined as grade III (target sign (31)) or grade IV/V (transmural perforation without or with contamination, respectively) (25). Pain was defined by the requirement of analgesia post-procedure. Long-term efficacy was defined by the absence of either endoscopic or histologic recurrence at SC. Study endpoints included: technical failure, SMIC, death, advanced age or comorbidities precluding ongoing SC, lost to follow-up and SC4.

Statistical Analysis

The primary outcome was technical success. Secondary outcomes were peri-procedural adverse events and recurrence (stratified by those who received margin STSC). Laterally spreading lesions at the anorectal junction were compared to the remaining cohort of rectal LSLs.

SPSS version 25.0 (IBM Corp, Armonk, NY, USA) was used for retrospective data analysis. Continuous variables were summarized using median (interquartile range (IQR)). Categorical variables were summarized as frequencies (%). To test for association between categorical variables, the Pearson x^2 or the Fisher Exact tests were used, where appropriate. For continuous variables, the Mann-Whitney U test was used. A probability (p) value < 0.05 was considered statistically significant.

Patient and Public Involvement

Patients were not involved in the design and execution of this study.

Results

Between July 2008 to August 2019, 128 ARJ-LSLs and 359 rectal LSLs were referred for endoscopic resection (Figure 3). Twenty lesions (5 ARJ-LSLs, 15 rectal LSLs) demonstrated features consistent with deep SMIC (> 1000 µm; D-SMIC) on optical evaluation and were referred directly to surgery. One rectal LSL had a concomitant sigmoid cancer and was referred to surgery. Fifty-three lesions (23 ARJ-LSLs, 30 rectal LSLs) were enrolled in a selective ESD protocol (clinicaltrials.gov identifier: NCT02198729). These lesions were excluded from analysis. Thirty-six lesions

(10 ARJ-LSLs; 26 rectal LSLs) were concomitantly enrolled in a randomized trial (clinicaltrials.gov identifier: NCT01789749) assessing the ability of margin thermal ablation to mitigate recurrence.

Patient and Lesion Characteristics

One-hundred ARJ-LSLs underwent EMR amongst 99 patients (Table 1). Eighty-two (82%) involved the dentate line. Median age was 64 years (IQR 55 to 73 years) with 53 (53.5%) being male. The majority were ASA I (37, 41.1%) or ASA II (43, 47.8%). Median lesion size was 40mm (IQR 35mm to 60mm). Eleven (11.0%) were previously attempted, all by snare-based resection techniques. On optical evaluation, Paris classification 0-IIa+Is was the predominant morphology (55, 55.0%). Eighty-eight (88.0%) showed granular topography. Ninety-seven (97%) showed either Kudo pit pattern III or IV.

Procedure Outcomes

Median procedure time was 30 minutes (IQR 15 to 55 minutes)(Table 2). Technical success was achieved in 98 (98%). Thermal ablation of the EMR margin was performed in 41 (41.0%). An auxiliary modality, to allow for complete removal of all polypoid tissue, was required in 12 (12.0%). Auxiliary modalities included: cold-avulsion with adjuvant snare-tip soft coagulation (CAST) 5 (41.7%); hot avulsion 2 (16.7%); other thermal techniques 5 (41.7%). Endoscopic mucosal resection was unsuccessful in 2 (2.0%). In one case, submucosal fibrosis was secondary to SMIC, with subsequent referral to surgery. In the other case, severe submucosal fibrosis was encountered, due

to previously attempted resection. Technical success was achieved by CAST after

rescue two-stage resection. Nineteen (19.2%) required hospital admission post-

procedure: 11 (57.9%) for observation after extensive endoscopic resection, 1 (5.4%)

due to comorbid disease management, 1 (5.4%) due to rigors post-procedure, 2

(10.5%) for CSPEB, and 4 (21.1%) for social reasons. None were due to post-

procedure pain.

On histopathology, the majority (69, 69.0%) were tubulovillous adenomas. The

frequency of low-grade dysplasia and high-grade dysplasia were 74 (76.3%), and 20

(20.6%), respectively. Submucosal invasive cancer was identified in 3 (3.0%) and were

subsequently referred to surgery or to multi-disciplinary team (MDT) discussion.

Adverse Events

Clinically significant intra-procedural bleeding was encountered in 6 (6.0%).

Hemostasis was achieved in all cases by either coagulation forceps (4, 66.7%) or

mechanical clip placement (2, 33.3%). No cases of DMI III-V occurred. Five (6.1%)

patients required post-procedural analgesia. One (1.0%) patient experienced rigors with

subsequent admission to hospital for intravenous antibiotics.

Clinically significant post-EMR bleeding occurred in 11 (11.1%). In 4 (36.4%), this

was conservatively managed with 7 (63.6%), undergoing endoscopic re-evaluation with

or without endoscopic re-intervention. No cases of delayed perforation occurred.

Long-term Outcomes

      86, 69, 37 and 10 were eligible for SC1 to SC4, respectively; of which 78 (90.7%), 59 (85.5%), 27 (73.0%) and 10 (100.0%) underwent endoscopic follow-up (Table 3). From index EMR, median time to follow-up for SC1 to SC4 was 5 months (IQR 4 to 7 months), 19 months (IQR 14 to 23 months), 39 months (IQR 28 to 57 months) and 54 months (IQR 33 to 83 months), respectively. Recurrence was identified in 12 (15.4%) at SC1, 4 (6.8%) at SC2, 1 (3.7%) at SC3 and 0 (0.0%) at SC4. Surgery was avoided in all but 1 case which was due to extensive recurrence at SC2.

      Amongst 30 ARJ-LSLs which underwent margin STSC to mitigate the risk of recurrence and underwent SC, no recurrence was identified at SC1 vs. 12 (25%; p = 0.002) which did not receive STSC (Table 4). Only 1 case of recurrence was identified amongst ARJ-LSLs which underwent STSC between SC1 to SC4. This was in a 70mm 0-IIa+Is lesion, with significant fibrosis requiring hot avulsion to achieve technical success.

ARJ-LSLs vs. Rectal LSLs

      When comparing outcomes between ARJ-LSLs and rectal LSLs, there was no significant difference for technical success, requiring an auxiliary modality to complete endoscopic resection, pain, direct hospital admission, CSIPB, CSPEB, delayed perforation, and recurrence at SC1 to SC4. Significant differences in procedure duration (ARJ-LSLs 30 minutes; IQR 15 – 55 minutes vs. rectal LSLs 25 minutes; IQR 12 – 50 minutes; p = 0.045) and DMI (ARJ-LSLs 0, 0.0% vs. rectal LSLs 14, 4.5%; p = 0.027) were identified.

Discussion

Endoscopic mucosal resection has revolutionized the management of early colorectal neoplasia. After confirming its superior safety (3) and cost-effectiveness (4) to surgery, the technique has continued to evolve; manifesting in the ability to predict, mitigate and manage intra-procedural and post-procedural adverse outcomes (18, 23-26, 29-34). Alongside site-specific modifications in technique, high-quality EMR has surmounted physician-imposed boundaries by effectively treating peri-appendiceal (35), ileocecal (36), circumferential (37) and non-lifting lesions (38). Our study highlights another major advancement; the ability of a site-specific EMR technique (supplemental video 1) to effectively, efficiently, and safely manage ARJ-LSLs in a multi-center observational cohort. Accentuated by the absence of comparable evidence for alternative techniques, EMR should be considered a first-line resection modality for the majority of these lesions.

Despite this lack of comparable evidence, many endoscopists advocate for the utilization of ESD. This is based on small retrospective cohorts, largely evaluating short-term outcomes (13, 14, 39-43). A perceived benefit of ESD for ARJ-LSLs is a lower frequency of recurrence (44). Comparing previous EMR (6, 7) and ESD (13, 14, 39-43) cohorts, the frequency of recurrence has ranged from 18% to 22% and 0% to 8%, respectively. This disparity is likely driven by the unique anatomical characteristics of the anorectal junction. Rectal fold convergence can limit endoscopic visualization, thus increasing the risk of diminutive foci of residual polyp remaining in situ unbeknownst to the endoscopist. Moreover, endoscopists may be reluctant to obtain a healthy margin of normal tissue at the dentate line in fear of precipitating pain. In our study, while the

frequency of recurrence at SC1 was 15.4%, with the application of thermal ablation

therapy to the margin, no recurrence was identified at SC1. Margin STSC is supported

by a recent multi-center randomized controlled trial, which reduced recurrence at SC1

from 21% to 5% ($p < 0.001$) (18). This effect on recurrence has now been reproduced in

a North American cohort (45). By negating a primary advantage of ESD, it naturally

directs one's focus to its negatives. This includes increased technical difficulty,

prolonged procedure times, and a heightened risk of post-procedural bleeding and

perforation, with estimates as high as 29% (13) and 4% (14), respectively.

Another advantage of ESD is the ability to perform size-independent en bloc

resection, as lesions ≥ 20mm are not reliably removed en bloc by EMR (8). If S-SMIC is

identified without any high-risk features (poor differentiation, lymphovascular invasion,

high-grade tumor budding), R0 resection is curative (8, 9). This allows ESD to be a

surgery-sparing technique for early colorectal cancer, which is of the utmost importance

in the rectum; given the heightened risk of morbidity, mortality and stoma formation with

distal rectal surgery (1). However, in a recent systematic review and meta-analysis (11),

evaluating 51 studies and 11,260 colorectal lesions, the frequency of S-SMIC was only

8%. With the frequency of curative endoscopic resection being 75%, this decreased the

frequency of lesions with S-SMIC which would be cured to 6% with a number needed to

treat of 17. These findings directly question the indiscriminate application of ESD in the

colorectum.

Clearly, the universal application of either EMR or ESD is not appropriate and a

rectum-specific selective resection algorithm is needed. With the vast majority of lesions

being benign, EMR should be the primary resection modality within this algorithm. If

features suggestive of S-SMIC are identified during optical evaluation, ESD would be indicated whereas if features suggestive of D-SMIC are identified, referral to surgery is appropriate. In an attempt to stratify the risk of invisible or "covert" SMIC, a recent study from the ACE consortium (17) evaluated 2277 LSLs ≥ 20mm. After excluding lesions with visible or overt features of SMIC, size, location, non-granularity and Paris classification 0-Is and 0-IIa+Is morphology were significantly associated with SMIC on multivariable analysis. Importantly, by using a combination of morphology, topography and location, lesions could be effectively stratified into a high (> 10%) covert SMIC grouping; thereby identifying potential candidates for ESD, particularly in the rectum. A selective resection algorithm, based on these premises has been shown to be the most cost-effective treatment strategy (46). Only 43 ESD procedures were required per 1000 patients.

An alternative local excision strategy is TES, which includes conventional trans-anal excision (TAE), trans-anal endoscopic microsurgery (TEM), and trans-anal minimally invasive surgery (TAMIS). Procedural outcomes for TES, specifically TEM, appear comparable to ESD (47) and it shares the benefit of performing en bloc resection of rectal LSLs and therefore carries the potential for curative resection of early colorectal cancers. In a recent multi-center randomized trial comparing EMR vs. TEM (48) for rectal LSLs, although EMR was less costly, non-inferiority could not be reached. This was due to an unexpectantly high frequency of recurrence in both groups (EMR 15% vs. TEM 11%). Of note, margin STSC was not performed. Within our cohort, the frequency of recurrence at SC1 was significantly lower for ARJ-LSLs (0.0% STSC vs. 25.0% no STSC; p = 0.002) and rectal LSLs (5.9% STSC vs. 17.5% no STSC; p =

0.041) amongst those receiving STSC. Therefore, a subsequent trial, with superiority design in favour of EMR, should be considered.

Another major limitation of TEM and TAMIS is that their respective platforms obscure the anorectal junction, thus limiting their applicability for ARJ-LSLs. Colorectal surgeons are commonly forced to revert to TAE with conventional retractors. This can limit visualization and exposure to facilitate en bloc resection. In a retrospective evaluation of 171 lesions which underwent TES (89 TAE, 82 TEM) (49), the frequency of adverse events, specimen fragmentation and recurrence for TAE were 17%, 35% and 27%, respectively. These findings have been supported in a recent meta-analysis of 6 comparative studies (435 TAE, 492 TEM), with significant differences in favor of TEM compared to TAE, for specimen fragmentation, negative resection margins, and recurrence (50). Accordingly, the European Association for Endoscopic Surgery (EAES) recommends that TAE should only be considered in very select cases (10). Therefore, until technological advances in TES facilitate its application near the dentate line, these modalities should not be applied for ARJ-LSLs outside the confines of a well-defined research protocol.

Unique to the anorectum is the concern for pain due to the distinct anatomy of the anal transition zone. To achieve a healthy margin of normal tissue during resection, the endoscopist will invariably resect below the dentate line into the somatically innervated squamous epithelium. Interestingly, no significant difference in the frequency of pain was identified between ARJ-LSLs and rectal LSLs (6.1% vs. 3.8%; $p = 0.366$). This supports the effectiveness of incorporating local anesthetic into the submucosal injectate at the distal resection margin, which is consistent with the majority of the

endoscopic tissue resection literature for ARJ-LSLs (6, 13, 14, 39, 40, 42, 43). However, it is imperative to always approach post-procedure pain with caution and distinguish between peri-anal pain and abdominal pain; as the latter can be precipitated by gaseous distension, transmural injection, serositis/post-polypectomy syndrome and perforation.

Another unique feature of this area is the risk of bacteremia. A submucosal plexus resides in the anal transition zone. As the hemorrhoidal plexus drains directly into the systemic circulation, the distal rectum is vulnerable to bacterial translocation during multifocal submucosal injection; a core component to high-quality EMR technique. This is in contrast to the middle rectum which is better protected by its porto-venous drainage. In this study, one patient developed rigors prior to the universal administration of prophylactic antibiotics, which is now our standard of practice. This is consistent with recommendations for the application of TES (51, 52). Although there is weak evidence to support this practice, this is a relatively low-risk and inexpensive intervention. Thus, given the infrequency of this adverse event, higher quality evidence either supporting or contradicting antibiotic use is unlikely to emerge.

An unexpected finding was a heightened frequency of CSPEB (11.1% vs. 6.2%) (32) and endoscopic re-evaluation (63.6% vs. 43.5%) (30) amongst ARJ-LSLs compared to previous estimates of the ACE consortium; especially as proximal location has been identified as an independent predictor of CSPEB (32). This is likely driven, in part, by the rich vascular network of the distal rectum alongside a lack of appreciation for the significance of ARJ-LSLs in previous evaluations (20). Another likely contributor is that bleeding at the anorectal junction is readily apparent and easily accessed;

therefore, predisposing the patient to seek out medical attention and the endoscopist to intervene. Unfortunately, CSPEB remains a major drawback of minimally invasive resection techniques with prophylactic vessel coagulation (53) and prophylactic clip closure (54) having limited roles for these specific lesions.

This study is not without limitations. The design lead to a moderate frequency of patients who did not complete surveillance, including those lost to follow-up. However, these results reflect the real-world application of EMR, as colorectal LSLs commonly afflict patients of advanced age and therefore are more likely to have comorbid disease states. Patients no longer followed in this context should not be viewed as a negative EMR outcome. Moreover, by including all patients irregardless of their stage of follow-up facilitated the analysis of pertinent clinical outcomes including technical success, adverse events, and recurrence. Another limitation is that while set SC intervals are recommended, colonoscopies within the ACE consortium are recorded sequentially with intervals at the discretion of the endoscopist performing surveillance. Irregardless, median time from index to SC4 was 54 months which, to our knowledge, is the longest description of follow-up in the EMR literature. Site-specific high-quality EMR technique did vary over time, with technical innovations in EMR being adopted as the evidence to support them emerged. However, given the evolution of high-quality EMR, performance outcomes in this study are likely an underestimate of the currently applied technique. Moreover, the primary focus of our study was to evaluate technical success and not to evaluate the efficacy of thermal ablation therapy to mitigate the risk of recurrence. As ARJ-LSLs which received margin STSC was a sample of the overall population, further evaluation in this area is needed. Lastly, a significant discrepancy in

the frequency of SMIC was identified between ARJ-LSLs (3.0%) vs. rectal LSLs (12.5%). This is likely explained by the exclusion of lesions due to the optical features of D-SMIC and enrolment in a selective ESD protocol (21.8% ARJ-LSLs vs. 12.8% rectal LSLs). It is unlikely that ARJ-LSLs have a unique pathobiological behavior.

In conclusion, EMR is an effective strategy for ARJ-LSLs, given its ability to efficiently and safely manage these lesions. By incorporating key advancements in this space, specifically thermal ablation therapy to the resection margin, recurrence has been effectively mitigated at this historically high-risk site. While ESD and TEM/TAMIS are exciting additions to the management of rectal neoplasia, their application must be founded in evidence and not overshadow logical clinical benefit. Carefully designed randomized clinical trials, with clearly defined inclusion criteria and endpoints, will be the definitive mechanism for deciding how these modalities should be utilized. Until a definitive rectum-specific selective resection algorithm can be delineated, EMR should be viewed as a first-line modality for the majority of these lesions.

Acknowledgements

Table 1: Patient and Lesion Characteristics

	All Rectal LSLs (n = 413; n, %)	ARJ-LSLs (n = 100; n, %)	Rectal LSLs (n = 313; n, %)
Patient Characteristics			
Age (median, IQR, years)	66 (58 – 74)	64 (55 – 73)	67 (59 – 75)
Male sex (n, %)	221 (54.0)	53 (53.5)	168 (54.2)
ASA classification (n, %)*			
I	166 (45.4)	37 (41.1)	129 (46.7)
II	158 (43.2)	43 (47.8)	115 (41.7)
III	42 (11.5)	10 (11.1)	32 (11.6)
Lesion Characteristics			
Size (median, IQR, mm)	40 (30 – 60)	40 (35 – 60)	40 (30 – 60)
Previously Attempted (n, %)	54 (13.1)	11 (11.0)	43 (13.7)
Paris classification (n, %)			
0-IIa	111 (26.9)	32 (32.0)	79 (25.2)
0-IIb	4 (1.0)	0 (0.0)	4 (1.3)
0-Is	73 (17.7)	11 (11.0)	62 (19.8)
0-IIa+Is	216 (52.3)	55 (55.0)	161 (51.4)
Any 0-IIc component	9 (2.2)	2 (2.0)	7 (2.2)
Topography (n, %)**			
Granular	329 (80.6)	88 (88.0)	241 (78.2)
Non-granular	41 (10.0)	5 (5.0)	36 (11.7)
Mixed	35 (8.6)	7 (7.0)	28 (9.1)
Serrated Topography	3 (0.7)	0 (0.0)	3 (1.0)
Kudo Pit Pattern (n, %)***			
I	2 (0.5)	0 (0.0)	2 (0.6)
II	7 (1.7)	1 (1.0)	6 (1.9)
III	82 (20.0)	14 (14.3)	68 (21.9)
IV	304 (74.3)	83 (84.7)	221 (71.1)
V	14 (3.4)	0 (0.0)	14 (4.5)
Histopathology (n, %)			
Tubular adenoma	39 (9.4)	6 (6.0)	33 (10.5)
Tubulovillous adenoma	277 (67.1)	69 (69.0)	208 (66.5)
Villous adenoma	11 (2.7)	2 (2.0)	9 (2.9)
Serrated	21 (5.1)	13 (13.0)	8 (2.6)
Submucosal Invasive Cancer	42 (10.2)	3 (3.0)	39 (12.5)
Other	23 (5.6)	7 (7.0)	16 (5.1)
Dysplasia (n, %)			
None	8 (2.2)	3 (3.1)	5 (1.8)
Low-grade dysplasia	261 (70.4)	74 (76.3)	187 (68.2)
High-grade dysplasia	102 (27.5)	20 (20.6)	82 (29.9)

ASA, American Society of Anesthesiologists
*43 participants ASA was not classified; **5 lesions topography was not classified; ***4 lesions Kudo pit pattern was not classified

Table 2: Procedural Outcomes

	All Rectal LSLs (n = 413; n, %)	ARJ-LSLs (n = 100; n, %)	Rectal LSLs (n = 313; n, %)	P-Value
Duration (median, IQR, minutes)*	25 (15 – 50)	30 (15 – 55)	25 (12 – 50)	**0.045**
Technical success (n, %)	402 (97.3)	98 (98.0)	304 (97.1)	1.000
Auxiliary modality (n, %)	58 (14.0)	12 (12.0)	46 (14.7)	0.499
Margin thermal ablation (n, %)	133 (32.2)	41 (41.0)	92 (29.4)	**0.031**
CSIPB (n, %)	24 (5.8)	6 (6.0)	18 (5.8)	0.926
Deep mural injury III-V (n, %)	14 (3.4)	0 (0.0)	14 (4.5)	**0.027**
Pain**	15 (4.3)	5 (6.1)	10 (3.8)	0.366
Direct hospital admission (n, %)***	72 (17.6)	19 (19.2)	53 (17.1)	0.634
CSPEB (n, %)	32 (7.8)	11 (11.1)	21 (6.8)	0.162
Delayed Perforation (n, %)	1 (0.2)	0 (0.0)	1 (0.3)	1.000

CSIPB, Clinically significant intra-procedural bleeding; CSPEB, Clinically significant post-EMR bleeding
*41 lesions missing procedural duration
**62 participants missing pain
**8 participants were admitted due to post-procedure pain, of which all were rectal LSLs

Table 3: Outcomes after EMR

	All Rectal LSLs (n = 413; n, %)	ARJ-LSLs (n = 100; n, %)	Rectal LSLs (n = 313; n, %)	P-Value
SC1				
Eligible (n)	331	86	245	
Underwent SC1 (n, %)	289 (87.3)	78 (90.7)	211 (86.1)	
Months to SC1 (median, IQR)	5 (4 – 7)	5 (4 – 7)	5 (4 – 7)	
Recurrence at SC1 (n, %)	43 (14.9)	12 (15.4)	31 (14.7)	0.883
Surgery at SC1 (n, %)	1 (0.3)	0 (0.0)	1 (0.5)	
SC2				
Eligible (n)	264	69	195	
Underwent SC2 (n, %)	215 (81.4)	59 (85.5)	156 (80.0)	
Months to SC2 (median, IQR)	19 (14 – 23)	19 (14 – 23)	18 (15 – 23)	
Recurrence at SC2 (n, %)	15 (7.0)	4 (6.8)	11 (7.1)	1.000
Surgery at SC2 (n, %)	1 (0.5)	1 (1.7)	0 (0.0)	
SC3				
Eligible (n)	162	37	125	
Underwent SC3 (n, %)	111 (68.5)	27 (73.0)	84 (67.2)	
Months to SC3 (median, IQR)	40 (29 – 53)	39 (28 – 57)	41 (29 – 51)	
Recurrence at SC3 (n, %)	3 (2.7)	1 (3.7)	2 (2.4)	0.570
Surgery at SC3 (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	
SC4				
Eligible (n)	40	10	30	
Underwent SC4 (n, %)	31 (77.5)	10 (100.0)	21 (70.0)	
Months to SC4 (median, IQR)	55 (41 – 69)	54 (33 – 83)	56 (42 – 69)	
Recurrence at SC4 (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Surgery at SC4 (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	

SC, Surveillance colonoscopy

Table 4: Outcomes after EMR, stratified by margin thermal ablation therapy

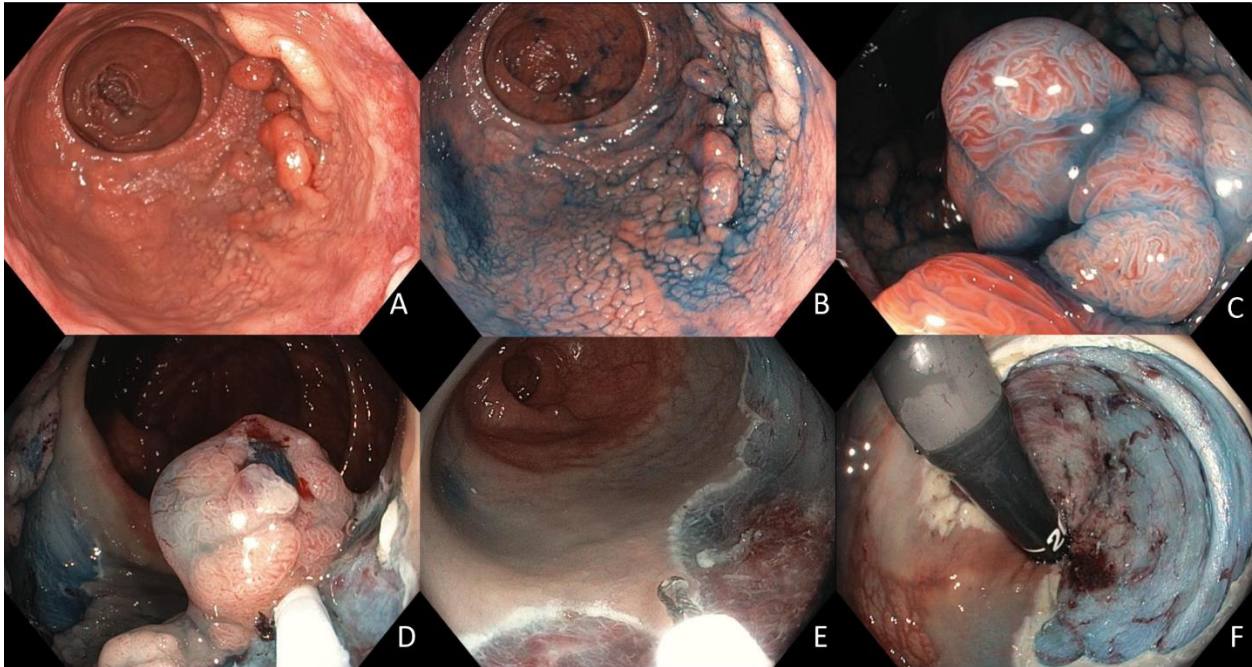|	ARJ-LSLs			Rectal LSLs		
	STSC	No STSC	P-value	STSC	No STSC	P-value
SC1 Recurrence (n/N, %)	0/30 (0.0)	12/48 (25.0)	**0.002**	3/51 (5.9)	28/160 (17.5)	**0.041**
SC2 Recurrence (n/N, %)	1/14 (7.1)	3/45 (6.7)	1.000	1/26 (3.8)	10/130 (7.5)	0.692
SC3 Recurrence (n/N, %)	0/3 (0.0)	1/24 (4.2)	1.000	0/8 (0.0)	2/76 (2.6)	1.000
SC4 Recurrence (n/N, %)	0/1 (0.0)	0/9 (0.0)	NA	0/1 (0.0)	0/20 (0.0)	NA

Figure 1. A: A 70mm 50% circumferential 0-IIa+Is granular laterally spreading lesion with the distal margin abutting the dentate line. **B:** Lesion margins best seen under chromoendoscopy. **C:** Kudo IV pit pattern, NICE type II, JNET type IIa on optical evaluation. **D:** High-quality endoscopic mucosal resection performed in a systematic manner. **E-F:** Margin thermal ablation performed to mitigate the risk of recurrence. Final histology confirmed a tubulovillous adenoma.
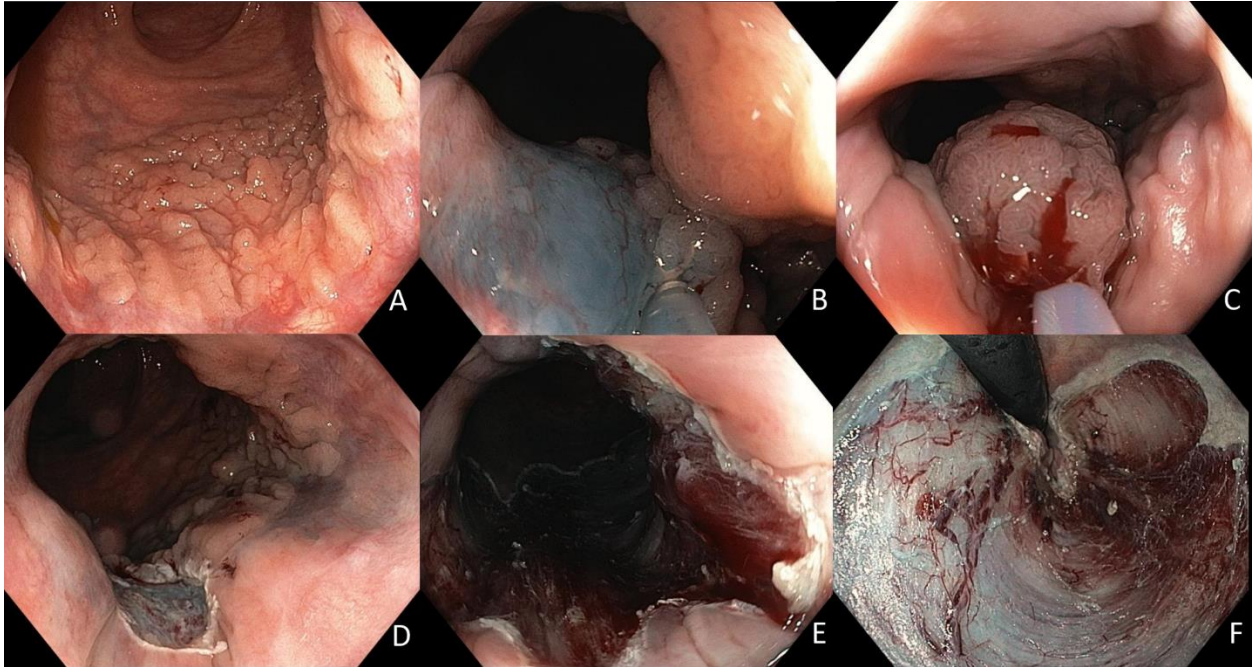
Figure 2. A: A 60mm 75% circumferential 0-IIa granular laterally spreading lesion with the distal margin crossing the dentate line. **B-E:** High-quality endoscopic mucosal resection with resection at the anorectal junction. **F:** Post-margin thermal ablation defect evaluation, showing no deep mural injury. Final histology confirmed a tubulovillous adenoma.
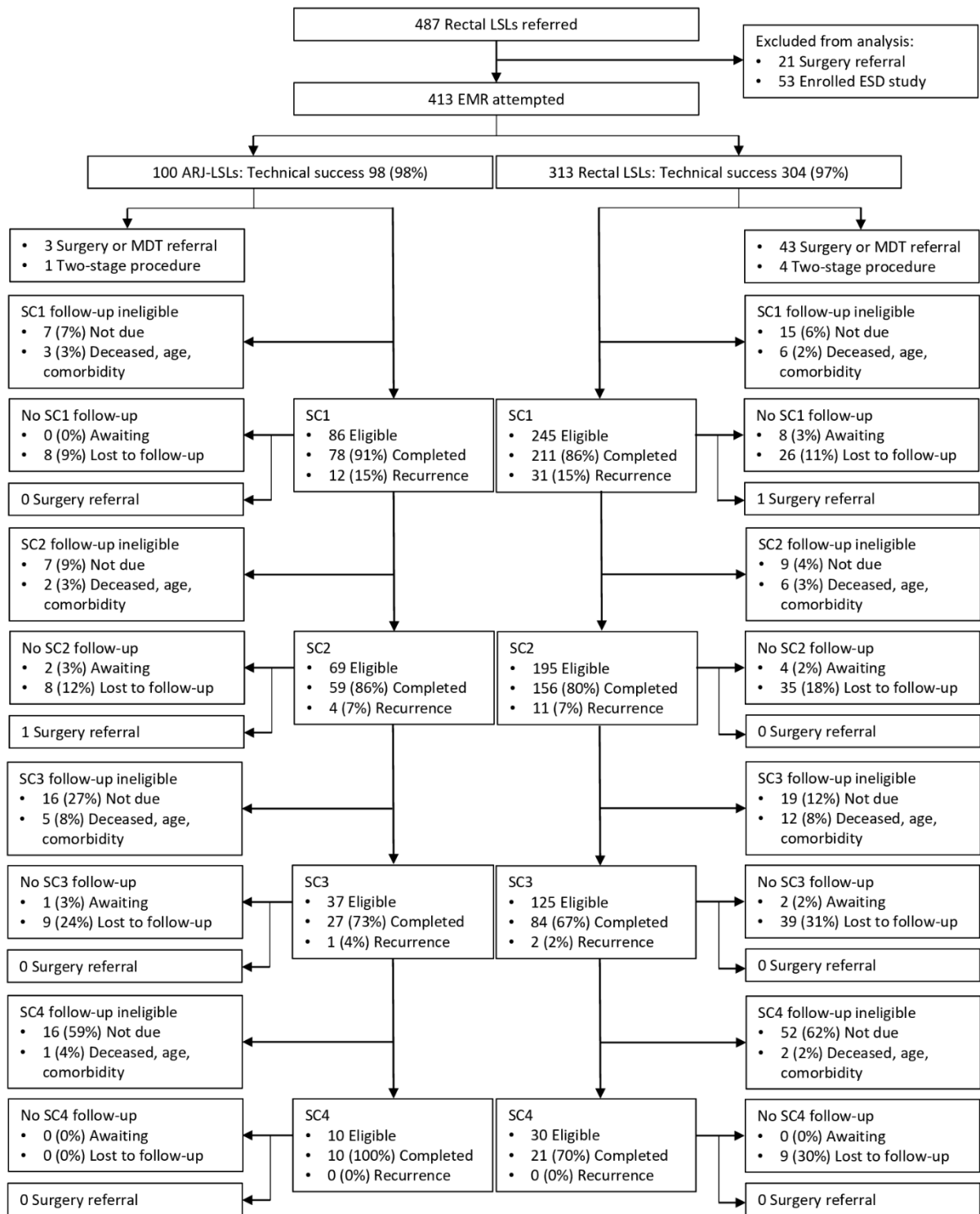
```
                          ┌─────────────────────────────┐
                          │   487 Rectal LSLs referred   │        ┌──────────────────────────────┐
                          └─────────────────────────────┘        │ Excluded from analysis:      │
                                        │                        │ •  21 Surgery referral       │
                          ┌─────────────────────────────┐        │ •  53 Enrolled ESD study     │
                          │     413 EMR attempted        │        └──────────────────────────────┘
                          └─────────────────────────────┘
```

| 100 ARJ-LSLs: Technical success 98 (98%) | 313 Rectal LSLs: Technical success 304 (97%) |

- 3 Surgery or MDT referral
- 1 Two-stage procedure

- 43 Surgery or MDT referral
- 4 Two-stage procedure

SC1 follow-up ineligible
- 7 (7%) Not due
- 3 (3%) Deceased, age, comorbidity

SC1 follow-up ineligible
- 15 (6%) Not due
- 6 (2%) Deceased, age, comorbidity

No SC1 follow-up
- 0 (0%) Awaiting
- 8 (9%) Lost to follow-up

SC1
- 86 Eligible
- 78 (91%) Completed
- 12 (15%) Recurrence

SC1
- 245 Eligible
- 211 (86%) Completed
- 31 (15%) Recurrence

No SC1 follow-up
- 8 (3%) Awaiting
- 26 (11%) Lost to follow-up

0 Surgery referral

1 Surgery referral

SC2 follow-up ineligible
- 7 (9%) Not due
- 2 (3%) Deceased, age, comorbidity

SC2 follow-up ineligible
- 9 (4%) Not due
- 6 (3%) Deceased, age, comorbidity

No SC2 follow-up
- 2 (3%) Awaiting
- 8 (12%) Lost to follow-up

SC2
- 69 Eligible
- 59 (86%) Completed
- 4 (7%) Recurrence

SC2
- 195 Eligible
- 156 (80%) Completed
- 11 (7%) Recurrence

No SC2 follow-up
- 4 (2%) Awaiting
- 35 (18%) Lost to follow-up

1 Surgery referral

0 Surgery referral

SC3 follow-up ineligible
- 16 (27%) Not due
- 5 (8%) Deceased, age, comorbidity

SC3 follow-up ineligible
- 19 (12%) Not due
- 12 (8%) Deceased, age, comorbidity

No SC3 follow-up
- 1 (3%) Awaiting
- 9 (24%) Lost to follow-up

SC3
- 37 Eligible
- 27 (73%) Completed
- 1 (4%) Recurrence

SC3
- 125 Eligible
- 84 (67%) Completed
- 2 (2%) Recurrence

No SC3 follow-up
- 2 (2%) Awaiting
- 39 (31%) Lost to follow-up

0 Surgery referral

0 Surgery referral

SC4 follow-up ineligible
- 16 (59%) Not due
- 1 (4%) Deceased, age, comorbidity

SC4 follow-up ineligible
- 52 (62%) Not due
- 2 (2%) Deceased, age, comorbidity

No SC4 follow-up
- 0 (0%) Awaiting
- 0 (0%) Lost to follow-up

SC4
- 10 Eligible
- 10 (100%) Completed
- 0 (0%) Recurrence

SC4
- 30 Eligible
- 21 (70%) Completed
- 0 (0%) Recurrence

No SC4 follow-up
- 0 (0%) Awaiting
- 9 (30%) Lost to follow-up

0 Surgery referral

0 Surgery referral

Figure 3. Flow diagram of consecutive rectal laterally spreading lesions referred for

endoscopic resection

ARJ-LSL, laterally spreading lesion at the anorectal junction; EMR, endoscopic mucosal

resection; ESD, endoscopic submucosal dissection; LSL, laterally spreading lesion; SC,

surveillance colonoscopy.

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Chapter 2: A rectum-specific selective resection algorithm optimizes oncologic outcomes for large non-pedunculated rectal polyps

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Summary: Among 480 large non-pedunculated rectal polyps (LNPRPs), a selective resection algorithm (SRA) vs. a universal EMR algorithm increased curative oncologic resection and decreased piecemeal resection of cancer without affecting technical success or adverse events; thus, demonstrating the effectiveness of a SRA which incorporates both EMR and ESD for LNPRPs.

A rectum-specific selective resection algorithm optimizes oncologic outcomes for large non-pedunculated rectal polyps

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Abbreviations:

ASA, American Society of Anesthesiologists

CSPEB, clinically significant post-endoscopic resection bleeding

DMI, deep mural injury

D-SMIC, deep submucosal invasive cancer

EMR, endoscopic mucosal resection

ESD, endoscopic submucosal dissection

IQR, interquartile range

LNPCP, large non-pedunculated colorectal polyp

LNPRP, large non-pedunculated rectal polyp

MDT, multi-disciplinary team

SC, surveillance colonoscopy

SMIC, submucosal invasive cancer

SRA, selective resection algorithm

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

STSC, snare-tip soft coagulation

S-SMIC, superficial submucosal invasive cancer

UEA, universal endoscopic mucosal resection algorithm

Abstract

Background and aims: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are complementary techniques for large (≥ 20mm) non-pedunculated rectal polyps (LNPRPs). A mechanism for appropriate technique selection has not been described.

Methods: We evaluated the performance of a selective resection algorithm (SRA; 08/2017-04/2021) compared to a universal EMR algorithm (UEA; 07/2008-07/2017) for LNPRPs within a prospective observational study. In the SRA, LNPRPs with features of superficial submucosal invasive cancer (SMIC < 1000μm; S-SMIC; Kudo pit pattern Vi), or with an increased risk of SMIC (Paris 0-Is or 0-IIa+Is non-granular, 0-IIa+Is granular with a dominant nodule ≥ 10mm) underwent ESD. The remaining LNPRPs underwent EMR. Algorithm performance was evaluated by SMIC identified after EMR, curative oncologic resection (R0 resection, S-SMIC, absence of negative histologic features), technical success, adverse events, and recurrence at first surveillance colonoscopy.

Results: 480 LNPRPs were evaluated (290 UEA, 190 SRA). Median lesion size was 40mm (IQR 30-60mm). SMIC was identified in 56 (11.7%) LNPRPs. Significant differences in SMIC after EMR (SRA 1 (1.0%) vs. UEA 35 (12.1%); p = 0.001), and curative oncologic resection (SRA 7 (33.3%) vs. UEA 2 (5.7%); p = 0.010) were identified. No significant differences in technical success or adverse events were identified (all p > 0.137). Among LNPRPs with SMIC amenable to curative oncologic resection and which underwent ESD, 100% (7/7) were cured.

Conclusions: A rectum-specific SRA optimizes oncologic outcomes for LNPRPs and mitigates the risk of piecemeal resection of cancers.

Key Words: Adenoma, Cancer, Colonoscopy, Polyp, Surgery

What You Need to Know

Background: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are complementary techniques. A mechanism for appropriate technique selection for large (≥ 20mm) non-pedunculated rectal polyps (LNPRPs) has not been described.

Findings: Among 480 LNPRPs, a selective resection algorithm (SRA) vs. a universal EMR algorithm increased curative oncologic resection and decreased piecemeal resection of cancer without affecting technical success or adverse events.

Implications for Patient Care: A rectum-specific SRA, based on real-time optical evaluation, optimizes oncologic outcomes for LNPRPs.

Short Summary

Analyzing 480 large rectal polyps, using both endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) increased the chances of curing early rectal cancers, compared to using only EMR.

Introduction

Large non-pedunculated colorectal polyps (LNPCPs) are a critical component of colorectal cancer screening. This is due to their incidence on screening colonoscopy, the complexity of their management, and the associated costs on the healthcare system (1). Large non-pedunculated rectal polyps (LNPRPs) are especially important as they have a two-fold risk of submucosal invasive cancer (SMIC) (2). Moreover, there is a heightened risk of morbidity, mortality and permanent ostomy formation associated with distal colorectal surgery (3).

Endoscopic mucosal resection (EMR) is now the first-line resection modality for LNPCPs due to its efficacy, efficiency and safety compared to surgery and alternative resection techniques (1, 4-6). The primary limitation of EMR is that for larger lesions, piecemeal resection is required due to technical limitations and safety concerns (7). In the event SMIC is detected, surgery is generally recommended as R0, and therefore curative oncologic resection, cannot be ascertained. This highlights the synergistic role of en bloc resection techniques such as endoscopic submucosal dissection (ESD) (8). Economic analyses have shown that a selective resection algorithm (SRA), incorporating EMR and ESD, is the most cost-effective strategy (9). However, how to select which lesions should undergo EMR vs. ESD has not been delineated.

Real-time optical evaluation of a lesion's pit and microvascular surface pattern can detect SMIC prior to endoscopic resection. Recent evidence suggests that optical evaluation has modest performance characteristics (10, 11). To negate the risk of missed or covert SMIC, lesion morphology can be used to further risk-stratify these lesions, and thus facilitate technique selection (2, 12). We therefore sought to evaluate

whether optical evaluation, in conjunction with covert SMIC risk stratification, can be used to effectively select between EMR and ESD for large non-pedunculated polyps within the rectum.

Methods

This manuscript is in keeping with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (13).

Study Design

Consecutive patients referred for the management of a LNPRP ≥ 20mm at a single center between July 2008 to April 2021 were evaluated as part of a prospectively collected, observational cohort (clinicaltrials.gov identifier: NCT01368289). Institutional Review Board approval was obtained. Written informed consent was obtained from each patient prior to study participation.

Two cohorts were defined according to the resection techniques applied during their respective timeframes: 1) Universal EMR algorithm (UEA): July 2008 to July 2017; 2) Selective resection algorithm (SRA): August 2017 to April 2021 (clinicaltrials.gov identifier: NCT04008407). In both the UEA and SRA, lesions with optical features of deep SMIC (≥ 1000 µm; D-SMIC; Kudo pit pattern Vn) were referred to multi-disciplinary team (MDT) review for consideration of surgery. In the UEA, all remaining LNPRPs were considered for EMR. In the SRA, LNPRPs with features consistent with superficial SMIC (< 1000µm; S-SMIC; Kudo pit pattern Vi) or with an increased risk of SMIC based on covert SMIC risk stratification (Paris 0-Is or 0-IIa+Is non-granular, Paris 0-IIa+Is

granular with a dominant nodule ≥ 10mm approximated relative to an open snare of known dimensions) underwent ESD (2). The remaining LNPRPs underwent EMR.

Procedural Details

All endoscopic procedures were performed by either a study investigator (accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their supervision. Currently, all colorectal endoscopic resections are performed using high-definition gastroscopes or colonoscopes (Olympus, Tokyo, Japan). Carbon dioxide is used for insufflation. Technical innovations in EMR and ESD were adopted as the evidence to support them emerged. Anti-platelet and anti-coagulation medications are held pre-procedure, in accordance with consensus recommendations (14).

After lesion identification, optical evaluation under high-definition white-light and narrow-band imaging is performed. Lesion location, size, Paris classification, granularity, and Kudo pit pattern classification are described in real-time.

Endoscopic Mucosal Resection

A standardized previously described inject and resect EMR technique was used (Figure 1) (15). In a systematic fashion, a submucosal cushion is created with injection of succinylated gelatin (Gelofusine; B. Braun, Bella Vista, Australia) with 0.4% indigo carmine and 1:100,000 epinephrine. Using a microprocessor-controlled generator (Endo Cut Q, Effect 3; ERBE, Tubingen, Germany)) snare excision is performed.

After complete resection, the defect is examined to ensure no neoplastic tissue remains and to assess for deep mural injury (DMI) (7). Areas of significant deep injury (DMI III-V) are subsequently treated with mechanical clips. Thermal ablation of the resection margin is performed using snare-tip soft coagulation (STSC) (Soft Coag, 80W, Effect 4) creating a 2 to 3mm rim of ablated tissue (16, 17)

Endoscopic Submucosal Dissection

With distal cap attachment (Olympus, Tokyo, Japan), a submucosal injection of succinylated gelatin with 0.4% indigo carmine and 1:100,000 epinephrine is introduced (Figure 1) (8). Marking of the margin was generally not performed. This is followed by mucosal incision (Dry Cut, 30W, Effect 2) and subsequent dissection (Swift Coag, 30W, Effect 2) underneath the lesion in the submucosal plane, using an electrosurgical knife (Dual-Knife-J; Olympus, Tokyo, Japan; Hybrid Knife; ERBE, Tubingen Germany). Dissection is most commonly performed in a retroflexed position. External traction techniques are used, where appropriate, to facilitate dissection.

After complete resection, prophylactic vessel coagulation of non-bleeding visible vessels is performed using coagulation forceps.

Post-Procedure

After procedure completion, patients are observed for 4 hours. If well, they are subsequently discharged on a clear fluid diet overnight. At 2 weeks, patients are contacted by a study coordinator and undergo a structured telephone interview to identify peri-procedural adverse events. First surveillance colonoscopy (SC1) is

performed at 6 months. During SC, patients undergo a standardized evaluation of the endoscopic resection scar. Biopsies are routinely performed.

Histopathology Evaluation

After endoscopic resection, specimens were collected and processed for histopathology review. Endoscopic submucosal dissection specimens were pinned. Histopathology review was completed by board-certified expert gastrointestinal pathologists. Cancer was defined by neoplastic invasion into the submucosa. Where appropriate, histopathology was confirmed with surgical specimen evaluation.

Data Extraction

Collected data included: 1) Patient characteristics: age, sex, American Society of Anesthesiologists (ASA) classification; 2) Lesion characteristics: size, morphology, surface granularity, Kudo pit pattern, histopathology; 3) Procedure outcomes: technical success, en bloc resection, R0 resection, curative oncologic resection, peri-procedural adverse events, recurrence, referral to surgery.

Technical success was defined as complete removal of all visible neoplastic tissue during index resection. En Bloc resection was defined as removal of all visible neoplastic tissue as a single specimen. R0 resection was defined as removal of all visible neoplastic tissue as a single specimen with negative histologic margins. Curative oncologic resection was defined as R0 resection in the absence of negative prognostic features (submucosal invasion ≥ 1000 μm, poor differentiation, lymphovascular invasion, tumor budding). Clinically significant post-endoscopic resection bleeding

(CSPEB) was defined as any bleeding after the procedure which required emergency room presentation, hospitalization, or re-intervention (endoscopy, angiography, surgery). Significant DMI, as per the Sydney DMI classification, was defined as grade III (muscularis propria injury) or grade IV/V (transmural perforation without or with contamination, respectively). Recurrence was evaluated at SC1. Study endpoints included: technical failure, death, non-curative SMIC, advanced age or comorbidities precluding ongoing SC, lost to follow-up and SC1.

Statistical Analysis

The primary outcome was the frequency of SMIC after EMR. Secondary outcomes were the frequencies of en bloc resection, R0 resection, curative oncologic resection, technical success, peri-procedural adverse outcomes (DMI III-V, CSPEB, delayed perforation), recurrence at SC1 and procedural duration. Outcomes between the SRA and the UEA were compared.

SPSS version 28 (IBM, Armonk, USA) was used for data analysis. Variables were analyzed per participant. If 2 or more eligible lesions were identified in a single participant, the largest lesion was selected for analysis. Lesions which underwent ESD, due to an out-of-protocol indication (eg. suspected D-SMIC in a non-surgical candidate), were excluded from analysis.

Continuous variables were summarized using median (interquartile range (IQR)). Categorical variables were summarized as frequencies (%). All analyses were exploratory and 2-tailed tests with a 5% significance level were used throughout. To test for association between categorical variables, the Pearson x^2 or the Fisher Exact tests

were used, where appropriate. For continuous variables, the Mann-Whitney U test was used.

Results

Between July 2008 to April 2021, 525 LNPRPs were referred for endoscopic resection (Figure 2). Forty-five LNPRPs were excluded from analysis (7 Synchronous LNPRPs, 1 synchronous cancer, 14 out of protocol ESD, 23 D-SMIC). Four hundred and eighty LNPRPs in 480 patients were included for analysis (290 UEA, 190 SRA).

Patient and Lesion Characteristics

Median patient age was 67 years (IQR 59-74 years) and 260 (54.2%) were male (Table 1). The majority of patients were ASA I-II (390, 90.1%).

Median lesion size was 40mm (IQR 30-60mm), with 120 (25.0%) located at the anorectal junction (≤ 20mm from the dentate line). Paris classification 0-IIa+Is was the most frequent morphology (273, 56.9%). Three hundred and eighty-seven (81.3%) were granular. On histopathology, the majority (323, 67.3%) were tubulovillous adenomas. High-grade dysplasia and SMIC were identified in 108 (22.5%) and 56 (11.7%), respectively. The frequencies of high-risk features are reported in Table 1.

Comparing the SRA and UEA cohorts, significant differences in ASA ($p = 0.004$) and Kudo pit pattern ($p < 0.001$) were identified.

Between the EMR vs. ESD subgroups within the SRA, significant differences in Paris classification ($p < 0.001$), granularity ($p = 0.006$), Kudo pit pattern ($p < 0.001$) and histopathology ($p < 0.001$) were identified (Supplemental Table 1).

Selective Resection vs. Universal Endoscopic Mucosal Resection Algorithms

For procedural outcomes (Table 2), when comparing the SRA vs. the UEA, significant differences in median resection duration (45 minutes, IQR 25-78 minutes vs. 29 minutes, IQR 15-50 minutes; p <0.001), margin thermal ablation of those which underwent EMR (98, 95.1% vs. 66, 22.8%; p <0.001), and SC1 recurrence (2, 1.6% vs. 40, 17.2%; p <0.001) were identified, respectively. When stratifying LNPRPs which underwent EMR and margin thermal ablation, no significant difference in recurrence between the SRA vs. the UEA was identified (1, 1.4% vs. 3, 5.2%; p = 0.321). No differences in technical success, DMI III-V, CSPEB, or delayed perforation were identified.

For oncologic outcomes (Table 3), when comparing the SRA vs. the UEA, significant differences in the frequencies of SMIC after EMR (1, 1.0% vs. 35, 12.1%; p = 0.001), en bloc resection (19, 90.5% vs. 4, 11.4%; p < 0.001), R0 resection (18, 85.7% vs. 2, 5.7%; p < 0.001), and curative oncologic resection (7, 33.3% vs. 2, 5.7%; p = 0.010) were identified, respectively. No difference in the frequency of LNPRPs with SMIC amenable to curative oncologic resection were identified (8, 38.1% vs. 12, 41.4%; p = 0.815)

Selective Resection Algorithm: Procedural Outcomes

Of the 190 LNPRPs within the SRA, 103 (54.2%) underwent EMR and 87 (45.8%) underwent ESD. Median resection duration was 45 minutes (IQR 25-78 minutes; Table 2). Technical success was achieved in 188 (98.9%) with technical failure

in 2 (1.2%): Both due to significant submucosal fibrosis. All cases were referred for MDT review or two-stage procedure.

Deep mural injury types III-V occurred in 11 (5.8%): 10 were successfully closed endoscopically with mechanical clip placement and one was left untreated due to distal location. Clinically significant post-endoscopic resection bleeding occurred in 19 (10.0%): 7 (36.8%) were managed conservatively and 12 (63.1%) underwent endoscopic re-evaluation with or without endoscopic intervention. Delayed perforation did not occur in any cases.

One hundred and forty-nine patients were eligible for SC1 (Figure 2, Table 2). One hundred and twenty-seven (85.2%) underwent surveillance colonoscopy with a median interval of 7 months (IQR 6-9 months). Recurrence was identified in 2 (1.6%). No patients were referred for surgery at SC1.

Between the EMR vs. ESD subgroups within the SRA, a significant difference in procedure duration was identified (40 minutes, IQR 25-60 minutes vs. 90 minutes, IQR 70-136 minutes; $p < 0.001$; Supplemental Table 2). No significant differences in technical success, DMI III-V, CSPEB, delayed perforation or recurrence were identified (all $p \geq 0.548$).

Selective Resection Algorithm: Oncologic Outcomes

Of the 21 LNPRPs with SMIC (Table 3) within the SRA, 20 (95.2%) were appropriately resected by ESD and 1 (4.5%) was resected by EMR (Table 4). Of those, 8 were potential candidates for curative oncologic resection (7 ESD, 1 EMR). En bloc resection and R0 resection were achieved in 19 (90.5%) and 18 (85.7%), respectively.

Three LNPRPs did not achieve R0 status: 1 due to piecemeal EMR, 2 due to deep margin positivity with SM2 depth of invasion.

Curative oncologic resection occurred in 7 (33.3%). Of the 14 non-curative resections: 1 due to piecemeal EMR, 4 due to ≥ SM2 depth of invasion, 2 due to lymphovascular invasion, 7 with ≥ 2 negative prognostic features. Among potentially curable malignant LNPRPs which underwent ESD, 100% (7/7) were cured. Within the SRA, the number of ESDs needed to cure 1 LNPRP with SMIC was 12.

Discussion

Minimally invasive endoscopic resection techniques are now the primary management strategy for early rectal neoplasia (1). This is due to the efficacy, efficiency and safety of these techniques, in contrast to the morbidity, mortality and permanent ostomy formation associated with distal colorectal surgery (3-6). Endoscopic mucosal resection is the preeminent endoscopic resection modality (1); however, a key limitation, especially in the rectum, is the risk of piecemeal resection of endoscopically curable rectal cancers. This has stimulated the development of en bloc resection techniques, such as ESD, which have the potential for organ-sparing curative oncologic resection (8). Cost-effectiveness analyses have shown that a SRA using EMR and ESD is the optimal approach (9). However, a mechanism to facilitate modality selection has not been delineated (18). To our knowledge, this study is the first to show that a rectum-specific SRA, based on real-time optical evaluation and covert SMIC risk stratification, increases the frequency of curative oncologic resection and minimizes the risk of malignant piecemeal resection for LNPRPs.

A key premise of minimally invasive endoscopic resection techniques is the avoidance of unnecessary surgery and its negative sequalae. Piecemeal resection of endoscopically curable malignant LNPRPs negates the very benefit that they are intended to provide. To avoid malignant piecemeal resection, optical evaluation of the lesion's pit and microvascular surface pattern can be used to predict SMIC prior to resection technique selection (10, 11). However, in a recent prospective trial of 343 LNPCPs, its sensitivity and specificity for SMIC was 78.7% and 94.2%, respectively (10). To mitigate the risk of invisible or covert SMIC, in a multicenter prospective cohort of 2277 LNPCPs, after excluding lesions with optical features of SMIC, size, distal location, non-granularity and 0-Is and 0-IIa+Is morphology were significantly associated with SMIC on multivariable logistic regression analysis (2). Furthermore, a high covert SMIC risk group was identified (0-Is or 0-IIa+Is non-granular, distal 0-IIa+Is granular). In this study, using analogous optical evaluation and covert SMIC risk stratification criteria, only 1 (1.0%) malignant LNPRP underwent piecemeal resection within the SRA. This is a pivotal advance in the application of minimally invasive endoscopic resection techniques. It demonstrates an effective approach to optical evaluation; thereby, delineating which LNPRPs can be effectively, efficiently and safely managed by EMR compared to those which may derive benefit from ESD.

Due to the procedural complexity of ESD and the onus to optimize endoscopy resource utilization, ESD should be reserved for lesions with suspected S-SMIC or a heightened risk of SMIC based on covert SMIC risk stratification (19). From a recent systematic review and meta-analysis, the frequency of en bloc and R0 resection after colorectal ESD was 91.0% and 82.9% respectively (20), with this study showing

comparable results. However, it is imperative to understand that R0 resection while being a core component of the definition of a curative oncologic resection is just that, only a component. It does not fully address depth of submucosal invasion or the absence of other evidence-based prognostic features such as poor differentiation, lymphovascular invasion or tumor budding (21). This highlights another important finding of this study, which is the frequency of curative resection after ESD. At 33.3%, this represents a critical improvement in patient outcomes and the application of minimally invasive endoscopic resection techniques; especially when taking into consideration the potential negative ramifications of distal colorectal surgery (3) and evidence showing that endoscopic resection does not impair subsequent surgical intervention (22). As the impact of negative histologic features on the risk of recurrent disease is better understood, as facilitated by the evaluation of outcomes after non-curative endoscopic resection, it is anticipated that the definition of curative oncologic resection will be refined (23). Moreover, with the emerging role of neoadjuvant/adjuvant chemoradiation therapy, the frequency of curative resection with increase; thus reinforcing the importance of appropriate patient selection and its anticipated evolution over time.

Concerning procedure outcomes, a significant difference in recurrence at SC1 was identified (SRA 2, 1.6% vs. UEA 40, 17.2%; $p < 0.001$). Although this can in part be attributed to ESD, which has historically been associated with a lower frequency of recurrence (20), a key driver is margin thermal ablation. In a multi-center randomized trial, SC1 recurrence was significantly reduced for LNPCPs which received margin thermal ablation (5% vs. 21%; $p < 0.001$) (16); with no adverse events. These findings

have now been reproduced, and with experience improved upon, in an international multi-center validation cohort of over 1000 LNPCPs (17). Recurrence was 1.4% of those receiving complete margin thermal ablation. Moreover, these results have also been reproduced for complex lesion subgroups such as previously attempted LNPCPs (5) as well as those at the anorectal junction (4) and the ileocecal valve (6). When comparing the SRA and the EUA for only those lesions which underwent margin thermal ablation, no significant difference in SC1 recurrence was identified. Taking these findings together, margin thermal ablation should now be viewed as an integral component of high-quality EMR and should be universally applied.

This study is not without limitations. The analysis was undertaken at a single expert center in minimally invasive endoscopic resection techniques. Therefore, reproducibility of these findings is needed. As the study was completed across different time periods, it is susceptible to selection bias due to changes in practice over time. This is demonstrated by the differences in ASA and Kudo pit pattern classification between the UEA and SRA; likely highlighting that in the UEA patients with concerning optical features were more likely to be referred to surgery alongside an inclination towards endoscopic resection for patients with comorbid disease within the SRA. Lastly, alternative en bloc resection techniques for malignant LNPRPs were not evaluated, such as endoscopic full-thickness resection (EFTR) or trans-anal endoscopic surgery (TES); the latter of which is currently being evaluated in randomized control trials.

In conclusion, a rectum-specific SRA, based on real-time optical evaluation and covert SMIC risk-stratification, effectively negates the risk of piecemeal resection of malignant LNPRPs and increases the frequency of curative oncologic resection. This

highlights another critical advance in the management of LNPRPs with the continued

refinement of their clinical trajectory through the avoidance of unnecessary surgery.

Future algorithm refinement is anticipated, such as LNPRP size and morphology criteria

as well as through further understanding of the curative potential of piecemeal EMR;

therefore, potentially optimizing the utilization of EMR given its proven efficacy,

efficiency and safety. Nevertheless, it is imperative to develop tissue resection centers

with expertise not only in the application of minimally invasive resection techniques but

optical evaluation and covert SMIC risk stratification. Moreover, all endoscopists must

embrace the expanding role of these resection techniques and a SRA with referral of

LNPRPs to a tissue resection center prior to referral for surgery.

Table 1: Patient and Lesion Characteristics

	Overall LNPRPs (N = 480, %)	UEA LNPRPs (N = 290, %)	SRA LNPRPs (N = 190, %)	P-value
Age, years (median, IQR)	67 (59-74)	66 (58-75)	67 (60-74)	0.602
Male sex (n, %)	260 (54.2)	167 (57.6)	93 (48.9)	0.063
ASA (n, %)*				**0.004**
I-II	390 (90.1)	234 (93.6)	156 (85.2)	
III	43 (9.9)	16 (6.4)	27 (14.8)	
Size, mm (median, IQR)	40 (30-60)	45 (35-60)	40 (30-60)	0.810
Location (n, %)				0.106
Anorectal junction	120 (25.0)	65 (22.4)	55 (28.9)	
Rectum	360 (75.0)	225 (77.6)	135 (71.1)	
Paris classification (n, %)				0.420
0-Is	58 (12.1)	38 (13.1)	20 (10.5)	
0-IIa	134 (27.9)	77 (26.6)	57 (30.0)	
0-IIb	4 (0.8)	4 (1.4)	0 (0.0)	
0-IIa+Is	273 (56.9)	165 (56.9)	108 (56.8)	
Any 0-IIc	11 (2.3)	6 (2.1)	5 (2.6)	
Granularity (n, %)**				0.862
Granular	387 (81.3)	232 (80.8)	155 (82.0)	
Non-granular	55 (11.6)	33 (11.5)	22 (11.6)	
Mixed	34 (7.1)	22 (7.7)	12 (6.3)	
Kudo Pit Pattern (n, %)				**<0.001**
I-II	10 (2.1)	8 (2.8)	2 (1.1)	
III-IV	438 (91.3)	274 (94.5)	164 (86.3)	
Vi	32 (6.7)	8 (2.8)	24 (12.6)	
Histopathology (n, %)				0.864
Tubular adenoma	49 (10.2)	28 (9.7)	21 (11.1)	
Tubulovillous adenoma	323 (67.3)	196 (67.6)	127 (66.8)	
Villous adenoma	9 (1.9)	5 (1.7)	4 (2.1)	
Serrated	12 (2.5)	9 (3.1)	3 (1.6)	
Submucosal invasive cancer	56 (11.7)	35 (12.1)	21 (11.1)	
Other	31 (6.5)	17 (5.9)	14 (7.4)	
High-grade dysplasia (n, %)	108 (22.5)	62 (21.4)	46 (24.2)	0.468
High-risk features (n, %)**				
Depth of invasion ≥ SM2	25 (50.0)	15 (51.7)	10 (47.6)	0.774
Poor differentiation	10 (20.0)	5 (17.2)	5 (23.8)	0.723
Lymphovascular invasion	8 (16.0)	5 (17.2)	3 (14.3)	1.000
Tumor budding	7 (14.0)	3 (10.3)	4 (19.0)	0.434

ASA, American Society of Anesthesiologists; IQR, interquartile range; LNPRP, large non-pedunculated rectal polyp; SRA, selective resection algorithm; UEA, universal EMR algorithm

*47 participants ASA not classified; **4 participants granularity not classified;
***Denominator: LNPRPs with SMIC. 6 participants incomplete high-risk feature reporting

Table 2: Procedural Outcomes

	Overall LNPRPs (N = 480 %)	UEA LNPRPs (N = 290, %)	SRA LNPRPs (N = 190, %)	P-value
Duration, min (median, IQR)*	30 (15-60)	29 (15-50)	45 (25-78)	**<0.001**
Technical success (n, %)	468 (97.5)	280 (96.6)	188 (98.9)	0.137
Margin thermal ablation (n, %)**	164 (41.7)	66 (22.8)	98 (95.1)	**<0.001**
Deep mural injury III-V (n, %)	23 (4.8)	12 (4.1)	11 (5.8)	0.407
CSPEB (n, %)	40 (8.3)	21 (7.2)	19 (10.0)	0.285
Delayed perforation (n, %)	1 (0.2)	1 (0.3)	0 (0.0)	1.000
SC1				
Eligible (n)	393	244	149	
Underwent SC1 (n, %)	360 (91.6)	233 (95.5)	127 (85.2)	**<0.001**
Months to SC1 (median, IQR)	6 (5-8)	5 (4-7)	7 (6-9)	**<0.001**
Recurrence	42 (11.7)	40 (17.2)	2 (1.6)	**<0.001**

CSPEB, clinically significant post-endoscopic resection bleeding; IQR, interquartile range; LNPRP, large non-pedunculated rectal polyp; Min, minutes; SC1, surveillance colonoscopy 1; SRA, selective resection algorithm; UEA, universal EMR algorithm
*116 participants duration not classified
**Denominator: LNPRPs which underwent EMR

Table 3: Oncologic Outcomes

	Overall LNPRPs (N = 56, %)	UEA LNPRPs (N = 35, %)	SRA LNPRPs (N = 21, %)	P-value
SMIC after EMR*	36 (9.2)	35 (12.1)	1 (1.0)	**0.001**
En Bloc Resection	23 (41.1)	4 (11.4)	19 (90.5)	**<0.001**
R0 Resection	20 (35.7)	2 (5.7)	18 (85.7)	**<0.001**
Curative Resection	9 (16.1)	2 (5.7)	7 (33.3)	**0.010**

EMR, endoscopic mucosal resection; LNPRP, large non-pedunculated rectal polyp; SMIC, submucosal invasive cancer; SRA, selective resection algorithm; UEA, universal EMR algorithm
*Denominator: LNPRPs which underwent EMR

Supplemental Table 1: Patient and Lesion Characteristics within the Selective Resection Algorithm

	SRA LNPRPs (N = 190, %)	LNPRPs - EMR (N = 103, %)	LNPRPs - ESD (N = 87, %)	P-value
Age, years (median, IQR)	67 (60-74)	67 (61-73)	68 (58-74)	0.698
Male sex (n, %)	93 (48.9)	50 (48.5)	43 (49.4)	0.904
ASA (n, %)*				0.390
I-II	156 (85.2)	89 (87.3)	67 (82.7)	
III	27 (14.8)	13 (12.7)	14 (17.3)	
Size, mm (median, IQR)	40 (30-60)	40 (30-60)	50 (35-70)	0.071
Location (n, %)				0.062
Anorectal Junction	55 (28.9)	24 (23.3)	31 (35.6)	
Rectum	135 (71.1)	79 (76.7)	56 (64.4)	
Paris classification (n, %)				**<0.001**
0-Is	20 (10.5)	15 (14.6)	5 (5.7)	
0-IIa	57 (30.0)	40 (38.8)	17 (19.5)	
0-IIb	0 (0.0)	0 (0.0)	0 (0.0)	
0-IIa+Is	108 (56.8)	48 (46.6)	60 (69.0)	
Any 0-IIc	5 (2.6)	0 (0.0)	5 (5.7)	
Granularity (n, %)**				**0.006**
Granular	155 (82.0)	92 (90.2)	63 (72.4)	
Non-granular	22 (11.6)	7 (6.9)	15 (17.2)	
Mixed	12 (6.3)	3 (2.9)	9 (10.3)	
Kudo Pit Pattern (n, %)				**<0.001**
I-II	2 (1.1)	2 (1.9)	0 (0.0)	
III-IV	164 (86.3)	101 (98.1)	63 (72.4)	
Vi	24 (12.6)	0 (0.0)	24 (27.6)	
Histopathology (n, %)				**<0.001**
Tubular adenoma	21 (11.1)	16 (15.5)	5 (5.7)	
Tubulovillous adenoma	127 (66.8)	76 (73.8)	51 (58.6)	
Villous adenoma	4 (2.1)	1 (1.0)	3 (3.4)	
Serrated	3 (1.6)	2 (1.9)	1 (1.1)	
Submucosal invasive cancer	21 (11.1)	1 (1.0)	20 (23.0)	
Other	14 (7.4)	7 (6.8)	7 (8.0)	
High-grade dysplasia (n, %)	46 (24.2)	24 (23.3)	22 (25.3)	0.750

ASA, American Society of Anesthesiologists; IQR, interquartile range; LNPRP, large non-pedunculated rectal polyp

*7 participants ASA not classified; **1 participant granularity not classified

Supplemental Table 2: Patient Outcomes within the Selective Resection Algorithm

	SRA LNPRPs (N = 190, %)	LNPRPs - EMR (N = 103, %)	LNPRPs - ESD (N = 87, %)	P-value
Duration, min (median, IQR)*	45 (25-78)	40 (25-60)	90 (70-136)	**<0.001**
Technical success (n, %)	188 (98.9)	102 (99.0)	86 (98.9)	1.000
Margin thermal ablation (n, %)**	98 (95.1)	98 (95.1)	NA	NA
Deep mural injury III-V (n, %)	11 (5.8)	5 (4.9)	6 (6.9)	0.548
CSPEB (n, %)	19 (10.0)	10 (9.7)	9 (10.3)	0.884
Delayed perforation (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	NA
SC1				
Eligible (n)	149	90	59	
Underwent SC1 (n, %)	127 (85.2)	76 (84.4)	51 (86.4)	0.737
Months to SC1 (median, IQR)	7 (6-9)	8 (6-10)	7 (6-8)	**0.007**
Recurrence	2 (1.6)	1 (1.3)	1 (2.0)	1.000

CSPEB, clinically significant post-endoscopic resection bleeding; IQR, interquartile range; LNPRP, large non-pedunculated rectal polyp; Min, minutes; SC1, surveillance colonoscopy 1

*85 participants duration not classified

**Denominator: LNPRPs which underwent EMR
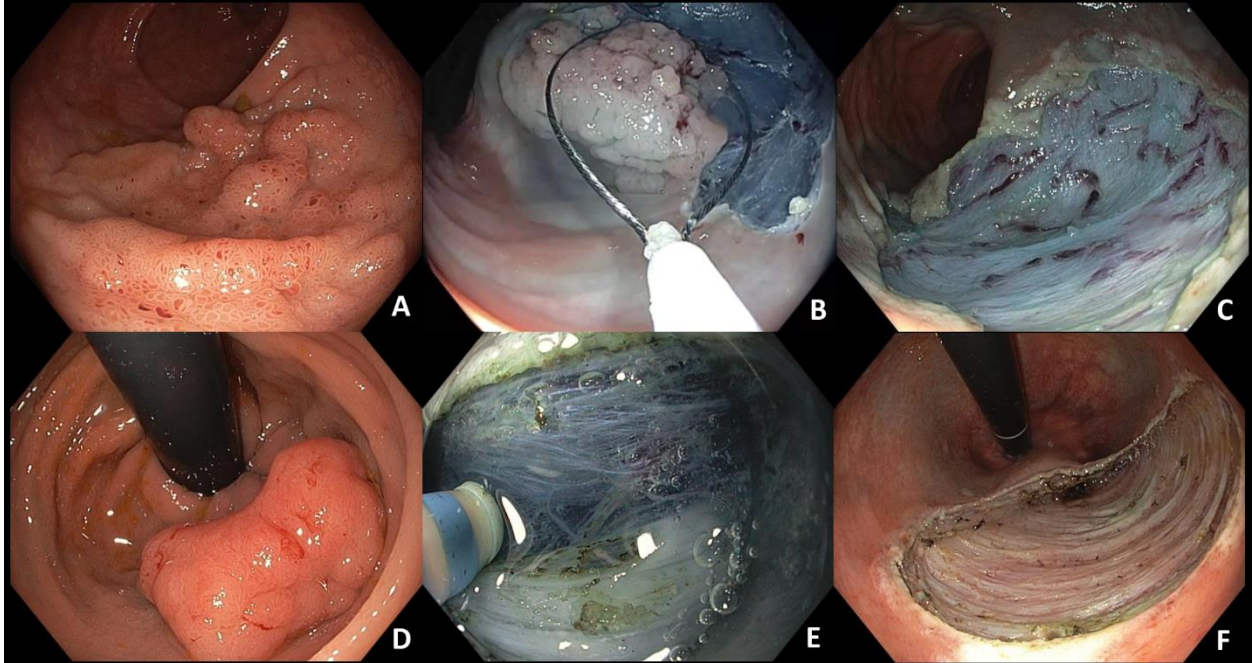
Figure 1. Minimally Invasive Endoscopic Resection Techniques. A-C: Endoscopic

mucosal resection; **D-F:** Endoscopic submucosal dissection
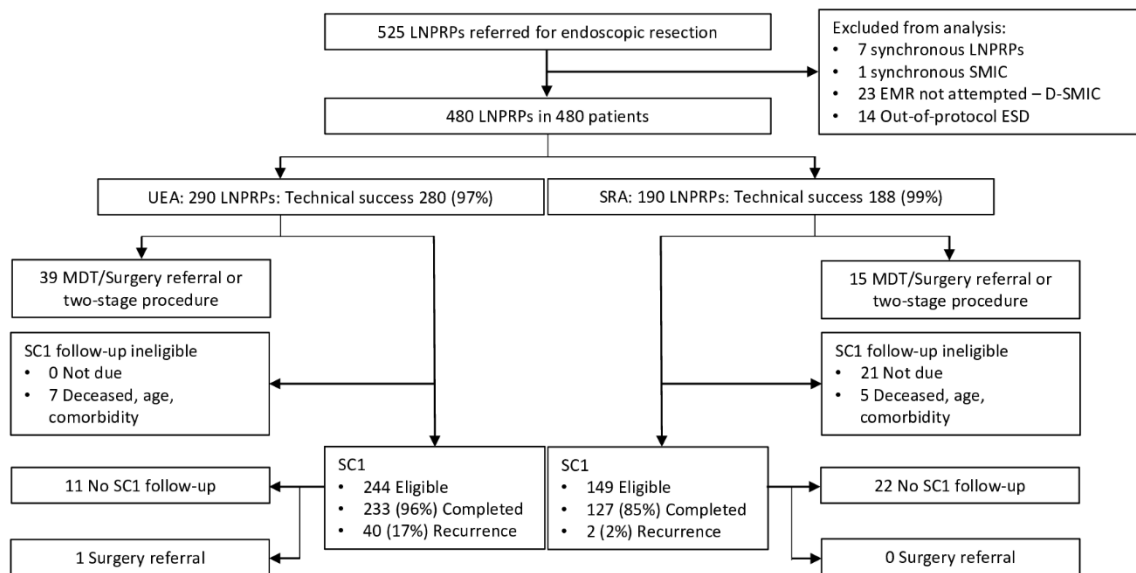
Figure 2. Flow Diagram of Consecutive Large Non-Pedunculated Rectal Polyps referred for Endoscopic Resection.

D-SMIC, deep submucosal invasive cancer; ESD, endoscopic submucosal dissection; LNPRP, large non-pedunculated rectal polyp; MDT, multi-disciplinary team; SC1, surveillance colonoscopy 1; SMIC, submucosal invasive cancer; SRA, selective resection algorithm; UEA, universal EMR algorithm

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Chapter 3: Previously attempted large non-pedunculated colorectal polyps are effectively managed by endoscopic mucosal resection

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Summary: In comparing 158 previously attempted large non-pedunculated colorectal polyps (PA-LNPCPs) to 1134 naïve LNPCPs (N-LNPCPs) which underwent endoscopic mucosal resection (EMR), we demonstrated high technical success with no difference in adverse events or recurrence. Importantly, margin thermal ablation was able to mitigate the frequency of recurrence establishing EMR as a first line treatment strategy for recalcitrant LNPCPs.

Previously attempted large non-pedunculated colorectal polyps are effectively managed by endoscopic mucosal resection

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Conflicts of Interest Disclosure

Abbreviations

ACE, Australian Colonic Endoscopic Resection

ASA, American Society of Anesthesiologists

CAST, cold-forceps avulsion with adjuvant snare-tip soft coagulation

CSPEB, clinically significant post-endoscopic mucosal resection bleeding

CSIPB, clinically significant intra-procedural bleeding

DMI, deep mural injury

EMR, endoscopic mucosal resection

ESD, endoscopic submucosal dissection

EFTR, endoscopic full-thickness resection

IQR, interquartile range

LNPCP, large non-pedunculated colorectal polyp

MDT, multi-disciplinary team

NBI, narrow-band imaging

N-LNPCP, naïve large non-pedunculated colorectal polyp

PA-LNPCP, previously attempted large non-pedunculated colorectal polyp

P-CSP, piecemeal cold-snare polypectomy

SC, surveillance colonoscopy

SMIC, submucosal invasive cancer

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

STSC, snare-tip soft coagulation

TSC, topical submucosal chromoendoscopy

Study Highlights

What is known

- Limited data exists concerning the management of previously attempted large (≥ 20mm) non-pedunculated colorectal polyps (PA-LNPCPs).

- The best approach for the treatment of PA-LNPCPs is unknown.

What is new here

- High technical success and low recurrence frequencies are achievable with EMR for PA-LNPCPs. However, auxiliary techniques such as cold-forceps avulsion with adjuvant snare-tip soft coagulation and margin thermal ablation are required.

Abstract

Objective: Endoscopic mucosal resection (EMR) is an effective therapy for naïve large non-pedunculated colorectal polyps (N-LNPCPs). The best approach for the treatment of previously attempted LNPCPs (PA-LNPCPs) is undetermined.

Methods: EMR performance for PA-LNPCPs was evaluated in a prospective observational cohort of LNPCPs ≥ 20mm. Efficacy was measured by technical success (removal of all visible polypoid tissue during index EMR) and recurrence at first surveillance colonoscopy (SC1). Safety was assessed by clinically significant intra-procedural bleeding, deep mural injury types III-V, clinically significant post-EMR bleeding and delayed perforation.

Results: From January-2012 to October-2019, 158 PA-LNPCPs and 1134 N-LNPCPs underwent EMR. Median PA-LNPCP size was 30mm (IQR 25-46mm). Technical success was 93.0% and increased to 95.6% after adjusting for two-stage EMR. Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) was required for non-lifting polypoid tissue in 73 (46.2%). Median time to SC1 was 6 months (IQR 5-7 months). Recurrence occurred in 9 (7.8%). No recurrence was identified among 65 PA-LNPCPs which underwent margin thermal ablation at SC1 vs. 9 (18.0%; $p<0.001$) which did not. There were significant differences in resection duration (35 minutes vs. 25 minutes; $p<0.001$), technical success (93.0% vs. 96.6%; $p=0.026$) and use of CAST (46.2% vs. 7.6%; $p<0.001$), between PA-LNPCPs and N-LNPCPs. When adjusting for two-stage EMR, no difference in technical success was identified (95.6% vs. 97.8%; $p=0.100$). No differences in adverse events or recurrence were identified.

Conclusion: Endoscopic mucosal resection, using auxiliary techniques where necessary, can achieve high technical success and low recurrence frequencies for PA-LNPCPs.

Introduction

Endoscopic mucosal resection (EMR) is advocated as the preferred treatment strategy for large (≥ 20mm) non-pedunculated colorectal polyps (LNPCPs) by international consensus guidelines (1, 2). These recommendations are based on high-quality evidence showing that EMR can effectively, efficiently and safely manage the vast majority of LNPCPs (3-6). Moreover, EMR is safer, less resource intensive and less expensive than surgery or endoscopic submucosal dissection (ESD) (7-9).

A requisite to successful EMR is submucosal fluid expansion to allow for effective and safe tissue capture. Prior attempts at endoscopic resection, which occurs in upwards of 16% of LNPCP referrals (10), invariably precipitate fibrosis and potentially obliterate the submucosal plane. This may render these lesions recalcitrant to subsequent EMR and prompts the need for advanced resection techniques such as ESD, endoscopic full-thickness resection (EFTR) and surgery; all of which increase costs and carry a greater risk of adverse events (11-13).

Auxillary techniques to complement EMR and treat non-lifting polypoid tissue have been described (14-18). However, the majority of evaluations are small single-arm retrospective cohorts which focus on technique description. There is limited evidence concerning the overall management of previously attempted LNPCPs (PA-LNPCPs). Moreover, critical advancements designed to mitigate EMR-related adverse outcomes, such as margin thermal ablation to prevent recurrence, have not been assessed (19). Therefore, we sought to evaluate EMR outcomes for PA-LNPCPs, in comparison to naïve LNPCPs (N-LNPCPs), in a single-center prospective observational cohort.

Methods

This manuscript is in keeping with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (20).

Study Design

Consecutive patients enrolled at single center between January 2012 to October 2019 were evaluated as part of a prospectively collected, observational cohort of patients referred for managing LNPCPs ≥ 20mm (clinicaltrials.gov identifier: NCT01368289). Institutional Review Board approval was obtained. Written informed consent was obtained from each patient prior to study participation.

Previously attempted LNPCPs were defined as those where the referring endoscopist had attempted endoscopic resection (either by conventional polypectomy or EMR) but was unable to successfully remove all visible polypoid tissue. All other lesions were considered naïve LNPCPs.

Endoscopic Mucosal Resection Technique

All endoscopic procedures were performed by a study investigator (accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal EMR) or a senior interventional endoscopy fellow under supervision. Technical innovations in EMR were adopted as the evidence to support them emerged. Anti-platelet and anti-coagulation medications were held pre-procedure, in accordance with consensus recommendations (21).

A standardized previously described inject and resect EMR technique was used

(22). Currently, all colorectal EMRs are performed using high-definition Olympus 190

series variable-stiffness colonoscopes (Olympus, Tokyo, Japan). Carbon dioxide is

used for insufflation (23). After lesion identification, optical evaluation under high-

definition white-light and narrow-band imaging (NBI) is performed to exclude features of

submucosal invasive cancer (SMIC). In a systematic fashion, a submucosal cushion is

created with injection of succinylated gelatin (Gelofusine; B. Braun, Bella Vista,

Australia) (24) with 0.4% indigo carmine and 1:100,000 epinephrine. Using a

microprocessor-controlled generator (ERBE VIO ENDO CUT Q, Effect 3 (ERBE,

Tubingen, Germany)) snare excision is performed.

After complete resection, the defect is carefully examined to ensure no polypoid

tissue remains and to assess for deep mural injury (DMI) (25). Areas of significant deep

injury (DMI III-V) are subsequently treated by mechanical clip closure. Thermal ablation

of the resection margin to mitigate the risk of recurrence is performed using snare-tip

soft coagulation (STSC) (ERBE VIO SOFT COAG: 80W, Effect 4) to create a 2 to 3mm

rim of ablated tissue (19). Clinically significant intra-procedural bleeding (CSIPB) is

treated with coagulation forceps or mechanical hemostasis. Resection specimens are

collected and evaluated by specialist gastrointestinal pathologists. Where appropriate,

histopathology was confirmed with surgical specimen evaluation.

After completion of the procedure, patients are observed for 4 hours. If well, they

are subsequently discharged on a clear fluid diet overnight. At 2 weeks, patients are

contacted by a study coordinator and undergo a structured telephone interview to

identify peri-procedural adverse events. Intervals between subsequent colonoscopies

are at the discretion of the endoscopist performing surveillance with recommended first

surveillance colonoscopy (SC1) at 6 months. During SC, patients undergo a

standardized evaluation of the EMR scar (26). Biopsies are routinely performed.

Technical aspects specific to PA-LNPCPs and non-lifting polypoid tissue are as

follows (Figures 1-3, Supplemental Video 1) (15):

1. **Scar identification:** Prior to commencing tissue resection, optical evaluation

    is performed to identify intra-lesional or adjacent scarring consistent with

    previously attempted resection.

2. **Endoscopic mucosal resection:** All lifting polypoid tissue is first removed.

    This is to isolate non-lifting polypoid tissue and free its lateral margins. Often

    normal mucosa at the margin of the lesion is removed to allow entry into the

    submucosal plane. Once isolation is achieved, EMR can be attempted with

    caution, bearing in mind the increased risk of DMI associated with

    submucosal fibrosis. Luminal gas is completely aspirated during snare

    closure. This is to decrease colorectal wall tension and facilitate tissue

    capture. After each successful resection, the EMR defect is carefully

    evaluated for DMI. If an unstained area of submucosa is exposed topical

    submucosal chromoendoscopy (TSC) is performed to facilitate DMI detection

    (27).

3. **Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST):**

    If EMR is not appropriate for or is unsuccessful at removing the non-lifting

    scarred residual polypoid tissue, it is meticulously and systematically avulsed

with cold forceps (Radial Jaw Biopsy Forceps; Boston Scientific, Massachusetts, USA). The exposed submucosa of the avulsion site and its margins are then treated with STSC (ERBE VIO SOFT COAG: 80W, Effect 4) as previously described (15). Type II DMI is frequently seen post-CAST and prophylactic mechanical clips are placed to mitigate the small risk of delayed perforation (25).

Data Extraction

Collected data included: 1) Patient characteristics: age, sex, American Society of Anesthesiologists (ASA) classification; 2) Lesion characteristics: size, morphology, surface granularity, Kudo pit pattern, histopathology; 3) Procedure outcomes: technical success, peri-procedural adverse events, recurrence.

Technical success was defined as complete removal of all visible polypoid tissue during index EMR. Clinically significant intra-procedural bleeding was defined by oozing or spurting blood loss for ≥ 60 seconds, not responding to water jet irrigation and requiring either coagulation forceps or mechanical hemostasis. Clinically significant post-EMR bleeding (CSPEB) was defined as any bleeding which occurred after the procedure and required emergency room presentation, hospitalization, or re-intervention (endoscopy, angiography, surgery). Significant deep mural injury was defined as grade III (muscularis propria injury, specimen target sign, defect target sign) or grade IV/V (transmural perforation without or with contamination, respectively). Recurrence was evaluated at SC1. Study endpoints included: technical failure, SMIC, death, advanced age or comorbidities precluding ongoing SC, lost to follow-up and SC1.

Statistical Analysis

The primary outcome was technical success. Secondary outcomes were resection duration, use of CAST, peri-procedural adverse events (CSIPB, DMI III-V, CSPEB, delayed perforation) and recurrence (stratified by those who received margin STSC). Previously attempted LNPCPs were compared to N-LNPCPs.

SPSS version 26.0 (IBM, Armonk, USA) was used for data analysis. Variables were analyzed per participant. If 2 or more eligible lesions were identified in a single participant, the largest lesion was selected for analysis. Lesions which underwent ESD, due to a heightened risk of SMIC based SMIC risk stratification, or piecemeal cold-snare polypectomy (P-CSP) were excluded from analysis.

Continuous variables were summarized using median (interquartile range (IQR)). Categorical variables were summarized as frequencies (%). All analyses were exploratory and 2-tailed tests with a 5% significance level were used throughout. To test for association between categorical variables, the Pearson x^2 or the Fisher Exact tests were used, where appropriate. For continuous variables, the Mann-Whitney U test was used.

Results

From January 2012 to October 2019, 1649 LNPCPs were referred for endoscopic resection (Figure 4). Three hundred and fifty-seven LNPCPs were excluded from analysis (110 resected by ESD or P-CSP as part of alternative research protocols, 168 synchronous lesions, 79 EMR not attempted due to concern for SMIC or technical

reasons). One thousand two-hundred and ninety-two LNPCPs (158 PA-LNPCPs, 1134 N-LNPCPs) in 1292 patients were included for analysis.

Patient and Lesion Characteristics

One-hundred and fifty-eight PA-LNPCPs underwent EMR in 158 patients (Table 1). Median patient age was 70 years (IQR 62 to 76 years) and 90 (57.0%) were male. The majority of patients were ASA I (48, 35.3%) or ASA II (66, 48.5%).

Median lesion size was 30mm (IQR 25 to 46mm). Paris classification 0-IIa was the most frequent morphology (89, 56.3%). Sixty-one (39.1%) PA-LNPCPs were non-granular or mixed.

Procedure Outcomes

Median resection duration was 35 minutes (IQR 25 to 60 minutes) (Table 2). Technical success was achieved in 147 (93.0%). From May 2016 thermal ablation to the post-EMR margin was routinely performed, comprising 81 lesions (51.3%). Cold-forceps avulsion with adjuvant snare-tip soft coagulation was required in 73 (46.2%). Technical success was not achieved in 11 (7.0%): 1 submucosal fibrosis secondary to SMIC, 1 involvement of the ileocecal valve and DMI IV with successful mechanical clip closure, 2 intra-procedural identification of intra-diverticular extension, 3 extensive submucosal fibrosis and difficult positioning. All cases were referred to multi-disciplinary team (MDT) review for consideration of surgery. In the remaining 4 cases, two-stage EMR was performed as previously described (28) with technical success achieved in all 4 cases. Adjusting for successful two-stage EMR, technical success was achieved in

151 (95.6%). Six (3.8%) patients required hospital admission: 2 observation after extensive endoscopic resection, 1 post-procedure pain, 1 CSPEB, 2 DMI III-V.

The majority (88, 55.7%) of PA-LNPCPs were tubulovillous adenomas. Submucosal invasive cancer and high-grade dysplasia were identified in 12 (7.6%) and 16 (10.1%), respectively. All PA-LNPCPs with SMIC were subsequently referred to MDT review for consideration of surgery.

Adverse Events

Clinically significant intra-procedural bleeding occurred in 11 (7.0%). Endoscopic hemostasis was achieved in all cases by coagulation forceps (7, 63.6%) or mechanical clip placement (4, 36.4%). Deep mural injury III-V was identified in 4 (2.5%) and all were successfully closed endoscopically with mechanical clip placement.

Clinically significant post-EMR bleeding occurred in 13 (8.2%): 10 (76.9%) were managed conservatively and 3 (23.1%) underwent endoscopic re-evaluation with or without endoscopic intervention. Delayed perforation did not occur in any cases.

Recurrence

One hundred and twenty-seven patients were eligible for SC1 (Figure 4, Table 2). One-hundred and fifteen (90.6%) underwent surveillance colonoscopy with a median interval of 6 months (IQR 5 to 7 months). Recurrence was identified in 9 (7.8%). No patients were referred for surgery at SC1.

In 65 PA-LNPCPs which received margin STSC, no recurrence was identified vs. 9 (18.0%; p < 0.001) which did not undergo margin STSC (Table 3). On further sub-

analysis, in 39 PA-LNPCPs where CAST was used and margin STSC was performed, no recurrence was identified vs. 5 (31.3%; p = 0.001) which did not receive margin STSC (Table 4).

Comparison with Naïve Large Non-Pedunculated Colorectal Polyps

Between PA-LNPCPs and N-LNPCPs, there were significant differences in resection duration (35 minutes vs. 25 minutes; p < 0.001), technical success (93.0% vs. 96.6%; p = 0.026) and the use of CAST (46.2% vs. 7.6%; p < 0.001), respectively. When adjusting for two-stage EMR, no difference in technical success was identified (95.6% vs. 97.8%; p = 0.100). No differences in CSIPB, DMI III-V, CSPEB, delayed perforation, or recurrence were identified.

Discussion

Evidence-based innovations in minimally invasive endoscopic resection techniques have transformed the management of LNPCPs. Site-specific technical modifications in high-quality EMR can effectively and safely treat circumferential LNPCPs (5) and those involving the ileocecal valve (3), the appendiceal orifice (4) and the anorectal junction (6). Moreover, complementary techniques and management strategies such as margin thermal ablation (19), DMI classification (25) and two-stage EMR (28) have largely mitigated recurrence, perforation, and technical failure, respectively. This study demonstrates another major advance. Endoscopic mucosal resection, in combination with margin thermal ablation and CAST where necessary, can achieve high technical success and low recurrence frequencies for PA-LNPCPs.

Snare-based resection techniques are inherently limited in removing non-lifting polypoid tissue as they are predicated on submucosal expansion to achieve tissue capture. In this study, complete removal of all polypoid tissue was achieved in 93.0% of PA-LNPCPs at index EMR. This can be largely attributed to CAST, which was required in 46.2% of cases. As CAST is based on equipment (biopsy forceps, snare) available in all endoscopy units and techniques (cold avulsion, STSC) familiar to endoscopists who perform colorectal EMR, it represents an easily adoptable auxiliary technique. With no difference in adverse outcomes compared to N-LNPCPs, these results further cement CAST as an essential technique for treating non-lifting polypoid tissue. Of note, a significant difference in technical success was identified between PA-LNPCPs and N-LNPCPs (93.0% vs. 96.6%; p = 0.026). While statistically significant, this difference may not be clinically meaningful. Moreover, when affording for two-stage EMR, technical success increased to 95.6% and no difference compared to N-LNPCPs was identified (p = 0.100). Therefore, EMR should be considered a first-line strategy for the treatment of PA-LNPCPs.

A critical advance in high-quality EMR technique is the ability of margin thermal ablation to prevent recurrence. In a randomized control trial, margin STSC decreased recurrence at SC1 from 21.0% to 5.2% (p < 0.001) (19). These results have been reproduced in LNPCPs involving the anorectal junction (6), which represents another complex lesion subgroup, as well as in North American cohorts (29). In this study, among 65 PA-LNPCPs which received margin STSC and underwent SC1, no recurrence was identified vs. 9 (18.0%; p < 0.001) which did not receive margin STSC. Similarly, in 39 PA-LNPCPs where CAST and margin STSC were performed, no

recurrence was identified vs. 5 (31.3%; p = 0.001) which did not receive margin STSC. Given these findings, margin thermal ablation should be viewed as an integral component of high-quality EMR. It should be universally applied independent of lesion complexity, consistent with current international guidelines (1).

Alternative auxiliary techniques have been developed for the management of non-lifting polypoid tissue including: 1) ablative techniques, 2) hot avulsion; and 3) curetting techniques. Ablative modalities, including argon plasma coagulation and STSC, when used for visible polypoid tissue are associated with a substantial risk of recurrence (10). Moreover, they preclude histopathology assessment. In the era of effective auxillary techniques, ablative techniques should be discouraged. Hot avulsion is a comparative technique to CAST, except that hot biopsy forceps with cutting current are used to avulse the area of concern. In a recent retrospective analysis of 112 lesions which required hot avulsion compared to 425 which did not, no difference in recurrence or adverse events were identified (all p > 0.15) (16). Although hot avulsion appears effective the frequency of recurrence was 17.5%, in comparison to 0% of lesions in this study which received CAST and margin STSC. To appropriately compare hot avulsion and CAST, a comparative analysis in the era of margin thermal ablation is therefore needed. The EndoRotor (Interscope Medical, Worcester, USA) is a novel through-the-scope non-thermal curetting device. In a pilot study of 19 rectosigmoid polyps, technical success was 52.6% after one attempt and increased to 84.1% after two attempts (30). Although a recent retrospective analysis of 28 colorectal lesions has shown more promising results (17), further evaluation of this new technology should be within the confines of a well-designed research study.

Endoscopic submucosal dissection, including hybrid techniques, and EFTR have also been evaluated (13, 18). While ESD continues to be adopted by western endoscopy centers, it is imperative to remember that the benefit of ESD is largely derived from its ability to perform R0 and therefore curative resections for superficially invasive SMIC. As with EMR, ESD is dependent on submucosal expansion. Therefore, ESD for PA-LNPCPs is extremely challenging, even in expert hands, with a heightened risk of adverse events and may not be appropriate for the current western skillset. Endoscopic full-thickness resection is a logical solution for non-lifting polypoid tissue as it circumvents the need for submucosal expansion. In a prospective multi-center study, which included 104 non-lifting lesions, EFTR showed promising results (13). However, the frequency of emergency surgery was 2.2%. Therefore, as safer alternatives for PA-LNPCPs exist, EFTR should be reserved for lesions unamenable to avulsion techniques.

This study is not without limitations. It is a single center analysis. Moreover, as the study was performed at an expert center in minimally invasive tissue resection techniques, reproducibility of these results in other centers are needed. Time between previous attempt by the referring endoscopist and index EMR was not quantified. Furthermore, comparative analyses based on the number of EMR specimens per LNPCPs were not performed. Lastly, CAST was exclusively used for non-lifting polypoid tissue during the study period and therefore no comparative analyses with alternative endoscopic resection techniques or alternative auxiliary modalities were performed. It is therefore critical for future studies to perform comparative analyses of different

endoscopic resection techniques and different auxiliary modalities for PA-LNPCP management.

In conclusion, EMR, in combination with CAST where necessary, is an effective and safe treatment for PA-LNPCPs affording high frequencies of technical success. It should now be viewed as a first-line modality for the vast majority of these lesions. By integrating margin thermal ablation into high-quality EMR technique, recurrence is essentially negated, even in this historically complex subgroup. Importantly, PA-LNPCP management should be reserved for tertiary tissue resection centers with N-LNPCPs only treated by endoscopists competent in high-quality EMR technique.

Table 1: Patient and Lesion Characteristics

	Overall LNPCPs (n=1292, %)	N-LNPCPs (n=1134, %)	PA-LNPCPs (n=158, %)
Age, years (median, IQR)	69 (61-76)	69 (60-75)	70 (62-76)
Male sex (n, %)	681 (52.7)	591 (52.1)	90 (57.0)
ASA (n, %)*			
I	397 (36.7)	349 (36.9)	48 (35.3)
II	532 (49.2)	466 (49.3)	66 (48.5)
III	151 (14.0)	129 (13.7)	22 (16.2)
IV	1 (0.1)	1 (0.1)	0 (0.0)
Size, mm (median, IQR)	35 (30-50)	35 (30-50)	30 (25-46)
Location (n, %)			
Recto-sigmoid	369 (28.6)	315 (27.8)	54 (34.2)
Proximal	923 (71.4)	819 (72.2)	104 (65.8)
Paris classification (n, %)			
0-Is	106 (8.2)	96 (8.5)	10 (6.3)
0-IIa	690 (53.4)	601 (53.0)	89 (56.3)
0-IIb	58 (4.5)	46 (4.1)	12 (7.6)
0-IIa+Is	413 (32.0)	373 (32.9)	40 (25.3)
Any 0-IIc	25 (1.9)	18 (1.6)	7 (4.4)
Granularity (n, %)**			
Granular	777 (61.3)	686 (61.7)	91 (58.3)
Non-granular	366 (28.9)	314 (28.2)	52 (33.3)
Mixed	66 (5.2)	57 (5.1)	9 (5.8)
Serrated	59 (4.7)	55 (4.9)	4 (2.6)
Kudo Pit Pattern (n, %)*			
I	1 (0.1)	1 (0.1)	0 (0.0)
II	97 (7.7)	89 (8.0)	8 (5.1)
III	290 (22.9)	255 (23.0)	35 (22.3)
IV	837 (66.1)	728 (65.6)	109 (69.4)
V	42 (3.3)	37 (3.3)	5 (3.2)
Histopathology (n, %)			
Tubular adenoma	314 (24.3)	270 (23.8)	44 (27.8)
Tubulovillous adenoma	713 (55.2)	625 (55.1)	88 (55.7)
Villous adenoma	9 (0.7)	6 (0.5)	3 (1.9)
Serrated	155 (12.0)	145 (12.8)	10 (6.3)
Submucosal invasive cancer	84 (6.5)	72 (6.3)	12 (7.6)
Other	17 (1.3)	16 (1.4)	1 (0.6)
High-grade dysplasia (n, %)	173 (13.4)	157 (13.8)	16 (10.1)

ASA, American Society of Anesthesiologists; IQR, interquartile range; LNPCP, large non-pedunculated colorectal polyp; N-LNPCP, naïve large non-pedunculated colorectal polyp; PA-LNPCP, previously att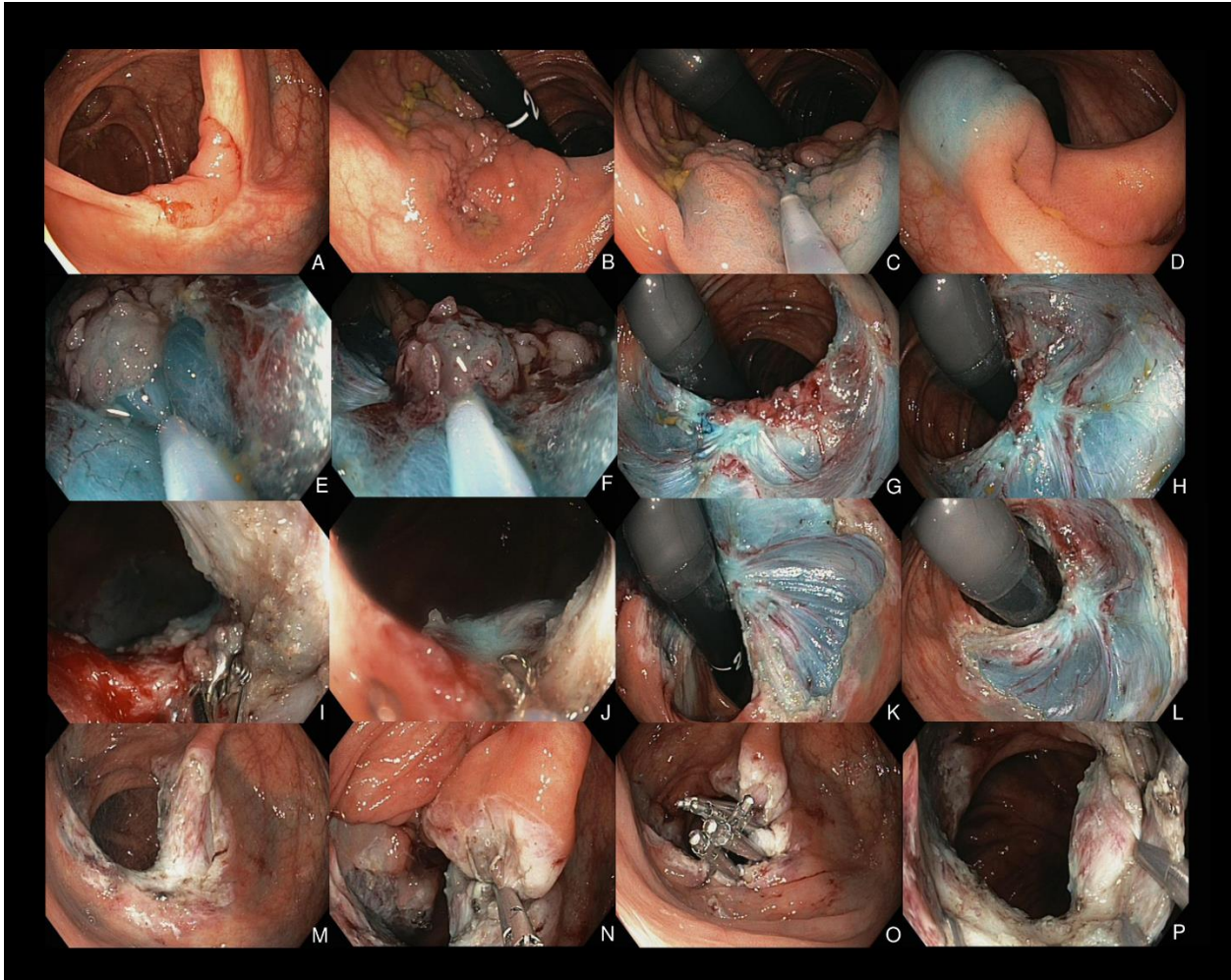empted large non-pedunculated colorectal polyp; *211 participants ASA not classified; **24 participants granularity not classified; ***25 participants Kudo pit pattern not classified

Table 2: Procedural Outcomes

	Overall LNPCPs (n=1292, %)	N-LNPCPs (n=1134, %)	PA-LNPCPs (n=158, %)	P-value
Duration, min (median, IQR)	30 (15-45)	25 (15-40)	35 (25-60)	**< 0.001**
Technical success (n, %)	1243 (96.2)	1096 (96.6)	147 (93.0)	**0.026**
Auxiliary modality (n, %)	159 (12.3)	86 (7.6)	73 (46.2)	**< 0.001**
Margin thermal ablation (n, %)	602 (46.6)	521 (45.9)	81 (51.3)	0.209
CSIPB (n, %)	63 (4.9)	52 (4.6)	11 (7.0)	0.194
Deep mural injury III-V (n, %)	46 (3.6)	42 (3.7)	4 (2.5)	0.456
CSPEB (n, %)	101 (7.8)	88 (7.8)	13 (8.2)	0.837
Delayed perforation (n, %)	4 (0.3)	4 (0.4)	0 (0.0)	1.000
SC1				
Eligible (n)	1009	882	127	
Underwent SC1 (n, %)	932 (92.4)	817 (92.6)	115 (90.6)	0.409
Months to SC1 (median, IQR)	6 (5-7)	6 (5-7)	6 (5-7)	0.805
Recurrence	93 (10.0)	84 (10.3)	9 (7.8)	0.411

CSIPB, clinically significant intra-procedural bleeding; CSPEB, clinically significant post-EMR bleeding; IQR, interquartile range; LNPCP, large non-pedunculated colorectal polyp; Min, minutes; N-LNPCP, naïve large non-pedunculated colorectal polyp; PA-LNPCP, previously attempted large non-pedunculated colorectal polyp; SC1, surveillance colonoscopy 1

Table 3: Recurrence Sub-Analysis of LNPCPs by Margin STSC

	N-LNPCPs			PA-LNPCPs		
	No STSC	**STSC**	**P-value**	**No STSC**	**STSC**	**P-value**
Recurrence (n/N, %)	82/481 (17.0)	2/336 (0.6)	**< 0.001**	9/50 (18.0)	0/65 (0.0)	**< 0.001**

LNPCP, large non-pedunculated colorectal polyp; N-LNPCP, naïve large non-pedunculated colorectal polyp; PA-LNPCP, previously attempted large non-pedunculated colorectal polyp; STSC, snare-tip soft coagulation

Table 4: Recurrence Sub-Analysis of LNPCPs requiring CAST by Margin STSC

	N-LNPCPs			PA-LNPCPs		
	No STSC	**STSC**	**P-value**	**No STSC**	**STSC**	**P-value**
Recurrence (n/N, %)	7/38 (18.4)	0/22 (0.0)	**0.040**	5/16 (31.3)	0/39 (0.0)	**0.001**

LNPCP, large non-pedunculated colorectal polyp; N-LNPCP, naïve large non-pedunculated colorectal polyp; PA-LNPCP, previously attempted large non-pedunculated colorectal polyp; STSC, snare-tip soft coagulation

Figure 1. A-B: 50mm 0-IIa mixed previously attempted large non-pedunculated colorectal polyp in the ascending colon. **C-F:** Endoscopic mucosal resection. **G-J:** Non-lifting polypoid tissue removed by cold-forceps avulsion with adjuvant snare-tip soft coagulation. **K-M:** status-post margin thermal ablation with deep mural injury type II. **N-P:** Successful prophylactic mechanical clip placement
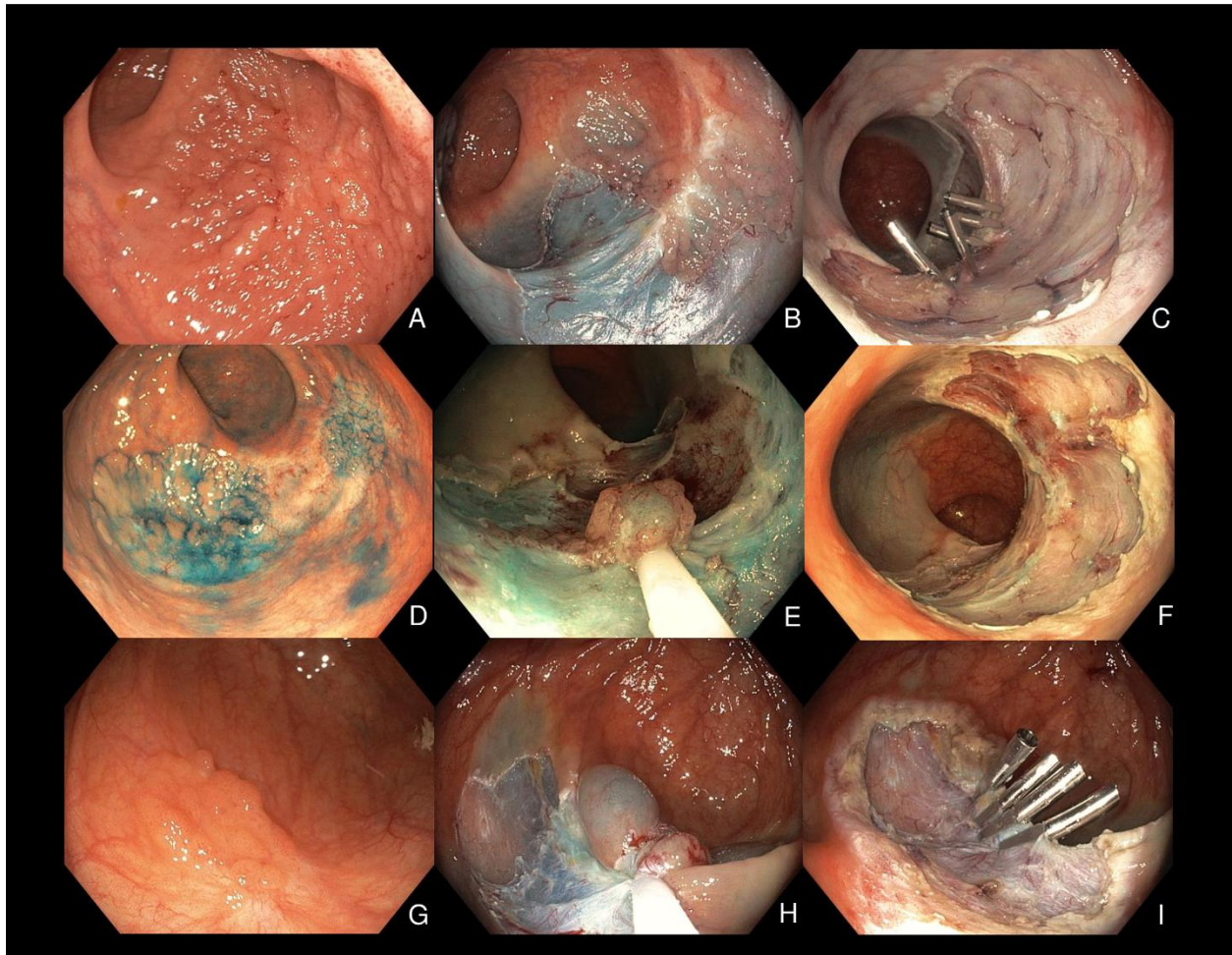
Figure 2. A-C: 60mm 0-IIa granular previously attempted large non-pedunculated colorectal polyp in the rectum. Removed by endoscopic mucosal resection with cold-forceps avulsion and adjuvant snare-tip soft coagulation. **D-F:** 40mm 0-IIa granular previously attempted large non-pedunculated colorectal polyp in the rectum. Removed by endoscopic mucosal resection with cold-forceps avulsion and adjuvant snare-tip soft coagulation. **G-I:** 20mm 0-IIa granular previously attempted large non-pedunculated colorectal polyp in the cecum. Removed by endoscopic mucosal resection.
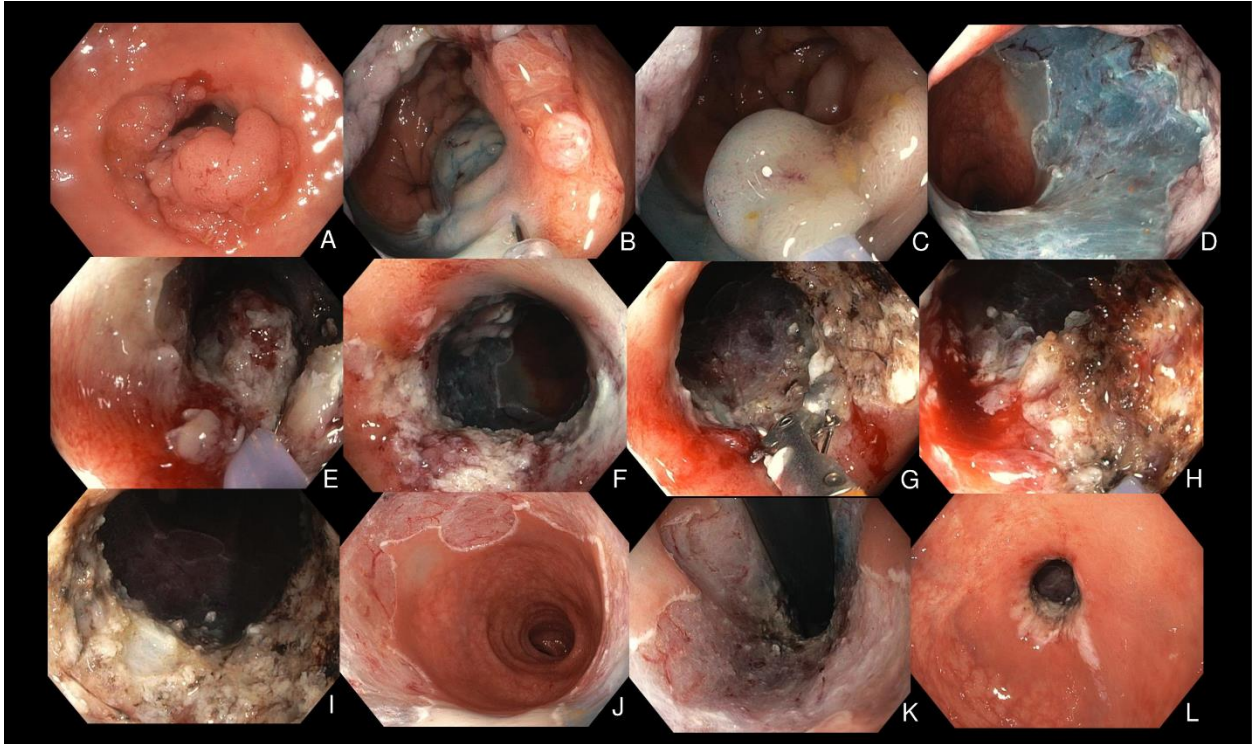
Figure 3. A: 50mm circumferential 0-IIa+Is granular previously attempted large non-pedunculated colorectal polyp in the rectum. **B-F:** Endoscopic mucosal resection. **G-I:** Non-lifting polypoid tissue removed by cold-forceps avulsion with adjuvant snare-tip soft coagulation. **J-L:** Resection defect evaluation prior to margin thermal ablation.

Figure 4. Flow diagram of consecutive large non-pedunculated colorectal polyps referred for endoscopic resection

CSP, cold snare polypectomy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LNPCP, large non-pedunculated colorectal polyp; MDT, multi-disciplinary team; N-LNPCP, naïve large non-pedunculated colorectal polyp; PA-LNPCP, previously attempted large non-pedunculated colorectal polyp; SC1, surveillance colonoscopy 1; SMIC, submucosal invasive cancer

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Chapter 4: Outcomes of deep mural injury after endoscopic resection: An international cohort of 3717 large non-pedunculated colorectal polyps

Summary: In a multi-center observational cohort of 3717 LNPCPs, significant deep mural injury occurred in 101 (2.7%). Defect closure was achieved in 98 (97.0%) with no difference in technical success or recurrence compared to LNPCPs without S-DMI; highlighting that S-DMI is readily managed by through-the-scope-clips.

Outcomes of deep mural injury after endoscopic resection: An international cohort of 3717 large non-pedunculated colorectal polyps

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Abbreviations

ACE, Australian Colonic Endoscopic Resection

AE, Adverse event

ASA, American Society of Anesthesiologists

ASGE, American Society for Gastrointestinal Endoscopy

CSPEB, clinically significant post-EMR bleeding

DMI, deep mural injury

EMR, endoscopic mucosal resection

ESD, endoscopic submucosal dissection

ESGE, European Society of Gastrointestinal Endoscopy

IQR, interquartile range

LNPCP, large non-pedunculated colorectal polyp

NBI, narrow-band imaging

S-DMI, significant deep mural injury

SC, surveillance colonoscopy

SMIC, submucosal invasive cancer

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

TTSC, through-the-scope clip

What You Need to Know

Background

Perforation is the most feared adverse event associated with endoscopic mucosal resection for large (≥ 20mm) non-pedunculated colorectal polyps (LNPCPs). Limited data exists concerning its management.

Findings

In a multi-center observational cohort of 3717 LNPCPs, significant deep mural injury occurred in 101 (2.7%). Defect closure was achieved in 98 (97.0%) with no difference in technical success or recurrence compared to LNPCPs without S-DMI.

Implications for Patient Care

Significant deep mural injury is readily managed by through-the-scope clips to achieve defect closure.

Abstract

Background and Aims: Although perforation is the most feared adverse event associated with endoscopic mucosal resection (EMR), limited data exists concerning its management. Therefore, we sought to evaluate the short- and long-term outcomes of intra-procedural deep mural injury (DMI) in an international multi-center observational cohort of large (≥ 20mm) non-pedunculated colorectal polyps (LNPCPs).

Methods: Consecutive patients who underwent EMR for a LNPCP ≥ 20mm were evaluated. Significant DMI (S-DMI), was defined as Sydney DMI Classification type III (muscularis propria injury, target sign) or type IV/V (perforation without or with contamination, respectively). The primary outcome was successful S-DMI defect closure. Secondary outcomes included technical success (removal of all visible polypoid tissue during index EMR), surgical referral and recurrence at first surveillance colonoscopy (SC1).

Results: Between July 2008 to May 2020, 3717 LNPCPs underwent EMR. Median lesion size was 35mm (interquartile range (IQR) 25 to 45mm). Significant DMI was identified in 101 cases (2.7%), with successful defect closure in 98 (97.0%) using a median of 4 through-the-scope clips (TTSCs; IQR 3 to 6 TTSCs). 3 (3.0%) patients underwent S-DMI-related urgent surgery. Technical success was achieved in 94 (93.1%) patients, with 46 (45.5%) admitted to hospital (median duration 1 day; IQR 1 to 2 days). Comparing LNPCPs with and without S-DMI, no differences in technical success (94 (93.1%) vs. 3316 (91.7%) $p = 0.62$) or SC1 recurrence (12 (20.0%) vs. 363 (13.6%); $p = 0.15$) were identified.

Conclusion: Significant DMI is readily managed endoscopically and does not appear to affect technical success or recurrence.

Key words:

Adverse Event; Colonoscopy; Complication; Endoscopy; Perforation

Introduction

Endoscopic mucosal resection (EMR) is established as the preferred resection technique for large (≥ 20mm) non-pedunculated colorectal polyps (LNPCPs) (1-3). While equally efficacious, it is safer and less costly compared to surgery (4-6).

Nevertheless, perforation remains the most feared EMR-related adverse event (AE), with an estimated frequency of 1 to 2% (7). Although endoscopic defect closure is feasible, as limited data exists, its efficacy and impact on short- and long-term outcomes are largely unknown. Current consensus recommendations (2, 3, 8) advocating for mechanical defect closure are predominantly based on small retrospective series (9-14). Therefore, we sought to evaluate the short- and long-term outcomes of intra-procedural deep mural injury (DMI) in an international multi-center observational cohort of consecutive LNPCPs.

Methods

This manuscript was produced, with guidance from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (15) recommendations.

The Australian Colonic Endoscopic Resection Cohort

The Australian Colonic Endoscopic Resection (ACE) cohort (clinicaltrials.gov identifiers: NCT01368289; NCT02000141) is a multi-center, observational cohort of consecutive patients referred for the management of LNPCPs ≥ 20mm. Center-specific Institutional Review Board approval is maintained at each participating site. Written informed consent is obtained from each participant prior to enrollment.

Between July 2008 and May 2020, consecutive participants enrolled at one of ten ACE sites who underwent EMR for a LNPCP, were considered for inclusion. All endoscopic procedures were performed by either a study investigator (accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their supervision. Endoscopic mucosal resection was performed using a standardized previously described inject and resect EMR technique at all centers (1). Technical innovations in EMR were adopted as the evidence to support them emerged.

Patient follow-up was performed at 14-days post-index procedure by dedicated research staff using a structured telephone interview to collect data regarding post-procedural AEs consistent with American Society for Gastrointestinal Endoscopy (ASGE) guidelines (16). Additional follow-up data was obtained at first surveillance colonoscopy (SC1) at 6 months and thereafter.

Significant Deep Mural Injury

Significant DMI (S-DMI) was defined as Sydney DMI Classification (17) type III (muscularis propria (MP) injury as evidenced by specimen target sign (18) or defect target sign), type IV (actual hole in the MP within a white cautery ring with no observed contamination), or type V (actual hole in the MP within a white cautery ring with observed contamination) (Figures 1 and 2). Data on S-DMI were prospectively collected from March 2010, after the description of the target sign (18). Prior to March 2010, retrospective review from procedure charts and comprehensive photo records was

performed independently by two investigators. In the case of discordance, a third investigator was used for arbitration.

Intra-procedural and post-procedural management decisions were at the discretion of the endoscopist. This included: 1) TTSC defect closure; 2) radiographic evaluation; 3) antibiotic therapy; 4) hospital admission and 5) surgical referral.

Data extraction

Collected data included: 1) Patient characteristics: age, sex, American Society of Anesthesiologists (ASA) classification; 2) Lesion characteristics: location, size, Paris classification, surface granularity; 3) Resection characteristics: attempted en-bloc resection, 4) Histopathology evaluation; 5) Post-procedural AE: clinically significant post-EMR bleeding (CSPEB), perforation, hospitalization, referral to surgery; 6) Surveillance: endoscopic/histologic recurrence.

Outcomes and analysis

The primary outcome was successful S-DMI defect closure. This was defined as complete capture and apposition of the area of concern with TTSCs, confirmed by inspection of both the proximal and distal margins. Secondary outcomes included technical success (complete removal of all visible polypoid tissue during index EMR), surgical referral, and recurrence (absence of endoscopic/histologic recurrence at SC1).

SPSS version 26.0 (IBM Corp, Armonk, NY, USA) was used for retrospective data analysis. Variables were analyzed per participant. If 2 or more eligible lesions were identified in a single participant, the lesion with DMI was selected for analysis. If no DMI

occurred, the smaller lesion(s) were excluded from analysis. Lesions which underwent

endoscopic submucosal dissection (ESD) or piecemeal cold snare polypectomy (P-

CSP) were excluded from analysis.

Continuous variables were summarized as median (interquartile range (IQR)).

Categorical variables were summarized as frequencies (%). All analyses were

exploratory and 2-tailed tests with a 5% significance level were used throughout.

Pearson x^2 test was used for categorical variables.

Results

Between July 2008 and May 2020 4545 LNPCPs in 4078 patients were referred

for endoscopic resection (Figure 3). 828 LNPCPs were excluded from analysis (295

resected by P-CSP or ESD, 365 synchronous lesions, 168 EMR not attempted due to

concern for submucosal invasive cancer (SMIC) or technical reasons). 3717 LNPCPs in

3717 patients underwent EMR (median age 68 years (IQR 61 to 76 years), male sex

53.3%) (Table 1). Median lesion size was 35mm (IQR 25 to 45mm), with the majority of

lesions located in the right colon (53.7%) or the rectum (17.6%). Piecemeal EMR was

performed in 3256 (87.6%). Overall technical success was achieved in 3410 (91.7%).

Submucosal invasive cancer was identified in 274 (7.4%).

Primary Outcome

Significant DMI was identified in 101 patients (2.7%) (Figure 4). Of these, 71

patients (70.3%) had an MP injury or target sign (DMI III). Thirty patients had a full-

thickness perforation: 28 (27.7%) without observed contamination (DMI IV) and 2 (2.0%) with contamination (DMI V).

Defect closure was attempted in 99 patients (98.0%). A selective closure of the area of concern was performed in 67 (67.7%) patients, with the remaining 32 (32.3%) undergoing closure of the entire resection defect. Successful defect closure was achieved in 98 patients (97.0%) with a median of 4 TTSCs (IQR 3 to 6 TTSCs). Of the remaining 3 patients, two underwent urgent surgery within 48 hours and the third patient had DMI type IV located in the distal rectum, below the peritoneal reflection. Closure was not attempted and the patient was treated conservatively with antibiotics.

Secondary Outcomes

Technical success was achieved in 94 (93.1%) patients with S-DMI. Of the 7 where technical success was not achieved, this was due to: suspected SMIC 1, technical considerations (significant submucosal fibrosis and/or difficult positioning) 4, and primarily related to S-DMI 2.

46 patients (45.5%) were admitted to hospital for observation. Median hospital stay was 1 day (IQR 1 to 2 days). Intravenous antibiotics were administered in 46 patients (45.5%). Imaging was performed in 17 patients (16.8%; computed tomography 10, plane X-ray 5, both modalities 2. Four of these patients were discharged on the day of procedure after reassuring imaging studies.

Five (4.9%) patients were referred for urgent surgery (< 48 hours): 1 defect closure not attempted; 1 successful defect closure not achieved, 1 peritonitis, 1 SMIC, 1 CSPEB after successful defect closure. 18 (17.8%) patients were referred for elective

surgery: 12 due to SMIC on histopathology and 6 due to other reasons (4 incomplete EMR due to significant submucosal fibrosis and/or difficult positioning, 2 concomitant lesions with SMIC).

65 patients were eligible for SC1 of which 60 (92.3%) underwent endoscopic follow-up. One patient was lost to follow-up and 4 patients are pending SC1, as the due date occurred during the COVID-19 pandemic. Reasons for ineligibility included: 23 post-surgery, 5 comorbid disease or death unrelated to S-DMI or colorectal neoplasia, 8 SC1 not due. From index EMR, median time to follow-up was 6 months (IQR 5 to 7 months). Recurrence was identified in 12 patients (20%).

Lesions with and without significant deep mural injury

Comparing outcomes of LNPCPs with and without S-DMI, no significant difference in technical success (94 (93.1%) vs. 3316 (91.7%); p = 0.62), or SC1 recurrence (12 (20%) vs. 363 (13.6%); p = 0.15) were identified.

Discussion

Endoscopic mucosal resection has emerged as the primary resection modality for LNPCPs (2, 3). Site-specific technical modifications in high-quality EMR and the development of auxiliary techniques now allow for the effective, efficient and safe removal of complex lesions (19, 20). Moreover, thermal ablation to the EMR margin and prophylactic clip closure of the resection defect, specifically for proximal lesions, have mitigated the risk of recurrence and CSPEB, respectively (21, 22). Despite these innovations, perforation remains the most feared EMR-related AE. Consensus

guidelines advocate for endoscopic defect closure (2, 3, 8). However, these recommendations are largely based on small retrospective cohorts which commonly do not provide colorectal EMR-specific short- and long-term outcomes (9-14, 23-25). In this study, we demonstrate that EMR-related S-DMI can be effectively managed with TTSCs in the overwhelming majority.

The importance of S-DMI management relates to the heightened morbidity of emergency surgery in this setting; therefore, emphasizing the potential for endoscopic defect closure to have a meaningful effect on clinical outcomes. In this study, successful TTSC closure was achieved in 97.0% of patients with 45.5% admitted to hospital for a median of 1 day (IQR 1 to 2 days). Only 3 (3.0%) patients underwent S-DMI-related urgent surgery (< 48 hours): 1 where defect closure was not attempted, 1 due to unsuccessful defect closure and 1 due to peritonitis. Furthermore, no significant differences in technical success (93.1% vs. 91.7%; p = 0.62), or SC1 recurrence (20% vs. 13.6%; p = 0.15) were identified. It is important to note that the lack of statistical significance, specifically for recurrence, may be due to the study being underpowered for this outcome. However, given the overall findings, TTSC defect closure should be considered the standard of care for colorectal EMR-related S-DMI.

Procedural success is predicated on a protocolized approach to high-quality EMR and the management of potential AEs (Figure 5; Supplemental Video 1). Pre-procedure, the endoscopist must ensure that TTSCs are appropriately stocked and readily available within the endoscopy suite for use by a competent endoscopy team. Moreover, EMR should only be performed with carbon dioxide insufflation, to mitigate the risk of tension pneumoperitoneum while allowing the endoscopist to treat the area of

concern with a considered and strategic approach in a controlled environment. In the era of carbon dioxide insufflation, the primary objective is complete and effective closure rather than speed which was necessary when air insufflation was used.

Once the procedure has begun, all residual debris should be aspirated, including in the colorectal segments above and below, where applicable. Prior to commencing tissue resection, the patient should be repositioned to manipulate the fluid pool to the opposing colorectal wall. In the event of intra-procedural bleeding or S-DMI, fluid does not pool over the working field, free access to the point of interest is maintained, and the risk of peritoneal contamination is minimized. After tissue capture, acquiring the snare handle from the assistant provides important tactile feedback. Firstly, the completely closed snare should feel "spongy". If firm, inadvertent MP capture may have occurred which can be addressed by gently elevating the captured tissue to the center of the lumen. Then the snare is opened slightly to release the MP, while simultaneously insufflating, followed by snare closure. Secondly, the snare catheter can be manipulated and the captured tissue should move freely compared to the colorectal wall. Thirdly, tissue transection should be achieved in 1-3 pulses of fractionated current. Greater than 3 pulses should raise concern for S-DMI.

After each resection, the defect should be expanded by waterjet irrigation to facilitate DMI identification. A homogenous blue surface of intersecting obliquely oriented submucosal fibers with or without flat non-bleeding blood vessels or herniating blood vessels, consistent with submucosal tissue stained with injectate, is expected. Any non-stained areas should prompt evaluation for DMI, as described by the Sydney DMI Classification (17). Topical submucosal chromoendoscopy (TSC) can be performed

by irrigating injectate into the area of concern without needle deployment (26). This should confirm homogenous blue staining of the previously unstained area if S-DMI is absent.

Significant DMI (Sydney DMI Classification types III-V) manifests as a partial or full-thickness transverse defect in the MP, with the long-axis of the defect invariably perpendicular to the long axis of the colon. In general, closure need only address the area of injury as attempting to close the entire resection site is more complex, and may risk incomplete closure of the area of S-DMI. It is important to work sequentially from one side of the defect to the other with TTSCs opposing the edges of the wound. Initial TTSC placement must take into account two important factors: 1) the orientation of the working channel, bearing in mind that with a colonoscope the working channel is at 5 o'clock and it is therefore easiest to work from left to right; 2) the impact of gravity which can be judged by the position of the fluid pool. The latter is important because as TTSCs are placed, the stems will fall towards the fluid pool. It is therefore easier to place additional TTSCs if the stems fall away from the site of subsequent TTSC placement. The first TTSC must be placed just outside the defect to raise up a small tissue mound. The TTSC is positioned perpendicular to the defect and gentle pressure is applied while aspirating luminal gas. The aim is to enable tissue to rise up into the TTSC. This method ensures maximal tissue capture to achieve serosa to serosa apposition. This technique is repeated with sequential TTSCs placed next to one another 1-2 mm apart so that a defect of < 10mm will generally require less than 6 TTSCs. The last TTSC is placed on uninjured submucosal tissue just outside the area of S-DMI. Once closure is achieved, the endoscope is passed beyond the defect and

used to gently deflect the TTSCs backwards. Successful defect closure is confirmed by verifying apposition of the two edges of the defect in between the adjacent TTSCs.

Critical to the management of S-DMI is an appreciation of its risk factors. In an analysis of 911 LNPCPs (17), attempted en bloc resection, advanced histopathology (high-grade dysplasia or SMIC) and transverse colon location were significantly associated with S-DMI on multivariable logistic regression analysis. Attempting an en bloc resection is an intuitive risk factor. Increasing lesion size will invariably increase the risk of capturing the MP during snare closure. Importantly, in a matched cohort of LNPCPs 20 to 25mm, en bloc resection was still associated with S-DMI (3.5% vs. 1.0%; p = 0.05) (27). Although recurrence at SC1 was higher (2.0% vs. 5.7%; p = 0.04), no difference was present on subsequent surveillance. Advanced histopathology is also logical, as it is associated with desmoplasia which may obliterate the submucosal plane. This emphasizes the importance of optical evaluation to quantify the risk of SMIC, and to inform therapeutic decisions regarding en bloc vs. piecemeal resection techniques. Transverse colon location, although less intuitive, is likely related to it being a highly mobile intra-peritoneal segment with a redundant mesentery; which may facilitate full-thickness capture of the colonic wall. Medium size snares (≤ 15mm) are therefore preferred for lesions proximal to the descending colon.

Many endoscopic defect closure techniques have been described including T-tags, (28), plicators (29), and suturing devices (30). The two predominant techniques within the colorectum are TTSCs and over-the-scope clips (OTSCs) (31). The European Society of Gastrointestinal Endoscopy (ESGE) currently recommends TTSCs for small defects and OTSCs for large defects. All defects within this study were assessed as

small (< 10mm) in size. This is partly due to the electrosurgical effect on the transected

area, leading the MP to be temporarily drawn together. Appropriate technique, as

described above, further facilitates successful closure. Although OTSC defect closure

appears comparable to TTSC defect closure (31), its impact on short- and long-term

outcomes are largely unknown. Moreover, it requires removal of the endoscope,

attachment of the OTSC, reinsertion of the endoscope and re-identification of the defect

which creates a time lag and an opportunity for peritoneal contamination. Endoscope

reinsertion necessitates gas insufflation and manipulation of the colon which may further

amplify the risk of peritoneal contamination. This highlights an intrinsic advantage of

TTSCs; alongside a likely significant cost-savings given the median number of TTSCs

(4 TTSCs, IQR 3 to 6 TTSCs) required for successful defect closure. Therefore, TTSCs

should be regarded as a first-line approach for colorectal EMR-related S-DMI, with

OTSCs used as a rescue approach when TTSC closure is not feasible or unsuccessful.

This study is not without limitations. Data on S-DMI were prospectively collected

from March 2010 onwards after the description of the target sign (18). Prior to this,

retrospective review from procedure charts and comprehensive photo records was

performed independently by two investigators, with arbitration by a third investigator if

discordance occurred. Secondly, alternative closure techniques including OTSC and

endoscopic suturing were not evaluated in this analysis. However, as TTSC closure is

relatively inexpensive, expedient and highly effective in this large cohort, it seems

unlikely that these alternative techniques will prove superior for EMR-related S-DMI.

Lastly, statistical analyses to compare selective vs. non-selective defect closure as well

as DMI III vs. DMI IV/V were not performed due to small sample sizes.

In conclusion, this study marks another evolution in minimally invasive endoscopic resection techniques. Significant DMI is readily managed by TTSC closure. Indeed, in the era of carbon dioxide insufflation and reliable clip closure, it should not be feared by experienced tissue resection endoscopists as our multi-center experience demonstrates that S-DMI is readily closed without adverse sequelae. Alongside an appreciation for S-DMI risk factors and the Sydney DMI Classification, TTSC closure carries the potential to mitigate perforation-related surgery and its associated morbidity. Intrinsic to this is the importance of a meticulous assessment of the post-EMR defect and a protocolized approach to EMR and its associated AEs.

Table 1: Patient and Lesion Characteristics

	All LNPCPs (N = 3717; n, %)	LNPCPs with S-DMI (n = 101; n, %)	LNPCPs without S-DMI (n = 3616; n, %)
Patient Characteristics			
Age (median, IQR, years)	68 (61-76)	69 (58-78)	68 (61-75)
Male sex (n, %)	1983 (53.3)	54 (53.5)	1929 (53.4)
ASA (n, %)*			
I	1119 (32.6)	30 (32.3)	1089 (32.6)
II	1747 (50.8)	47 (50.5)	1700 (50.8)
III-V	571 (16.6)	16 (17.2)	555 (16.6)
Lesion Characteristics			
Size (median, IQR, mm)	35 (25-45)	35 (25-50)	35 (25-45)
Location (n, %)			
Right Colon (Cecum to Hepatic Flexure)	1995 (53.7)	42 (41.6)	1953 (54.0)
Transverse Colon	429 (11.5)	15 (14.9)	414 (11.4)
Left Colon (Splenic Flexure to Sigmoid Colon)	637 (17.1)	31 (30.7)	606 (16.8)
Rectum	656 (17.6)	13 (12.9)	643 (17.8)
Morphology (n, %)**			
0-IIa or 0-IIb	1863 (50.7)	45 (44.6)	1818 (50.9)
0-Is	712 (19.4)	21 (20.8)	691 (19.4)
0-IIa+Is	971 (26.5)	30 (29.7)	941 (26.4)
Any 0-IIc component	124 (3.4)	5 (5.0)	119 (3.3)
Granularity (n, %)***			
Granular	2099 (68.7)	52 (63.4)	2047 (68.9)
Non-granular	735 (24.1)	22 (26.8)	713 (24.0)
Mixed	205 (6.7)	6 (7.3)	199 (6.7)
Serrated	12 (0.4)	2 (2.4)	10 (0.3)
Attempted en bloc resection (n, %)	461 (12.4)	22 (21.8)	439 (12.1)
Histopathology (n, %)			
Tubular adenoma	919 (24.7)	17 (16.8)	902 (24.9)
Tubulovillous adenoma	2128 (57.2)	66 (65.3)	2062 (57.0)

Villous adenoma	95 (2.6)	0 (0.0)	95 (2.6)
Sessile serrated polyp	490 (13.2)	15 (14.9)	475 (13.1)
Traditional serrated adenoma	62 (1.7)	3 (3.0)	59 (1.6)
Other	23 (0.6)	0 (0.0)	23 (0.6)
Submucosal invasive cancer	274 (7.4)	17 (16.8)	257 (7.1)
Dysplasia			
None	405 (10.9)	11 (10.9)	394 (10.9)
Low-grade dysplasia	2353 (63.3)	57 (56.4)	2296 (63.5)
High-grade dysplasia	959 (25.8)	33 (32.7)	926 (25.6)

ASA, American Society of Anesthesiologists; IQR, interquartile range; LNPCP, large non-pedunculated colorectal polyp; n, number; S-DMI, significant deep mural injury
*280 ASA not classified; **47 morphology not classified; ***Granularity assessment for adenomatous LNPCPs. 91 granularity not classified
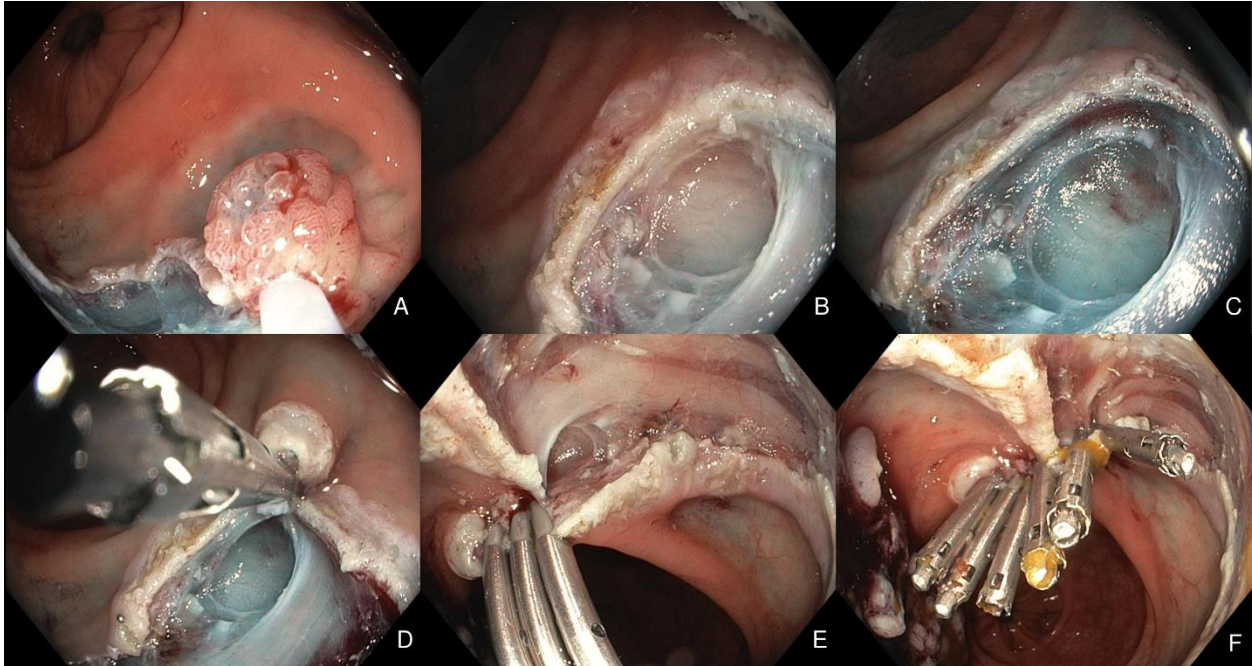
Figure 1. A: Endoscopic mucosal resection of a 40mm 0-IIa+Is granular large non-pedunculated colorectal polyp. **B-C:** Suspected significant deep mural injury confirmed with topical submucosal chromoendoscopy. **D-F:** Successful through-the-scope clip closure
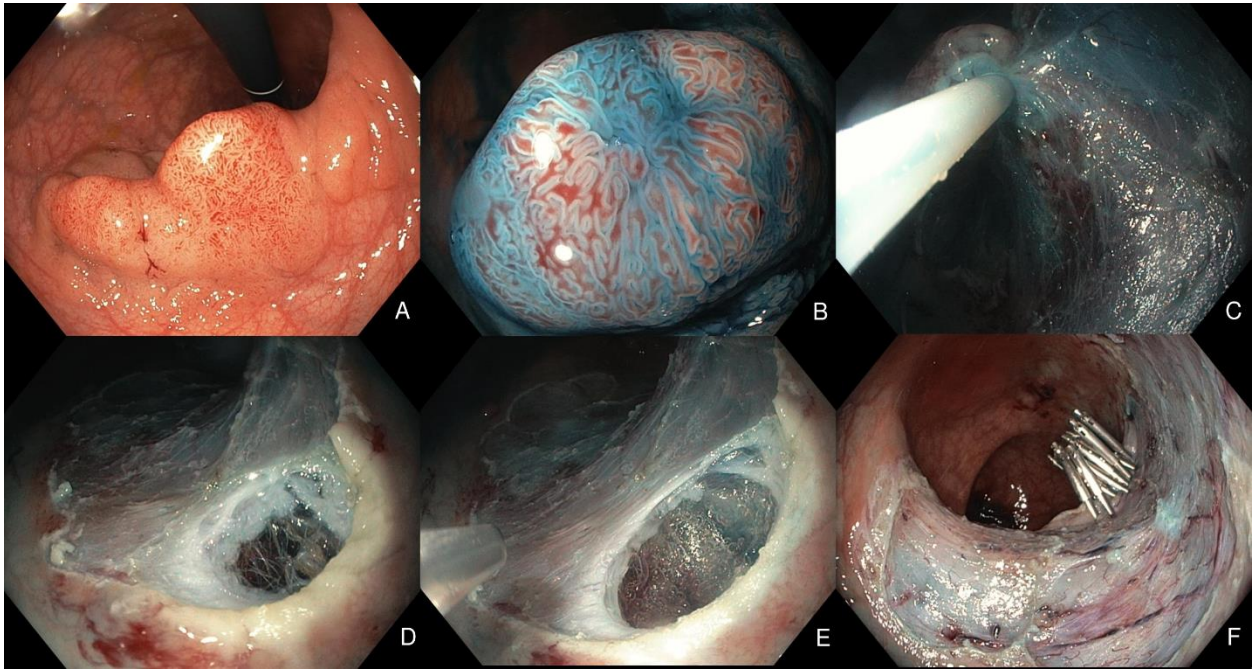
Figure 2. A-C: Endoscopic mucosal resection of a 40mm 0-IIa granular large non-pedunculated colorectal polyp. **D-E:** Suspected significant deep mural injury confirmed with topical submucosal chromoendoscopy. **F:** Successful through-the-scope clip closure.
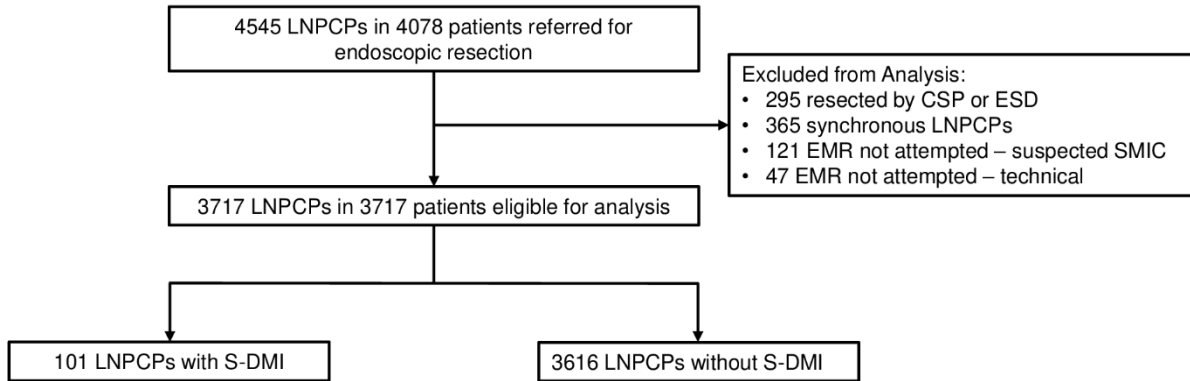
Figure 3. Flow diagram of consecutive large non-pedunculated colorectal polyps referred for endoscopic resection. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LNPCP, large non-pedunculated colorectal polyp; CSP, cold snare polypectomy; S-DMI, significant deep mural injury; SMIC, submucosal invasive cancer.
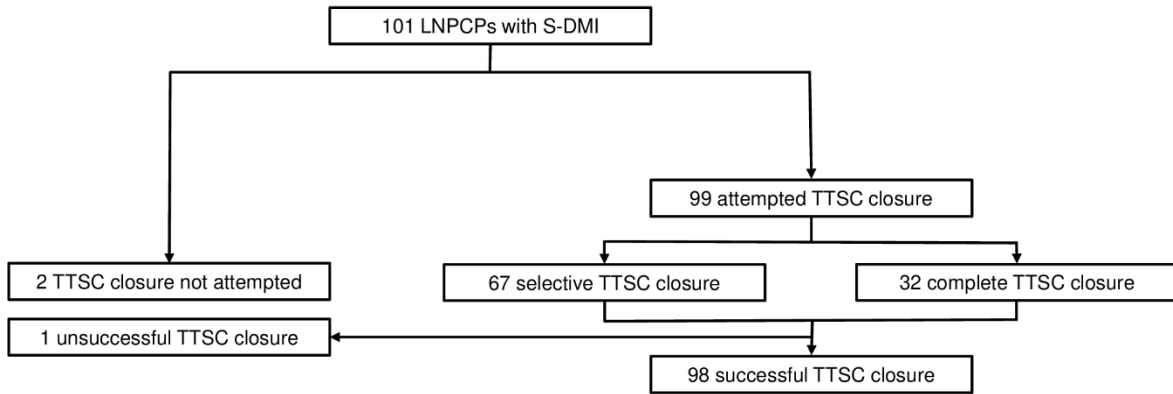
Figure 4. Flow diagram of significant deep mural injury management. EMR,

endoscopic mucosal resection; LNPCP, large non-pedunculated colorectal polyp; S-

DMI, significant deep mural injury; TTSC, through-the-scope clip
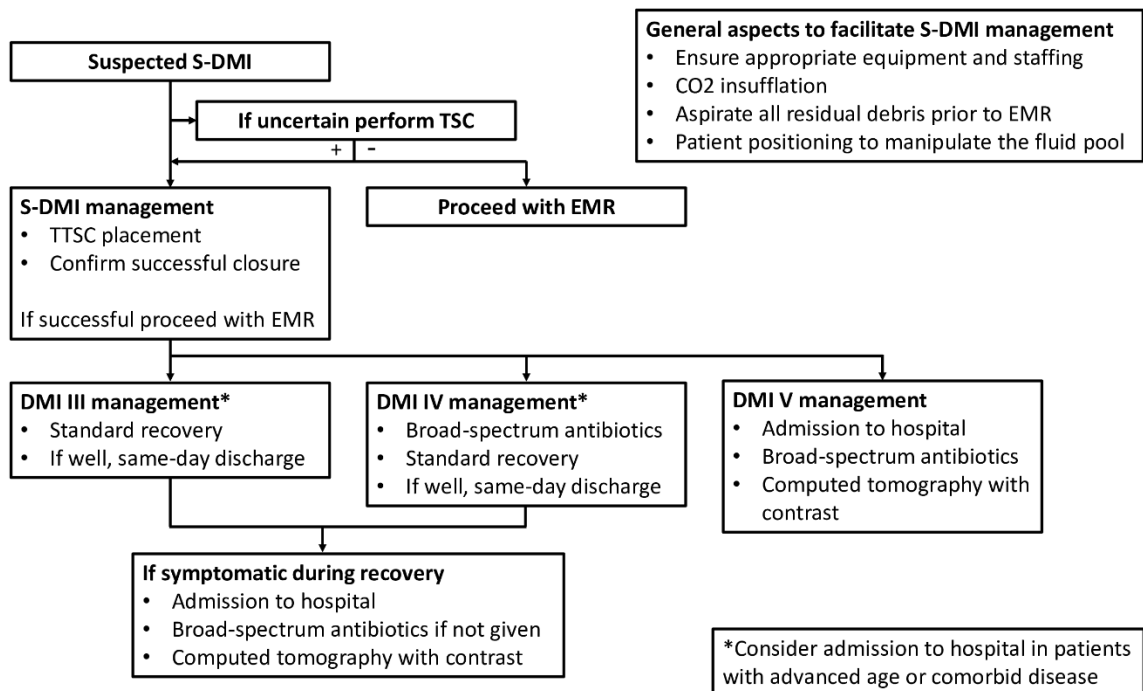
Figure 5. Proposed algorithm for significant deep mural injury management. DMI, deep mural injury; EMR, endoscopic mucosal resection; S-DMI, significant deep mural injury; TSC, topical submucosal chromoendoscopy; TTSC, through-the-scope clip. Standard recovery: Patients are observed for 4 hours. If well, they are subsequently discharged.

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Chapter 5: Optical evaluation for predicting cancer in large non-pedunculated colorectal polyps is accurate for flat lesions

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Summary: In a prospective multicenter evaluation of 1583 large non-pedunculated colorectal polyps (LNPCPs), real-time optical evaluation to detect the presence of submucosal invasive cancer (SMIC) showed excellent performance when assessing flat lesions and modest performance for nodular lesions; therefore, in the absence of optical features consistent with SMIC, endoscopic mucosal resection should be considered as the preferred first-option for treating all flat lesions in the colorectum.

Title: Optical evaluation for predicting cancer in large non-pedunculated colorectal polyps is accurate for flat lesions

Short Title: Optical evaluation for colorectal neoplasia

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Conflict of Interest

Michael J. Bourke: Research Support: Olympus Medical, Cook Medical, Boston Scientific.

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Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Writing Assistance

None

Abbreviations

ACE, Australian Colonic Endoscopic Resection

ASA, American Society of Anesthesiologists

CI, confidence interval

D-SMIC, deep submucosal invasive cancer

EMR, endoscopic mucosal resection

ESD, endoscopic submucosal dissection

IQR, interquartile range

LNPCP, large non-pedunculated colorectal polyp

NBI, narrow-band imaging

OR, odds ratio

SMIC, submucosal invasive cancer

S-SMIC, superficial submucosal invasive cancer

STARD, Standards for Reporting of Diagnostic Accuracy Studies

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

Acknowledgements

Abstract

Background and Aims: The ability of optical evaluation to diagnose submucosal invasive cancer (SMIC) prior to endoscopic resection of large (≥ 20mm) non-pedunculated colorectal polyps (LNPCPs) is critical to inform therapeutic decisions. Prior studies suggest that it is insufficiently accurate to detect SMIC. It is unknown whether lesion morphology influences optical evaluation performance.

Methods: LNPCPs ≥ 20mm referred for endoscopic resection, within a prospective, multi-center, observational cohort were evaluated. Optical evaluation was performed prior to endoscopic resection with the optical prediction of SMIC based on established features (Kudo V pit pattern, depressed morphology, rigidity/fixation, ulceration). Optical evaluation performance outcomes were calculated. Outcomes were reported by dominant morphology: nodular (Paris 0-Is/0-IIa+Is) vs. flat (Paris 0-IIa/0-IIb) morphology.

Results: From July 2013-July 2019, 1583 LNPCPs (median size 35mm; IQR 25-50mm; 855 flat, 728 nodular) were assessed. SMIC was identified in 146 (9.2%, 95%CI 7.9-10.8%). Overall sensitivity and specificity were 67.1% (95%CI 59.2-74.2%) and 95.1% (95%CI 93.9-96.1%), respectively. The overall SMIC miss rate was 3.0% (95%CI 2.3-4.0%). Significant differences in sensitivity (90.9% vs. 52.7%), specificity (96.3% vs. 93.7%) and SMIC miss rate (0.6% vs. 5.9%) between flat and nodular LNPCPs were identified (all p < 0.027). Multiple logistic regression identified size ≥ 40mm (OR 2.0; 95%CI 1.0-3.8), rectosigmoid location (OR 2.0; 95%CI 1.1-3.7) and nodular morphology (OR 7.2; 95%CI 2.8-18.9) as predictors of missed SMIC (all p < 0.039).

Conclusions: Optical evaluation performance is dependent on lesion morphology. In the absence of features suggestive of SMIC, flat lesions can be presumed benign and be managed accordingly.

Key Words: Adenoma, Colonoscopy, Endoscopy, Polyp

What you need to know

Background

While real-time optical evaluation has emerged as the predominant method for predicting submucosal invasion prior to endoscopic resection of colorectal lesions, evaluating ≥ 20mm lesions can be challenging, with existing data suggesting only modest performance characteristics.

Findings

This study demonstrates that optical evaluation is predicated on lesion morphology, with excellent performance demonstrated when assessing flat lesions. In contrast, optical evaluation has only decent performance in nodular lesions.

Implications for patient care

In the absence of optical features consistent with submucosal invasive cancer, endoscopic mucosal resection should be considered as the preferred first-option for treating all flat lesions in the colorectum. However, for nodular lesions we need algorithms, in addition to optical evaluation, to select lesions for the appropriate treatment.

Introduction

The ability of real-time optical evaluation of large (≥ 20mm) non-pedunculated colorectal polyps (LNPCPs) to accurately predict submucosal invasive cancer (SMIC) is crucial as it enables the endoscopist to appropriately select between endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and surgery. This is done by identifying characteristic surface and morphological features. Although recent evidence suggests that optical evaluation is effective at diagnosing SMIC (1,2), of those studies solely evaluating LNPCPs ≥ 20mm (3), modest performance was observed. Moreover, the complexity of quantifying the pre-test probability of SMIC based on patient and lesion characteristics (4), alongside the multitude of optical evaluation classifications for LNPCPs, has hindered its widespread adoption and application among all endoscopists who perform colonoscopy. Therefore, refining and simplifying the application of optical evaluation is needed.

As lesions grow in size, it is intuitive that optical features of SMIC could be missed. This may be heightened in lesions with a nodular component, as the identification of these features may be hindered or may be absent on the lesions' surface. Stratifying optical evaluation by lesion morphology may facilitate the implementation of a selective resection algorithm by identifying lesion subgroups with accurate optical evaluation performance characteristics. Therefore, we sought to evaluate the performance of optical evaluation, stratified by lesion morphology, in a prospective, multi-center, observational cohort of LNPCPs ≥ 20mm referred for endoscopic resection.

Materials and Methods

This manuscript was produced, with guidance from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (5), and the Standards for Reporting of Diagnostic Accuracy Studies (STARD) recommendations (6).

The Australian Colonic Endoscopic Resection Cohort

The Australian Colonic Endoscopic Resection (ACE) cohort (clinicaltrials.gov identifiers: NCT01368289; NCT02000141) is a prospective, multi-center, observational cohort of consecutive patients referred for the management of LNPCPs ≥ 20mm. Center-specific Institutional Review Board approval is maintained at each center. Written informed consent is obtained from each participant prior to enrollment.

Between July 2013 to July 2019, consecutive participants enrolled at 1 of 4 sites, were considered for inclusion. All endoscopic procedures were performed by either a study investigator (accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their supervision. Endoscopic mucosal resection was performed in a standardized fashion across all centers (7). Technical innovations in EMR were adopted as the evidence to support them emerged. A sub-group of lesions underwent ESD as part of a selective ESD protocol (clinicaltrials.gov identifiers: NCT02198729). Endoscopic submucosal dissection was performed in accordance with established international technical recommendations (8). Lesions believed to be unamenable to endoscopic resection were referred directly to surgery.

Optical Evaluation

Colonoscopy was performed using Olympus high-definition variable-stiffness colonoscopes (Olympus; Tokyo, Japan). Optical evaluation was performed in a standardized fashion across all centers. This included lesion evaluation under white-light and narrow-band imaging (NBI). Lesion location, size, Paris classification (9), granularity, Kudo pit pattern classification (10) and SMIC prediction were described in real-time. The latter was based on the presence of any of the following established endoscopic features consistent with invasive disease including: 1) Kudo pit pattern V; 2) depression (Paris 0-IIc morphology); 3) ulceration; and 4) fixation or rigidity.

Histopathology Evaluation

Specimens were collected and processed for histopathology review, in accordance with the Australasian Gastrointestinal Pathology Society guidelines (11). Histopathology review was completed by board-certified expert gastrointestinal pathologists, at their respective site. Cancer was defined by neoplastic invasion into the submucosa. Where appropriate, histopathology was confirmed with surgical specimen evaluation.

Data Extraction and Analysis

Prospectively collected data included: 1) Patient characteristics: age, sex, American Society of Anesthesiologists (ASA) classification; 2) Lesion characteristics: location, size, Paris classification, granularity, Kudo pit pattern, SMIC prediction; 3) Histopathology evaluation.

Lesions with incomplete optical evaluation were excluded. Lesions with serrated histopathology were also excluded, as optical evaluation of serrated lesions (12), as well as their biological behavior (13) differ from adenomatous neoplasia. The largest LNPCPs ≥ 20mm in each patient was selected for this study.

Optical evaluation performance outcomes were calculated with histopathology as the reference gold standard. SMIC miss rate was calculated with the denominator being all LNPCPs within the respective grouping. Lesions were grouped into flat (Paris 0-IIa or 0-IIb) and nodular (Paris 0-Is or 0-IIa+Is) morphology. If depression (any 0-IIc component) was present, the lesion in question was grouped by its predominant morphology.

Statistical Analysis

SPSS version 26.0 (IBM Corp, Armonk, NY, USA) was used for data analysis. Continuous variables were summarized as median (IQR) and categorical variables as frequencies (%). Wilson's method was used to calculate 95% confidence intervals (CI) for proportions.

All analyses were exploratory. Two-tailed tests with a 5% significance level were used throughout. Mann-Whitney U tests were used to test for differences in the distribution of age and lesion size. Pearson x^2 or Fisher's exact test were used, as appropriate, to test for association between categorical variables. Exact permutation test was used to assess for heterogeneity between endoscopists.

Multiple logistic regression with backward stepwise variable selection, was used to identify independent predictors of the outcome of interest (missed SMIC on optical evaluation). Candidate variables for inclusion in the model were those with p-values for

univariable association <0.1. Odds ratios (OR) and their 95% CIs were used to quantify the strength of association.

A decision tree classification model for missed SMIC on optical evaluation was developed for comparison with the multiple logistic regression model as it can highlight hidden relationships between variables which might otherwise be overlooked. The same candidate variables were included for the decision tree along with the continuous variables age and lesion size. Chi-squared Automatic Interaction Detection using Bonferroni-adjusted significance values (CHAID) was used to grow the tree to a maximum of three levels beneath the root node with the minimum number of cases for parent and child nodes set at 100 and 50 respectively. Ten-fold cross validation was used to produce the final tree model.

Patient and Public Involvement

Patients and the public were not involved in the design and execution of this study.

Results

Between July 2013 and July 2019, 2112 LNPCPs ≥ 20mm were referred for endoscopic resection. 294 were serrated-class lesions on histopathology and were excluded from analysis. 159 had incomplete optical evaluation data and were excluded from analysis. 71 participants had 2 or more lesions. The largest lesion per subject was selected for analysis resulting in a further 76 lesions being excluded. The final cohort comprised 1583 participants and 1583 LNPCPs managed by one of seven study investigators or a senior interventional endoscopy fellow under their supervision.

Median years of endoscopy experience for study investigators at study onset was 15 years (IQR: 6-18 years). Median lesions per study investigator was 99 lesions (IQR: 20-271 lesions). Optical evaluation performance (% correct diagnosis) ranged from 86.4% to 93.8% for individual endoscopists with no evidence of significant heterogeneity between endoscopists (p = 0.532).

The majority of lesions were removed by EMR 1467 (92.7%), of which 1361 (92.8%) underwent piecemeal resection. The remaining 48 (3.0%) and 68 (4.3%) underwent ESD and surgery, respectively.

Demographic and Lesion Characteristics

Median age was 69 years (IQR; 62-76 years), with 54.6% of participants being male (Table 1, Supplemental Table 1). The majority of participants were ASA I (309, 19.5%) or ASA II (737, 46.6%).

Median lesion size was 35mm (IQR: 25-50mm). Cecum (364, 23.0%), ascending colon (361, 22.8%), and rectum (323, 20.4%) were the most common locations. 855 (54.0%) and 728 (46.0%) LNPCPs had flat and nodular morphology (Figures 1 and 2), respectively. The majority of LNPCPs were granular (1012, 63.9%). On histopathology, tubulovillous adenoma was the most frequent diagnosis (989, 62.5%). Submucosal invasive cancer was identified in 146 (9.2%) LNPCPs.

In comparing LNPCPs with flat vs. nodular morphology, there were differences in median size (30mm; IQR: 25-40mm vs. 40mm; IQR: 30-50mm), location (recto-sigmoid location: 17.2%; 95% CI 14.8-19.9% vs. 46.8%; 95% CI 43.2-50.5%) and granularity (granular: 53.8%; 95% CI 50.5-57.1% vs. 75.8%; 95% CI 72.6-78.8%), respectively. The

frequency of SMIC was significantly higher in nodular (12.5%; 95% CI 10.3-15.1%) vs. flat (6.4%; 95% CI 5.0-8.3%) LNPCPs.

Optical Evaluation Performance

Overall sensitivity and specificity of optical evaluation to diagnose SMIC were 67.1% (95% CI 59.2-74.2%) and 95.1% (95% CI 93.9-96.1%), respectively (Table 2). When stratified by lesion morphology, there were significant differences between flat vs. nodular LNPCPs in sensitivity (90.9% 95% CI 80.4-96.1% vs. 52.7% 95% CI 42.6-62.7%; p < 0.001) and specificity (96.3% 95% CI 94.7-97.4% vs. 93.7% 95% CI 91.6-95.4%; p = 0.027). Positive predictive value and negative predictive value estimates for SMIC are provided in Table 2.

Diagnostic performance of individual endoscopic features of SMIC are provided in Supplemental Table 2.

Missed Submucosal Invasive Cancer on Optical Evaluation

Submucosal invasive cancer was missed on optical evaluation in 48 lesions overall, with a SMIC miss rate of 3.0% (95% CI 2.3-4.0%) (Table 3). This varied by lesion granularity with miss rates of 3.2% (95% CI 2.3-4.4%), 2.2% (95% CI 1.2-4.0%), and 5.2% (95% CI 2.4-10.9%) for granular, non-granular and mixed lesions, respectively. Of the 460 flat granular LNPCPs, no cases of SMIC were missed. The SMIC miss rates on optical evaluation when solely evaluating malignant LNPCPs is provided in Supplemental Table 3.

There was a significant difference in the SMIC miss rate between flat (0.6% 95% CI 0.3-1.4%) vs. nodular (5.9% 95% CI 4.4-7.9%) LNPCPs (p < 0.001). This difference remained significant when further stratifying by granularity (both p < 0.047).

On univariable logistic regression (Supplemental Table 4), nodular morphology (OR 10.7; 95% CI 4.2-27.1; p < 0.001), rectosigmoid location (OR 3.6 95% CI 2.0-6.5; p < 0.001) and size ≥ 40 mm (OR 3.2; 95% CI 1.7-6.0; p < 0.001) were significantly associated with missed SMIC on optical evaluation. Multiple logistic regression analysis (Table 4) identified nodular morphology (OR 7.2; 95% CI 2.8-18.9; p < 0.001), rectosigmoid location (OR 2.0; 95% CI 1.1-3.7; p = 0.026) and size ≥ 40 mm (OR 2.0; 95% CI 1.0-3.8; p = 0.039) as independent predictors of missed SMIC on optical evaluation.

The decision tree classification model identified lesion morphology (flat vs. nodular) to be the critical variable when searching for missed SMIC on optical evaluation (Supplemental Figure 1); therefore, confirming the findings of the multivariable logistic regression analysis.

Discussion

Minimally invasive resection techniques have revolutionized the management of early colorectal neoplasia (7,14-17). This is due to evidence-based site-specific modifications in high-quality EMR and the development of ancillary techniques when snare resection is not feasible (18). Moreover, technical innovations have largely alleviated the risk of clinically significant post-EMR bleeding (19-20), deep mural injury (21) and recurrence (22). With the overwhelming majority of colorectal LNPCPs being benign (4), EMR has rightly positioned itself as the primary endoscopic modality for the

colorectum (14). However, it is unable to reliably achieve curative resection in lesions ≥ 20mm with superficial SMIC (≤ 1000µm; S-SMIC). This emphasizes its natural synergism with ESD, as an organ-sparing, curative endoscopic resection technique. The benefits of a selective resection algorithm are intuitive and it has been shown to be the optimal strategy based on cost-effectiveness analyses (23). This has placed the onus on optical evaluation to reliably select the appropriate resection technique by identifying characteristic surface features consistent with SMIC. However, there is a paucity of data evaluating LNPCPs ≥ 20mm (3,4), with existing data suggesting only modest performance characteristics (2,3). Our findings show that optical evaluation of LNPCPs ≥ 20mm, while modest overall, is dependent on lesion morphology with excellent performance demonstrated when assessing flat lesions. This marks an easily implementable and critical step towards the adoption of a selective resection algorithm in the colorectum.

Two previous studies have solely focused on optical evaluation of LNPCPs (3,4). In a previous analysis of 2277 LNPCPs (mean size 36.9mm), the sensitivity and specificity for SMIC using Kudo pit pattern V was 40.4% (95% CI 33.3-47.8%) and 97.5% (95% CI 96.7-98.1%), respectively (4). In an alternative study, the Hiroshima classification was evaluated in a multi-center prospective cohort of 343 LNPCPs ≥ 20mm (median size 30mm; IQR 25-40mm) (3). Sensitivity and specificity were 79.7% (95% CI 64.3-89.3%), and 94.2% (95% CI 90.9-96.6%), respectively. With modest performance, it was concluded that the application of optical evaluation requires further optimization.

Our findings identify that the crux of optical evaluation is lesion morphology. It is an independent predictor of performance on multiple logistic regression and was

identified as the critical variable in classification tree analysis. Sensitivity, specificity and SMIC miss rates amongst flat lesions were 90.9% (95% CI 80.4-96.1%), 96.3% (95% CI 94.7-97.4%) and 0.6% (95% CI 0.3-1.4%), respectively. With further stratification, optical evaluation performance continued to improve amongst flat granular lesions (sensitivity 100%, 95% CI 67.6-100%; specificity 98.7%, 95% CI 97.1-99.4%). Notably, no cases of SMIC were missed. Therefore, if features of S-SMIC are identified on optical evaluation, ESD should be considered; although this decision is dependent on lesion location, endoscopic resources and operator expertise. Otherwise, EMR should be performed. With flat LNPCPs making up 54.0% of the cohort, and 93.6% being benign, this further cements EMR as the primary resection modality in the colorectum.

In contrast, when assessing nodular lesions, optical evaluation performance was significantly hindered. Sensitivity and SMIC miss rates were 52.7% (95% CI 42.6-62.7%) and 5.9% (95% CI 4.4-7.9%), respectively. This is likely due to the malignant focus not being expressed on the mucosal surface, thereby rendering optical evaluation obsolete in these circumstances. Moreover, the surface expression of SMIC may be inaccessible and go undetected. These findings further reinforce the concept of invisible or "covert" neoplasia. First described by the ACE consortium in an analysis of 2277 LNPCPs ≥ 20mm (4). After excluding lesions with visible or overt SMIC, lesion size, location, non-granularity and Paris 0-Is and 0-IIa+Is morphology were significantly associated with SMIC on multiple logistic regression. When stratified by lesion location, morphology and granularity, 0-Is non-granular, 0-IIa+Is non-granular, and distal 0-IIa+Is granular lesions were identified as high-risk (> 10%) for covert SMIC. This is further supported by the recent analysis of 693 granular mixed type lesions by D'Amico and colleagues (24), whereby increasing lesion size and rectal location were independently

associated with covert SMIC on multivariable logistic regression analysis. In the absence of optical features of D-SMIC, these lesions are ideal ESD candidates; specifically, in the rectum given the elevated risk of morbidity, mortality, and permanent ostomy formation associated with distal colorectal surgery. The application of a selective resection algorithm, based on these premises, would require 43 ESD procedures per 1000 patients (23).

Both size and rectosigmoid location were also identified as independent predictors of missed SMIC on optical evaluation. The influence of lesion size is instinctual, with the likelihood of missing optical features of SMIC increasing as lesion surface area increases. This emphasizes that optical evaluation must be both systematic and meticulous. Concerning rectosigmoid location, despite confounding due to an increased frequency of nodular morphology in the distal colorectum, this remained an independent predictor of optical evaluation performance. The sigmoid colon is a challenging location for the management of early colorectal neoplasia. This is due to lumen caliber, concomitant diverticular disease, and acute angulations related to variability in the length and mobility of the sigmoid mesentery; thus, limiting visualization during optical evaluation and endoscopic tissue resection.

Our study is not without limitations. Given the study's premise, lesions were grouped by their predominant morphology. Lesion morphology classification can be subjective, however, in a recent analysis it showed substantial inter-rater reliability (25). Moreover, it is imperative to appreciate that morphology in itself is associated with SMIC and that depressed morphology represents a high-risk lesion subgroup. Secondly, the creation of the ACE consortium precedes the establishment of both the NICE and JNET classifications. Optical evaluation criteria for SMIC were therefore

largely based on the identification of Kudo V pit pattern (10). While pit pattern classification was initially described using traditional magnifying chromoendoscopy, it can be discerned with high-definition endoscopes, particularly when using electronic image-enhanced techniques; although, this has not been validated experimentally. We also did not differentiate between Kudo V pit pattern sub-types (Vi or Vn) nor between S-SMIC and D-SMIC and focused on the diagnosis of SMIC. As EMR is the preferred tissue resection technique, as recommended in both North American (26) and European (14) consensus guidelines, the viewpoint of this study is from that of the community gastroenterologist. Endoscopic mucosal resection is commonly performed in the community setting, with the critical question being whether a lesion is benign and can be safely removed by EMR or whether referral to a tissue resection specialist is appropriate. Moreover, this is also an important question from the perspective of the tissue resection specialist. With the widespread adoption of ESD, endoscopic tissue resection specialists are increasingly referred non-surgical candidates with lesions demonstrating features of SMIC; for which the differentiation between features of S-SMIC and D-SMIC can be challenging. D-SMIC discovered in the resection specimen still carries the potential for curative endoscopic resection and empowers the patient alongside their clinical decision team regarding further therapeutic decisions. In the event of a non-curative diagnosis, it may modify the natural history of disease by mitigating the risk of future luminal adverse events related to luminal neoplasia. Performance validation of the participating endoscopists were not assessed and is therefore a potential source of bias. Lastly, due to the low frequency of SMIC in specific lesion subgroups or the low frequency of specific lesion subtypes, such as mixed

LNPCPs, the application of these findings within these subgroups needs to be approached with caution.

In conclusion, as optical evaluation has become the linchpin for the management of early colorectal neoplasia our study shows that its performance is predicated on lesion morphology. Optical evaluation has high sensitivity, high specificity and low SMIC miss rates when assessing flat neoplasia. Therefore, in the absence of optical features consistent with SMIC, all flat lesions should be removed by high-quality EMR, applying site-specific modifications and ancillary techniques where needed. In contrast, optical evaluation has modest performance in nodular lesions. While lesion location, morphology and granularity can be used to stratify the risk of covert SMIC, further refinement is needed to robustly apply a selective resection algorithm irrespective of lesion morphology. Nevertheless, it is imperative that all endoscopists embrace optical evaluation in everyday clinical practice; thus, harnessing its proven ability to influence resection technique selection and the associated clinical and economic ramifications.

Table 1: Demographic and Lesion Characteristics

	All LNPCPs (n = 1583)	Flat LNPCPs (n = 855)	Nodular LNPCPs (n = 728)	p-value
Age (median, IQR, years)	69 (62-76)	70 (64-77)	67 (61-75)	0.581
Male sex (n, %)	864 (54.6)	464 (54.3)	400 (54.9)	0.811
ASA classification (n, %)*				<0.001
I	309 (19.5)	140 (16.4)	169 (23.2)	
II	737 (46.6)	392 (45.8)	345 (47.4)	
III	284 (17.9)	171 (20.0)	113 (15.5)	
Size (median, IQR, mm)	35 (25-50)	30 (25-40)	40 (30-50)	<0.001
Location (n, %)				<0.001
Rectum	323 (20.4)	84 (9.8)	239 (32.8)	
Sigmoid	165 (10.4)	63 (7.4)	102 (14.0)	
Descending	80 (5.1)	50 (5.8)	30 (4.1)	
Splenic flexure	33 (2.1)	22 (2.6)	11 (1.5)	
Transverse	169 (10.6)	121 (14.2)	48 (6.6)	
Hepatic flexure	88 (5.6)	49 (5.7)	39 (5.4)	
Ascending	361 (22.8)	220 (25.7)	141 (19.4)	
Cecum	364 (23.0)	246 (28.8)	118 (16.2)	
Morphology (n, %)				
Flat	855 (54.0)	855 (100.0)	-	
Nodular	728 (46.0)	-	728 (100.0)	
Granularity (n, %)				<0.001
Granular	1012 (63.9)	460 (53.8)	552 (75.8)	
Non-granular	456 (28.8)	355 (41.5)	101 (13.9)	
Mixed granularity	115 (7.3)	40 (4.7)	75 (10.3)	
Histopathology (n, %)				<0.001
Tubular adenoma	402 (25.4)	237 (27.8)	165 (22.7)	
Tubulovillous adenoma	989 (62.5)	541 (63.3)	448 (61.5)	
Villous adenoma	46 (2.9)	22 (2.6)	24 (3.3)	
SMIC	146 (9.2)	55 (6.4)	91 (12.5)	
Features of Invasion (n, %)				
Kudo V pit pattern	129 (8.1)	74 (8.7)	55 (7.6)	0.427
Depression	85 (5.4)	70 (8.2)	15 (2.1)	<0.001
Ulceration	18 (1.1)	10 (1.2)	8 (1.1)	0.034
Fixed or rigid	116 (7.3)	64 (7.5)	52 (7.2)	0.820

ASA, American Society of Anesthesiologists; LNPCPs, large non-pedunculated colorectal polyps; n, number; SMIC, submucosal invasive cancer
*253 (16.9%) participants were missing ASA classification data

Table 2: Optical evaluation performance outcomes for predicting submucosal invasive cancer overall and stratified by lesion morphology and granularity.

	All LNPCPs (n = 1583)	Flat LNPCPs (n = 855)	Nodular LNPCPs (n = 728)
Sensitivity (%, n/N, 95% CI)	**67.1**% (98/146) (59.2 – 74.2)	**90.9**% (50/55) (80.4-96.1)	**52.7**% (48/91) (42.6 – 62.7)
Specificity (%, n/N, 95% CI)	**95.1**% (1367/1437) (93.9 – 96.1)	**96.3**% (770/800) (94.7 – 97.4)	**93.7**% (597/637) (91.6 – 95.4)
Positive predictive value (%, 95% CI)	**58.3**% (52.0-64.3)	**62.4`**% (53.6-70.4)	**54.6**% (45.6-63.2)
Negative predictive value (%, 95% CI)	**96.6**% (95.8-97.3)	**99.4**% (98.5-99.7)	**93.3**% (91.8-94.5)
Granular LNPCPs			
Sensitivity (%, n/N, 95% CI)	**51.5**% (34/66) (39.7 – 63.2)	**100**% (8/8) (67.6-100)	**44.8**% (26/58) (32.8 – 57.5)
Specificity (%, n/N, 95% CI)	**96.6**% (914/946) (95.3 – 97.6)	**98.7**% (446/452) (97.1 – 99.4)	**94.7**% (468/494) (92.4 – 96.4)
Positive predictive value (%, 95% CI)	**51.4**% (41.2-61.6)	**56.6**% (37.0-74.3)	**50.0**% (38.4-61.5)
Negative predictive value (%, 95% CI)	**96.6**% (95.7-97.4)	**100**% (NA)	**93.6**% (92.1-94.9)
Non-granular LNPCPs			
Sensitivity (%, n/N, 95% CI)	**83.1**% (49/59) (71.5 – 90.5)	**88.9**% (40/45) (76.5 – 95.2)	**64.3**% (9/14) (38.8 – 83.7)
Specificity (%, n/N, 95% CI)	**92.7**% (368/397) (89.7 – 94.9)	**92.9**% (288/310) (89.5 – 95.3)	**92.0**% (80/87) (84.3 – 96.1)
Positive predictive value (%, 95% CI)	**62.7**% (53.8-70.9)	**64.6**% (54.6-73.4)	**56.3**% (36.5-74.4)
Negative predictive value (%, 95% CI)	**97.4**% (95.5-98.5)	**98.3**% (96.2-99.2)	**94.1**% (88.7-97.0)
Mixed-granular LNPCPs			
Sensitivity (%, n/N, 95% CI)	**71.4**% (15/21) (50.0 – 86.2)	**100**% (2/2) (34.2 – 100)	**68.4**% (13/19) (46.0 – 84.6)
Specificity (%, n/N, 95% CI)	**90.4**% (85/94) (82.8 – 94.9)	**94.7**% (36/38) (82.7 – 98.6)	**87.5**% (49/56) (76.4 – 93.8)
Positive predictive value (%, 95% CI)	**62.6**% (45.9-76.7)	**50.0**% (20.6-79.4)	**65.0**% (46.5-79.8)
Negative predictive value (%, 95% CI)	**93.4**% (87.8-96.5)	**100**% (NA)	**89.1**% (80.7-94.1)

CI, confidence interval; LNPCPs, large non-pedunculated colorectal polyps; n, number

Table 3: Miss rates for submucosal invasive cancer on optical evaluation overall and stratified by lesion morphology, granularity, lesion size and location

	All LNPCPs (n = 1583)	Flat LNPCPs (n = 855)	Nodular LNPCPs (n = 728)	p-value
All LNPCPs (%, n/N, 95% CI)	**3.0**% (48/1583) (2.3 – 4.0)	**0.6**% (5/855) (0.3 – 1.4)	**5.9**% (43/728) (4.4 – 7.9)	<0.001
Granularity				
Granular (%, n/N, 95% CI)	**3.2**% (32/1012) (2.3 – 4.4)	**0.0**% (0/460) (0.0 – 0.8)	**5.8**% (32/552) (4.1 – 8.1)	<0.001
Non-granular (%, n/N, 95% CI)	**2.2**% (10/445) (1.2 – 4.0)	**1.4**% (5/355) (0.6 – 3.3)	**5.0**% (5/101) (2.1 – 11.1)	0.047
Mixed (%, n/N, 95% CI)	**5.2**% (6/115) (2.4 – 10.9)	**0.0**% (0/40) (0.0 – 8.8)	**8.0**% (6/75) (3.7 – 16.4)	0.090
Size				
< 40 mm	**1.6**% (14/887) (0.9 - 2.6)	**0.3**% (2/580) (0.1 – 1.2)	**3.9**% (12/307) (2.3 – 6.7)	<0.001
≥ 40 mm	**4.9**% (34/696) (3.5 – 6.8)	**1.1**% (3/275) (0.4 – 3.2)	**7.4**% (31/421) (5.2 – 10.3)	<0.001
Location				
Proximal colon*	**1.7**% (19/1095) (1.1 – 2.7)	**0.6**% (4/708) (0.2 – 1.4)	**3.9**% (15/387) (2.4 – 6.3)	<0.001
Rectosigmoid	**5.9**% (29/488) (4.2 – 8.4)	**0.7**% (1/147) (0.1 – 3.8)	**8.2**% (28/341) (5.7 – 11.6)	0.001

CI, confidence interval; LNPCPs, large non pedunculated colorectal polyps; n, number
*Proximal colon includes Cecum, ascending colon, transverse colon and descending colon
Denominator: LNPCPs with or without SMIC

Table 4: Best-fitting multiple logistic regression model showing independent predictors of missed submucosal invasive cancer on optical evaluation with adjusted odds ratios and p-values

	Odds Ratio (95% CI)	p-value
Nodular morphology	7.2 (2.8 – 18.9)	<0.001
Rectosigmoid location	2.0 (1.1 – 3.7)	0.026
Lesion size ≥ 40 mm	2.0 (1.0 – 3.8)	0.039

CI, confidence interval

Supplemental Table 1: Demographic and lesion characteristics stratified by submucosal invasive cancer

	SMIC (n = 146)	No SMIC (n = 1437)
Age (median, IQR, years)	70 (64-77)	67 (61-75)
Male (n, %)	90 (61.6)	774 (53.9)
ASA classification (n, %)*		
I	28 (19.2)	281 (19.6)
II	71 (48.6)	666 (46.3)
III	22 (15.1)	262 (18.2)
Size (median, IQR, mm)	40 (30 –50)	35 (25-45)
Location (n, %)		
Rectum	58 (39.7)	265 (18.5)
Sigmoid	32 (21.9)	133 (9.3)
Descending	9 (6.2)	71 (4.9)
Splenic flexure	1 (0.7)	32 (2.2)
Transverse	8 (5.5)	161 (11.2)
Hepatic flexure	5 (3.4)	83 (5.8)
Ascending	20 (13.7)	341 (23.7)
Cecum	13 (8.9	351 (24.4)
Morphology (n, %)		
Flat	55 (37.7)	800 (55.7)
Nodular	91 (62.3)	637 (44.3)
Granularity (n, %)		
Granular	66 (45.2)	946 (65.8)
Non-granular	59 (40.4)	397 (27.6)
Mixed granularity	21 (14.4)	94 (6.6)
Features of Invasion (n, %)		
Kudo V pit pattern	83 (56.8)	46 (3.2)
Depression (0-IIc)	31 (21.2)	54 (3.8)
Ulceration	11 (7.5)	7 (0.5)
Fixed or Rigid	33 (22.6)	83 (5.8)

ASA, American Society of Anesthesiologists; n, number; SMIC, submucosal invasive cancer

*253 (16.9%) participants were missing ASA classification

Supplemental Table 2: Diagnostic accuracy of endoscopic features associated with submucosal invasive cancer

	All LNPCPs (n = 1583)	Flat LNPCPs (n = 855)	Nodular LNPCPs (n = 728)
Kudo V pit pattern (%, n/N, 95% CI)	64.3% (83/129) (55.8 – 72.1)	63.5% (47/74) (52.1 – 73.6)	65.5% (36/55) (52.3 – 76.6)
Depression (%, n/N, 95% CI)	36.5% (31/85) (27.0 – 47.1)	34.3% (24/70) (24.3 – 46.0)	46.7% (7/15) (24.8 – 69.9)
Rigid/Fixed (%, n/N, 95% CI)	28.5% (33/116) (21.0 – 37.3)	20.3% (13/64) (12.3 – 31.7)	38.5% (20/52) (26.5 – 52.0)
Ulceration (%, n/N, 95% CI)	61.1 (11/18) (38.6 – 79.7)	60.0% (6/10) (31.3 – 83.2)	62.5% (5/8) (30.6 – 86.3)
Kudo V pit pattern and ≥ 1 additional feature* (%, n/N, 95% CI)	66.2% (45/68) (54.3 – 76.9)	69.6% (32/46) (55.2 – 80.9)	59.1% (13/22) (38.7 – 78.5)

CI, confidence interval; LNPCPs, large non-pedunculated colorectal polyps; n, number
*Additional feature(s) included: depression, rigid/fixed, ulceration.

Supplemental Table 3: Miss rates for submucosal invasive cancer overall and stratified by lesion morphology, granularity, lesion size and location for malignant large non-pedunculated colorectal polyps

	All malignant LNPCPs (n = 146)	Flat malignant LNPCPs (n = 55)	Nodular malignant LNPCPs (n = 91)	p-value
All LNPCPs (%, n/N)	**32.9** (48/146)	**9.1** (5/55)	**47.3** (43/91)	<0.001
Granularity				
Granular (%, n/N)	**48.5** (32/66)	**0.0** (0/8)	**55.2** (32/58)	<0.001
Non-granular (%, n/N)	**16.9** (10/59)	**11.1** (5/45)	**35.7** (5/14)	0.034
Mixed (%, n/N)	**28.6** (6/21)	**0.0**% (0/2)	**31.6** (6/19)	0.359
Size				
< 40 mm	**24.1** (14/58)	**5.6** (2/36)	**54.5** (12/22)	<0.001
≥ 40 mm	**38.6** (34/88)	**15.8** (3/19)	**44.9** (31/69)	0.022
Location				
Proximal colon*	**33.9** (19/56)	**13.8** (4/29)	**55.6** (15/27)	0.001
Rectosigmoid	**32.2** (29/90)	**3.8** (1/26)	**43.8** (28/64)	<0.001

CI, confidence interval; LNPCPs, large non pedunculated colorectal polyps; n, number
*Proximal colon includes Cecum, Ascending colon, Transverse colon and Descending colon

Supplemental Table 4: Univariable analysis of association with missed submucosal invasive cancer on optical evaluation

	n	SMIC missed (n, %)	Odds ratio (95% CI)	p-value
Sex				
Male	864	23 (2.7)	1	
Female	719	25 (3.5)	1.3 (0.7-2.3)	0.348
Age				
> 70 years	717	15 (2.1)	1	
≤ 70 years	866	33 (3.8)	1.9 (1.0-3.4)	0.050
Location				
Proximal to rectosigmoid	1095	19 (1.7)	1	
Rectosigmoid	488	29 (5.9)	3.6 (2.0-6.5)	<0.001
Morphology				
Flat	855	5 (0.6)	1	
Nodular	728	43 (5.9)	10.7 (4.2-27.1)	<0.001
Granularity				
Non-granular	456	10 (2.2)	1	
Mixed	115	6 (5.2)	2.5 (0.9-6.9)	0.089
Granular	1012	32 (3.2)	1.5 (0.7-3.0)	0.305
Lesion Size				
< 40 mm	887	14 (1.6)	1	
≥ 40 mm	696	34 (4.9)	3.2 (1.7-6.0)	<0.001
Previously attempted				
Yes	153	3 (2.0)	1	
No	1430	45 (3.1)	1.6 (0.5-5.3)	0.421

CI, confidence interval; n, number; SMIC, submucosal invasive cancer
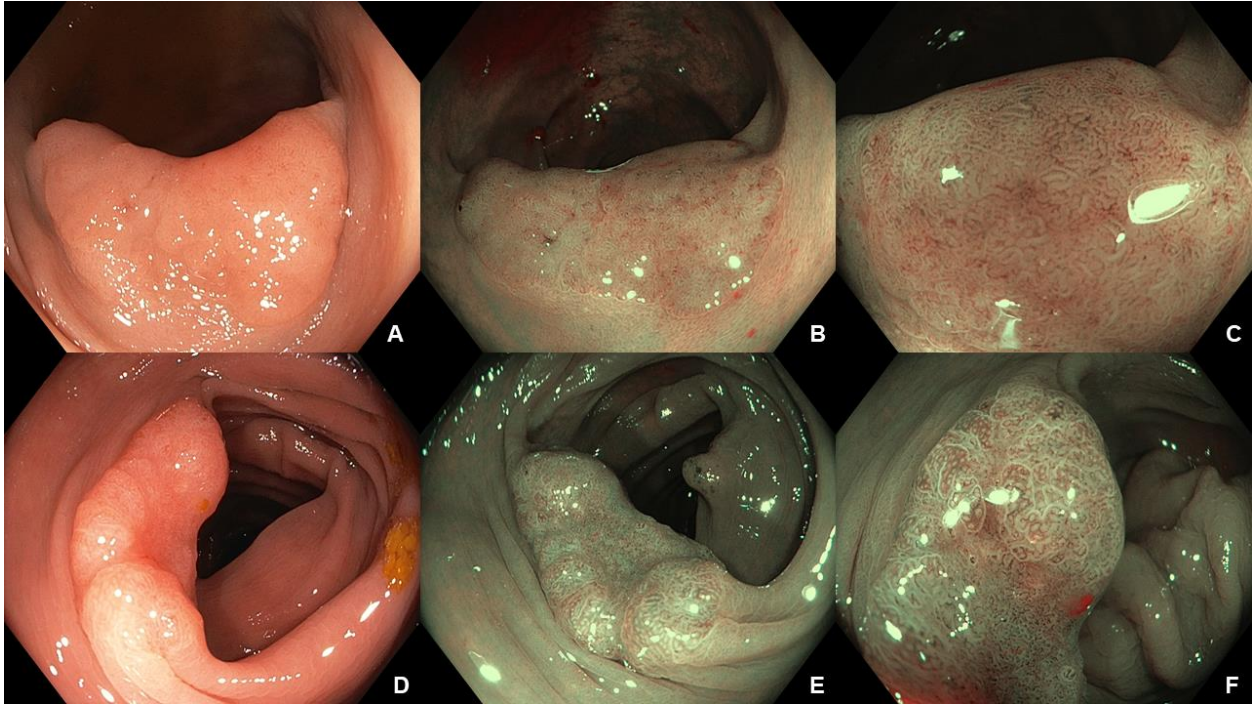
Figure 1: Optical evaluation of flat lesions. A: A 25mm 0-IIa non-granular large non-pedunculated colorectal polyp in the transverse colon. **B-C:** On narrow-band imaging, a homogenous pit (Kudo pit pattern III/IV) and microvascular pattern are identified. Histology confirmed a tubular adenoma with low-grade dysplasia. **D:** A 25mm 0-IIa+c non-granular large non-pedunculated colorectal polyp in the transverse colon. **E-F:** On narrow-band imaging, a demarcation line is readily apparent with disruption of the pit (Kudo pit pattern V) and microvascular pattern. Histology confirmed a superficial submucosal invasive cancer in the absence of other high-risk histologic features.
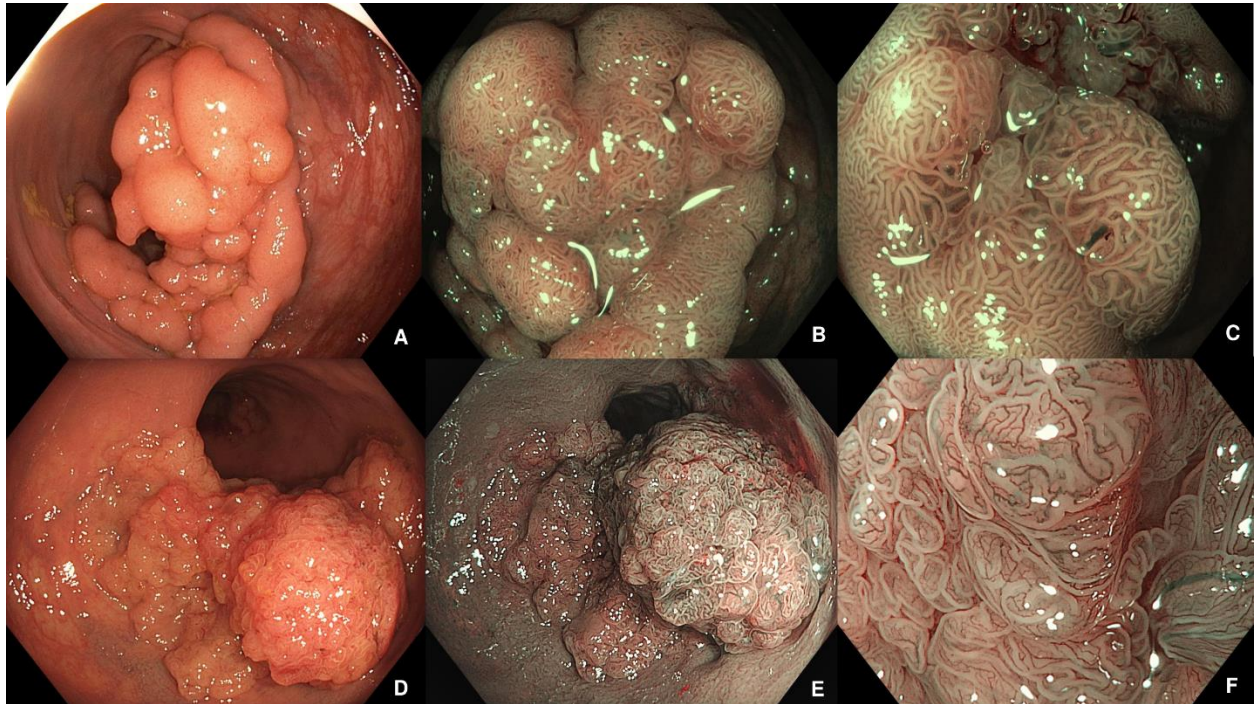
Figure 2: Optical evaluation of nodular lesions. **A:** A 50mm 0-IIa+Is mixed large non-pedunculated colorectal polyp in the proximal rectum. **B-C:** On narrow-band imaging, a homogenous. pit pattern (Kudo pit pattern IV) and microvascular pattern are identified. Histology confirmed a tubulovillous adenoma with high-grade dysplasia. **D:** A 60mm 0-IIa+Is granular large non-pedunculated colorectal polyp in the distal sigmoid colon. **E-F:** On narrow-band imaging, a homogenous pit and microvascular pattern are identified. Histology identified a superficial submucosal invasive cancer with lymphovascular invasion.
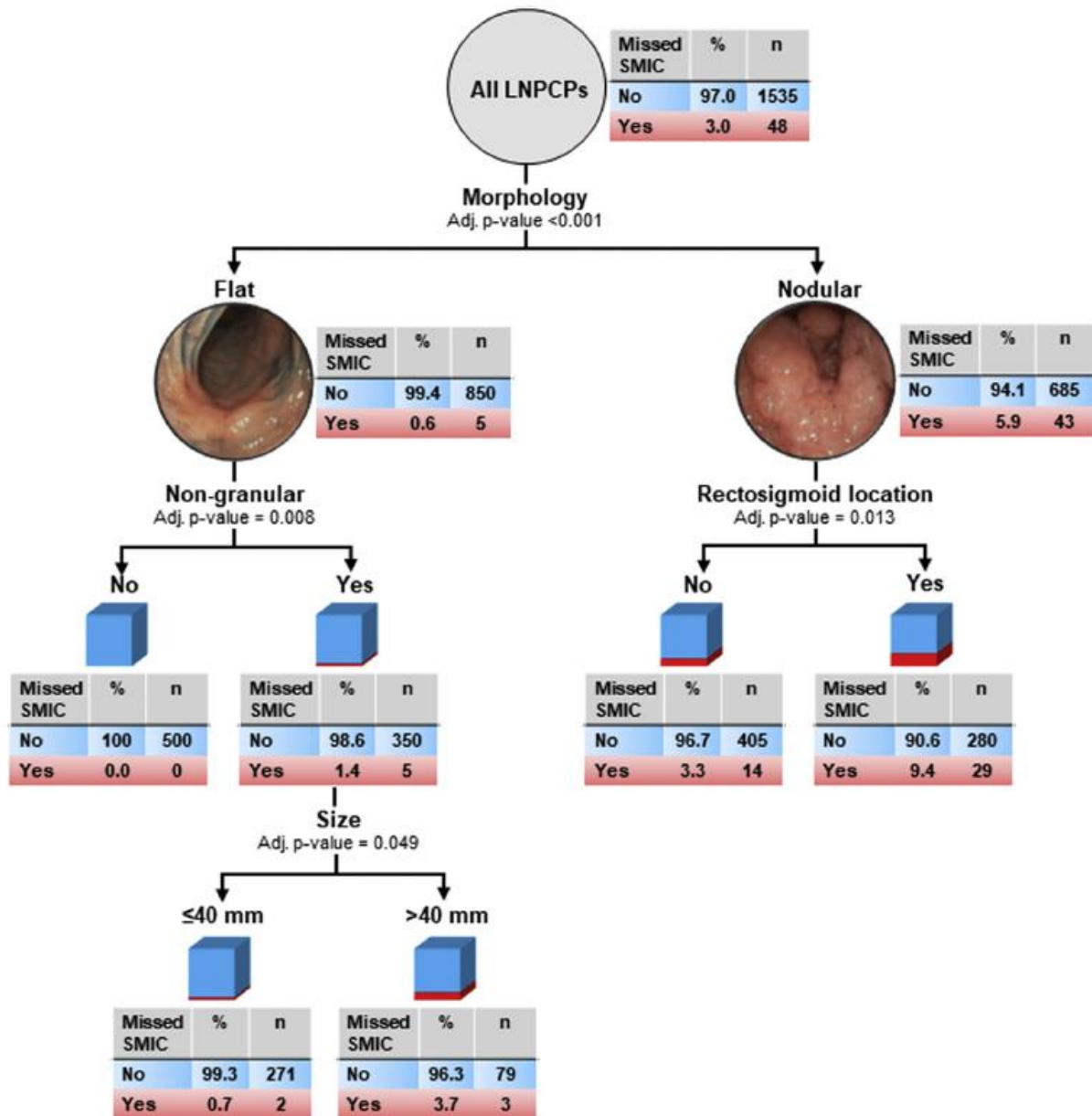
Supplemental Figure 1: Classification tree analysis for missed submucosal invasive cancer. LNPCPs, large non-pedunculated colorectal polyps; n, number; SMIC, submucosal invasive cancer

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Integrative Discussion

Endoscopic mucosal resection (EMR) has transformed large non-pedunculated colorectal polyps (LNPCPs) from a surgical to an endoscopic disease process. The 5 chapters of this thesis address key deficits in the literature on existing challenges in LNPCP management; thereby empowering endoscopists to improve patient outcomes and resource utilization. Taken together, they highlight that the vast majority of LNPCPs, regardless of lesion complexity, can be managed by EMR.

Large Non-Pedunculated Colorectal Polyps at the Anorectal Junction

To our knowledge, this is the world's largest description on the management of large non-pedunculated colorectal polyps at the anorectal junction (ARJ-LNPCPs) (1). It highlights several key findings. Firstly, with site-specific technical modifications, EMR is effective and safe for ARJ-LNPCPs with no difference in adverse outcomes compared to large non-pedunculated rectal polyps (LNPRPs) outside of significant deep mural injury (S-DMI; 0% ARJ-LNPCPs vs. 4.5% LNPRPs; p = 0.027). Secondly, with the introduction of EMR with margin thermal ablation (EMR-T), recurrence was essentially negative (0.0% EMR-T vs. 25.0% EMR; p = 0.002). Therefore, EMR should be considered a primary resection modality for benign appearing ARJ-LNPCPs; especially given the adverse event profiles of ESD and comparative limitations of transanal endoscopic surgeries (TES).

Non-Curative Piecemeal Resection of Low-Risk Colorectal Cancers

With site-specific technical modifications in high-quality EMR technique, alongside auxiliary techniques and management strategies mitigating the risk of

technical failure, recurrence and adverse events, non-curative piecemeal resection of low-risk submucosal invasive cancer (SMIC) remains the primary limitations of EMR. Therefore, a selective resection algorithm incorporating piecemeal and en bloc resection techniques are needed. This is the first study to apply a selective resection algorithm (SRA) to the management of LNPRPs (2). It demonstrates that in comparison, to a universal EMR algorithm (UEA), a selective resection algorithm (SRA), incorporating real-time optical evaluation to select between EMR and ESD, leads to a significant differences in SMIC after EMR (UEA 12.1% vs. SRA 1.0%; p = 0.001) and curative oncologic resection (UEA 5.7% vs. SRA 33.3%; p = 0.010). Moreover, no significant differences in technical success of adverse events were identified (all p > 0.137). These findings represent a paradigm shift in the management of LNPRPs. It provides a framework for a SRA, dependent on local endoscopic expertise and resources, which harnesses the efficacy, efficiency and safety of EMR with the curative potential for low-risk SMIC of ESD.

Previously Attempted Large Non-Pedunculated Colorectal Polyps

Previously attempted large non-pedunculated colorectal polyps (PA-LNPCPs) are a frequently encountered challenging LNPCP subgroup. In this study (3), we demonstrate that in comparison to naïve LNPCPs (N-LNPCPs), there were significant differences in resection duration (median; 35 minutes IQR 25-60 minutes vs. 25 minutes IQR 15-40 minutes; p < 0.001), technical success (93.0% vs. 96.6%; p = 0.026), and need for auxiliary modality (46.2% vs. 7.6%; p < 0.001). Although statistically significant, the difference in technical success may not be clinically relevant. Moreover, when allowing for two-stage EMR, no difference in technical success was identified (95.6%

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vs. 97.8%). Furthermore, no difference in adverse events or recurrence were identified. Lastly, EMR-T negated the risk of recurrence at first surveillance colonoscopy (SC1), regardless if cold forceps avulsion with adjuvant snare-tip soft coagulation (CAST) was required (0.0% EMR-T vs. 18.0% EMR; $p < 0.001$; 0.0% EMR-T + CAST vs. 31.3% EMR + CAST; $p = 0.001$). In conjunction with the findings for ARJ-LNPCPs, EMR has now been evaluated and shown to effective and safe across the gamut of complex LNPCPs including circumferential LNPCPs, and those involving the appendiceal orifice and ileocecal valve.

Significant Deep Mural Injury

Significant deep mural injury is of critical concern, with limited evidence for EMR-related short term and long-term outcomes. This multicenter evaluation of 3717 LNPCPs demonstrates a number of important findings (4). Firstly, successful defect closure with through-the-scope mechanical clips (TTSCs) was achieved in 98 of 101 patients (97.0%). Moreover, when comparing LNPCPs with and without S-DMI, no difference in technical success (93.1 vs. 91.7%; $p = 0.62$) or SC1 recurrence (20.0% vs. 13.6%; $p = 0.15$) were identified. Therefore, S-DMI is readily managed with TTSCs and generally does not affect EMR-related short-term and long-term outcomes. We also provide a management framework for suspected S-DMI and recommendations stratified by DMI severity and patients' characteristics. Based on these findings and the financial implications of OTSC defect closure, OTSC should be reserved for cases unamenable to TTSC defect closure.

Optical Evaluation to Differentiate between Benign and Malignant Large Non-Pedunculated Colorectal Polyps

Optical evaluation is the crux of LNPCP management as it informs therapeutic decisions. However, it is currently limited due to modest performance to accurately predict SMIC. Herein, we reaffirm the modest performance characteristics of LNPCPs (sensitivity 67.1%, 95% CI 59.2-74.2%; specificity 95.1%, 95% CI 93.9-96.1%; SMIC miss rate 3.0%, 95% CI 2.3-4.0%) (5). However, significant differences in sensitivity (90.9% vs. 52.7%), specificity (96.3% vs. 93.7%), and SMIC miss rate (0.6% vs. 5.9%) between flat and nodular LNPCPs were identified (all p < 0.027). These findings are supported by multivariable regression analysis and decision tree classification modelling. Notably, flat granular LNPCPs showed excellent optical evaluation performance (sensitivity 100% 95% CI 67.6-100%; specificity 98.7%, 95% CI 97.1-99.4%; SMIC miss rate 0.0%, 95% CI 0.0-0.8%). Therefore, we demonstrate excellent optical evaluation performance for flat LNPCPs and in the absence of optical features consistent with SMIC, it is safe to proceed with EMR. Alternatively, future research to refine optical evaluation performance needs to be directed at nodular LNPCPs.

Future Research

Although this thesis has addressed multiple challenges in the application of minimally invasive endoscopic resection techniques, a number of pertinent questions remain:

- Performance of EMR and ESD for inflammatory bowel disease-related neoplasia
- Programmatic LNPCP outcomes in universal colorectal cancer screening programs

- Optimization of optical evaluation for nodular LNPCPs, including the role of artificial intelligence to address operator-dependent limitations

- International validation of EMR outcomes for complex LNPCPs

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    *Denotes co-first author

Conclusions

Innovations in the pre-resection, resection and post-resection phases of large non-pedunculated colorectal polyp (LNPCP) management continue to improve patient outcomes, allow for organ preservation, and improve healthcare resource utilization. The thesis continues this theme of innovation by addressing of number of ongoing challenges in the application of endoscopic mucosal resection (EMR): 1) EMR is effective for LNPCPs at the anorectal junction and for previously attempted LNPCPs; 2) A rectum-specific selection resection algorithm addresses the key limitation of EMR; which is non-curative piecemeal resection of LNPCPs with low-risk submucosal invasive cancer (SMIC); 3) Significant deep mural injury is now readily managed by through-the-scope mechanical clips and does not impact technical success or recurrence; 4) Optical evaluation has excellent performance for flat LNPCPs and in the absence of optical features of SMIC, can be readily managed by EMR.

These findings continue to redirect the clinical trajectory of challenging LNPCPs away from unnecessary surgery. Consistent with current consensus recommendations, the majority of LNPCPs, regardless of complexity, can be managed by EMR.

Appendices

Publications Related to PhD During Candidacy

1. **Shahidi N**, Sidhu M, Vosko S, van Hattem WA, Bar-Yishay I, Schoeman S, Tate DJ, Holt B, Hourigan L, Lee EYT, Burgess N, Bourke MJ. Endoscopic mucosal resection is effective for laterally spreading lesions at the anorectal junction. Gut 2020;69:673-680

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Abstracts Related to PhD During Candidacy

1. Vosko S, **Shahidi N**, Sidhu M, Hourigan LF, Singh R, Moss AC, Van Hattem A, Bar-Yishay I, Schoeman S, Burgess N, Bourke MJ. Lesion morphology and topography influence the prediction and miss rates of submucosal invasive cancer in colorectal laterally spreading lesions. J Gastroenterol Hepatol 2019;34:224

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Awards During Candidacy

1. United European Gastroenterology Travel Award 2019

2. United European Gastroenterology Week Poster of Excellence Award 2019

3. Gastroenterology Society of Australia Travel Award 2019

4. University of Syndey Completion Tuition Award 2022

5. University of Sydney Completion Stipend Award 2022

Other Publications During Candidacy

1. **Shahidi N**, Bourke MJ. Endoscopic full-thickness resection for invasive colorectal neoplasia: Hype or here to stay? Gastrointest Endosc 2019;89:1190-1192

2. **Shahidi N**, Sidhu M, Bar-Yishay I, Bourke MJ. Mind the gap: Submucosal diffusion of tattoo into the resection defect. Gastrointest Endosc 2019;90:856-858

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ORIGINAL RESEARCH

Endoscopic mucosal resection is effective for laterally spreading lesions at the anorectal junction

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ABSTRACT

Objective The optimal approach for removing large laterally spreading lesions at the anorectal junction (ARJ-LSLs) is unknown. Endoscopic mucosal resection (EMR) is a definitive therapy for colorectal LSLs. It is unclear whether it is an effective modality for ARJ-LSLs.
Design EMR outcomes for ARJ-LSLs (distal margin of ≤20 mm from the dentate line) in comparison with rectal LSLs (distal margin of >20 mm from the dentate line) were evaluated within a multicentre observational cohort of LSLs of ≥20 mm. Technical success was defined as the removal of all polypoid tissue during index EMR. Safety was evaluated by the frequencies of intraprocedural bleeding, delayed bleeding, deep mural injury (DMI) and delayed perforation. Long-term efficacy was evaluated by the absence of recurrence (either endoscopic or histologic) at surveillance colonoscopy (SC).
Results Between July 2008 and August 2019, 100 ARJ-LSLs and 313 rectal LSLs underwent EMR. ARJ-LSL median size was 40 mm (IQR 35–60 mm). Median follow-up at SC4 was 54 months (IQR 33–83 months). Technical success was 98%. Cancer was present in three (3%). Recurrence occurred in 15.4%, 6.8%, 3.7% and 0% at SC1–SC4, respectively. Among 30 ARJ-LSLs that received margin thermal ablation, no recurrence was identified at SC1 (0.0% vs 25.0%, p=0.002). Technical success, recurrence and adverse events were not different between groups, except for DMI (ARJ-LSLs 0% vs rectal LSLs 4.5%, p=0.027).
Conclusion EMR is an effective technique for ARJ-LSLs and should be considered a first-line resection modality for the majority of these lesions.

INTRODUCTION

Large (≥20 mm) laterally spreading lesions at the anorectal junction (ARJ-LSLs) have historically been referred to surgery due to the unique anatomical, sensory and physiological characteristics of this area. However, distal colorectal surgery carries a significant risk of morbidity, mortality and permanent ostomy formation.[1] With evidence supporting the efficacy, safety and cost-effectiveness of minimally invasive resection techniques,[2–5] distal colorectal surgery for early colorectal neoplasia should be discouraged.

Nevertheless, the optimal minimally invasive strategy for removing ARJ-LSLs remains unknown. This is due to a lack of randomised trials comparing different local excision modalities and a lack of

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Significance of this study

What is already known on this subject?
► While endoscopic mucosal resection (EMR), endoscopic submucosal dissection and transanal endoscopic surgery are existing techniques for resecting large colorectal laterally spreading lesions at the anorectal junction (ARJ-LSLs), the optimal strategy is unknown.

What are the new findings?
► This study demonstrates that EMR is an effective, efficient and safe method for treating ARJ-LSLs.

How might it impact on clinical practice in the foreseeable future?
► EMR should be viewed as a first-line option for treating ARJ-LSLs.

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long-term observational data. As the primary resection modality for the colorectum, evidence demonstrating the short-term efficacy of endoscopic mucosal resection (EMR) for treating ARJ-LSLs exists.[6 7] Modifications in EMR technique are required to successfully treat the distal resection margin. This is due to rectal fold convergence, presence of the haemorrhoidal plexus and somatic innervation at the squamous epithelium.

Two alternative strategies, endoscopic submucosal dissection (ESD) and transanal endoscopic surgery (TES), are currently used to treat ARJ-LSLs. Both can perform en bloc resection of lesions of ≥20 mm. Therefore, they carry the ability to perform curative resection for superficial submucosal invasive cancer (S-SMIC) (≤1000 µm), in the absence of other high-risk histological features.[8–10] However, the infrequency of S-SMIC in colorectal LSLs, coupled with the modest R0 resection frequencies of ESD and TES, directly questions their universal application.[11 12] Moreover, concerning ARJ-LSLs, there are limited retrospective data supporting the utility of these techniques.[13 14]

With major advances in optical evaluation allowing for effective submucosal invasive cancer (SMIC) risk stratification[15–17] alongside thermal ablation techniques mitigating the risk of recurrence after EMR,[18] we sought to evaluate its efficacy for
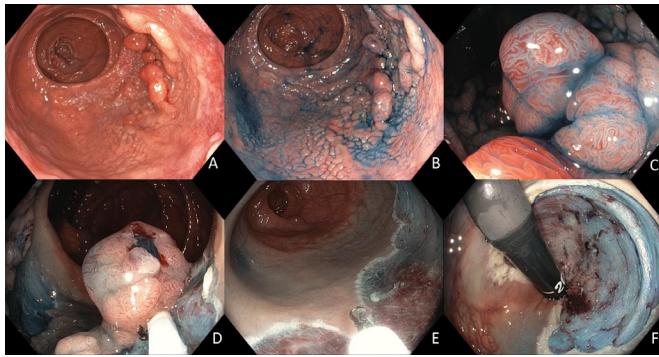
Figure 1 (A) A 70 mm 50% circumferential 0-IIa+Is granular laterally spreading lesion with the distal margin abutting the dentate line. (B) Lesion margins best seen under chromoendoscopy. (C) Kudo IV pit pattern, Narrow-band Imaging International Colorectal Endoscopic type II, Japan Narrow-band Imaging Expert Team type IIA on optical evaluation. (D) High-quality endoscopic mucosal resection performed in a systematic manner. (E,F) Margin thermal ablation performed to mitigate the risk of recurrence. Final histology confirmed a tubulovillous adenoma.

treating ARJ-LSLs in a retrospective analysis of a prospectively collected multicentre observational cohort.

METHODS

This manuscript was created in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[19]

The Australian Colonic Endoscopic Resection (ACE) study

The ACE study (clinicaltrials.gov identifiers: NCT01368289; NCT02000141) is a prospectively collected, multicentre, observational cohort of consecutive patients referred for managing colorectal LSLs of ≥20 mm (July 2008–present).

Consecutive rectal LSLs enrolled at two sites in the ACE study between July 2008 and August 2019 were evaluated. ARJ-LSLs were defined as those either crossing or within 20 mm of the dentate line. Consistent with previous descriptions,[6 7] an anatomically and clinically relevant cut-off of ≤20 mm was selected to define ARJ-LSLs. Anatomically, although variable, the anal transition zone is commonly defined as the proximal 20 mm above the dentate line.[20] Histologically, it shares characteristics of columnar and squamous epithelium. Longitudinal mucosal folds, known as the columns of Morgagni, occupy the anal transition zone. These harbour a submucosal plexus, which forms the hemorrhoidal plexus. This area is therefore clinically relevant for the management of distal colorectal lesions and the application of minimally invasive resection techniques due to (1) impaired endoscopic visualisation as the columns of Morgagni converge towards the dentate line; (2) the risk of precipitating pain, given the somatic innervation of squamous epithelium in the context of obtaining a healthy margin of normal tissue during high-quality EMR; (3) the risk of bacteraemia due to the relative lack of protection by the reticuloendothelial function of the portal lymphovenous drainage system; (4) the implications of achieving an adequate surgical resection margin and thus appropriately selecting between sphincter-sparing surgery and abdominal perineal resection.[21]

Technique

All endoscopic procedures were performed by one of four study investigators (an accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal EMR) or a senior interventional endoscopy fellow under supervision. Endoscopic resections were performed in a standardised fashion across all centres.[5] Technical innovations in EMR were adopted as the evidence to support them emerged. Antiplatelet and anticoagulation medications were held preprocedure, in accordance with consensus recommendations.[22]

A standardised, previously described inject and resect EMR technique was used at all centres.[5] Currently, all colorectal EMRs are performed using high-definition Olympus 190 series variable-stiffness colonoscopes (Olympus, Tokyo, Japan). Carbon dioxide is used for insufflation.[23] After lesion identification, optical evaluation under high-definition white-light and narrow-band imaging is performed to exclude features of SMIC. In a systematic fashion, a submucosal cushion is created with injection of succinylated gelatin[24] (Gelofusine; B. Braun, Bella Vista, Australia) with 0.4% indigo carmine and 1:100 000 epinephrine. Using a microprocessor-controlled generator (ERBE VIO ENDO CUT Q, effect 3; ERBE, Tubingen, Germany), snare excision is performed.

After complete resection, the defect is carefully examined to ensure no polypoid tissue remains and to assess for deep mural injury (DMI).[25] Areas of deep injury (DMI III–V) are subsequently treated by mechanical clip closure. Thermal ablation of the resection margin to mitigate the risk of recurrence is performed using snare-tip soft coagulation (STSC) (ERBE VIO SOFT COAG: 80 W, effect 4) to create a rim of ablated tissue of 2–3 mm.[18] Clinically significant intraprocedural bleeding (CSIPB) is treated with coagulation forceps or mechanical haemostasis. Resection specimens are collected and evaluated by specialist GI pathologists at their respective centres.

After completion of the procedure, patients are observed for 4 hours. If well, they are subsequently discharged on a clear fluid diet overnight. At 2 weeks, patients are contacted by an ACE study coordinator and undergo a structured telephone interview to identify periprocedural adverse events. Intervals between subsequent colonoscopies are at the discretion of the endoscopist performing surveillance with recommended surveillance colonoscopy (SC) intervals of 6, 12, 36 and 60 months (SC1–SC4,
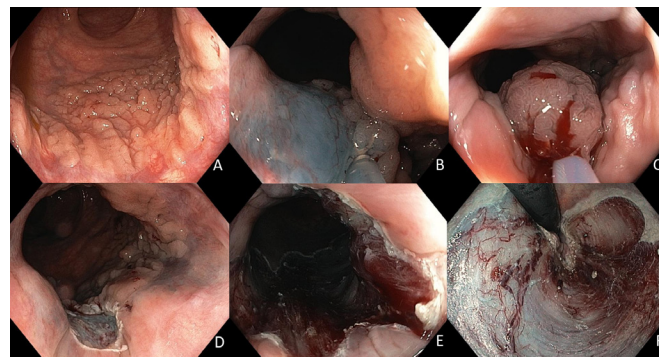

Figure 2 (A) A 60 mm 75% circumferential 0-IIa granular laterally spreading lesion with the distal margin crossing the dentate line. (B–E) High-quality endoscopic mucosal resection with resection at the anorectal junction. (F) Post margin thermal ablation defect evaluation showing no deep mural injury. Final histology confirmed a tubulovillous adenoma.
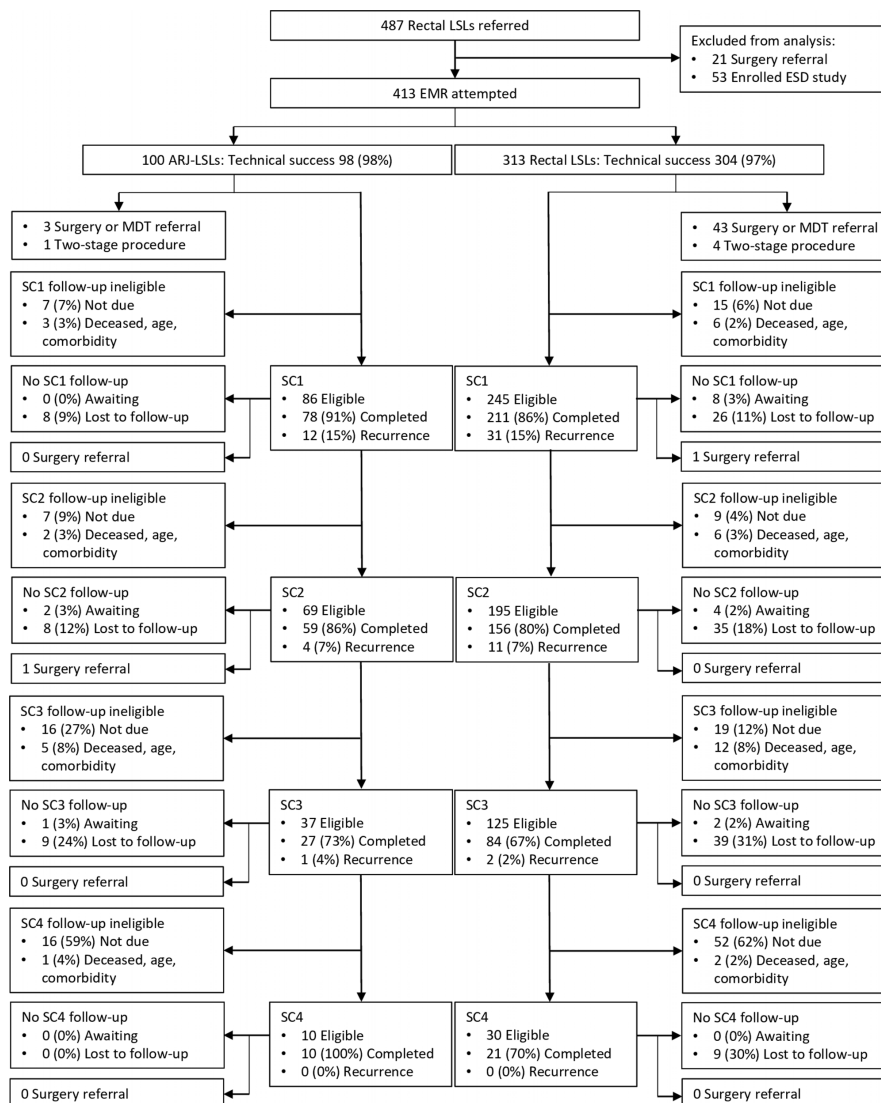
Figure 3 Flow diagram of consecutive rectal laterally spreading lesions referred for endoscopic resection. ARJ-LSL, laterally spreading lesion at the anorectal junction; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LSL, laterally spreading lesion; MDT, multidisciplinary team; SC, surveillance colonoscopy.

respectively). During SC, patients undergo a standardised evaluation of the EMR scar.[26] Biopsies are routinely performed.

Specific procedural aspects for EMR at the anorectal junction are as follows (figures 1 and 2 and online supplementary video 1)[6]:

1. *Prophylactic antibiotics*: antibiotics (ceftriaxone 1000 mg intravenous and metronidazole 500 mg intravenous) are administered intraprocedurally, given the theoretical risk of bacterial translocation. Continued antibiotic prophylaxis postprocedure is not routinely provided.

2. *Lesion access*: a gastroscope with cap attachment can be used to maximise manoeuvrability in the retroflexed position and to optimise visibility by deflecting mucosal folds at the anorectal junction, respectively.

3. *Pain management*: at the distal margin, long-acting local anaesthetic (ropivacaine 0.5%, maximum dose of 40 mg) is added to the submucosal injectate to provide anaesthesia (4 hours) and analgesia (24 hours). Cardiac monitoring is required. Oral paracetamol every 4–6 hours as needed is prescribed to all patients at discharge.

4. *Resection over haemorrhoidal columns*: anterograde tangential submucosal injection is performed to facilitate adequate submucosal expansion away from the haemorrhoidal plexus. Resection is initiated at the distal margin, with meticulous snare placement and tissue capture with a rim of normal tissue of 2–3 mm irregardless of proximity to the dentate line.

5. *Margin thermal ablation*: using identical settings and technique in the colorectum, STSC is carefully performed along the distal resection margin, being mindful of the somatic innervation of the squamous epithelium.

Data extraction

Collected data included (1) patient characteristics: sex, age and American Society of Anesthesiologists (ASA) classification; (2) lesion characteristics: size, Paris classification,[27] surface topography, Kudo pit pattern[28] and histopathology; and (3) procedure outcomes: technical success, periprocedural adverse events and recurrence.

Technical success was defined as complete removal of all polypoid tissue during index EMR. CSIPB was defined by

oozing or spurting blood loss for ≥60 s, not responding to water jet irrigation, and requiring either coagulation forceps or mechanical haemostasis.[29] Clinically significant postendoscopic mucosal resection bleeding (CSPEB) was defined as any bleeding that occurred after the procedure and required emergency room presentation, hospitalisation or reintervention (endoscopy, angiography and surgery).[30] DMI was defined as grade III (target sign[31]) or grade IV/V (transmural perforation without or with contamination, respectively).[25] Pain was defined by the requirement of analgesia postprocedure. Long-term efficacy was defined by the absence of either endoscopic or histologic recurrence at SC. Study endpoints included technical failure, SMIC, death, advanced age or comorbidities precluding ongoing SC, being lost to follow-up and SC4.

Statistical analysis

The primary outcome was technical success. Secondary outcomes were periprocedural adverse events and recurrence (stratified by those who received margin STSC). ARJ-LSLs were compared with the remaining cohort of rectal LSLs.

SPSS V.25.0 was used for retrospective data analysis. Continuous variables were summarised using median (IQR). Categorical variables were summarised as frequencies (%). To test for association between categorical variables, the Pearson χ^2 or the Fisher exact test was used, where appropriate. For continuous variables, the Mann-Whitney U test was used. A probability (p) value of <0.05 was considered statistically significant.

Patient and public involvement

Patients were not involved in the design and execution of this study.

RESULTS

Between July 2008 and August 2019, 128 ARJ-LSLs and 359 rectal LSLs were referred for endoscopic resection (figure 3). Twenty lesions (5 ARJ-LSLs and 15 rectal LSLs) demonstrated features consistent with deep submucosal invasive cancer (D-SMIC) (>1000 μm) on optical evaluation and were referred directly to surgery. One rectal LSL had a concomitant sigmoid cancer and was referred to surgery. Fifty-three lesions (23 ARJ-LSLs and 30 rectal LSLs) were enrolled in a selective ESD protocol (clinicaltrials.gov identifier: NCT02198729). These lesions were excluded from analysis. Thirty-six lesions (10 ARJ-LSLs and 26 rectal LSLs) were concomitantly enrolled in a randomised trial (clinicaltrials.gov identifier: NCT01789749) assessing the ability of margin thermal ablation to mitigate recurrence.

Patient and lesion characteristics

One-hundred ARJ-LSLs underwent EMR among 99 patients (table 1). Eighty-two (82%) involved the dentate line. The median age was 64 years (IQR 55–73 years), with 53 (53.5%) being male. The majority were ASA I (37, 41.1%) or ASA II (43, 47.8%). The median lesion size was 40 mm (IQR 35–60mm). Eleven (11.0%) were previously attempted, all by snare-based resection techniques. On optical evaluation, Paris classification 0-IIa+Is was the predominant morphology (55, 55.0%). Eighty-eight (88.0%) showed granular topography. Ninety-seven (97%) showed either Kudo pit pattern III or IV.

Procedure outcomes

The median procedure time was 30 min (IQR 15–55 min) (table 2). Technical success was achieved in 98 (98%). Thermal ablation of the EMR margin was performed in 41 (41.0%).

Table 1 Patient and lesion characteristics

	All rectal LSLs (n=413) n (%)	ARJ-LSLs (n=100) n (%)	Rectal LSLs (n=313) n (%)
Patient characteristics			
Age (years), median (IQR)	66 (58–74)	64 (55–73)	67 (59–75)
Male sex, n (%)	221 (54.0)	53 (53.5)	168 (54.2)
ASA classification, n (%)*			
I	166 (45.4)	37 (41.1)	129 (46.7)
II	158 (43.2)	43 (47.8)	115 (41.7)
III	42 (11.5)	10 (11.1)	32 (11.6)
Lesion characteristics			
Size (mm), median (IQR)	40 (30–60)	40 (35–60)	40 (30–60)
Previously attempted, n (%)	54 (13.1)	11 (11.0)	43 (13.7)
Paris classification, n (%)			
0-IIa	111 (26.9)	32 (32.0)	79 (25.2)
0-IIb	4 (1.0)	0 (0.0)	4 (1.3)
0-Is	73 (17.7)	11 (11.0)	62 (19.8)
0-IIa+Is	216 (52.3)	55 (55.0)	161 (51.4)
Any 0-IIc component	9 (2.2)	2 (2.0)	7 (2.2)
Topography, n (%)†			
Granular	329 (80.6)	88 (88.0)	241 (78.2)
Non-granular	41 (10.0)	5 (5.0)	36 (11.7)
Mixed	35 (8.6)	7 (7.0)	28 (9.1)
Serrated topography	3 (0.7)	0 (0.0)	3 (1.0)
Kudo pit pattern, n (%)‡			
I	2 (0.5)	0 (0.0)	2 (0.6)
II	7 (1.7)	1 (1.0)	6 (1.9)
III	82 (20.0)	14 (14.3)	68 (21.9)
IV	304 (74.3)	83 (84.7)	221 (71.1)
V	14 (3.4)	0 (0.0)	14 (4.5)
Histopathology, n (%)			
Tubular adenoma	39 (9.4)	6 (6.0)	33 (10.5)
Tubulovillous adenoma	277 (67.1)	69 (69.0)	208 (66.5)
Villous adenoma	11 (2.7)	2 (2.0)	9 (2.9)
Serrated	21 (5.1)	13 (13.0)	8 (2.6)
Submucosal invasive cancer	42 (10.2)	3 (3.0)	39 (12.5)
Other	23 (5.6)	7 (7.0)	16 (5.1)
Dysplasia, n (%)			
None	8 (2.2)	3 (3.1)	5 (1.8)
Low-grade dysplasia	261 (70.4)	74 (76.3)	187 (68.2)
High-grade dysplasia	102 (27.5)	20 (20.6)	82 (29.9)

*43 participants; ASA was not classified.
†5 lesions; topography was not classified.
‡4 lesions; Kudo pit pattern was not classified.
ARJ-LSL, laterally spreading lesion at the anorectal junction; ASA, American Society of Anesthesiologists; LSL, laterally spreading lesion.

An auxiliary modality, to allow for complete removal of all polypoid tissue, was required in 12 (12.0%). Auxiliary modalities included cold avulsion with adjuvant snare-tip soft coagulation (CAST) in five (41.7%); hot avulsioin in two (16.7%) and other thermal techniques in five (41.7%). EMR was unsuccessful in two (2.0%). In one case, submucosal fibrosis was secondary to SMIC, with subsequent referral to surgery. In the other case, severe submucosal fibrosis was encountered due to a previously attempted resection. Technical success was achieved by CAST after rescue two-stage resection. Nineteen (19.2%) required hospital admission postprocedure: 11 (57.9%) for observation after extensive endoscopic resection, 1 (5.4%) due to comorbid disease management, 1 (5.4%) due to rigours postprocedure, 2 (10.5%) for CSPEB and 4 (21.1%) for social reasons. None were due to postprocedure pain.

On histopathology, the majority (69, 69.0%) were tubulovillous adenomas. The frequencies of low-grade dysplasia and

Table 2 Procedural outcomes

	All rectal LSLs (n=413) n (%)	ARJ-LSLs (n=100) n (%)	Rectal LSLs (n=313) n (%)	P value
Duration (min), median (IQR)*	25 (15–50)	30 (15–55)	25 (12–50)	0.045
Technical success, n (%)	402 (97.3)	98 (98.0)	304 (97.1)	1.000
Auxiliary modality, n (%)	58 (14.0)	12 (12.0)	46 (14.7)	0.499
Margin thermal ablation, n (%)	133 (32.2)	41 (41.0)	92 (29.4)	0.031
CSIPB, n (%)	24 (5.8)	6 (6.0)	18 (5.8)	0.926
Deep mural injuries III–V, n (%)	14 (3.4)	0 (0.0)	14 (4.5)	0.027
Pain, n (%)†	15 (4.3)	5 (6.1)	10 (3.8)	0.366
Direct hospital admission, n (%)‡	72 (17.6)	19 (19.2)	53 (17.1)	0.634
CSPEB, n (%)	32 (7.8)	11 (11.1)	21 (6.8)	0.162
Delayed perforation, n (%)	1 (0.2)	0 (0.0)	1 (0.3)	1.000

*41 lesions missing procedural duration.
†62 participants missing pain.
‡8 participants were admitted due to postprocedure pain, of which all were rectal LSLs.
ARJ-LSL, laterally spreading lesion at the anorectal junction; CSIPB, clinically significant intraprocedural bleeding; CSPEB, clinically significant postendoscopic mucosal resection bleeding; LSL, laterally spreading lesion.

high-grade dysplasia were 74 (76.3%) and 20 (20.6%), respectively. Submucosal invasive cancer was identified in three (3.0%), which were subsequently referred to surgery or to multidisciplinary team discussion.

Adverse events

CSIPB was encountered in 6 (6.0%). Haemostasis was achieved in all cases by either coagulation forceps (four, 66.7%) or mechanical clip placement (two, 33.3%). No cases of DMI III–V occurred. Five (6.1%) patients required postprocedural analgesia. One (1.0%) patient experienced rigours with subsequent admission to hospital for intravenous antibiotics.

CSPEB occurred in 11 (11.1%). In four (36.4%), this was conservatively managed, with seven (63.6%) undergoing endoscopic re-evaluation with or without endoscopic reintervention. No cases of delayed perforation occurred.

Long-term outcomes

Eighty-six, 69, 37 and 10 were eligible for SC1–SC4, respectively, of which 78 (90.7%), 59 (85.5%), 27 (73.0%) and 10 (100.0%) underwent endoscopic follow-up (table 3). From index EMR, median time to follow-up for SC1–SC4 was 5 months (IQR 4–7 months), 19 months (IQR 14–23 months), 39 months (IQR 28–57 months) and 54 months (IQR 33–83 months), respectively. Recurrence was identified in 12 (15.4%) at SC1, 4 (6.8%) at SC2, 1 (3.7%) at SC3 and 0 (0.0%) at SC4. Surgery was avoided in all but one case, which was due to extensive recurrence at SC2.

Among 30 ARJ-LSLs that underwent margin STSC to mitigate the risk of recurrence and underwent SC, no recurrence was identified at SC1 versus 12 (25%, p=0.002), which did not undergo STSC (table 4). Only one case of recurrence was identified among ARJ-LSLs, which underwent STSC between SC1 and SC4. This was in a 70 mm 0-IIa+Is lesion, with significant fibrosis requiring hot avulsion to achieve technical success.

ARJ-LSLs versus rectal LSLs

When comparing outcomes between ARJ-LSLs and rectal LSLs, there was no significant difference for technical success, requiring an auxiliary modality to complete endoscopic resection, pain, direct hospital admission, CSIPB, CSPEB, delayed perforation and recurrence at SC1–SC4. Significant differences in procedure duration (ARJ-LSLs 30 min, IQR 15–55 min, vs rectal LSLs 25 min, IQR 12–50 min; p=0.045) and DMI (ARJ-LSLs 0, 0.0%, vs rectal LSLs 14, 4.5%; p=0.027) were identified.

DISCUSSION

EMR has revolutionised the management of early colorectal neoplasia. After confirming its superior safety[3] and cost-effectiveness[4] to surgery, the technique has continued to evolve, manifesting in the ability to predict, mitigate and manage intraprocedural and postprocedural adverse outcomes.[18 23–26 29–34] Alongside site-specific modifications in technique, high-quality EMR has surmounted physician-imposed boundaries by effectively treating periappendiceal,[35] ileocecal,[36] circumferential[37] and non-lifting lesions.[38] Our study highlights another major

Table 3 Outcomes after endoscopic mucosal resection

	All rectal LSLs (n=413) n (%)	ARJ-LSLs (n=100) n (%)	Rectal LSLs (n=313) n (%)	P value
SC1				
Eligible (n)	331	86	245	
Underwent SC1, n (%)	289 (87.3)	78 (90.7)	211 (86.1)	
Months to SC1, median (IQR)	5 (4–7)	5 (4–7)	5 (4–7)	
Recurrence at SC1, n (%)	43 (14.9)	12 (15.4)	31 (14.7)	0.883
Surgery at SC1, n (%)	1 (0.3)	0 (0.0)	1 (0.5)	
SC2				
Eligible (n)	264	69	195	
Underwent SC2, n (%)	215 (81.4)	59 (85.5)	156 (80.0)	
Months to SC2, median (IQR)	19 (14–23)	19 (14–23)	18 (15–23)	
Recurrence at SC2, n (%)	15 (7.0)	4 (6.8)	11 (7.1)	1.000
Surgery at SC2, n (%)	1 (0.5)	1 (1.7)	0 (0.0)	
SC3				
Eligible (n)	162	37	125	
Underwent SC3, n (%)	111 (68.5)	27 (73.0)	84 (67.2)	
Months to SC3, median (IQR)	40 (29–53)	39 (28–57)	41 (29–51)	
Recurrence at SC3, n (%)	3 (2.7)	1 (3.7)	2 (2.4)	0.570
Surgery at SC3, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
SC4				
Eligible (n)	40	10	30	
Underwent SC4, n (%)	31 (77.5)	10 (100.0)	21 (70.0)	
Months to SC4, median (IQR)	55 (41–69)	54 (33–83)	56 (42–69)	
Recurrence at SC4, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Surgery at SC4, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	

ARJ-LSL, laterally spreading lesion at the anorectal junction; LSL, laterally spreading lesion; NA, not applicable; SC, surveillance colonoscopy.

Table 4 Outcomes after endoscopic mucosal resection, stratified by margin thermal ablation therapy

	ARJ-LSLs			Rectal LSLs		
	STSC	No STSC	P value	STSC	No STSC	P value
SC1 recurrence, n/N (%)	0/30 (0.0)	12/48 (25.0)	0.002	3/51 (5.9)	28/160 (17.5)	0.041
SC2 recurrence, n/N (%)	1/14 (7.1)	3/45 (6.7)	1.000	1/26 (3.8)	10/130 (7.5)	0.692
SC3 recurrence, n/N (%)	0/3 (0.0)	1/24 (4.2)	1.000	0/8 (0.0)	2/76 (2.6)	1.000
SC4 recurrence, n/N (%)	0/1 (0.0)	0/9 (0.0)	NA	0/1 (0.0)	0/20 (0.0)	NA

ARJ-LSL, laterally spreading lesion at the anorectal junction; LSL, laterally spreading lesion; STSC, snare-tip soft coagulation.

advancement: the ability of a site-specific EMR technique (online supplementary video 1) to effectively, efficiently and safely manage ARJ-LSLs in a multicentre observational cohort. Accentuated by the absence of comparable evidence for alternative techniques, EMR should be considered a first-line resection modality for the majority of these lesions.

Despite this lack of comparable evidence, many endoscopists advocate for the use of ESD. This is based on small retrospective cohorts, largely evaluating short-term outcomes.[13 14 39–43] A perceived benefit of ESD for ARJ-LSLs is a lower frequency of recurrence.[44] Comparing previous EMR[6 7] and ESD[13 14 39–43] cohorts, the frequency of recurrence has ranged from 18% to 22% and from 0% to 8%, respectively. This disparity is likely driven by the unique anatomical characteristics of the anorectal junction. Rectal fold convergence can limit endoscopic visualisation, thus increasing the risk of diminutive foci of residual polyp remaining in situ unbeknownst to the endoscopist. Moreover, endoscopists may be reluctant to obtain a healthy margin of normal tissue at the dentate line in fear of precipitating pain. In our study, while the frequency of recurrence at SC1 was 15.4%, with the application of thermal ablation therapy to the margin, no recurrence was identified at SC1. Margin STSC is supported by a recent multicentre randomised controlled trial, which reduced recurrence at SC1 from 21% to 5% (p<0.001).[18] This effect on recurrence has now been reproduced in a North American cohort.[45] By negating a primary advantage of ESD, it naturally directs one's focus to its negatives. This includes increased technical difficulty, prolonged procedure times and a heightened risk of postprocedural bleeding and perforation, with estimates as high as 29%[13] and 4%,[14] respectively.

Another advantage of ESD is the ability to perform size-independent en bloc resection, as lesions of ≥20 mm are not reliably removed en bloc by EMR.[8] If S-SMIC is identified without any high-risk features (poor differentiation, lymphovascular invasion and high-grade tumour budding), R0 resection is curative.[8 9] This allows ESD to be a surgery-sparing technique for early colorectal cancer, which is of the utmost importance in the rectum, given the heightened risk of morbidity, mortality and stoma formation with distal rectal surgery.[1] However, in a recent systematic review and meta-analysis[11] evaluating 51 studies and 11 260 colorectal lesions, the frequency of S-SMIC was only 8%. With the frequency of curative endoscopic resection being 75%, this decreased the frequency of lesions with S-SMIC, which would be cured to 6% with a number needed to treat of 17. These findings directly question the indiscriminate application of ESD in the colorectum.

Clearly, the universal application of either EMR or ESD is not appropriate, and a rectum-specific selective resection algorithm is needed. With the vast majority of lesions being benign, EMR should be the primary resection modality within this algorithm. If features suggestive of S-SMIC are identified during optical evaluation, ESD would be indicated, whereas if features suggestive of D-SMIC are identified, referral to surgery is appropriate. In an attempt to stratify the risk of invisible or 'covert' SMIC, a recent study from the ACE consortium[17] evaluated 2277 LSLs of ≥20 mm. After excluding lesions with visible or overt features of SMIC, size, location, non-granularity and Paris classification 0-Is and 0-IIa+Is morphology were significantly associated with SMIC on multivariable analysis. Importantly, by using a combination of morphology, topography and location, lesions could be effectively stratified into a high (>10%) covert SMIC grouping, thereby identifying potential candidates for ESD, particularly in the rectum. A selective resection algorithm based on these premises has been shown to be the most cost-effective treatment strategy.[46] Only 43 ESD procedures were required per 1000 patients.

An alternative local excision strategy is TES, which includes conventional transanal excision (TAE), transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS). Procedural outcomes for TES, specifically TEM, appear comparable to ESD,[47] and it shares the benefit of performing en bloc resection of rectal LSLs and therefore carries the potential for curative resection of early colorectal cancers. In a recent multicentre randomised trial comparing EMR with TEM[48] for rectal LSLs, although EMR was less costly, non-inferiority could not be reached. This was due to an unexpectedly high frequency of recurrence in both groups (EMR 15% vs TEM 11%). Of note, margin STSC was not performed. Within our cohort, the frequency of recurrence at SC1 was significantly lower for ARJ-LSLs (0.0% STSC vs 25.0% no STSC, p=0.002) and rectal LSLs (5.9% STSC vs 17.5% no STSC, p=0.041) among those undergoing STSC. Therefore, a subsequent trial, with superiority design in favour of EMR, should be considered.

Another major limitation of TEM and TAMIS is that their respective platforms obscure the anorectal junction, thus limiting their applicability for ARJ-LSLs. Colorectal surgeons are commonly forced to revert to TAE with conventional retractors. This can limit visualisation and exposure to facilitate en bloc resection. In a retrospective evaluation of 171 lesions that underwent TES (89 TAE and 82 TEM),[49] the frequency of adverse events, specimen fragmentation and recurrence for TAE were 17%, 35% and 27%, respectively. These findings have been supported in a recent meta-analysis of six comparative studies (435 TAE and 492 TEM), with significant differences in favour of TEM compared with TAE, for specimen fragmentation, negative resection margins and recurrence.[50] Accordingly, the European Association for Endoscopic Surgery (EAES) recommends that TAE should only be considered in very select cases.[10] Therefore, until technological advances in TES facilitate its application near the dentate line, these modalities should not be applied for ARJ-LSLs outside the confines of a well-defined research protocol.

Unique to the anorectum is the concern for pain due to the distinct anatomy of the anal transition zone. To achieve a healthy margin of normal tissue during resection, the endoscopist will invariably resect below the dentate line into the somatically innervated squamous epithelium. Interestingly, no significant difference in the frequency of pain was identified between ARJ-LSLs and rectal LSLs (6.1% vs 3.8%, p=0.366). This supports

the effectiveness of incorporating local anaesthetic into the submucosal injectate at the distal resection margin, which is consistent with the majority of the endoscopic tissue resection literature for ARJ-LSLs.[6 13 14 39 40 42 43] However, it is imperative to always approach postprocedure pain with caution and to distinguish between perianal pain and abdominal pain, as the latter can be precipitated by gaseous distension, transmural injection, serositis/postpolypectomy syndrome and perforation.

Another unique feature of this area is the risk of bacteraemia. A submucosal plexus resides in the anal transition zone. As the haemorrhoidal plexus drains directly into the systemic circulation, the distal rectum is vulnerable to bacterial translocation during multifocal submucosal injection, a core component to high-quality EMR technique. This is in contrast to the middle rectum, which is better protected by its portovenous drainage. In this study, one patient developed rigours prior to the universal administration of prophylactic antibiotics, which is now our standard of practice. This is consistent with recommendations for the application of TES.[51 52] Although there is weak evidence to support this practice, this is a relatively low-risk and inexpensive intervention. Thus, given the infrequency of this adverse event, higher quality evidence either supporting or contradicting antibiotic use is unlikely to emerge.

An unexpected finding was a heightened frequency of CSPEB (11.1% vs 6.2%)[32] and endoscopic re-evaluation (63.6% vs 43.5%)[30] among ARJ-LSLs compared with previous estimates of the ACE consortium, especially as proximal location has been identified as an independent predictor of CSPEB.[32] This is likely driven, in part, by the rich vascular network of the distal rectum alongside a lack of appreciation for the significance of ARJ-LSLs in previous evaluations.[20] Another likely contributor is that bleeding at the anorectal junction is readily apparent and easily accessed, therefore predisposing the patient to seek out medical attention and the endoscopist to intervene. Unfortunately, CSPEB remains a major drawback of minimally invasive resection techniques, with prophylactic vessel coagulation[53] and prophylactic clip closure[54] having limited roles for these specific lesions.

This study is not without limitations. The design led to a moderate frequency of patients who did not complete surveillance, including those lost to follow-up. However, these results reflect the real-world application of EMR, as colorectal LSLs commonly afflict patients of advanced age and therefore are more likely to have comorbid disease states. Patients no longer followed up in this context should not be viewed as a negative EMR outcome. Moreover, including all patients irregardless of their stage of follow-up facilitated the analysis of pertinent clinical outcomes, including technical success, adverse events and recurrence. Another limitation is that while set SC intervals are recommended, colonoscopies within the ACE consortium are recorded sequentially with intervals at the discretion of the endoscopist performing surveillance. Regardless, the median time from index to SC4 was 54 months, which, to our knowledge, is the longest description of follow-up in the EMR literature. Site-specific high-quality EMR technique did vary over time, with technical innovations in EMR being adopted as the evidence to support them emerged. However, given the evolution of high-quality EMR, performance outcomes in this study are likely an underestimation of the currently applied technique. Moreover, the primary focus of our study was to evaluate technical success and not to evaluate the efficacy of thermal ablation therapy to mitigate the risk of recurrence. As ARJ-LSLs which received margin STSC was a sample of the overall population, further evaluation in this area is needed. Lastly, a significant discrepancy in the frequency of SMIC was identified between ARJ-LSLs (3.0%) and rectal LSLs (12.5%). This is likely

explained by the exclusion of lesions due to the optical features of D-SMIC and enrolment in a selective ESD protocol (21.8% ARJ-LSLs vs 12.8% rectal LSLs). It is unlikely that ARJ-LSLs have a unique pathobiological behaviour.

In conclusion, EMR is an effective strategy for ARJ-LSLs, given its ability to efficiently and safely manage these lesions. By incorporating key advancements in this space, specifically thermal ablation therapy to the resection margin, recurrence has been effectively mitigated at this historically high-risk site. While ESD and TEM/TAMIS are exciting additions to the management of rectal neoplasia, their application must be founded in evidence and not overshadow logical clinical benefit. Carefully designed randomised clinical trials, with clearly defined inclusion criteria and endpoints, will be the definitive mechanism for deciding how these modalities should be used. Until a definitive rectum-specific selective resection algorithm can be delineated, EMR should be viewed as a first-line modality for the majority of these lesions.

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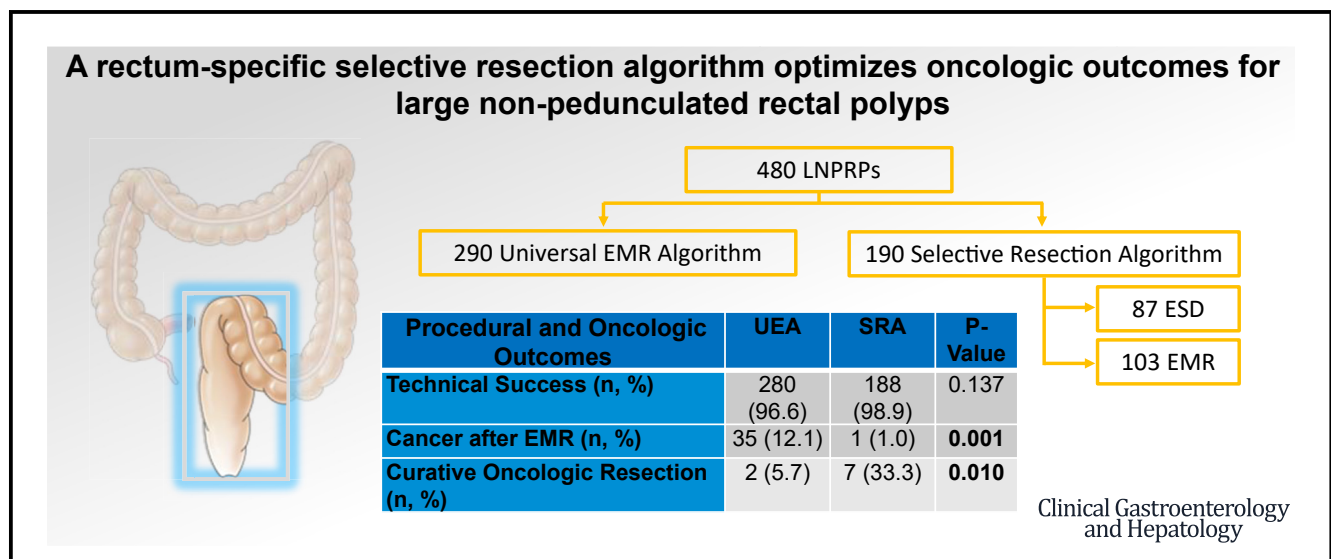Mayenaaz Sidhu http://orcid.org/0000-0001-8994-1680

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A Rectum-Specific Selective Resection Algorithm Optimizes Oncologic Outcomes for Large Nonpedunculated Rectal Polyps

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A rectum-specific selective resection algorithm optimizes oncologic outcomes for large non-pedunculated rectal polyps

480 LNPRPs

290 Universal EMR Algorithm

190 Selective Resection Algorithm

87 ESD

103 EMR

Procedural and Oncologic Outcomes	UEA	SRA	P-Value
Technical Success (n, %)	280 (96.6)	188 (98.9)	0.137
Cancer after EMR (n, %)	35 (12.1)	1 (1.0)	**0.001**
Curative Oncologic Resection (n, %)	2 (5.7)	7 (33.3)	**0.010**

Clinical Gastroenterology and Hepatology

BACKGROUND AND AIMS: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are complementary techniques for large (≥20 mm) nonpedunculated rectal polyps (LNPRPs). A mechanism for appropriate technique selection has not been described.

METHODS: We evaluated the performance of a selective resection algorithm (SRA) (August 2017 to April 2021) compared with a universal EMR algorithm (UEA) (July 2008 to July 2017) for LNPRPs within a prospective observational study. In the SRA, LNPRPs with features of superficial submucosal invasive cancer (SMIC) (<1000 μm; Kudo pit pattern Vi), or with an increased risk of SMIC (Paris 0-Is or 0-IIa+Is nongranular, 0-IIa+Is granular with a dominant nodule ≥10 mm) underwent ESD. The remaining LNPRPs underwent EMR. Algorithm performance was evaluated by SMIC identified after EMR, curative oncologic resection (R0 resection, superficial SMIC, absence of negative histologic features), technical success, adverse events, and recurrence at first surveillance colonoscopy.

RESULTS: A total of 480 LNPRPs were evaluated (290 UEA, 190 SRA). Median lesion size was 40 (interquartile range, 30–60) mm. SMIC was identified in 56 (11.7%) LNPRPs. Significant differences in

SMIC after EMR (SRA 1 [1.0%] vs UEA 35 [12.1%]; $P = .001$) and curative oncologic resection (SRA n = 7 [33.3%] vs UEA n = 2 [5.7%]; $P = .010$) were identified. No significant differences in technical success or adverse events were identified (all $P > .137$). Among LNPRPs with SMIC amenable to curative oncologic resection and which underwent ESD, 100% (n = 7 of 7) were cured.

CONCLUSIONS: A rectum-specific SRA optimizes oncologic outcomes for LNPRPs and mitigates the risk of piecemeal resection of cancers.

Key Words: Adenoma; Cancer; Colonoscopy; Polyp; Surgery.

Large nonpedunculated colorectal polyps (LNPCPs) are a critical component of colorectal cancer screening. This is due to their incidence on screening colonoscopy, the complexity of their management, and the associated costs on the healthcare system.[1] Large nonpedunculated rectal polyps (LNPRPs) are especially important, as they have a 2-fold risk of submucosal invasive cancer (SMIC).[2] Moreover, there is a heightened risk of morbidity, mortality, and permanent ostomy formation associated with distal colorectal surgery.[3]

Endoscopic mucosal resection (EMR) is now the first-line resection modality for LNPCPs due to its efficacy, efficiency, and safety compared with surgery and alternative resection techniques.[1,4–6] The primary limitation of EMR is that for larger lesions, piecemeal resection is required due to technical limitations and safety concerns.[7] In the event SMIC is detected, surgery is generally recommended as R0, and therefore curative oncologic resection cannot be ascertained. This highlights the synergistic role of en bloc resection techniques such as endoscopic submucosal dissection (ESD).[8] Economic analyses have shown that a selective resection algorithm (SRA), incorporating EMR and ESD, is the most cost-effective strategy.[9] However, how to select which lesions should undergo EMR vs ESD has not been delineated.

Real-time optical evaluation of a lesion's pit and microvascular surface pattern can detect SMIC prior to endoscopic resection. Recent evidence suggests that optical evaluation has modest performance characteristics.[10,11] To negate the risk of missed or covert SMIC, lesion morphology can be used to further risk-stratify these lesions and thus facilitate technique selection.[2,12] We therefore sought to evaluate whether optical evaluation, in conjunction with covert SMIC risk stratification, can be used to effectively select between EMR and ESD for large nonpedunculated polyps within the rectum.

Materials and Methods

This manuscript is in keeping with the recommendations of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[13]

Study Design

Consecutive patients referred for the management of a LNPRP ≥20 mm at a single center between July 2008 to April 2021 were evaluated as part of a prospectively collected, observational cohort (NCT01368289). Institutional Review Board approval was obtained. Written informed consent was obtained from each patient prior to study participation.

Two cohorts were defined according to the resection techniques applied during their respective time frames: (1) universal EMR algorithm (UEA) from July 2008 to July 2017; and (2) SRA from August 2017 to April 2021 (NCT04008407). In both the UEA and SRA, lesions with optical features of deep SMIC (D-SMIC) (≥1000 μm; Kudo pit pattern Vn) were referred to multidisciplinary team review for consideration of surgery. In the UEA, all remaining LNPRPs were considered for EMR. In the SRA, LNPRPs with features consistent with superficial SMIC (S-SMIC) (<1000 μm; Kudo pit pattern Vi) or with an increased risk of SMIC based on covert SMIC risk stratification (Paris 0-Is or 0-IIa+Is nongranular, Paris 0-IIa+Is granular with a dominant nodule ≥10 mm approximated relative to an open snare of known dimensions) underwent ESD.[2] The remaining LNPRPs underwent EMR.

Procedural Details

All endoscopic procedures were performed by either a study investigator (accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their supervision. Currently, all colorectal endoscopic resections are performed using high-definition gastroscopes or colonoscopes (Olympus, Tokyo, Japan). Carbon dioxide is used for insufflation. Technical innovations in EMR and ESD were adopted as the evidence to support them emerged. Antiplatelet and anticoagulation medications are held preprocedure, in accordance with consensus recommendations.[14]

After lesion identification, optical evaluation under high-definition white-light and narrow-band imaging is

performed. Lesion location, size, Paris classification, granularity, and Kudo pit pattern classification are described in real time.

Endoscopic Mucosal Resection

A standardized previously described inject and resect EMR technique was used (Figure 1).[15] In a systematic fashion, a submucosal cushion is created with injection of succinylated gelatin (Gelofusine; B. Braun, Bella Vista, Australia) with 0.4% indigo carmine and 1:100,000 epinephrine. Using a microprocessor-controlled generator (Endo Cut Q, Effect 3; ERBE, Tübingen, Germany), snare excision is performed.

After complete resection, the defect is examined to ensure no neoplastic tissue remains and to assess for deep mural injury (DMI).[7] Areas of significant deep injury (DMI III–V) are subsequently treated with mechanical clips. Thermal ablation of the resection margin is performed using snare-tip soft coagulation (Soft Coag, 80 W, Effect 4; ERBE) creating a 2- to 3-mm rim of ablated tissue.[16,17]

Endoscopic Submucosal Dissection

With distal cap attachment (Olympus), a submucosal injection of succinylated gelatin with 0.4% indigo carmine and 1:100,000 epinephrine is introduced (Figure 1).[8] Marking of the margin was generally not performed. This is followed by mucosal incision (Dry Cut, 30 W, Effect 2; ERBE) and subsequent dissection (Swift Coag, 30 W, Effect 2; ERBE) underneath the lesion in the submucosal plane, using an electrosurgical knife (Dual-Knife-J [Olympus]; Hybrid Knife [ERBE]). Dissection is most commonly performed in a retroflexed position. External traction techniques are used, where appropriate, to facilitate dissection.

After complete resection, prophylactic vessel coagulation of nonbleeding visible vessels is performed using coagulation forceps.

Postprocedure

After procedure completion, patients are observed for 4 hours. If well, they are subsequently discharged on a clear fluid diet overnight. At 2 weeks, patients are contacted by a study coordinator and undergo a structured telephone interview to identify periprocedural adverse events. First surveillance colonoscopy (SC1) is performed at 6 months. During SC, patients undergo a standardized evaluation of the endoscopic resection scar. Biopsies are routinely performed.

Histopathology Evaluation

After endoscopic resection, specimens were collected and processed for histopathology review. ESD specimens

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What You Need to Know

Background

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection are complementary techniques. A mechanism for appropriate technique selection for large (≥20 mm) nonpedunculated rectal polyps (LNPRPs) has not been described.

Findings

Among 480 LNPRPs, a selective resection algorithm vs a universal EMR algorithm increased curative oncologic resection and decreased piecemeal resection of cancer without affecting technical success or adverse events.

Implications for Patient Care

A rectum-specific selective resection algorithm, based on real-time optical evaluation, optimizes oncologic outcomes for LNPRPs.

Short Summary

Analyzing 480 large rectal polyps, using both endoscopic mucosal resection and endoscopic submucosal dissection increased the chances of curing early rectal cancers, compared with using only endoscopic mucosal resection.

were pinned. Histopathology review was completed by board-certified expert gastrointestinal pathologists. Cancer was defined by neoplastic invasion into the submucosa. Where appropriate, histopathology was confirmed with surgical specimen evaluation.

Data Extraction

Collected data included (1) patient characteristics of age, sex, and American Society of Anesthesiologists (ASA) classification; (2) lesion characteristics of size, morphology, surface granularity, Kudo pit pattern, and histopathology; and (3) procedure outcomes of technical success, en bloc resection, R0 resection, curative oncologic resection, periprocedural adverse events, recurrence, and referral to surgery.

Technical success was defined as complete removal of all visible neoplastic tissue during index resection. En bloc resection was defined as removal of all visible neoplastic tissue as a single specimen. R0 resection was defined as removal of all visible neoplastic tissue as a single specimen with negative histologic margins. Curative oncologic resection was defined as R0 resection in the absence of negative prognostic features (submucosal invasion ≥1000 μm, poor differentiation, lymphovascular invasion, tumor budding). Clinically significant postendoscopic resection bleeding (CSPEB) was defined as any bleeding after the procedure which required emergency room presentation, hospitalization, or
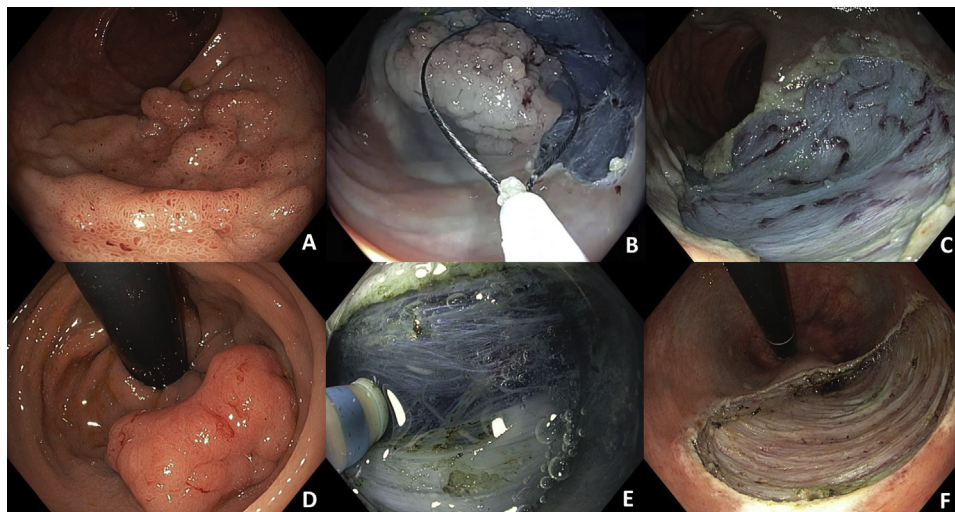
Figure 1. Minimally invasive endoscopic resection techniques. (*A–C*) EMR; (*D–F*) ESD.

reintervention (endoscopy, angiography, surgery). Significant DMI, as per the Sydney DMI classification, was defined as grade III (muscularis propria injury) or grade IV or V (transmural perforation without or with contamination, respectively). Recurrence was evaluated at SC1. Study endpoints included technical failure, death, noncurative SMIC, advanced age or comorbidities precluding ongoing SC, lost to follow-up, and SC1.

Statistical Analysis

The primary outcome was the frequency of SMIC after EMR. Secondary outcomes were the frequencies of en bloc resection, R0 resection, curative oncologic resection, technical success, periprocedural adverse outcomes (DMI III–V, CSPEB, delayed perforation), recurrence at SC1, and procedural duration. Outcomes between the SRA and the UEA were compared.

SPSS version 28 (IBM, Armonk, NY, USA) was used for data analysis. Variables were analyzed per participant. If 2 or more eligible lesions were identified in a single participant, the largest lesion was selected for analysis. Lesions that underwent ESD, owing to an out-of-protocol indication (eg. suspected D-SMIC in a nonsurgical candidate), were excluded from analysis.

Continuous variables were summarized using median (interquartile range [IQR]). Categorical variables were summarized as frequencies. All analyses were exploratory and 2-tailed tests with a 5% significance level were used throughout. To test for association between categorical variables, the Pearson chi-square or the Fisher exact tests were used, where appropriate. For continuous variables, the Mann-Whitney U test was used.

Results

Between July 2008 to April 2021, 525 LNPRPs were referred for endoscopic resection (Figure 2). A total of 45 LNPRPs were excluded from analysis (7 synchronous

LNPRPs, 1 synchronous cancer, 14 out-of-protocol ESD, 23 D-SMIC). A total of 480 LNPRPs in 480 patients were included for analysis (290 UEA, 190 SRA).

Patient and Lesion Characteristics

The median patient age was 67 (IQR, 59–74) years and 260 (54.2%) were male (Table 1). The majority of patients were ASA I–II (n = 390 [90.1%]).

The median lesion size was 40 (IQR, 30–60) mm, with 120 (25.0%) located at the anorectal junction (≤20 mm from the dentate line). Paris classification 0-IIa+Is was the most frequent morphology (n = 273 [56.9%]). A total of 327 (81.3%) were granular. On histopathology, the majority (n = 323 [67.3%]) were tubulovillous adenomas. High-grade dysplasia and SMIC were identified in 108 (22.5%) and 56 (11.7%), respectively. The frequencies of high-risk features are reported in Table 1.

Comparing the SRA and UEA cohorts, significant differences in ASA (P = .004) and Kudo pit pattern (P < .001) were identified.

Between the EMR vs ESD subgroups within the SRA, significant differences in Paris classification (P < .001), granularity (P = .006), Kudo pit pattern (P < .001), and histopathology (P < .001) were identified (Supplementary Table 1).

SRA vs UEA Algorithms

For procedural outcomes (Table 2), when comparing the SRA vs the UEA, significant differences in median resection duration (45 [IQR, 25–78] minutes vs 29 [IQR, 15–50] minutes; P < .001), margin thermal ablation of those which underwent EMR (n = 98 [95.1%] vs n = 66 [22.8%]; P < .001), and SC1 recurrence (n = 2 [1.6%] vs n = 40 [17.2%]; P < .001) were identified. When stratifying LNPRPs which underwent EMR and margin thermal ablation, no significant difference in recurrence between the SRA vs the UEA was identified (n = 1 [1.4%]
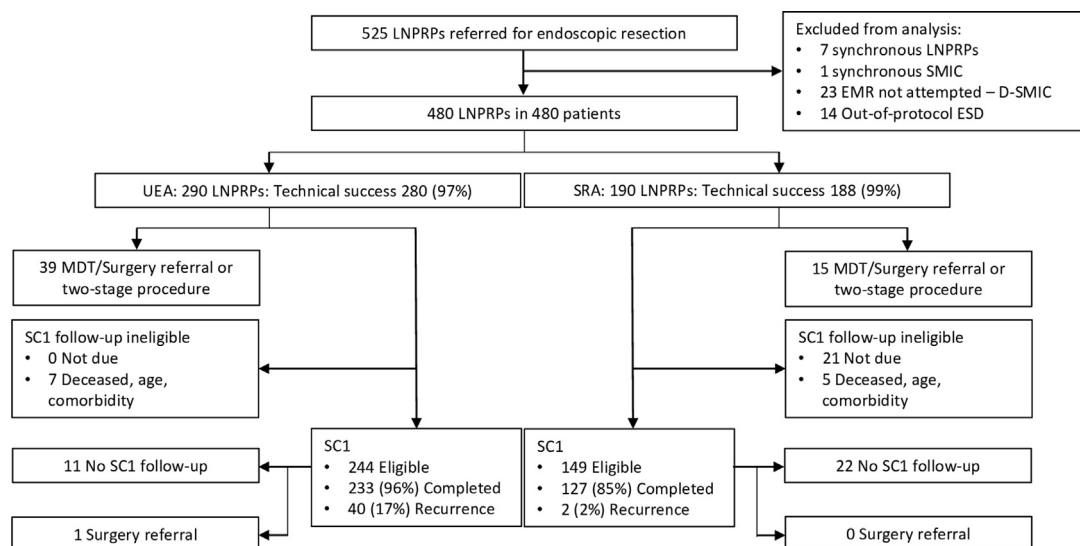
Figure 2. Flow diagram of consecutive LNPRPs referred for endoscopic resection. MDT, multidisciplinary team.

vs n = 3 [5.2%]; P = .321). No differences in technical success, DMI III–V, CSPEB, or delayed perforation were identified.

For oncologic outcomes (Table 3), when comparing the SRA vs the UEA, significant differences in the frequencies of SMIC after EMR (n = 1 [1.0%] vs n = 35 [12.1%]; P = .001), en bloc resection (n = 19 [90.5%] vs n = 4 [11.4%]; P < .001), R0 resection (n = 18 [85.7%] vs n = 2 [5.7%]; P < .001), and curative oncologic resection (n = 7 [33.3%] vs n = 2 [5.7%]; P = .010) were identified, respectively. No difference in the frequency of LNPRPs with SMIC amenable to curative oncologic resection were identified (n = 8 [38.1%] vs n = 12 [41.4%]; P = .815).

SRA: Procedural Outcomes

Of the 190 LNPRPs within the SRA, 103 (54.2%) underwent EMR and 87 (45.8%) underwent ESD. Median resection duration was 45 (IQR, 25–78) minutes (Table 2). Technical success was achieved in 188 (98.9%) with technical failure in 2 (1.2%), both owing to significant submucosal fibrosis. All cases were referred for multidisciplinary team review or 2-stage procedure.

DMI types III–V occurred in 11 (5.8%): 10 were successfully closed endoscopically with mechanical clip placement and 1 was left untreated due to distal location. Clinically significant postendoscopic resection bleeding occurred in 19 (10.0%): 7 (36.8%) were managed conservatively and 12 (63.1%) underwent endoscopic re-evaluation with or without endoscopic intervention. Delayed perforation did not occur in any cases.

A total of 149 patients were eligible for SC1 (Figure 2, Table 2). A total of 127 (85.2%) underwent SC with a median interval of 7 (IQR, 6–9) months. Recurrence was identified in 2 (1.6%). No patients were referred for surgery at SC1.

Between the EMR vs ESD subgroups within the SRA, a significant difference in procedure duration was identified (40 [IQR, 25–60] minutes vs 90 [IQR, 70–136] minutes; P < .001) (Supplementary Table 2). No significant differences in technical success, DMI III–V, CSPEB, delayed perforation, or recurrence were identified (all P ≥ .548).

SRA: Oncologic Outcomes

Of the 21 LNPRPs with SMIC (Table 3) within the SRA, 20 (95.2%) were appropriately resected by ESD and 1 (4.5%) was resected by EMR (Table 4). Of those, 8 were potential candidates for curative oncologic resection (7 ESD, 1 EMR). En bloc resection and R0 resection were achieved in 19 (90.5%) and 18 (85.7%), respectively. Three LNPRPs did not achieve R0 status: 1 owing to piecemeal EMR and 2 owing to deep margin positivity with SM2 depth of invasion.

Curative oncologic resection occurred in 7 (33.3%). Of the 14 noncurative resections: 1 owing to piecemeal EMR, 4 owing to ≥SM2 depth of invasion, 2 owing to lymphovascular invasion, and 7 with ≥2 negative prognostic features. Among potentially curable malignant LNPRPs that underwent ESD, 100% (n = 7 of 7) were cured. Within the SRA, the number of ESDs needed to cure 1 LNPRP with SMIC was 12.

Discussion

Minimally invasive endoscopic resection techniques are now the primary management strategy for early rectal neoplasia.[1] This is due to the efficacy, efficiency, and safety of these techniques, in contrast to the morbidity, mortality, and permanent ostomy formation associated with distal colorectal surgery.[3–6] EMR is the preeminent endoscopic resection modality[1]; however, a

Table 1. Patient and Lesion Characteristics

	Overall LNPRPs (n = 480)	UEA LNPRPs (n = 290)	SRA LNPRPs (n = 190)	P Value
Age, y	67 (59–74)	66 (58–75)	67 (60–74)	.602
Male	260 (54.2)	167 (57.6)	93 (48.9)	.063
ASA[a]				.004
I–II	390 (90.1)	234 (93.6)	156 (85.2)	
III	43 (9.9)	16 (6.4)	27 (14.8)	
Size, mm	40 (30–60)	45 (35–60)	40 (30–60)	.810
Location				.106
Anorectal junction	120 (25.0)	65 (22.4)	55 (28.9)	
Rectum	360 (75.0)	225 (77.6)	135 (71.1)	
Paris classification				.420
0-Is	58 (12.1)	38 (13.1)	20 (10.5)	
0-IIa	134 (27.9)	77 (26.6)	57 (30.0)	
0-IIb	4 (0.8)	4 (1.4)	0 (0.0)	
0-IIa+Is	273 (56.9)	165 (56.9)	108 (56.8)	
Any 0-IIc	11 (2.3)	6 (2.1)	5 (2.6)	
Granularity[b]				.862
Granular	387 (81.3)	232 (80.8)	155 (82.0)	
Nongranular	55 (11.6)	33 (11.5)	22 (11.6)	
Mixed	34 (7.1)	22 (7.7)	12 (6.3)	
Kudo pit pattern				<.001
I–II	10 (2.1)	8 (2.8)	2 (1.1)	
III–IV	438 (91.3)	274 (94.5)	164 (86.3)	
Vi	32 (6.7)	8 (2.8)	24 (12.6)	
Histopathology				.864
Tubular adenoma	49 (10.2)	28 (9.7)	21 (11.1)	
Tubulovillous adenoma	323 (67.3)	196 (67.6)	127 (66.8)	
Villous adenoma	9 (1.9)	5 (1.7)	4 (2.1)	
Serrated	12 (2.5)	9 (3.1)	3 (1.6)	
Submucosal invasive cancer	56 (11.7)	35 (12.1)	21 (11.1)	
Other	31 (6.5)	17 (5.9)	14 (7.4)	
High-grade dysplasia	108 (22.5)	62 (21.4)	46 (24.2)	.468
High-risk features[c]				
Depth of invasion ≥SM2	25 (50.0)	15 (51.7)	10 (47.6)	.774
Poor differentiation	10 (20.0)	5 (17.2)	5 (23.8)	.723
Lymphovascular invasion	8 (16.0)	5 (17.2)	3 (14.3)	1.000
Tumor budding	7 (14.0)	3 (10.3)	4 (19.0)	.434

Values are median (interquartile range) or n (%).
ASA, American Society of Anesthesiologists; LNPRP, large nonpedunculated rectal polyp; SRA, selective resection algorithm; UEA, universal endoscopic mucosal resection algorithm.
[a]47 participants ASA not classified.
[b]4 participants granularity not classified.
[c]Denominator: LNPRPs with SMIC. Six participants had incomplete high-risk feature reporting.

key limitation, especially in the rectum, is the risk of piecemeal resection of endoscopically curable rectal cancers. This has stimulated the development of en bloc resection techniques, such as ESD, which have the potential for organ-sparing curative oncologic resection.[8] Cost-effectiveness analyses have shown that a SRA using EMR and ESD is the optimal approach.[9] However, a mechanism to facilitate modality selection has not been delineated.[18] To our knowledge, this study is the first to show that a rectum-specific SRA, based on real-time optical evaluation and covert SMIC risk stratification,

increases the frequency of curative oncologic resection and minimizes the risk of malignant piecemeal resection for LNPRPs.

A key premise of minimally invasive endoscopic resection techniques is the avoidance of unnecessary surgery and its negative sequalae. Piecemeal resection of endoscopically curable malignant LNPRPs negates the very benefit that they are intended to provide. To avoid malignant piecemeal resection, optical evaluation of the lesion's pit and microvascular surface pattern can be used to predict SMIC prior to resection technique

Table 2. Procedural Outcomes

	Overall LNPRPs (n = 480)	UEA LNPRPs (n = 290)	SRA LNPRPs (n = 190)	P Value
Duration, min[a]	30 (15–60)	29 (15–50)	45 (25–78)	<.001
Technical success	468 (97.5)	280 (96.6)	188 (98.9)	.137
Margin thermal ablation[b]	164 (41.7)	66 (22.8)	98 (95.1)	<.001
Deep mural injury III–V	23 (4.8)	12 (4.1)	11 (5.8)	.407
CSPEB	40 (8.3)	21 (7.2)	19 (10.0)	.285
Delayed perforation	1 (0.2)	1 (0.3)	0 (0.0)	1.000
SC1				
Eligible	393	244	149	
Underwent SC1	360 (91.6)	233 (95.5)	127 (85.2)	<.001
Months to SC1	6 (5–8)	5 (4–7)	7 (6–9)	<.001
Recurrence	42 (11.7)	40 (17.2)	2 (1.6)	<.001

Values are n (%), median (interquartile range), or n.
CSPEB, clinically significant postendoscopic resection bleeding; LNPRP, large nonpedunculated rectal polyp; SC1, surveillance colonoscopy 1; SRA, selective resection algorithm; UEA, universal endoscopic mucosal resection algorithm.
[a]116 participants duration not classified.
[b]Denominator: LNPRPs which underwent EMR.

selection.[10,11] However, in a recent prospective trial of 343 LNPCPs, its sensitivity and specificity for SMIC was 78.7% and 94.2%, respectively.[10] To mitigate the risk of invisible or covert SMIC, in a multicenter prospective cohort of 2277 LNPCPs, after excluding lesions with optical features of SMIC, size, distal location, non-granularity, and 0-Is and 0-IIa+Is morphology were significantly associated with SMIC on multivariable lo-gistic regression analysis.[2] Furthermore, a high covert SMIC risk group was identified (0-Is or 0-IIa+Is nongranular, distal 0-IIa+Is granular). In this study, us-ing analogous optical evaluation and covert SMIC risk stratification criteria, only 1 (1.0%) malignant LNPRP underwent piecemeal resection within the SRA. This is a pivotal advance in the application of minimally invasive endoscopic resection techniques. It demonstrates an effective approach to optical evaluation; thereby, delineating which LNPRPs can be effectively, efficiently, and safely managed by EMR compared with those which may derive benefit from ESD.

Owing to the procedural complexity of ESD and the onus to optimize endoscopy resource utilization, ESD should be reserved for lesions with suspected S-SMIC or a heightened risk of SMIC based on covert SMIC risk stratification.[19] From a recent systematic review and meta-analysis, the frequency of en bloc and R0 resection after colorectal ESD was 91.0% and 82.9% respec-tively,[20] with this study showing comparable results. However, it is imperative to understand that R0 resec-tion while being a core component of the definition of a curative oncologic resection is just that, only a compo-nent. It does not fully address depth of submucosal in-vasion or the absence of other evidence-based prognostic features such as poor differentiation, lymphovascular

Table 3. Oncologic Outcomes

	Overall LNPRPs (n = 56)	UEA LNPRPs (n = 35)	SRA LNPRPs (n = 21)	P Value
SMIC after EMR[a]	36 (9.2)	35 (12.1)	1 (1.0)	.001
En bloc resection	23 (41.1)	4 (11.4)	19 (90.5)	<.001
R0 resection	20 (35.7)	2 (5.7)	18 (85.7)	<.001
Curative resection	9 (16.1)	2 (5.7)	7 (33.3)	.010

Values are n (%).
EMR, endoscopic mucosal resection; LNPRP, large nonpedunculated rectal polyp; SMIC, submucosal invasive cancer; SRA, selective resection algorithm; UEA, universal endoscopic mucosal resection algorithm.
[a]Denominator: LNPRPs that underwent EMR.

invasion, or tumor budding.[21] This highlights another important finding of this study, which is the frequency of curative resection after ESD. At 33.3%, this represents a critical improvement in patient outcomes and the application of minimally invasive endoscopic resection techniques; especially when taking into consideration the potential negative ramifications of distal colorectal surgery[3] and evidence showing that endoscopic resection does not impair subsequent surgical intervention.[22] As the impact of negative histologic features on the risk of recurrent disease is better understood, as facilitated by the evaluation of outcomes after noncurative endoscopic resection, it is anticipated that the definition of curative oncologic resection will be refined.[23] Moreover, with the emerging role of neoadjuvant or adjuvant chemoradiation therapy, the frequency of curative resection with increase, thus reinforcing the importance of appropriate patient selection and its anticipated evolution over time.

Concerning procedure outcomes, a significant difference in recurrence at SC1 was identified (SRA n = 2 [1.6%] vs UEA n = 40 [17.2%]; $P < .001$). Although this can in part be attributed to ESD, which has historically been associated with a lower frequency of recurrence,[20] a key driver is margin thermal ablation. In a multicenter randomized trial, SC1 recurrence was significantly reduced for LNPCPs that received margin thermal ablation (5% vs 21%; $P < .001$),[16] with no adverse events. These findings have now been reproduced, and with experience improved upon, in an international multicenter validation cohort of over 1000 LNPCPs.[17] Recurrence was 1.4% of those receiving complete margin thermal ablation. Moreover, these results have also been reproduced for complex lesion subgroups such as previously attempted LNPCPs[5] as well as those at the anorectal junction[4] and the ileocecal valve.[6] When comparing the SRA and the EUA for only those lesions that underwent margin thermal ablation, no significant difference in SC1 recurrence was identified. Taking these findings together, margin thermal ablation should now be viewed as an integral component of high-quality EMR and should be universally applied.

This study is not without limitations. The analysis was undertaken at a single expert center in minimally invasive endoscopic resection techniques. Therefore, reproducibility of these findings is needed. As the study was completed across different time periods, it is susceptible to selection bias due to changes in practice over time. This is demonstrated by the differences in ASA and Kudo pit pattern classification between the UEA and SRA; likely highlighting that in the UEA patients with concerning optical features were more likely to be referred to surgery alongside an inclination toward endoscopic resection for patients with comorbid disease within the SRA. Last, alternative en bloc resection techniques for malignant LNPRPs were not evaluated, such as endoscopic full-thickness resection or transanal endoscopic surgery; the latter of which is currently being evaluated in randomized control trials.

In conclusion, a rectum-specific SRA, based on real-time optical evaluation and covert SMIC risk stratification, effectively negates the risk of piecemeal resection of malignant LNPRPs and increases the frequency of curative oncologic resection. This highlights another critical advance in the management of LNPRPs with the continued refinement of their clinical trajectory through the avoidance of unnecessary surgery. Future algorithm refinement is anticipated, such as LNPRP size and morphology criteria, as well as through further understanding of the curative potential of piecemeal EMR; therefore, potentially optimizing the utilization of EMR given its proven efficacy, efficiency, and safety. Nevertheless, it is imperative to develop tissue resection centers with expertise in the application not only of minimally invasive resection techniques, but also of optical evaluation and covert SMIC risk stratification. Moreover, all endoscopists must embrace the expanding role of these resection techniques and a SRA with referral of LNPRPs to a tissue resection center prior to referral for surgery.

Supplementary Material

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Supplementary Table 1. Patient and Lesion Characteristics Within the SRA

	SRA LNPRPs (n = 190)	LNPRPs: EMR (n = 103)	LNPRPs: ESD (n = 87)	P Value
Age, y	67 (60–74)	67 (61–73)	68 (58–74)	.698
Male	93 (48.9)	50 (48.5)	43 (49.4)	.904
ASA[a]				.390
I-II	156 (85.2)	89 (87.3)	67 (82.7)	
III	27 (14.8)	13 (12.7)	14 (17.3)	
Size, mm	40 (30–60)	40 (30–60)	50 (35–70)	.071
Location				.062
Anorectal junction	55 (28.9)	24 (23.3)	31 (35.6)	
Rectum	135 (71.1)	79 (76.7)	56 (64.4)	
Paris classification				<.001
0-Is	20 (10.5)	15 (14.6)	5 (5.7)	
0-IIa	57 (30.0)	40 (38.8)	17 (19.5)	
0-IIb	0 (0.0)	0 (0.0)	0 (0.0)	
0-IIa+Is	108 (56.8)	48 (46.6)	60 (69.0)	
Any 0-IIc	5 (2.6)	0 (0.0)	5 (5.7)	
Granularity[b]				.006
Granular	155 (82.0)	92 (90.2)	63 (72.4)	
Nongranular	22 (11.6)	7 (6.9)	15 (17.2)	
Mixed	12 (6.3)	3 (2.9)	9 (10.3)	
Kudo pit pattern				<.001
I–II	2 (1.1)	2 (1.9)	0 (0.0)	
III–IV	164 (86.3)	101 (98.1)	63 (72.4)	
Vi	24 (12.6)	0 (0.0)	24 (27.6)	
Histopathology				<.001
Tubular adenoma	21 (11.1)	16 (15.5)	5 (5.7)	
Tubulovillous adenoma	127 (66.8)	76 (73.8)	51 (58.6)	
Villous adenoma	4 (2.1)	1 (1.0)	3 (3.4)	
Serrated	3 (1.6)	2 (1.9)	1 (1.1)	
Submucosal invasive cancer	21 (11.1)	1 (1.0)	20 (23.0)	
Other	14 (7.4)	7 (6.8)	7 (8.0)	
High-grade dysplasia	46 (24.2)	24 (23.3)	22 (25.3)	.750

Values are median (interquartile range) or n (%).
ASA, American Society of Anesthesiologists; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LNPRP, large non-pedunculated rectal polyp; SRA, selective resection algorithm.
[a]7 participants ASA not classified.
[b]1 participant granularity not classified.

Supplementary Table 2. Patient Outcomes within the SRA

	SRA LNPRPs (n = 190)	LNPRPs: EMR (n = 103)	LNPRPs: ESD (n = 87)	P Value
Duration, min[a]	45 (25–78)	40 (25–60)	90 (70–136)	<.001
Technical success	188 (98.9)	102 (99.0)	86 (98.9)	1.000
Margin thermal ablation[b]	98 (95.1)	98 (95.1)		
Deep mural injury III–V	11 (5.8)	5 (4.9)	6 (6.9)	.548
CSPEB	19 (10.0)	10 (9.7)	9 (10.3)	.884
Delayed perforation	0 (0.0)	0 (0.0)	0 (0.0)	
SC1				
Eligible	149	90	59	
Underwent SC1	127 (85.2)	76 (84.4)	51 (86.4)	.737
Months to SC1	7 (6–9)	8 (6–10)	7 (6–8)	.007
Recurrence	2 (1.6)	1 (1.3)	1 (2.0)	1.000

Values are median (interquartile range), n (%), or n.
CSPEB, clinically significant postendoscopic resection bleeding; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LNPRP, large nonpedunculated rectal polyp; SC1, surveillance colonoscopy 1; SRA, selective resection algorithm.
[a]85 participants duration not classified.
[b]Denominator: LNPRPs that underwent EMR.

ENDOSCOPY

Previously Attempted Large Nonpedunculated Colorectal Polyps Are Effectively Managed by Endoscopic Mucosal Resection

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INTRODUCTION: Endoscopic mucosal resection (EMR) is an effective therapy for naive large nonpedunculated colorectal polyps (N-LNPCPs). The best approach for the treatment of previously attempted LNPCPs (PA-LNPCPs) is undetermined.

METHODS: EMR performance for PA-LNPCPs was evaluated in a prospective observational cohort of LNPCPs ≥20 mm. Efficacy was measured by technical success (removal of all visible polypoid tissue during index EMR) and recurrence at first surveillance colonoscopy (SC1). Safety was assessed by clinically significant intraprocedural bleeding, deep mural injury types III–V, clinically significant post-EMR bleeding, and delayed perforation.

RESULTS: From January 2012 to October 2019, 158 PA-LNPCPs and 1,134 N-LNPCPs underwent EMR. Median PA-LNPCP size was 30 mm (interquartile range 25–46 mm). Technical success was 93.0% and increased to 95.6% after adjusting for 2-stage EMR. Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) was required for nonlifting polypoid tissue in 73 (46.2%). Median time to SC1 was 6 months (interquartile range 5–7 months). Recurrence occurred in 9 (7.8%). No recurrence was identified among 65 PA-LNPCPs which underwent margin thermal ablation at SC1 vs 9 (18.0%; *P* < 0.001) which did not. There were significant differences in resection duration (35 vs 25 minutes; *P* < 0.001), technical success (93.0% vs 96.6%; *P* = 0.026), and use of CAST (46.2% vs 7.6%; *P* < 0.001), between PA-LNPCPs and N-LNPCPs. When adjusting for 2-stage EMR, no difference in technical success was identified (95.6% vs 97.8%; *P* = 0.100). No differences in adverse events or recurrence were identified.

DISCUSSION: EMR, using auxillary techniques where necessary, can achieve high technical success and low recurrence frequencies for PA-LNPCPs.

Previously attempted large non-pedunculated colorectal polyps are effectively managed by endoscopic mucosal resection

Using evidence-based auxillary techniques, previously attempted LNPCPs ≥ 20mm are effectively managed by EMR
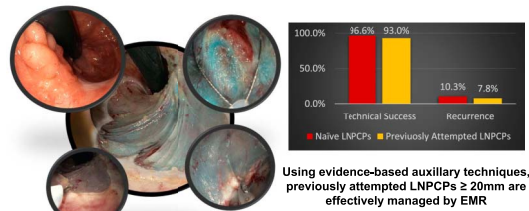
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INTRODUCTION

Endoscopic mucosal resection (EMR) is advocated as the preferred treatment strategy for large (≥20 mm) nonpedunculated colorectal polyps (LNPCPs) by international consensus guidelines (1,2). These recommendations are based on high-quality evidence showing that EMR can effectively, efficiently, and safely manage most LNPCPs (3–6). Moreover, EMR is safer, less resource intensive, and less expensive than surgery or endoscopic submucosal dissection (ESD) (7–9).

A requisite to successful EMR is submucosal fluid expansion to allow for effective and safe tissue capture. Previous attempts at endoscopic resection, which occurs in upward of 16% of LNPCP referrals (10), invariably precipitate fibrosis and potentially obliterate the submucosal plane. This may render these lesions recalcitrant to subsequent EMR and prompts the need for advanced resection techniques such as ESD, endoscopic full-thickness resection (EFTR), and surgery, all of which increase costs and carry a greater risk of adverse events (11–13).

Auxiliary techniques to complement EMR and treat nonlifting polypoid tissue have been described (14–18). However, most evaluations are small single-arm retrospective cohorts which focus on technique description. There is limited evidence concerning the overall management of previously attempted LNPCPs (PA-LNPCPs). Moreover, critical advancements designed to mitigate EMR-related adverse outcomes, such as margin thermal ablation to prevent recurrence, have not been assessed (19). Therefore, we sought to evaluate EMR outcomes for PA-LNPCPs, in comparison with naive LNPCPs (N-LNPCPs), in a single-center prospective observational cohort.

METHODS

This article is in keeping with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (20).

Study design

Consecutive patients enrolled at a single center between January 2012 to October 2019 were evaluated as part of a prospectively collected, observational cohort of patients referred for managing
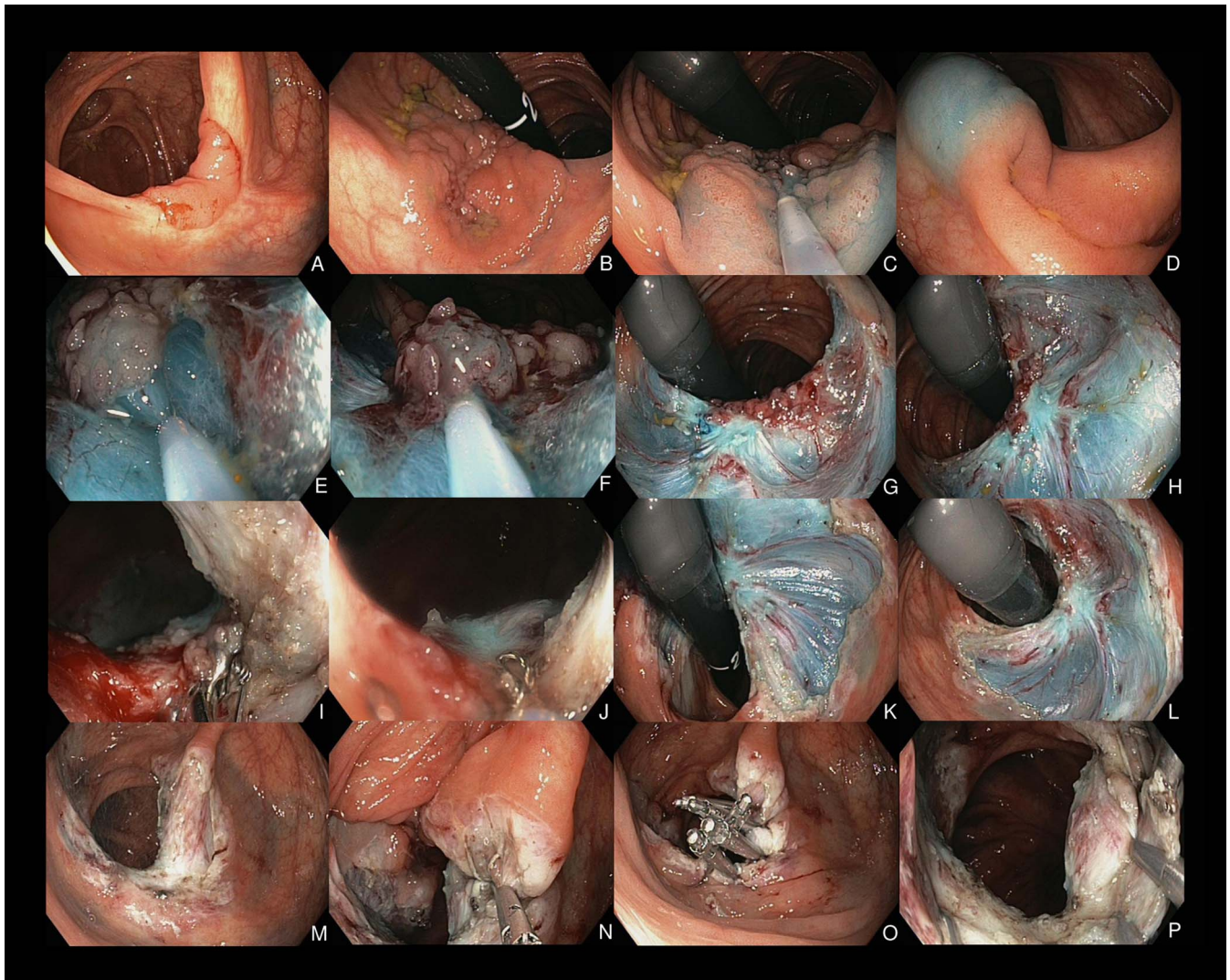
Figure 1. (**a** and **b**) A 50-mm 0-IIa mixed previously attempted large nonpedunculated colorectal polyp in the ascending colon. (**c–f**) Endoscpic mucosal resection. (**g–j**) Nonlifting polypoid tissue removed by cold-forceps avulsion with adjuvant snare-tip soft coagulation. (**k–m**) Status-post margin thermal ablation with deep mural injury type II. (**n–p**) Successful prophylactic mechanical clip placement.
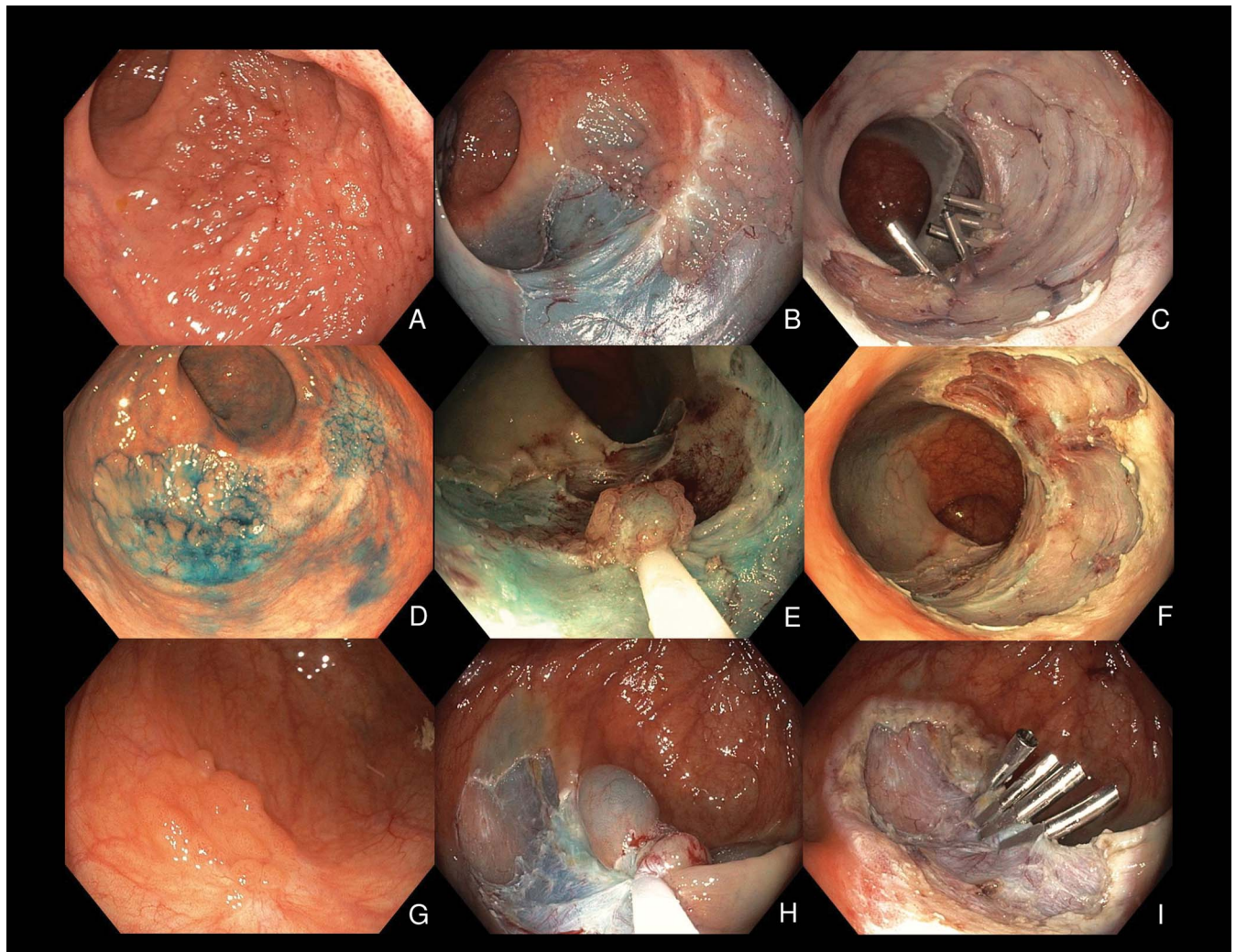
Figure 2. (**a–c**) A 60-mm 0-IIa granular previously attempted large nonpedunculated colorectal polyp in the rectum. Removed by endoscopic mucosal resection with cold-forceps avulsion and adjuvant snare-tip soft coagulation. (**d–f**) A 40-mm 0-IIa granular previously attempted large nonpedunculated colorectal polyp in the rectum. Removed by endoscopic mucosal resection with cold-forceps avulsion and adjuvant snare-tip soft coagulation. (**g–i**) A 20-mm 0-IIa granular previously attempted large nonpedunculated colorectal polyp in the cecum. Removed by endoscopic mucosal resection.

LNPCPs ≥20 mm (ClinicalTrials.gov identifier: NCT01368289). Institutional review board approval was obtained. Written informed consent was obtained from each patient before study participation.

PA-LNPCPs were defined as those where the referring endoscopist had attempted endoscopic resection (either by conventional polypectomy or EMR) but was unable to successfully remove all visible polypoid tissue. All other lesions were considered N-LNPCPs.

EMR technique

All endoscopic procedures were performed by a study investigator (accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal EMR) or a senior interventional endoscopy fellow under supervision. Technical innovations in EMR were adopted as the evidence to support them emerged. Antiplatelet and anticoagulation medications were held preprocedure, in accordance with consensus recommendations (21).

A standardized previously described inject and resect EMR technique was used (22). Currently, all colorectal EMRs are performed using high-definition Olympus 190 series variable-stiffness colonoscopes (Olympus, Tokyo, Japan). Carbon dioxide is used for insufflation (23). After lesion identification, optical evaluation under high-definition white-light and narrow-band imaging is performed to exclude features of submucosal invasive cancer (SMIC). In a systematic fashion, a submucosal cushion is created with injection of succinylated gelatin (Gelofusine; B. Braun, Bella Vista, Australia) (24) with 0.4% indigo carmine and 1:100,000 epinephrine. Using a microprocessor-controlled generator (ERBE VIO ENDO CUT Q, Effect 3; ERBE, Tubingen, Germany) snare excision is performed.

After complete resection, the defect is carefully examined to ensure no polypoid tissue remains and to assess for deep mural injury (DMI) (25). Areas of significant deep injury (DMI III–V) are subsequently treated by mechanical clip closure. Thermal ablation of the resection margin to mitigate the risk of recurrence is performed using snare-tip soft coagulation (STSC) (ERBE VIO SOFT COAG: 80W, Effect 4) to create a 2- to 3-mm rim of ablated tissue (19). Clinically significant intraprocedural bleeding (CSIPB) is treated with coagulation forceps or mechanical hemostasis. Resection specimens are collected and evaluated by
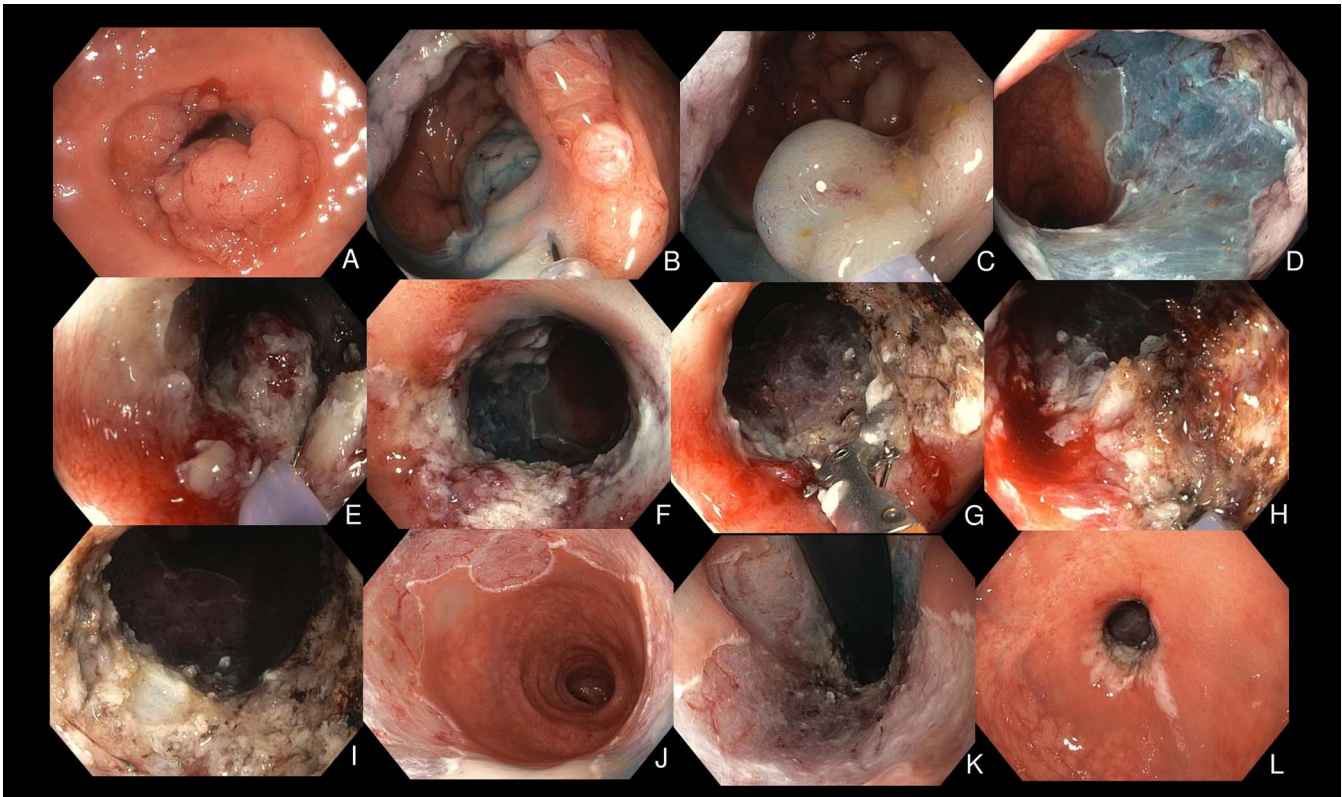
Figure 3. (**a**) A 50-mm circumferential 0-IIa + Is granular previously attempted large nonpedunculated colorectal polyp in the rectum. (**b–f**) Endoscopic mucosal resection. (**g–i**) Nonlifting polypoid tissue removed by cold-forceps avulsion with adjuvant snare-tip soft coagulation. (**j–l**) Resection defect evaluation before margin thermal ablation.

specialist gastrointestinal pathologists. Where appropriate, histopathology was confirmed with surgical specimen evaluation.

After completion of the procedure, patients are observed for 4 hours. If well, they are subsequently discharged on a clear fluid diet overnight. At 2 weeks, patients are contacted by a study coordinator and undergo a structured telephone interview to identify periprocedural adverse events. Intervals between subsequent colonoscopies are at the discretion of the endoscopist performing surveillance with recommended first surveillance colonoscopy (SC1) at 6 months. During SC, patients undergo a standardized evaluation of the EMR scar (26). Biopsies are routinely performed.

Technical aspects specific to PA-LNPCPs and nonlifting polypoid tissue are as follows (Figures 1–3, see Supplemental Video 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B927) (15):

1. Scar identification: Before commencing tissue resection, optical evaluation is performed to identify intralesional or adjacent scarring consistent with previously attempted resection.
2. EMR: All lifting polypoid tissue is first removed. This is to isolate nonlifting polypoid tissue and free its lateral margins. Often normal mucosa at the margin of the lesion is removed to allow entry into the submucosal plane. Once isolation is achieved, EMR can be attempted with caution, bearing in mind the increased risk of DMI associated with submucosal fibrosis. Luminal gas is completely aspirated during snare closure. This is to decrease colorectal wall tension and facilitate tissue capture. After each successful resection, the EMR defect is carefully evaluated for DMI. If an unstained area of

submucosa is exposed, topical submucosal chromoendoscopy is performed to facilitate DMI detection (27).

3. Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST): If EMR is not appropriate for or is unsuccessful at removing the nonlifting scarred residual polypoid tissue, it is meticulously and systematically avulsed with cold forceps (Radial Jaw Biopsy Forceps; Boston Scientific, Boston, MA). The exposed submucosa of the avulsion site and its margins are then treated with STSC (ERBE VIO SOFT COAG: 80W, Effect 4) as previously described (15). Type II DMI is frequently seen post-CAST, and prophylactic mechanical clips are placed to mitigate the small risk of delayed perforation (25).

Data extraction

Collected data included (i) patient characteristics: age, sex, and American Society of Anesthesiologists (ASA) classification; (ii) lesion characteristics: size, morphology, surface granularity, and Kudo pit pattern, histopathology; and (iii) procedure outcomes: technical success, periprocedural adverse events, and recurrence.

Technical success was defined as complete removal of all visible polypoid tissue during index EMR. Clinically significant intraprocedural bleeding was defined by oozing or spurting blood loss for ≥60 seconds, not responding to water jet irrigation and requiring either coagulation forceps or mechanical hemostasis. Clinically significant post-EMR bleeding (CSPEB) was defined as any bleeding which occurred after the procedure and required emergency department presentation, hospitalization, or reintervention (endoscopy, angiography, and surgery). Significant DMI
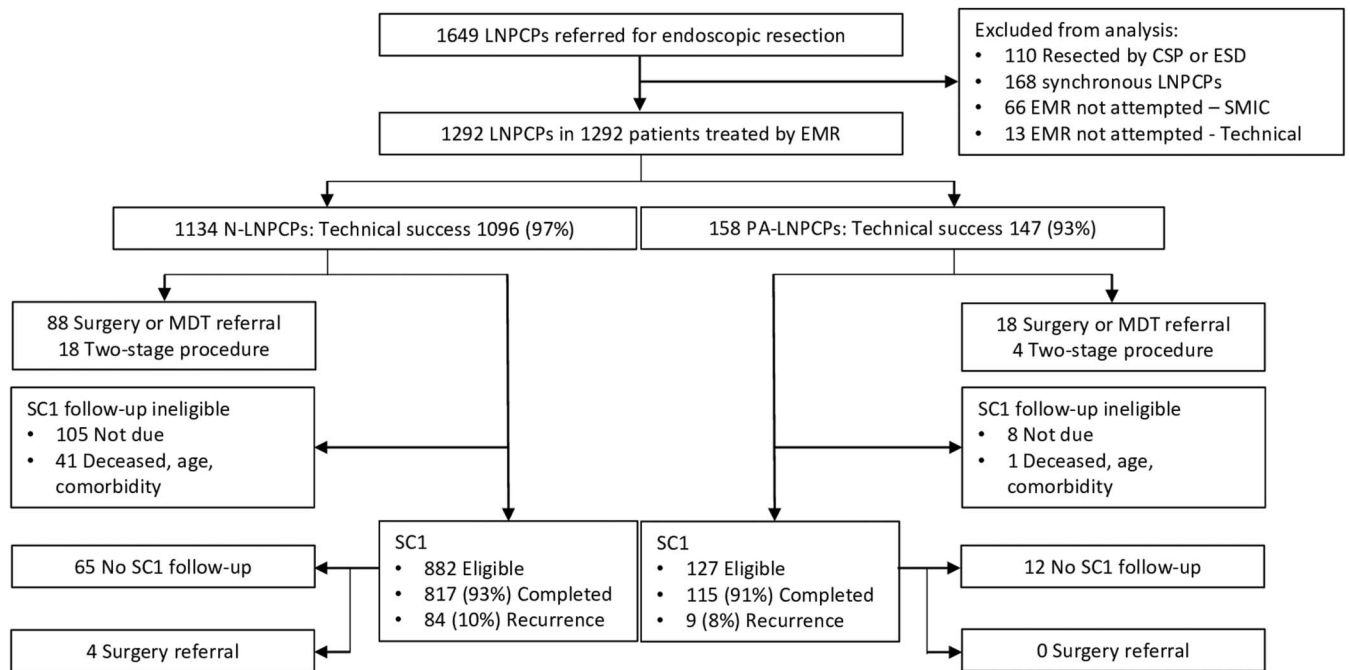
Figure 4. Flow diagram of consecutive LNPCPs referred for endoscopic resection. CSP, cold snare polypectomy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LNPCP, large nonpedunculated colorectal polyp; MDT, multidisciplinary team; N-LNPCP, naive large nonpedunculated colorectal polyp; PA-LNPCP, previously attempted large nonpedunculated colorectal polyp; SC1, surveillance colonoscopy 1; SMIC, submucosal invasive cancer.

was defined as grade III (muscularis propria injury, specimen target sign, and defect target sign) or grade IV/V (transmural perforation without or with contamination, respectively). Recurrence was evaluated at SC1. Study endpoints included technical failure, SMIC, death, advanced age, or comorbidities precluding ongoing SC, lost to follow-up, and SC1.

Statistical analysis

The primary outcome was technical success. Secondary outcomes were resection duration, use of CAST, periprocedural adverse events (CSIPB, DMI III-V, CSPEB, and delayed perforation) and recurrence (stratified by those who received margin STSC). PA-LNPCPs were compared with N-LNPCPs.

SPSS version 26.0 (IBM, Armonk, NY) was used for data analysis. Variables were analyzed per participant. If 2 or more eligible lesions were identified in a single participant, the largest lesion was selected for analysis. Lesions which underwent ESD, due to a heightened risk of SMIC-based SMIC risk stratification, or piecemeal cold-snare polypectomy were excluded from analysis.

Continuous variables were summarized using median (interquartile range [IQR]). Categorical variables were summarized as frequencies (%). All analyses were exploratory, and 2-tailed tests with a 5% significance level were used throughout. To test for association between categorical variables, the Pearson χ^2 or the Fisher exact tests were used, where appropriate. For continuous variables, the Mann-Whitney U test was used.

RESULTS

From January 2012 to October 2019, 1,649 LNPCPs were referred for endoscopic resection (Figure 4). Three hundred fifty-seven LNPCPs were excluded from analysis (110 resected by ESD or piecemeal cold-snare polypectomy as part of alternative

research protocols, 168 synchronous lesions, and 79 EMR not attempted due to concern for SMIC or technical reasons). One thousand two-hundred ninety-two LNPCPs (158 PA-LNPCPs and 1,134 N-LNPCPs) in 1,292 patients were included for analysis.

Patient and lesion characteristics

One hundred fifty-eight PA-LNPCPs underwent EMR in 158 patients (Table 1). Median patient age was 70 years (IQR 62–76 years), and 90 (57.0%) were men. The majority of patients were ASA I (48, 35.3%) or ASA II (66, 48.5%).

Median lesion size was 30 mm (IQR 25–46 mm). Paris classification 0-IIa was the most frequent morphology (89, 56.3%). Sixty-one (39.1%) PA-LNPCPs were nongranular or mixed.

Procedure outcomes

Median resection duration was 35 minutes (IQR 25–60 minutes) (Table 2). Technical success was achieved in 147 (93.0%). From May 2016, thermal ablation to the post-EMR margin was routinely performed, comprising 81 lesions (51.3%). Cold-forceps avulsion with adjuvant snare-tip soft coagulation was required in 73 (46.2%). Technical success was not achieved in 11 (7.0%): 1 submucosal fibrosis secondary to SMIC, 1 involvement of the ileocecal valve and DMI IV with successful mechanical clip closure, 2 intraprocedural identification of intradiverticular extension, and 3 extensive submucosal fibrosis and difficult positioning. All cases were referred to multidisciplinary team review for consideration of surgery. In the remaining 4 cases, 2-stage EMR was performed as previously described (28) with technical success achieved in all 4 cases. Adjusting for successful two-stage EMR, technical success was achieved in 151 (95.6%). Six (3.8%) patients required hospital admission: 2 observation after extensive endoscopic resection, 1 postprocedure pain, 1 CSPEB, and 2 DMI III-V.

Table 1. Patient and lesion characteristics

	Overall LNPCPs (n = 1,292, %)	N-LNPCPs (n = 1,134, %)	PA-LNPCPs (n = 158, %)
Age, yr, median (IQR)	69 (61–76)	69 (60–75)	70 (62–76)
Male sex, n (%)	681 (52.7)	591 (52.1)	90 (57.0)
ASA, n (%)[a]			
I	397 (36.7)	349 (36.9)	48 (35.3)
II	532 (49.2)	466 (49.3)	66 (48.5)
III	151 (14.0)	129 (13.7)	22 (16.2)
IV	1 (0.1)	1 (0.1)	0 (0.0)
Size, mm, median (IQR)	35 (30–50)	35 (30–50)	30 (25–46)
Location, n (%)			
Rectosigmoid	369 (28.6)	315 (27.8)	54 (34.2)
Proximal	923 (71.4)	819 (72.2)	104 (65.8)
Paris classification, n (%)			
0-Is	106 (8.2)	96 (8.5)	10 (6.3)
0-IIa	690 (53.4)	601 (53.0)	89 (56.3)
0-IIb	58 (4.5)	46 (4.1)	12 (7.6)
0-IIa + Is	413 (32.0)	373 (32.9)	40 (25.3)
Any 0-IIc	25 (1.9)	18 (1.6)	7 (4.4)
Granularity, n (%)[b]			
Granular	777 (61.3)	686 (61.7)	91 (58.3)
Nongranular	366 (28.9)	314 (28.2)	52 (33.3)
Mixed	66 (5.2)	57 (5.1)	9 (5.8)
Serrated	59 (4.7)	55 (4.9)	4 (2.6)
Kudo pit pattern, n (%)[c]			
I	1 (0.1)	1 (0.1)	0 (0.0)
II	97 (7.7)	89 (8.0)	8 (5.1)
III	290 (22.9)	255 (23.0)	35 (22.3)
IV	837 (66.1)	728 (65.6)	109 (69.4)
V	42 (3.3)	37 (3.3)	5 (3.2)
Histopathology, n (%)			
Tubular adenoma	314 (24.3)	270 (23.8)	44 (27.8)
Tubulovillous adenoma	713 (55.2)	625 (55.1)	88 (55.7)
Villous adenoma	9 (0.7)	6 (0.5)	3 (1.9)
Serrated	155 (12.0)	145 (12.8)	10 (6.3)
Submucosal invasive cancer	84 (6.5)	72 (6.3)	12 (7.6)
Other	17 (1.3)	16 (1.4)	1 (0.6)
High-grade dysplasia, n (%)	173 (13.4)	157 (13.8)	16 (10.1)

ASA, American Society of Anesthesiologists; IQR, interquartile range; LNPCP, large nonpedunculated colorectal polyp; N-LNPCP, naive large nonpedunculated colorectal polyp; PA-LNPCP, previously attempted large nonpedunculated colorectal polyp.
[a]Two hundred eleven participants ASA not classified.
[b]Twenty-four participants granularity not classified.
[c]Twenty-five participants Kudo pit pattern not classified.

The majority (88, 55.7%) of PA-LNPCPs were tubulovillous adenomas. SMIC and high-grade dysplasia were identified in 12 (7.6%) and 16 (10.1%), respectively. All PA-LNPCPs with SMIC were subsequently referred to multidisciplinary team review for consideration of surgery.

Adverse events

Clinically significant intraprocedural bleeding occurred in 11 (7.0%). Endoscopic hemostasis was achieved in all cases by coagulation forceps (7, 63.6%) or mechanical clip placement (4, 36.4%). DMI III-V was identified in 4 (2.5%), and all

Table 2. Procedural outcomes

	Overall LNPCPs (n = 1,292, %)	N-LNPCPs (n = 1,134, %)	PA-LNPCPs (n = 158, %)	*P*
Duration, min, median (IQR)	30 (15–45)	25 (15–40)	35 (25–60)	<**0.001**
Technical success, n (%)	1,243 (96.2)	1,096 (96.6)	147 (93.0)	**0.026**
Auxiliary modality, n (%)	159 (12.3)	86 (7.6)	73 (46.2)	<**0.001**
Margin thermal ablation, n (%)	602 (46.6)	521 (45.9)	81 (51.3)	0.209
CSIPB, n (%)	63 (4.9)	52 (4.6)	11 (7.0)	0.194
Deep mural injury III-V, n (%)	46 (3.6)	42 (3.7)	4 (2.5)	0.456
CSPEB, n (%)	101 (7.8)	88 (7.8)	13 (8.2)	0.837
Delayed perforation, n (%)	4 (0.3)	4 (0.4)	0 (0.0)	1.000
SC1				
Eligible, n	1,009	882	127	
Underwent SC1, n (%)	932 (92.4)	817 (92.6)	115 (90.6)	0.409
Months to SC1, median (IQR)	6 (5–7)	6 (5–7)	6 (5–7)	0.805
Recurrence	93 (10.0)	84 (10.3)	9 (7.8)	0.411

Bold values represent significant *P* values < 0.05.
CSIPB, clinically significant intraprocedural bleeding; CSPEB, clinically significant post-EMR bleeding; IQR, interquartile range; LNPCP, large nonpedunculated colorectal polyp; N-LNPCP, naive large nonpedunculated colorectal polyp; PA-LNPCP, previously attempted large nonpedunculated colorectal polyp; SC1, surveillance colonoscopy 1.

were successfully closed endoscopically with mechanical clip placement.

Clinically significant post-EMR bleeding occurred in 13 (8.2%): 10 (76.9%) were managed conservatively, and 3 (23.1%) underwent endoscopic re-evaluation with or without endoscopic intervention. Delayed perforation did not occur in any cases.

Recurrence

One hundred twenty-seven patients were eligible for SC1 (Table 2 and Figure 4). One hundred fifteen (90.6%) underwent SC with a median interval of 6 months (IQR 5–7 months). Recurrence was identified in 9 (7.8%). No patients were referred for surgery at SC1.

In 65 PA-LNPCPs which received margin STSC, no recurrence was identified vs 9 (18.0%; *P* < 0.001) which did not undergo margin STSC (Table 3). On further subanalysis, in 39 PA-LNPCPs where CAST was used and margin STSC was performed, no recurrence was identified vs 5 (31.3%; *P* = 0.001) which did not receive margin STSC (Table 4).

Comparison with N-LNPCPs

Between PA-LNPCPs and N-LNPCPs, there were significant differences in resection duration (35 vs 25 minutes; *P* < 0.001), technical success (93.0% vs 96.6%; *P* = 0.026), and the use of CAST (46.2% vs 7.6%; *P* < 0.001), respectively. When adjusting for 2-stage EMR, no difference in technical success was identified (95.6% vs 97.8%; *P* = 0.100). No differences in CSIPB, DMI III-V, CSPEB, delayed perforation, or recurrence were identified.

DISCUSSION

Evidence-based innovations in minimally invasive endoscopic resection techniques have transformed the management of LNPCPs. Site-specific technical modifications in high-quality EMR can effectively and safely treat circumferential LNPCPs (5) and those involving the ileocecal valve (3), the appendiceal orifice (4), and the anorectal junction (6). Moreover, complementary techniques and management strategies such as margin

thermal ablation (19), DMI classification (25), and 2-stage EMR (28) have largely mitigated recurrence, perforation, and technical failure, respectively. This study demonstrates another major advance. EMR, in combination with margin thermal ablation and CAST where necessary, can achieve high technical success and low recurrence frequencies for PA-LNPCPs.

Snare-based resection techniques are inherently limited in removing nonlifting polypoid tissue as they are predicated on submucosal expansion to achieve tissue capture. In this study, complete removal of all polypoid tissue was achieved in 93.0% of PA-LNPCPs at index EMR. This can be largely attributed to CAST, which was required in 46.2% of cases. As CAST is based on equipment (biopsy forceps and snare) available in all endoscopy units and techniques (cold avulsion and STSC) familiar to endoscopists who perform colorectal EMR, it represents an easily adoptable auxiliary technique. With no difference in adverse outcomes compared with N-LNPCPs, these results further cement CAST as an essential technique for treating nonlifting polypoid tissue. Of note, a significant difference in technical success was identified between PA-LNPCPs and N-LNPCPs (93.0% vs 96.6%; *P* = 0.026). Although statistically significant,

Table 3. Recurrence subanalysis of LNPCPs by margin STSC

	N-LNPCPs			PA-LNPCPs		
	No STSC	STSC	*P*	No STSC	STSC	*P*
Recurrence, n/N (%)	82/481 (17.0)	2/336 (0.6)	<**0.001**	9/50 (18.0)	0/65 (0.0)	<**0.001**

Bold values represent significant *P* values < 0.05.
LNPCP, large nonpedunculated colorectal polyp; N-LNPCP, naive large nonpedunculated colorectal polyp; PA-LNPCP, previously attempted large nonpedunculated colorectal polyp; STSC, snare-tip soft coagulation.

Table 4. Recurrence subanalysis of LNPCPs requiring CAST by margin STSC

	N-LNPCPs			PA-LNPCPs		
	No STSC	STSC	*P*	No STSC	STSC	*P*
Recurrence, n/N (%)	7/38 (18.4)	0/22 (0.0)	**0.040**	5/16 (31.3)	0/39 (0.0)	**0.001**

Bold values represent significant *P* values < 0.05.
LNPCP, large nonpedunculated colorectal polyp; N-LNPCP, naive large nonpedunculated colorectal polyp; PA-LNPCP, previously attempted large nonpedunculated colorectal polyp; STSC, snare-tip soft coagulation.

this difference may not be clinically meaningful. Moreover, when affording for 2-stage EMR, technical success increased to 95.6% and no difference compared with N-LNPCPs was identified (*P* = 0.100). Therefore, EMR should be considered a first-line strategy for the treatment of PA-LNPCPs.

A critical advance in high-quality EMR technique is the ability of margin thermal ablation to prevent recurrence. In a randomized control trial, margin STSC decreased recurrence at SC1 from 21.0% to 5.2% (*P* < 0.001) (19). These results have been reproduced in LNPCPs involving the anorectal junction (6), which represents another complex lesion subgroup, as well as in North American cohorts (29). In this study, among 65 PA-LNPCPs which received margin STSC and underwent SC1, no recurrence was identified vs 9 (18.0%; *P* < 0.001) which did not receive margin STSC. Similarly, in 39 PA-LNPCPs where CAST and margin STSC were performed, no recurrence was identified vs 5 (31.3%; *P* = 0.001) which did not receive margin STSC. Given these findings, margin thermal ablation should be viewed as an integral component of high-quality EMR. It should be universally applied independent of lesion complexity, consistent with current international guidelines (1).

Alternative auxiliary techniques have been developed for the management of nonlifting polypoid tissue including (i) ablative techniques, (ii) hot avulsion, and (iii) curetting techniques. Ablative modalities, including argon plasma coagulation and STSC, when used for visible polypoid tissue are associated with a substantial risk of recurrence (10). Moreover, they preclude histopathology assessment. In the era of effective auxiliary techniques, ablative techniques should be discouraged. Hot avulsion is a comparative technique to CAST, except that hot biopsy forceps with cutting current are used to avulse the area of concern. In a recent retrospective analysis of 112 lesions which required hot avulsion compared with 425 which did not, no difference in recurrence or adverse events was identified (all *P* > 0.15) (16). Although hot avulsion seems effective, the frequency of recurrence was 17.5%, in comparison with 0% of lesions in this study which received CAST and margin STSC. To appropriately compare hot avulsion and CAST, a comparative analysis in the era of margin thermal ablation is therefore needed. The EndoRotor (Interscope Medical, Worcester, MA) is a novel through-the-scope nonthermal curetting device. In a pilot study of 19 rectosigmoid polyps, technical success was 52.6% after 1 attempt and increased to 84.1% after 2 attempts (30). Although a recent retrospective analysis of 28 colorectal lesions has shown more promising results (17), further

evaluation of this new technology should be within the confines of a well-designed research study.

ESD, including hybrid techniques, and EFTR have also been evaluated (13,18). Although ESD continues to be adopted by western endoscopy centers, it is imperative to remember that the benefit of ESD is largely derived from its ability to perform R0 and therefore curative resections for superficially invasive SMIC. As with EMR, ESD is dependent on submucosal expansion. Therefore, ESD for PA-LNPCPs is extremely challenging, even in expert hands, with a heightened risk of adverse events and may not be appropriate for the current western skill set. EFTR is a logical solution for nonlifting polypoid tissue because it circumvents the need for submucosal expansion. In a prospective multicenter study, which included 104 nonlifting lesions, EFTR showed promising results (13). However, the frequency of emergency surgery was 2.2%. Therefore, as safer alternatives for PA-LNPCPs exist, EFTR should be reserved for lesions unamenable to avulsion techniques.

This study is not without limitations. It is a single-center analysis. Moreover, as the study was performed at an expert center in minimally invasive tissue resection techniques, reproducibility of these results in other centers is needed. Time between previous attempt by the referring endoscopist and index EMR was not quantified. Furthermore, comparative analyses based on the number of EMR specimens per LNPCPs were not performed. Finally, CAST was exclusively used for nonlifting polypoid tissue during the study period, and therefore, no comparative analyses with alternative endosocpic resection techniques or alternative auxiliary modalities were performed. It is therefore critical for future studies to perform comparative analyses of different endosocpic resection techniques and different auxiliary modalities for PA-LNPCP management.

In conclusion, EMR, in combination with CAST where necessary, is an effective and safe treatment for PA-LNPCPs affording high frequencies of technical success. It should now be viewed as a first-line modality for most lesions. By integrating margin thermal ablation into high-quality EMR technique, recurrence is essentially negated, even in this historically complex subgroup. Importantly, PA-LNPCP management should be reserved for tertiary tissue resection centers with N-LNPCPs only treated by endoscopists competent in high-quality EMR technique.

CONFLICTS OF INTEREST

ENDOSCOPY

Study Highlights

WHAT IS KNOWN

✓ Limited data exist concerning the management of previously attempted large (≥20 mm) nonpedunculated colorectal polyps (PA-LNPCPs).

✓ The best approach for the treatment of PA-LNPCPs is unknown.

WHAT IS NEW HERE

✓ High technical success and low recurrence frequencies are achievable with endoscopic mucosal resection for PA-LNPCPs. However, auxillary techniques such as cold-forceps avulsion with adjuvant snare-tip soft coagulation and margin thermal ablation are required.

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Outcomes of Deep Mural Injury After Endoscopic Resection: An International Cohort of 3717 Large Non-Pedunculated Colorectal Polyps

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Outcomes of deep mural injury after endoscopic resection: An international cohort of 3717 large non-pedunculated colorectal polyps
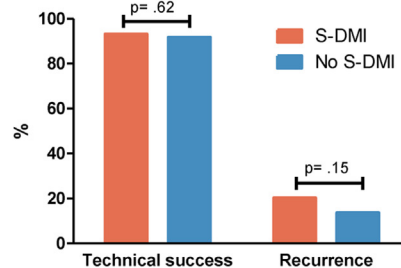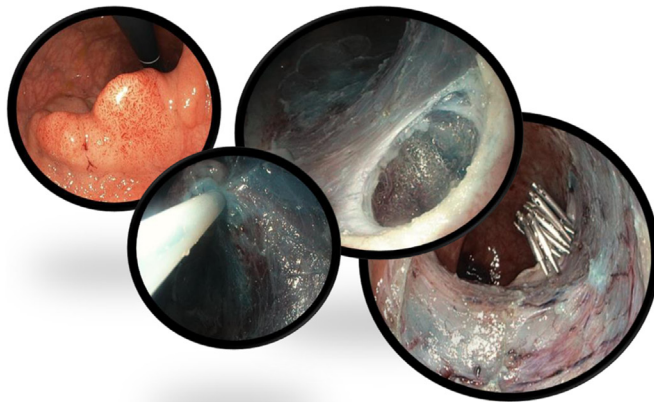
Significant deep mural injury (S-DMI) is readily managed endoscopically

Clinical Gastroenterology and Hepatology

BACKGROUND & AIMS: Although perforation is the most feared adverse event associated with endoscopic mucosal resection (EMR), limited data exists concerning its management. Therefore, we sought to evaluate the short- and long-term outcomes of intra-procedural deep mural injury (DMI) in an international multi-center observational cohort of large (≥20 mm) non-pedunculated colorectal polyps (LNPCPs).

Most current article

METHODS: Consecutive patients who underwent EMR for a LNPCP ≥20 mm were evaluated. Significant DMI (S-DMI) was defined as Sydney DMI Classification type III (muscularis propria injury, target sign) or type IV/V (perforation without or with contamination, respectively). The primary outcome was successful S-DMI defect closure. Secondary outcomes included technical success (removal of all visible polypoid tissue during index EMR), surgical referral and recurrence at first surveillance colonscopy (SC1).

RESULTS: Between July 2008 to May 2020, 3717 LNPCPs underwent EMR. Median lesion size was 35mm (interquartile range (IQR) 25 to 45mm). Significant DMI was identified in 101 cases (2.7%), with successful defect closure in 98 (97.0%) using a median of 4 through-the-scope clips (TTSCs; IQR 3 to 6 TTSCs). Three (3.0%) patients underwent S-DMI-related urgent surgery. Technical success was achieved in 94 (93.1%) patients, with 46 (45.5%) admitted to hospital (median duration 1 day; IQR 1 to 2 days). Comparing LNPCPs with and without S-DMI, no differences in technical success (94 (93.1%) vs 3316 (91.7%); P = .62) or SC1 recurrence (12 (20.0%) vs 363 (13.6%); P = .15) were identified.

CONCLUSIONS: Significant DMI is readily managed endoscopically and does not appear to affect technical success or recurrence.

Keywords: Adverse Event; Colonoscopy; Complication; Endoscopy; Perforation.

See editorial on page e19.

Endoscopic mucosal resection (EMR) is established as the preferred resection technique for large (≥20 mm) non-pedunculated colorectal polyps (LNPCPs).[1–3] Although equally efficacious, it is safer and less costly compared with surgery.[4–6]

Nevertheless, perforation remains the most feared EMR-related adverse event (AE), with an estimated frequency of 1%–2%.[7] Although endoscopic defect closure is feasible, because limited data exist, its efficacy and impact on short- and long-term outcomes are largely unknown. Current consensus recommendations[2,3,8] advocating for mechanical defect closure are predominantly based on small retrospective series.[9–14] Therefore, we sought to evaluate the short- and long-term outcomes of intra-procedural deep mural injury (DMI) in an international multicenter observational cohort of consecutive LNPCPs.

Methods

This article was produced with guidance from the Strengthening the Reporting of Observational Studies in Epidemiology[15] recommendations.

The Australian Colonic Endoscopic Resection Cohort

The Australian Colonic Endoscopic Resection (ACE) cohort (clinicaltrials.gov identifiers: NCT01368289, NCT02000141) is a multicenter, observational cohort of consecutive patients referred for the management of LNPCPs ≥20 mm. Center-specific Institutional Review Board approval is maintained at each participating site. Written informed consent is obtained from each participant before enrollment.

Between July 2008 and May 2020, consecutive participants enrolled at 1 of 10 ACE sites who underwent EMR for a LNPCP were considered for inclusion. All endoscopic procedures were performed by either a study investigator (accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their supervision. Endoscopic mucosal resection was performed by using a standardized previously described inject and resect EMR technique at all centers.[1] Technical innovations in EMR were adopted as the evidence to support them emerged.

Patient follow-up was performed at 14 days after index procedure by dedicated research staff using a structured telephone interview to collect data regarding post-procedural AEs consistent with American Society for Gastrointestinal Endoscopy guidelines.[16] Additional follow-up data were obtained at first surveillance colonoscopy (SC1) at 6 months and thereafter.

Significant Deep Mural Injury

Significant DMI (S-DMI) was defined as Sydney DMI Classification[17] type III (muscularis propria [MP] injury as evidenced by specimen target sign[18] or defect target sign), type IV (actual hole in the MP within a white cautery ring with no observed contamination), or type V (actual hole in the MP within a white cautery ring with observed contamination) (Figures 1 and 2). Data on S-DMI were prospectively collected from March 2010 after the description of the target sign.[18] Before March 2010, retrospective review from procedure charts and comprehensive photo records was performed independently by 2 investigators. In the case of discordance, a third investigator was used for arbitration.

Intraprocedural and post-procedural management decisions were at the discretion of the endoscopist. This included (1) through-the-scope clip (TTSC) defect closure, (2) radiographic evaluation, (3) antibiotic therapy, (4) hospital admission, and (5) surgical referral.

Data Extraction

Collected data included the following: (1) patient characteristics: age, sex, American Society of Anesthesiologists classification; (2) lesion characteristics: location, size, Paris classification, surface granularity; (3) resection characteristics: attempted en bloc resection; (4) histopathology evaluation; (5) post-procedural AEs: clinically significant post-EMR bleeding (CSPEB), perforation, hospitalization, referral to surgery; and (6) surveillance: endoscopic/histologic recurrence.

Outcomes and Analysis

The primary outcome was successful S-DMI defect closure. This was defined as complete capture and apposition of the area of concern with TTSCs, confirmed by inspection of both the proximal and distal margins. Secondary outcomes included technical success (complete removal of all visible polypoid tissue during index EMR), surgical referral, and recurrence (absence of endoscopic/histologic recurrence at SC1).

SPSS version 26.0 (IBM Corp, Armonk, NY) was used for retrospective data analysis. Variables were analyzed per participant. If 2 or more eligible lesions were identified in a

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What You Need to Know

Background

Perforation is the most feared adverse event associated with endoscopic mucosal resection for large ($\geq$ 20 mm) non-pedunculated colorectal polyps (LNPCPs). Limited data exist concerning its management.

Findings

In a multicenter observational cohort of 3717 LNPCPs, significant deep mural injury occurred in 101 (2.7%). Defect closure was achieved in 98 (97.0%), with no difference in technical success or recurrence compared with LNPCPs without S-DMI.

Implications for patient care

Significant deep mural injury is readily managed by through-the-scope clips to achieve defect closure.

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single participant, the lesion with DMI was selected for analysis. If no DMIs occurred, the smaller lesion(s) were excluded from analysis. Lesions that underwent endoscopic submucosal dissection (ESD) or piecemeal cold snare polypectomy were excluded from analysis.

Continuous variables were summarized as median (interquartile range [IQR]). Categorical variables were summarized as frequencies (%). All analyses were exploratory, and 2-tailed tests with 5% significance level were used throughout. Pearson χ^2 test was used for categorical variables.
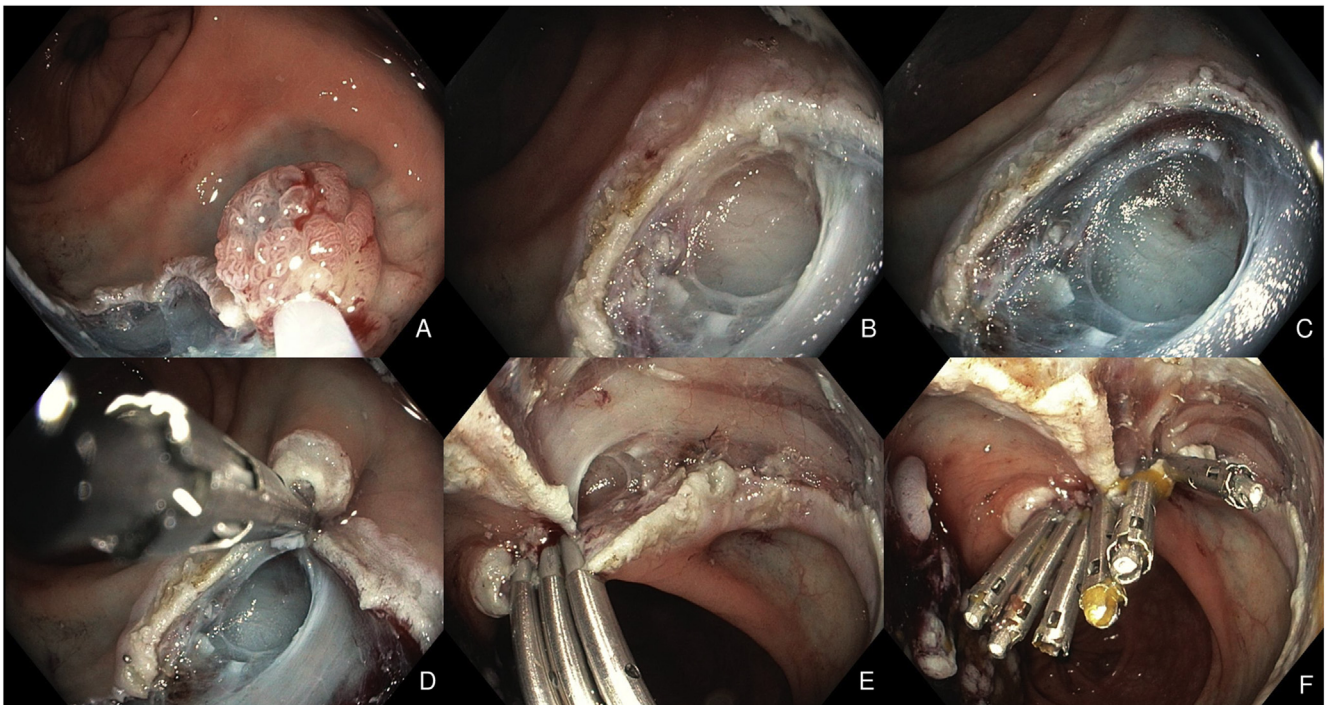

Figure 1. (*A*) Endoscopic mucosal resection of 40-mm 0-IIa+Is granular large non-pedunculated colorectal polyp. (*B* and *C*) Suspected significant deep mural injury confirmed with topical submucosal chromoendoscopy. (*D* and *F*) Successful through-the-scope clip closure.
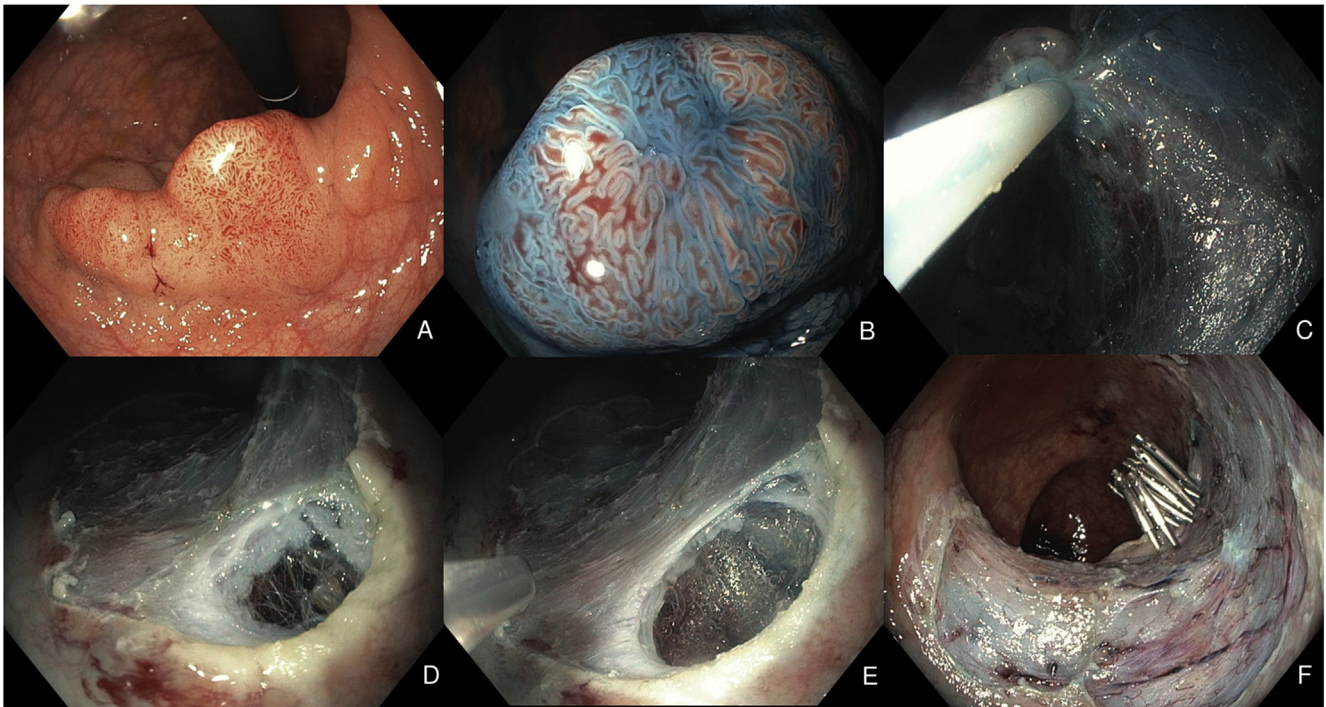
Figure 2. (*A–C*) Endoscopic mucosal resection of 40-mm 0-IIa granular large non-pedunculated colorectal polyp. (*D* and *E*) Suspected significant deep mural injury confirmed with topical submucosal chromoendoscopy. (*F*) Successful through-the-scope clip closure.

Results

Between July 2008 and May 2020, 4545 LNPCPs in 4078 patients were referred for endoscopic resection (Figure 3). Eight hundred twenty-eight LNPCPs were excluded from analysis (295 resected by piecemeal cold snare polypectomy or ESD, 365 synchronous lesions, 168 EMR not attempted because of concern for submucosal invasive cancer [SMIC] or technical reasons). Three thousand seven hundred seventeen LNPCPs in 3717 patients underwent EMR (median age, 68 years; IQR, 61–76 years; male sex, 53.3%) (Table 1). Median lesion size was 35 mm (IQR, 25–45 mm), with the majority of lesions located in the right colon (53.7%) or the rectum (17.6%). Piecemeal EMR was performed in 3256 (87.6%). Overall technical success was achieved in 3410 (91.7%). SMIC was identified in 274 (7.4%).

Primary Outcome

Significant DMI was identified in 101 patients (2.7%) (Figure 4). Of these, 71 patients (70.3%) had an MP injury or target sign (DMI III). Thirty patients had a full-thickness perforation, 28 (27.7%) without observed contamination (DMI IV) and 2 (2.0%) with contamination (DMI V).

Defect closure was attempted in 99 patients (98.0%). A selective closure of the area of concern was performed in 67 patients (67.7%), with the remaining 32 (32.3%) undergoing closure of the entire resection defect.

Successful defect closure was achieved in 98 patients (97.0%) with a median of 4 TTSCs (IQR, 3–6 TTSCs). Of the remaining 3 patients, 2 underwent urgent surgery within 48 hours, and the third patient had DMI type IV located in the distal rectum below the peritoneal reflection. Closure was not attempted, and the patient was treated conservatively with antibiotics.

Secondary Outcomes

Technical success was achieved in 94 patients (93.1%) with S-DMI. Of the 7 in whom technical success was not achieved, this was due to suspected SMIC 1, technical considerations (significant submucosal fibrosis and/or difficult positioning) 4, and primarily related to S-DMI 2.

Forty-six patients (45.5%) were admitted to hospital for observation. Median hospital stay was 1 day (IQR, 1–2 days). Intravenous antibiotics were administered in 46 patients (45.5%). Imaging was performed in 17 patients (16.8%; computed tomography 10, plane x-ray 5, both modalities 2. Four of these patients were discharged on the day of procedure after reassuring imaging studies.

Five patients (4.9%) were referred for urgent surgery (<48 hours): 1 defect closure not attempted, 1 successful defect closure not achieved, 1 peritonitis, 1 SMIC, 1 CSPEB after successful defect closure. Eighteen patients (17.8%) were referred for elective surgery: 12 because of SMIC on histopathology and 6 because of other reasons (4 incomplete EMR due to significant submucosal
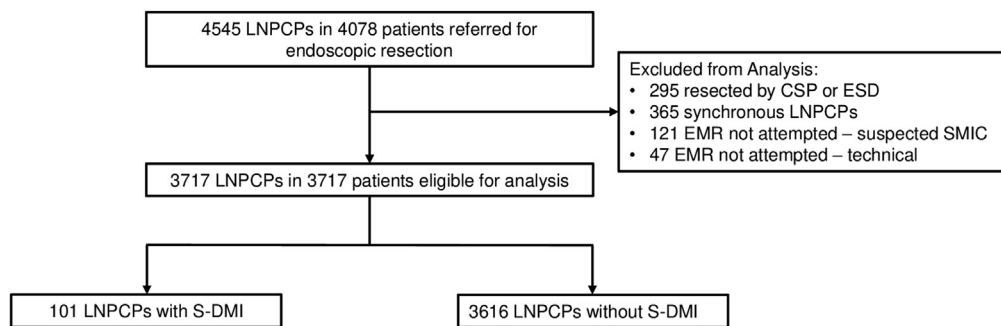
Figure 3. Flow diagram of consecutive large non-pedunculated colorectal polyps referred for endoscopic resection. CSP, cold snare polypectomy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LNPCP, large non-pedunculated colorectal polyp; S-DMI, significant deep mural injury; SMIC, submucosal invasive cancer.

fibrosis and/or difficult positioning, 2 concomitant lesions with SMIC).

Sixty-five patients were eligible for SC1, of whom 60 (92.3%) underwent endoscopic follow-up. One patient was lost to follow-up, and 4 patients are pending SC1, because the due date occurred during the coronavirus disease 2019 pandemic. Reasons for ineligibility included 23 post-surgery, 5 comorbid disease or death unrelated to S-DMI or colorectal neoplasia, 8 SC1 not due. From index EMR, median time to follow-up was 6 months (IQR, 5–7 months). Recurrence was identified in 12 patients (20%).

Lesions With and Without Significant Deep Mural Injury

Comparing outcomes of LNPCPs with and without S-DMI, no significant differences in technical success (94, 93.1% vs 3316, 91.7%; $P = .62$) or SC1 recurrence (12, 20% vs 363, 13.6%; $P = .15$) were identified.

Discussion

EMR has emerged as the primary resection modality for LNPCPs.[2,3] Site-specific technical modifications in high-quality EMR and the development of auxiliary techniques now allow for the effective, efficient, and safe removal of complex lesions.[19,20] Moreover, thermal ablation to the EMR margin and prophylactic clip closure of the resection defect, specifically for proximal lesions, have mitigated the risk of recurrence and CSPEB, respectively.[21,22] Despite these innovations, perforation remains the most feared EMR-related AE. Consensus guidelines advocate for endoscopic defect closure.[2,3,8] However, these recommendations are largely based on small retrospective cohorts that commonly do not provide colorectal EMR-specific short- and long-term outcomes.[9–14,23–25] In this study, we demonstrate that EMR-related S-DMI can be effectively managed with TTSCs in the overwhelming majority.

The importance of S-DMI management relates to the heightened morbidity of emergency surgery in this setting, therefore emphasizing the potential for endoscopic defect closure to have a meaningful effect on clinical outcomes. In this study, successful TTSC closure was achieved in 97.0% of patients, with 45.5% admitted to hospital for a median of 1 day (IQR, 1–2 days). Only 3 patients (3.0%) underwent S-DMI–related urgent surgery (<48 hours): 1 where defect closure was not attempted, 1 due to unsuccessful defect closure, and 1 due to peritonitis. Furthermore, no significant differences in technical success (93.1% vs 91.7%; $P = .62$), or SC1 recurrence (20% vs 13.6%; $P = .15$) were identified. It is important to note that the lack of statistical significance, specifically for recurrence, may be due to the study being underpowered for this outcome. However, because of the overall findings, TTSC defect closure should be considered the standard of care for colorectal EMR-related S-DMI.

Procedural success is predicated on a protocolized approach to high-quality EMR and the management of potential AEs (Figure 5, Supplementary Video 1). Pre-procedure, the endoscopist must ensure that TTSCs are appropriately stocked and readily available within the endoscopy suite for use by a competent endoscopy team. Moreover, EMR should only be performed with carbon dioxide insufflation to mitigate the risk of tension pneumoperitoneum, while allowing the endoscopist to treat the area of concern with a considered and strategic approach in a controlled environment. In the era of carbon dioxide insufflation, the primary objective is complete and effective closure rather than speed, which was necessary when air insufflation was used.

Once the procedure has begun, all residual debris should be aspirated, including in the colorectal segments above and below, where applicable. Before commencing tissue resection, the patient should be repositioned to manipulate the fluid pool to the opposing colorectal wall. In the event of intraprocedural bleeding or S-DMI, fluid does not pool over the working field, free access to the point of interest is maintained, and the risk of peritoneal contamination is minimized. After tissue capture, acquiring the snare handle from the assistant provides important tactile feedback. First, the completely closed snare should feel "spongy". If firm, inadvertent MP

Table 1. Patient and Lesion Characteristics

	All LNPCPs (N = 3717) (n, %)	LNPCPs with S-DMI (n = 101) (n, %)	LNPCPs without S-DMI (n = 3616) (n, %)
Patient characteristics			
Age (median, IQR, y)	68 (61–76)	69 (58–78)	68 (61–75)
Male sex (n, %)	1983 (53.3)	54 (53.5)	1929 (53.4)
ASA (n, %)[a]			
I	1119 (32.6)	30 (32.3)	1089 (32.6)
II	1747 (50.8)	47 (50.5)	1700 (50.8)
III–V	571 (16.6)	16 (17.2)	555 (16.6)
Lesion characteristics			
Size (median, IQR, mm)	35 (25–45)	35 (25–50)	35 (25–45)
Location (n, %)			
Right colon (cecum to hepatic flexure)	1995 (53.7)	42 (41.6)	1953 (54.0)
Transverse colon	429 (11.5)	15 (14.9)	414 (11.4)
Left colon (splenic flexure to sigmoid colon)	637 (17.1)	31 (30.7)	606 (16.8)
Rectum	656 (17.6)	13 (12.9)	643 (17.8)
Morphology (n, %)[b]			
0-IIa or 0-IIb	1863 (50.7)	45 (44.6)	1818 (50.9)
0-Is	712 (19.4)	21 (20.8)	691 (19.4)
0-IIa+Is	971 (26.5)	30 (29.7)	941 (26.4)
Any 0-IIc component	124 (3.4)	5 (5.0)	119 (3.3)
Granularity (n, %)[c]			
Granular	2099 (68.7)	52 (63.4)	2047 (68.9)
Non-granular	735 (24.1)	22 (26.8)	713 (24.0)
Mixed	205 (6.7)	6 (7.3)	199 (6.7)
Serrated	12 (0.4)	2 (2.4)	10 (0.3)
Attempted en bloc resection (n, %)	461 (12.4)	22 (21.8)	439 (12.1)
Histopathology (n, %)			
Tubular adenoma	919 (24.7)	17 (16.8)	902 (24.9)
Tubulovillous adenoma	2128 (57.2)	66 (65.3)	2062 (57.0)
Villous adenoma	95 (2.6)	0 (0.0)	95 (2.6)
Sessile serrated polyp	490 (13.2)	15 (14.9)	475 (13.1)
Traditional serrated adenoma	62 (1.7)	3 (3.0)	59 (1.6)
Other	23 (0.6)	0 (0.0)	23 (0.6)
Submucosal invasive cancer	274 (7.4)	17 (16.8)	257 (7.1)
Dysplasia			
None	405 (10.9)	11 (10.9)	394 (10.9)
Low-grade dysplasia	2353 (63.3)	57 (56.4)	2296 (63.5)
High-grade dysplasia	959 (25.8)	33 (32.7)	926 (25.6)

ASA, American Society of Anesthesiologists; IQR, interquartile range; LNPCP, large non-pedunculated colorectal polyp; S-DMI, significant deep mural injury.
[a]280, ASA not classified.
[b]47, morphology not classified.
[c]Granularity assessment for adenomatous LNPCPs. 91 granularity not classified.

capture may have occurred, that can be addressed by gently elevating the captured tissue to the center of the lumen. Then the snare is opened slightly to release the MP, while simultaneously insufflating, followed by snare closure. Second, the snare catheter can be manipulated, and the captured tissue should move freely compared
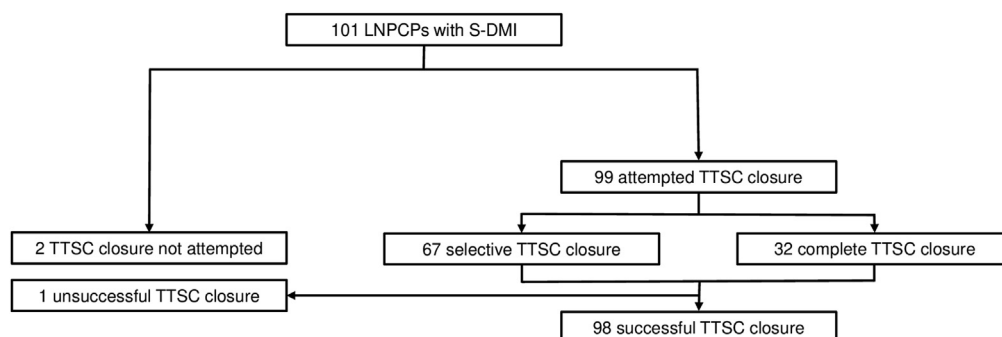

Figure 4. Flow diagram of significant deep mural injury management. EMR, endoscopic mucosal resection; LNPCP, large non-pedunculated colorectal polyp; S-DMI, significant deep mural injury; TTSC, through-the-scope clip.
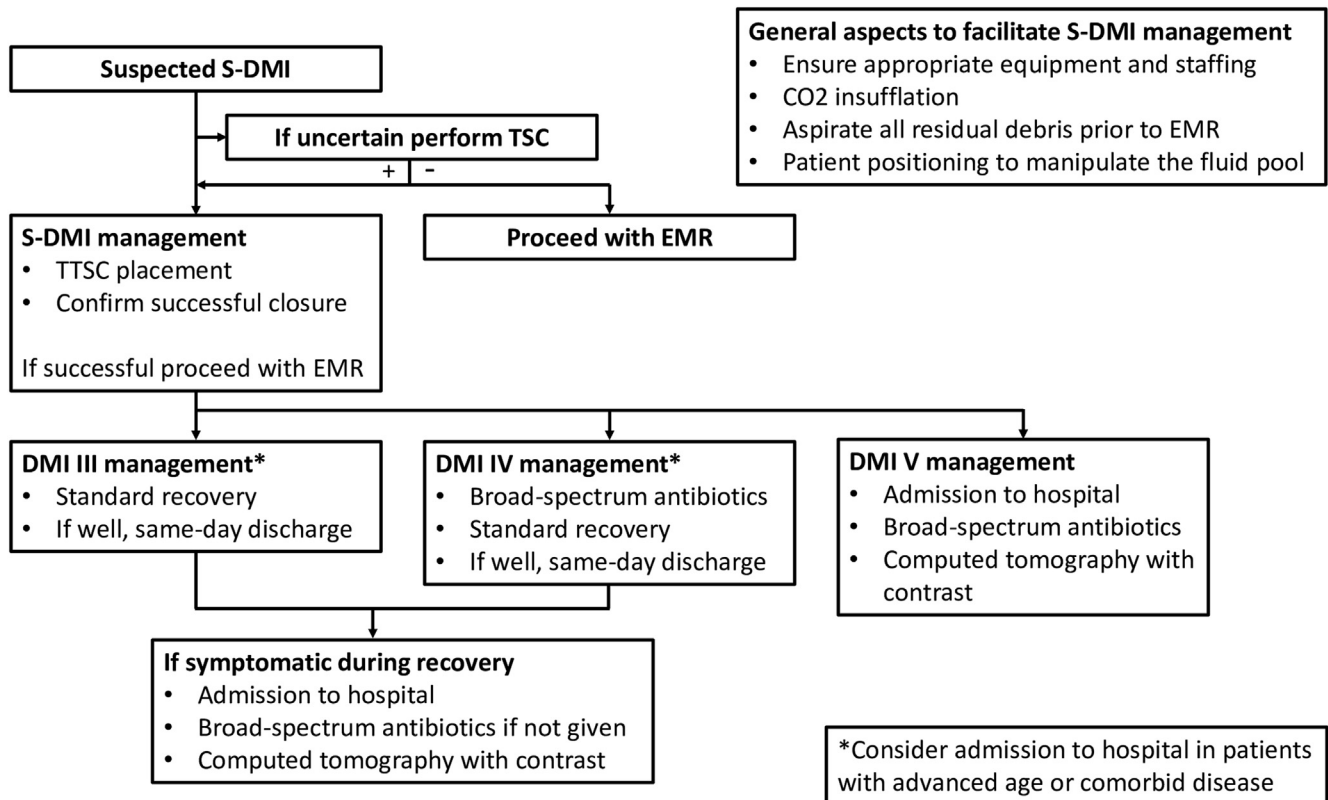
Suspected S-DMI

If uncertain perform TSC
+ | −

General aspects to facilitate S-DMI management
- Ensure appropriate equipment and staffing
- CO_2 insufflation
- Aspirate all residual debris prior to EMR
- Patient positioning to manipulate the fluid pool

S-DMI management
- TTSC placement
- Confirm successful closure

If successful proceed with EMR

Proceed with EMR

DMI III management*
- Standard recovery
- If well, same-day discharge

DMI IV management*
- Broad-spectrum antibiotics
- Standard recovery
- If well, same-day discharge

DMI V management
- Admission to hospital
- Broad-spectrum antibiotics
- Computed tomography with contrast

If symptomatic during recovery
- Admission to hospital
- Broad-spectrum antibiotics if not given
- Computed tomography with contrast

*Consider admission to hospital in patients with advanced age or comorbid disease

Figure 5. Proposed algorithm for significant deep mural injury management. DMI, deep mural injury; EMR, endoscopic mucosal resection; S-DMI, significant deep mural injury; TSC, topical submucosal chromoendoscopy; TTSC, through-the-scope clip. Standard recovery: patients are observed for 4 hours. If well, they are subsequently discharged.

with the colorectal wall. Third, tissue transection should be achieved in 1–3 pulses of fractionated current. More than 3 pulses should raise concern for S-DMI.

After each resection, the defect should be expanded by waterjet irrigation to facilitate DMI identification. A homogenous blue surface of intersecting obliquely oriented submucosal fibers with or without flat non-bleeding blood vessels or herniating blood vessels, consistent with submucosal tissue stained with injectate, is expected. Any non-stained areas should prompt evaluation for DMI, as described by the Sydney DMI Classification.[17] Topical submucosal chromoendoscopy can be performed by irrigating injectate into the area of concern without needle deployment.[26] This should confirm homogenous blue staining of the previously unstained area if S-DMI is absent.

Significant DMI (Sydney DMI Classification types III–V) manifests as a partial or full-thickness transverse defect in the MP, with the long axis of the defect invariably perpendicular to the long axis of the colon. In general, closure need only address the area of injury because attempting to close the entire resection site is more complex and may risk incomplete closure of the area of S-DMI. It is important to work sequentially from one side of the defect to the other, with TTSCs opposing the edges of the wound. Initial TTSC placement must take into account 2 important factors: (1) the orientation of the working channel, bearing in mind that with a colonoscope the working channel is at 5 o'clock and it is

therefore easiest to work from left to right, and (2) the impact of gravity, which can be judged by the position of the fluid pool. The latter is important because as TTSCs are placed, the stems will fall toward the fluid pool. It is therefore easier to place additional TTSCs if the stems fall away from the site of subsequent TTSC placement. The first TTSC must be placed just outside the defect to rise up a small tissue mound. The TTSC is positioned perpendicular to the defect, and gentle pressure is applied while aspirating luminal gas. The aim is to enable tissue to rise up into the TTSC. This method ensures maximal tissue capture to achieve serosa to serosa apposition. This technique is repeated with sequential TTSCs placed next to one another 1–2 mm apart so that a defect of <10 mm will generally require less than 6 TTSCs. The last TTSC is placed on uninjured submucosal tissue just outside the area of S-DMI. Once closure is achieved, the endoscope is passed beyond the defect and used to gently deflect the TTSCs backwards. Successful defect closure is confirmed by verifying apposition of the 2 edges of the defect in between the adjacent TTSCs.

Critical to the management of S-DMI is an appreciation of its risk factors. In an analysis of 911 LNPCPs,[17] attempted en bloc resection, advanced histopathology (high-grade dysplasia or SMIC), and transverse colon location were significantly associated with S-DMI on multivariable logistic regression analysis. Attempting an en bloc resection is an intuitive risk factor. Increasing

lesion size will invariably increase the risk of capturing the MP during snare closure. Importantly, in a matched cohort of LNPCPs 20–25 mm, en bloc resection was still associated with S-DMI (3.5% vs 1.0%; $P = .05$).[27] Although recurrence at SC1 was higher (2.0% vs 5.7%; $P = .04$), no difference was present on subsequent surveillance. Advanced histopathology is also logical because it is associated with desmoplasia, which may obliterate the submucosal plane. This emphasizes the importance of optical evaluation to quantify the risk of SMIC and to inform therapeutic decisions regarding en bloc vs piecemeal resection techniques. Although transverse colon location is less intuitive, it is likely related to it being a highly mobile intraperitoneal segment with a redundant mesentery, which may facilitate full-thickness capture of the colonic wall. Medium size snares (≤15 mm) are therefore preferred for lesions proximal to the descending colon.

Many endoscopic defect closure techniques have been described including T-tags,[28] plicators,[29] and suturing devices.[30] The 2 predominant techniques within the colorectum are TTSCs and over-the-scope clips (OTSCs).[31] The European Society of Gastrointestinal Endoscopy currently recommends TTSCs for small defects and OTSCs for large defects. All defects within this study were assessed as small (<10 mm) in size. This is partly due to the electrosurgical effect on the transected area, leading the MP to be temporarily drawn together. Appropriate technique, as described above, further facilitates successful closure. Although OTSC defect closure appears comparable to TTSC defect closure,[31] its impact on short- and long-term outcomes is largely unknown. Moreover, it requires removal of the endoscope, attachment of the OTSC, reinsertion of the endoscope, and re-identification of the defect, which creates a time lag and an opportunity for peritoneal contamination. Endoscope reinsertion necessitates gas insufflation and manipulation of the colon, which may further amplify the risk of peritoneal contamination. This highlights an intrinsic advantage of TTSCs, alongside a likely significant cost savings because of the median number of TTSCs (4 TTSCs; IQR, 3–6 TTSCs) required for successful defect closure. Therefore, TTSCs should be regarded as a first-line approach for colorectal EMR-related S-DMI, with OTSCs used as a rescue approach when TTSC closure is not feasible or unsuccessful.

This study is not without limitations. Data on S-DMI were prospectively collected from March 2010 onward after the description of the target sign.[18] Before this, retrospective review from procedure charts and comprehensive photo records was performed independently by 2 investigators, with arbitration by a third investigator if discordance occurred. Second, alternative closure techniques including OTSC and endoscopic suturing were not evaluated in this analysis. However, because TTSC closure is relatively inexpensive, expedient, and highly effective in this large cohort, it seems unlikely that these alternative techniques will prove superior for EMR-related S-DMI. Last, statistical analyses to compare selective vs nonselective defect closure as well as DMI III vs DMI IV/V were not performed because of small sample sizes.

In conclusion, this study marks another evolution in minimally invasive endoscopic resection techniques. Significant DMI is readily managed by TTSC closure. Indeed, in the era of carbon dioxide insufflation and reliable clip closure, it should not be feared by experienced tissue resection endoscopists because our multicenter experience demonstrates that S-DMI is readily closed without adverse sequelae. Alongside an appreciation for S-DMI risk factors and the Sydney DMI Classification, TTSC closure carries the potential to mitigate perforation-related surgery and its associated morbidity. Intrinsic to this is the importance of a meticulous assessment of the post-EMR defect and a protocolized approach to EMR and its associated AEs.

Supplementary Material

Note: To access the supplementary material accompanying this article, please click here.

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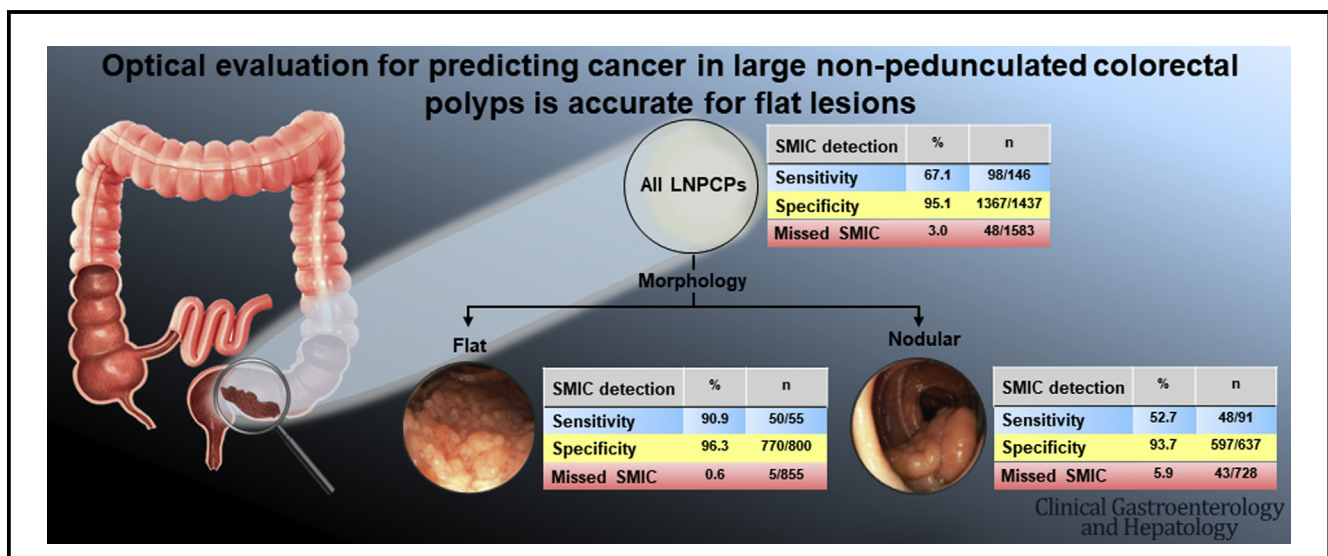
ENDOSCOPY

Optical Evaluation for Predicting Cancer in Large Nonpedunculated Colorectal Polyps Is Accurate for Flat Lesions

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BACKGROUND AND AIMS: The ability of optical evaluation to diagnose submucosal invasive cancer (SMIC) prior to endoscopic resection of large (≥20 mm) nonpedunculated colorectal polyps (LNPCPs) is critical to inform therapeutic decisions. Prior studies suggest that it is insufficiently accurate to detect SMIC. It is unknown whether lesion morphology influences optical evaluation performance.

METHODS: LNPCPs ≥20 mm referred for endoscopic resection within a prospective, multicenter, observational cohort were evaluated. Optical evaluation was performed prior to endoscopic resection with the optical prediction of SMIC based on established features (Kudo V pit pattern, depressed morphology, rigidity/fixation, ulceration). Optical evaluation performance outcomes

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were calculated. Outcomes were reported by dominant morphology: nodular (Paris 0–Is/0–IIa+Is) vs flat (Paris 0–IIa/0–IIb) morphology.

RESULTS: From July 2013 to July 2019, 1583 LNPCPs (median size 35 [interquartile range, 25–50] mm; 855 flat, 728 nodular) were assessed. SMIC was identified in 146 (9.2%; 95% confidence interval [CI], 7.9%–10.8%). Overall sensitivity and specificity were 67.1% (95% CI, 59.2%–74.2%) and 95.1% (95% CI, 93.9%–96.1%), respectively. The overall SMIC miss rate was 3.0% (95% CI, 2.3%–4.0%). Significant differences in sensitivity (90.9% vs 52.7%), specificity (96.3% vs 93.7%), and SMIC miss rate (0.6% vs 5.9%) between flat and nodular LNPCPs were identified (all $P < .027$). Multiple logistic regression identified size ≥40 mm (odds ratio [OR], 2.0; 95% CI, 1.0–3.8), rectosigmoid location (OR, 2.0; 95% CI, 1.1–3.7), and nodular morphology (OR, 7.2; 95% CI, 2.8–18.9) as predictors of missed SMIC (all $P < .039$).

CONCLUSIONS: Optical evaluation performance is dependent on lesion morphology. In the absence of features suggestive of SMIC, flat lesions can be presumed benign and be managed accordingly.

The ability of real-time optical evaluation of large (≥20 mm) nonpedunculated colorectal polyps (LNPCPs) to accurately predict submucosal invasive cancer (SMIC) is crucial, as it enables the endoscopist to appropriately select among endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and surgery. This is done by identifying characteristic surface and morphological features. Although recent evidence suggests that optical evaluation is effective at diagnosing SMIC,[1,2] of those studies solely evaluating LNPCPs ≥20 mm,[3] modest performance was observed. Moreover, the complexity of quantifying the pretest probability of SMIC based on patient and lesion characteristics,[4] alongside the multitude of optical evaluation classifications for LNPCPs, has hindered its widespread adoption and application among all endoscopists who perform colonoscopy. Therefore, refining and simplifying the application of optical evaluation is needed.

As lesions grow in size, it is intuitive that optical features of SMIC could be missed. This may be heightened in lesions with a nodular component, as the identification of these features may be hindered or may be absent on the lesions' surface. Stratifying optical evaluation by lesion morphology may facilitate the implementation of a selective resection algorithm by identifying lesion subgroups with accurate optical evaluation performance characteristics. Therefore, we sought to evaluate the performance of optical evaluation, stratified by lesion morphology, in a prospective, multicenter, observational cohort of LNPCPs ≥20 mm referred for endoscopic resection.

Materials and Methods

This manuscript was produced, with guidance from the Strengthening the Reporting of Observational Studies in Epidemiology[5] and the Standards for Reporting of Diagnostic Accuracy Studies recommendations.[6]

The Australian Colonic Endoscopic Resection Cohort

The Australian Colonic Endoscopic Resection (ACE) cohort (NCT01368289; NCT02000141) is a prospective, multicenter, observational cohort of consecutive patients referred for the management of LNPCPs ≥20 mm. Center-specific Institutional Review Board approval is maintained at each center. Written informed consent is obtained from each participant prior to enrollment.

Between July 2013 to July 2019, consecutive participants enrolled at 1 of 4 sites were considered for inclusion. All endoscopic procedures were performed by either a study investigator (accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their supervision. EMR was performed in a standardized fashion across all centers.[7] Technical innovations in EMR were adopted as the evidence to support them emerged. A subgroup of lesions underwent ESD as part of a selective ESD protocol (NCT02198729). ESD was performed in accordance with established international technical recommendations.[8] Lesions believed to be unamenable to endoscopic resection were referred directly to surgery.

Optical Evaluation

Colonoscopy was performed using Olympus high-definition variable-stiffness colonoscopes (Olympus, Tokyo, Japan). Optical evaluation was performed in a standardized fashion across all centers. This included lesion evaluation under white light and narrow-band imaging. Lesion location, size, Paris classification,[9] granularity, Kudo pit pattern classification,[10] and SMIC prediction were described in real time. The latter was based on the presence of any of the following established endoscopic features consistent with invasive disease

including (1) Kudo pit pattern V, (2) depression (Paris 0–IIc morphology), (3) ulceration, and (4) fixation or rigidity.

Histopathology Evaluation

Specimens were collected and processed for histopathology review, in accordance with the Australasian Gastrointestinal Pathology Society guidelines.[11] Histopathology review was completed by board-certified expert gastrointestinal pathologists at their respective sites. Cancer was defined by neoplastic invasion into the submucosa. Where appropriate, histopathology was confirmed with surgical specimen evaluation.

Data Extraction and Analysis

Prospectively collected data included (1) patient characteristics (age, sex, American Society of Anesthesiologists [ASA] classification), (2) lesion characteristics (location, size, Paris classification, granularity, Kudo pit pattern, SMIC prediction), and (3) histopathology evaluation.

Lesions with incomplete optical evaluation were excluded. Lesions with serrated histopathology were also excluded, as optical evaluation of serrated lesions,[12] as well as their biological behavior,[13] differs from adenomatous neoplasia. The largest LNPCP ≥20 mm in each patient was selected for this study.

Optical evaluation performance outcomes were calculated with histopathology as the reference gold standard. SMIC miss rate was calculated with the denominator being all LNPCPs within the respective grouping. Lesions were grouped into flat (Paris 0–IIa or 0–IIb) and nodular (Paris 0–Is or 0–IIa+Is) morphology. If depression (any 0–IIc component) was present, the lesion in question was grouped by its predominant morphology.

Statistical Analysis

SPSS version 26.0 (IBM, Armonk, NY) was used for data analysis. Continuous variables were summarized as median (interquartile range [IQR]) and categorical variables as frequency and percentage. Wilson's method was used to calculate 95% confidence intervals (CIs) for proportions.

All analyses were exploratory. Two-tailed tests with a 5% significance level were used throughout. Mann-Whitney U tests were used to test for differences in the distribution of age and lesion size. Pearson chi-square or Fisher's exact test were used, as appropriate, to test for association between categorical variables. Exact permutation test was used to assess for heterogeneity between endoscopists.

Multiple logistic regression with backward stepwise variable selection was used to identify independent

What You Need to Know

Background
While real-time optical evaluation has emerged as the predominant method for predicting submucosal invasion prior to endoscopic resection of colorectal lesions, evaluating ≥20-mm lesions can be challenging, with existing data suggesting only modest performance characteristics.

Findings
This study demonstrates that optical evaluation is predicated on lesion morphology, with excellent performance demonstrated when assessing flat lesions. In contrast, optical evaluation has only decent performance in nodular lesions.

Implications for patient care
In the absence of optical features consistent with submucosal invasive cancer, endoscopic mucosal resection should be considered as the preferred first option for treating all flat lesions in the colorectum. However, in the nodular group, we need additional optical evaluation algorithms to select lesions for the appropriate treatment.

predictors of the outcome of interest (missed SMIC on optical evaluation). Candidate variables for inclusion in the model were those with P values for univariable association <.1. Odds ratios (ORs) and their 95% CIs were used to quantify the strength of association.

A decision tree classification model for missed SMIC on optical evaluation was developed for comparison with the multiple logistic regression model, as it can highlight hidden relationships between variables which might otherwise be overlooked. The same candidate variables were included for the decision tree along with the continuous variables age and lesion size. Chi-square automatic interaction detection using Bonferroni-adjusted significance values was used to grow the tree to a maximum of 3 levels beneath the root node with the minimum number of cases for parent and child nodes set at 100 and 50, respectively. Ten-fold cross-validation was used to produce the final tree model.

Patient and Public Involvement

Patients and the public were not involved in the design and execution of this study.

Results

Between July 2013 and July 2019, 2112 LNPCPs ≥20 mm were referred for endoscopic resection. A total of 294 were serrated-class lesions on histopathology and were excluded from analysis, and 159 had incomplete

Table 1. Demographic and Lesion Characteristics

	All LNPCPs (n = 1583)	Flat LNPCPs (n = 855)	Nodular LNPCPs (n = 728)	P value
Age, y	69 (62–76)	70 (64–77)	67 (61–75)	.581
Male sex	864 (54.6)	464 (54.3)	400 (54.9)	.811
ASA classification[a]				<.001
I	309 (19.5)	140 (16.4)	169 (23.2)	
II	737 (46.6)	392 (45.8)	345 (47.4)	
III	284 (17.9)	171 (20.0)	113 (15.5)	
Size, mm	35 (25–50)	30 (25–40)	40 (30–50)	<.001
Location				<.001
Rectum	323 (20.4)	84 (9.8)	239 (32.8)	
Sigmoid	165 (10.4)	63 (7.4)	102 (14.0)	
Descending	80 (5.1)	50 (5.8)	30 (4.1)	
Splenic flexure	33 (2.1)	22 (2.6)	11 (1.5)	
Transverse	169 (10.6)	121 (14.2)	48 (6.6)	
Hepatic flexure	88 (5.6)	49 (5.7)	39 (5.4)	
Ascending	361 (22.8)	220 (25.7)	141 (19.4)	
Cecum	364 (23.0)	246 (28.8)	118 (16.2)	
Morphology				
Flat	855 (54.0)	855 (100.0)	-	
Nodular	728 (46.0)	-	728 (100.0)	
Granularity				<.001
Granular	1012 (63.9)	460 (53.8)	552 (75.8)	
Nongranular	456 (28.8)	355 (41.5)	101 (13.9)	
Mixed granularity	115 (7.3)	40 (4.7)	75 (10.3)	
Histopathology				<.001
Tubular adenoma	402 (25.4)	237 (27.8)	165 (22.7)	
Tubulovillous adenoma	989 (62.5)	541 (63.3)	448 (61.5)	
Villous adenoma	46 (2.9)	22 (2.6)	24 (3.3)	
SMIC	146 (9.2)	55 (6.4)	91 (12.5)	
Features of invasion				
Kudo V pit pattern	129 (8.1)	74 (8.7)	55 (7.6)	.427
Depression	85 (5.4)	70 (8.2)	15 (2.1)	<.001
Ulceration	18 (1.1)	10 (1.2)	8 (1.1)	.034
Fixed or rigid	116 (7.3)	64 (7.5)	52 (7.2)	.820

NOTE. Values are median (interquartile range) or n (%).
ASA, American Society of Anesthesiologists; LNPCP, large nonpedunculated colorectal polyp; SMIC, submucosal invasive cancer.
[a]253 (16.9%) participants were missing ASA classification data.

optical evaluation data and were excluded from analysis. A total of 71 participants had 2 or more lesions. The largest lesion per subject was selected for analysis, resulting in a further 76 lesions being excluded. The final cohort comprised 1583 participants and 1583 LNPCPs

managed by 1 of 7 study investigators or a senior interventional endoscopy fellow under their supervision. The median years of endoscopy experience for study investigators at study onset was 15 (IQR, 6–18). The median lesions per study investigator was 99 (IQR,
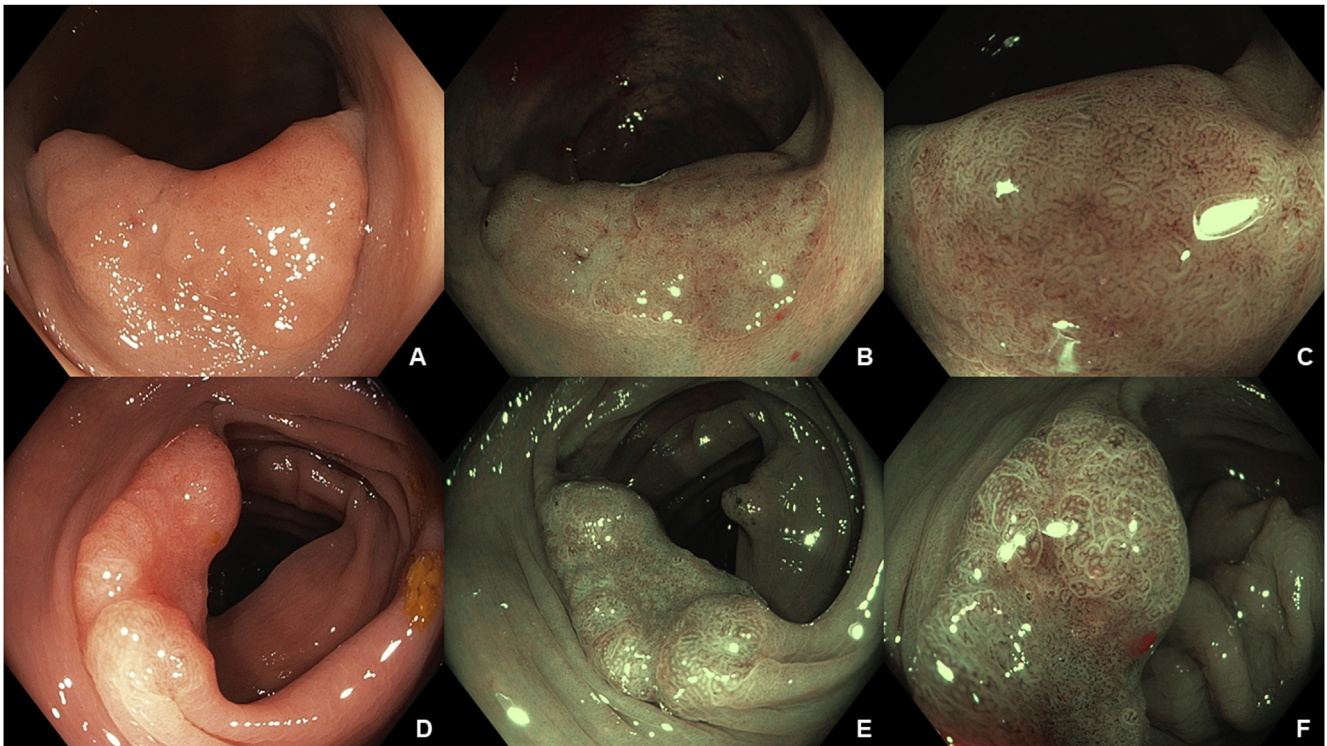
Figure 1. Optical evaluation of flat lesions. (*A*) A 25-mm 0–IIa nongranular transverse colon LNPCP. (*B*, *C*) On narrow-band imaging, a homogeneous surface pattern is identified. Histology confirmed a tubular adenoma. (*D*) A 25-mm 0–IIa+c nongranular transverse colon LNPCP. (*E*, *F*) On narrow-band imaging, a demarcation line is readily apparent with disruption of the surface pattern. Histology confirmed a superficial SMIC.

20–271). Optical evaluation performance (% correct diagnosis) ranged from 86.4% to 93.8% for individual endoscopists, with no evidence of significant heterogeneity between endoscopists ($P = .532$).

The majority of lesions were removed by EMR 1467 (92.7%), of which 1361 (92.8%) underwent piecemeal resection. The remaining 48 (3.0%) and 68 (4.3%) underwent ESD and surgery, respectively.

Demographic and Lesion Characteristics

Median age was 69 (IQR, 62–76) years, with 54.6% of participants being male (Table 1, Supplementary Table 1). The majority of participants were ASA I (n = 309, 19.5%) or ASA II (n = 737, 46.6%).

Median lesion size was 35 (IQR, 25–50) mm. Cecum (n = 364, 23.0%), ascending colon (n = 361, 22.8%), and rectum (n = 323, 20.4%) were the most common locations. A total of 855 (54.0%) and 728 (46.0%) LNPCPs had flat and nodular morphology (Figures 1 and 2), respectively. The majority of LNPCPs were granular (n = 1012, 63.9%). On histopathology, tubulovillous adenoma was the most frequent diagnosis (n = 989, 62.5%). SMIC was identified in 146 (9.2%) LNPCPs.

In comparing LNPCPs with flat vs nodular morphology, there were differences in median size (30 [IQR, 25–40] mm vs 40 [IQR, 30–50] mm), location (rectosigmoid location: 17.2%; 95% CI, 14.8%–19.9% vs 46.8%; 95% CI, 43.2%–50.5%), and granularity

(granular: 53.8%; 95% CI, 50.5%–57.1% vs 75.8%; 95% CI, 72.6%–78.8%), respectively. The frequency of SMIC was significantly higher in nodular (12.5%; 95% CI, 10.3%–15.1%) vs flat (6.4%; 95% CI, 5.0–8.3%) LNPCPs.

Optical Evaluation Performance

Overall sensitivity and specificity of optical evaluation to diagnose SMIC were 67.1% (95% CI, 59.2%–74.2%) and 95.1% (95% CI, 93.9%–96.1%), respectively (Table 2). When stratified by lesion morphology, there were significant differences between flat vs nodular LNPCPs in sensitivity (90.9%; 95% CI, 80.4%–96.1% vs 52.7%; 95% CI, 42.6%–62.7%; $P < .001$) and specificity (96.3%; 95% CI, 94.7%–97.4% vs 93.7%; 95% CI, 91.6%–95.4%; $P = .027$). Positive predictive value and negative predictive value estimates for SMIC are provided in Table 2.

Diagnostic performance of individual endoscopic features of SMIC are provided in Supplementary Table 2.

Missed SMIC on Optical Evaluation

SMIC was missed on optical evaluation in 48 lesions overall, with a SMIC miss rate of 3.0% (95% CI, 2.3%–4.0%) (Table 3). This varied by lesion granularity, with miss rates of 3.2% (95% CI, 2.3%–4.4%), 2.2% (95% CI, 1.2%–4.0%), and 5.2% (95% CI, 2.4%–10.9%) for
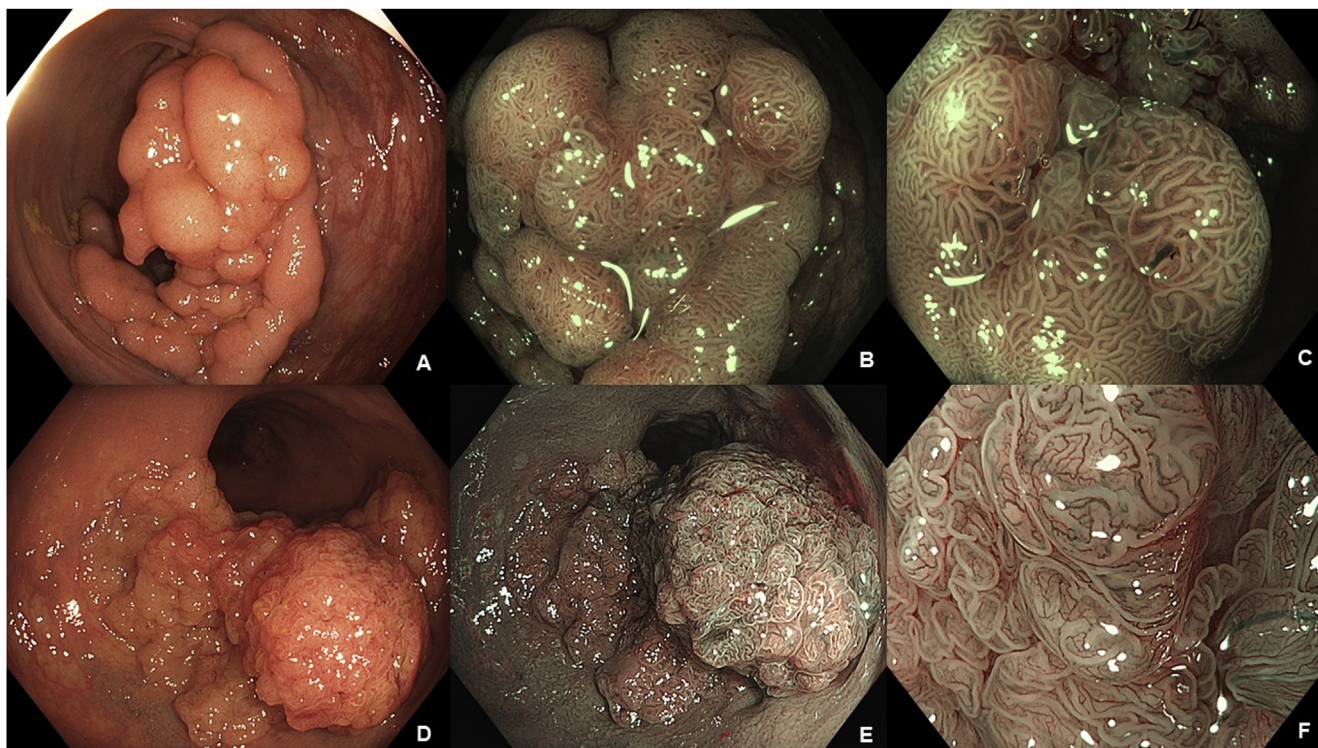
Figure 2. Optical evaluation of nodular lesions. (*A*) A 50-mm 0–IIa+Is mixed rectal LNPCP. (*B, C*) On narrow-band imaging, a homogeneous surface pattern is identified. Histology confirmed a tubulovillous adenoma. (*D*) A 60-mm 0–IIa+Is granular sigmoid colon LNPCP. (*E, F*) On narrow-band imaging, a homogeneous surface pattern is identified. Histology identified a superficial SMIC.

granular, nongranular and mixed lesions, respectively. Of the 460 flat granular LNPCPs, no cases of SMIC were missed. The SMIC miss rates on optical evaluation when solely evaluating malignant LNPCPs is provided in Supplementary Table 3.

There was a significant difference in the SMIC miss rate between flat (0.6%; 95% CI, 0.3%–1.4%) vs nodular (5.9%; 95% CI, 4.4%–7.9%) LNPCPs (*P* < .001). This difference remained significant when further stratifying by granularity (both *P* < .047).

On univariable logistic regression (Supplementary Table 4), nodular morphology (OR, 10.7; 95% CI, 4.2–27.1; *P* < .001), rectosigmoid location (OR, 3.6 95% CI, 2.0–6.5; *P* < .001), and size ≥40 mm (OR, 3.2; 95% CI, 1.7–6.0; *P* < .001) were significantly associated with missed SMIC on optical evaluation. Multiple logistic regression analysis (Table 4) identified nodular morphology (OR, 7.2; 95% CI, 2.8–18.9; *P* < .001), rectosigmoid location (OR, 2.0; 95% CI, 1.1–3.7; *P* = .026), and size ≥40 mm (OR, 2.0; 95% CI, 1.0–3.8; *P* = .039) as independent predictors of missed SMIC on optical evaluation.

The decision tree classification model identified lesion morphology (flat vs nodular) to be the critical variable when searching for missed SMIC on optical evaluation (Supplementary Figure 1), therefore confirming the findings of the multivariable logistic regression analysis.

Discussion

Minimally invasive resection techniques have revolutionized the management of early colorectal neoplasia.[7,14–17] This is due to evidence-based site-specific modifications in high-quality EMR and the development of ancillary techniques when snare resection is not feasible.[18] Moreover, technical innovations have largely alleviated the risk of clinically significant post-EMR bleeding,[19,20] deep mural injury,[21] and recurrence.[22] With the overwhelming majority of colorectal LNPCPs being benign,[4] EMR has rightly positioned itself as the primary endoscopic modality for the colorectum.[14] However, it is unable to reliably achieve curative resection in lesions ≥20 mm with superficial SMIC (S-SMIC) (≤1000 μm). This emphasizes its natural synergism with ESD, as an organ-sparing, curative endoscopic resection technique. The benefits of a selective resection algorithm are intuitive, and it has been shown to be the optimal strategy based on cost-effectiveness analyses.[23] This has placed the onus on optical evaluation to reliably select the appropriate resection technique by identifying characteristic surface features consistent with SMIC. However, there is a paucity of data evaluating LNPCPs ≥20 mm,[3,4] with existing data suggesting only modest performance characteristics.[2,3] Our findings show that optical evaluation of LNPCPs ≥20 mm, while modest overall, is dependent on lesion morphology, with

excellent performance demonstrated when assessing flat lesions. This marks an easily implementable and critical step toward the adoption of a selective resection algorithm in the colorectum.

Two previous studies have solely focused on optical evaluation of LNPCPs.[3,4] In a previous analysis of 2277 LNPCPs (mean size 36.9 mm), the sensitivity and specificity for SMIC using Kudo pit pattern V was 40.4% (95% CI, 33.3%–47.8%) and 97.5% (95% CI, 96.7%–98.1%), respectively.[4] In an alternative study, the Hiroshima classification was evaluated in a multicenter prospective cohort of 343 LNPCPs ≥20 mm (median size 30 [interquartile range, 25–40] mm).[3] Sensitivity and specificity were 79.7% (95% CI, 64.3%–89.3%) and 94.2% (95% CI, 90.9%–96.6%), respectively. With modest performance, it was concluded that the application of optical evaluation requires further optimization.

Our findings identify that the crux of optical evaluation is lesion morphology. It is an independent predictor of performance on multiple logistic regression and was identified as the critical variable in classification tree analysis. Sensitivity, specificity and SMIC miss rates among flat lesions were 90.9% (95% CI, 80.4%–96.1%), 96.3% (95% CI, 94.7%–97.4%), and 0.6% (95% CI, 0.3%–1.4%), respectively. With further stratification, optical evaluation performance continued to improve among flat granular lesions (sensitivity: 100%; 95% CI, 67.6%–100%; specificity: 98.7%; 95% CI, 97.1%–99.4%). Notably, no cases of SMIC were missed. Therefore, if features of S-SMIC are identified on optical evaluation, ESD should be considered, although this decision is dependent on lesion location, endoscopic resources and operator expertise. Otherwise, EMR should be performed. With flat LNPCPs making up 54.0% of the cohort,

Table 2. Optical Evaluation Performance Outcomes for Predicting Submucosal Invasive Cancer Overall and Stratified by Lesion Morphology and Granularity

	All LNPCPs (n = 1583)	Flat LNPCPs (n = 855)	Nodular LNPCPs (n = 728)
Sensitivity	67.1 (98/146) (59.2–74.2)	90.9 (50/55) (80.4–96.1)	52.7 (48/91) (42.6–62.7)
Specificity	95.1 (1367/1437) (93.9–96.1)	96.3 (770/800) (94.7–97.4)	93.7 (597/637) (91.6–95.4)
Positive predictive value	58.3 (52.0–64.3)	62.4 (53.6–70.4)	54.6 (45.6–63.2)
Negative predictive value	96.6 (95.8–97.3)	99.4 (98.5–99.7)	93.3 (91.8–94.5)
Granular LNPCPs			
Sensitivity	51.5 (34/66) (39.7–63.2)	100 (8/8) (67.6–100)	44.8 (26/58) (32.8–57.5)
Specificity	96.6 (914/946) (95.3–97.6)	98.7 (446/452) (97.1–99.4)	94.7 (468/494) (92.4–96.4)
Positive predictive value	51.4 (41.2–61.6)	56.6 (37.0–74.3)	50.0 (38.4–61.5)
Negative predictive value	96.6 (95.7–97.4)	100 (NA)	93.6 (92.06–94.9)
Nongranular LNPCPs			
Sensitivity	83.1 (49/59) (71.5–90.5)	88.9 (40/45) (76.5–95.2)	64.3 (9/14) (38.8–83.7)
Specificity	92.7 (368/397) (89.7–94.9)	92.9 (288/310) (89.5–95.3)	92.0 (80/87) (84.3–96.1)
Positive predictive value	62.7 (53.8–70.9)	64.6 (54.6–73.4)	56.3 (36.5–74.4)
Negative predictive value	97.4 (95.5–98.5)	98.3 (96.2–99.2)	94.1 (88.7–97.0)
Mixed-granular LNPCPs			
Sensitivity	71.4 (15/21) (50.0–86.2)	100 (2/2) (34.2–100)	68.4 (13/19) (46.0–84.6)
Specificity	90.4 (85/94) (82.8–94.9)	94.7 (36/38) (82.7–98.6)	87.5 (49/56) (76.4–93.8)
Positive predictive value	62.6 (45.9–76.7)	50 (20.6–79.4)	65.0 (46.5–79.8)
Negative predictive value	93.4 (87.8–96.5)	100 (NA)	89.1 (80.7–94.1)

NOTE. Values are % (n/n) (95% confidence interval) or % (95% confidence interval).
LNPCP, large nonpedunculated colorectal polyp; N/A, not available.

Table 3. Miss Rates for Submucosal Invasive Cancer on Optical Evaluation Overall and Stratified by Lesion Morphology, Granularity, Lesion Size, and Location

	All LNPCPs (n = 1583)	Flat LNPCPs (n = 855)	Nodular LNPCPs (n = 728)	P value
All LNPCPs	3.0 (48/1583) (2.3–4.0)	0.6 (5/855) (0.3–1.4)	5.9 (43/728) (4.4–7.9)	<.001
Granularity				
Granular	3.2 (32/1012) (2.3–4.4)	0.0 (0/460) (0.0–0.8)	5.8 (32/552) (4.1–8.1)	<.001
Nongranular	2.2 (10/445) (1.2–4.0)	1.4 (5/355) (0.6–3.3)	5.0 (5/101) (2.1–11.1)	.047
Mixed	5.2 (6/115) (2.4–10.9)	0.0 (0/40) (0.0–8.8)	8.0 (6/75) (3.7–16.4)	.090
Size				
<40 mm	1.6 (14/887) (0.9–2.6)	0.3 (2/580) (0.1–1.2)	3.9 (12/307) (2.3–6.7)	<.001
≥40 mm	4.9 (34/696) (3.5–6.8)	1.1 (3/275) (0.4–3.2)	7.4 (31/421) (5.2–10.3)	<.001
Location				
Proximal colon[a]	1.7 (19/1095) (1.1–2.7)	0.6 (4/708) (0.2–1.4)	3.9 (15/387) (2.4–6.3)	<.001
Rectosigmoid	5.9 (29/488) (4.2–8.4)	0.7 (1/147) (0.1–3.8)	8.2 (28/341) (5.7–11.6)	.001

NOTE. Values are % (n/n) (95% confidence interval). Denominator: LNPCPs with or without submucosal invasive cancer.
LNPCP, large nonpedunculated colorectal polyp.
[a]Proximal colon includes cecum, ascending colon, transverse colon, and descending colon.

and 93.6% being benign, this further cements EMR as the primary resection modality in the colorectum.

In contrast, when assessing nodular lesions, optical evaluation performance was significantly hindered. Sensitivity and SMIC miss rates were 52.7% (95% CI, 42.6%–62.7%) and 5.9% (95% CI, 4.4%–7.9%), respectively. This is likely due to the malignant focus not being expressed on the mucosal surface, thereby rendering optical evaluation obsolete in these circumstances. Moreover, the surface expression of SMIC may be inaccessible and go undetected. These findings further reinforce the concept of invisible or "covert" neoplasia, first described by the ACE consortium in an analysis of 2277 LNPCPs ≥20 mm.[4] After excluding lesions with visible or overt SMIC, lesion size, location, nongranularity, and Paris 0–Is and 0–IIa+Is morphology were significantly associated with SMIC on multiple logistic regression. When stratified by lesion location, morphology, and granularity, 0–Is nongranular, 0–IIa+Is nongranular, and distal 0–IIa+Is granular lesions were identified as high-risk (>10%) for covert SMIC. This is further supported by the recent analysis of 693 granular mixed type lesions by D'Amico et al,[24] whereby increasing lesion size and rectal location were independently associated with covert SMIC on multivariable logistic regression analysis. In the absence of optical features of deep SMIC (D-SMIC), these lesions are ideal ESD candidates, specifically in the rectum, given the elevated risk of morbidity, mortality, and permanent ostomy formation associated with distal colorectal surgery. The application of a selective resection algorithm, based on these premises, would require 43 ESD procedures per 1000 patients.[23]

Both size and rectosigmoid location were also identified as independent predictors of missed SMIC on optical evaluation. The influence of lesion size is instinctual, with the likelihood of missing optical features of SMIC increasing as lesion surface area increases. This emphasizes that optical evaluation must be both systematic and meticulous. Concerning rectosigmoid location, despite confounding due to an increased frequency of nodular morphology in the distal colorectum, this remained an independent predictor of optical evaluation performance. The sigmoid colon is a challenging location for the management of early colorectal neoplasia. This is due to lumen caliber, concomitant diverticular disease, and acute angulations related to variability in the length and mobility of the sigmoid mesentery, thus limiting visualization during optical evaluation and endoscopic tissue resection.

Table 4. Best-Fitting Multiple Logistic Regression Model Showing Independent Predictors of Missed Submucosal Invasive Cancer on Optical Evaluation With Adjusted Odds Ratios and P Values

	Odds Ratio (95% CI)	P value
Nodular morphology	7.2 (2.8–18.9)	<.001
Rectosigmoid location	2.0 (1.1–3.7)	.026
Lesion size ≥40 mm	2.0 (1.0–3.8)	.039

CI, confidence interval.

Our study is not without limitations. Given the study's premise, lesions were grouped by their predominant morphology. Lesion morphology classification can be subjective; however, in a recent analysis, it showed substantial interrater reliability.[25] Moreover, it is imperative to appreciate that morphology in itself is associated with SMIC and that depressed morphology represents a high-risk lesion subgroup.

Second, the creation of the ACE consortium precedes the establishment of both the NICE and Japan NBI Expert Team classifications. Optical evaluation criteria for SMIC were therefore largely based on the identification of Kudo V pit pattern.[10] While pit pattern classification was initially described using traditional magnifying chromoendoscopy, it can be discerned with high-definition endoscopes, particularly when using electronic image-enhanced techniques, although this has not been validated experimentally. We also did not differentiate between Kudo V pit pattern subtypes (Vi or Vn) or between S-SMIC and D-SMIC and focused on the diagnosis of SMIC. As EMR is the preferred tissue resection technique, as recommended in both North American[26] and European[14] consensus guidelines, the viewpoint of this study is from that of the community gastroenterologist. EMR is commonly performed in the community setting, with the critical question being whether a lesion is benign and can be safely removed by EMR or whether referral to a tissue resection specialist is appropriate. Moreover, this is also an important question from the perspective of the tissue resection specialist. With the widespread adoption of ESD, endoscopic tissue resection specialists are increasingly referred nonsurgical candidates with lesions demonstrating features of SMIC, for which the differentiation between features of S-SMIC and D-SMIC can be challenging. D-SMIC discovered in the resection specimen still carries the potential for curative endoscopic resection and empowers the patient alongside their clinical decision team regarding further therapeutic decisions. In the event of a noncurative diagnosis, it may modify the natural history of disease by mitigating the risk of future luminal adverse events related to luminal neoplasia. Performance validation of the participating endoscopists were not assessed and is therefore a potential source of bias. Last, owing to the low frequency of SMIC in specific lesion subgroups or the low frequency of specific lesion subtypes, such as mixed LNPCPs, the application of these findings within these subgroups needs to be approached with caution.

In conclusion, as optical evaluation has become the linchpin for the management of early colorectal neoplasia, our study shows that its performance is predicated on lesion morphology. Optical evaluation has high sensitivity, high specificity, and low SMIC miss rates when assessing flat neoplasia. Therefore, in the absence of optical features consistent with SMIC, all flat lesions should be removed by high-quality EMR, applying site-specific modifications and ancillary techniques where needed. In contrast, optical evaluation has modest performance in nodular lesions. While lesion location, morphology and granularity can be used to stratify the risk of covert SMIC, further refinement is needed to robustly apply a selective resection algorithm irrespective of lesion morphology. Nevertheless, it is imperative that all endoscopists embrace optical evaluation in everyday clinical practice, thus harnessing its proven ability to influence resection technique selection and the associated clinical and economic ramifications.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.05.017.

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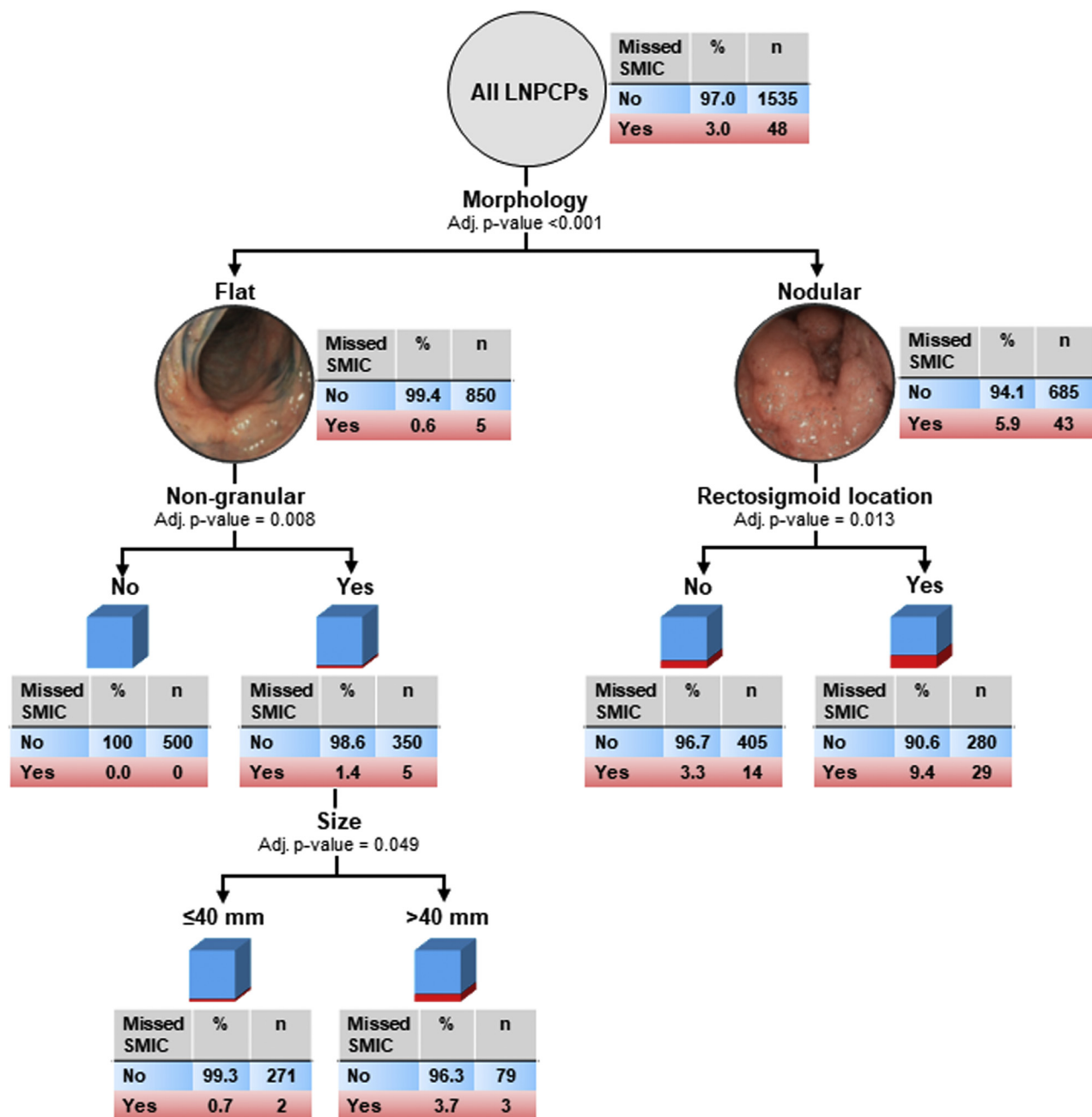**Supplementary Figure 1.** Classification tree analysis for missed submucosal invasive cancer (SMIC). LNPCP, large non-pedunculated colorectal polyp.

Supplementary Table 1. Demographic and Lesion Characteristics Stratified by SMIC

	SMIC (n = 146)	No SMIC (n = 1437)
Age, y	70 (64–77)	67 (61–75)
Male	90 (61.6)	774 (53.9)
ASA classification[a]		
I	28 (19.2)	281 (19.6)
II	71 (48.6)	666 (46.3)
III	22 (15.1)	262 (18.2)
Size, mm	40 (30–50)	35 (25–45)
Location		
Rectum	58 (39.7)	265 (18.5)
Sigmoid	32 (21.9)	133 (9.3)
Descending	9 (6.2)	71 (4.9)
Splenic flexure	1 (0.7)	32 (2.2)
Transverse	8 (5.5)	161 (11.2)
Hepatic flexure	5 (3.4)	83 (5.8)
Ascending	20 (13.7)	341 (23.7)
Cecum	13 (8.9	351 (24.4)
Morphology		
Flat	55 (37.7)	800 (55.7)
Nodular	91 (62.3)	637 (44.3)
Granularity		
Granular	66 (45.2)	946 (65.8)
Nongranular	59 (40.4)	397 (27.6)
Mixed granularity	21 (14.4)	94 (6.6)
Features of invasion		
Kudo V pit pattern	83 (56.8)	46 (3.2)
Depression (0–IIc)	31 (21.2)	54 (3.8)
Ulceration	11 (7.5)	7 (0.5)
Fixed or rigid	33 (22.6)	83 (5.8)

NOTE. Values are median (interquartile range) or n (%).
ASA, American Society of Anesthesiologists; SMIC, submucosal invasive cancer.
[a]253 (16.9%) participants were missing ASA classification.

Supplementary Table 2. Diagnostic Accuracy of Endoscopic Features Associated With Submucosal Invasive Cancer

	All LNPCPs (n = 1583)	Flat LNPCPs (n = 855)	Nodular LNPCPs (n = 728)
Kudo V pit pattern	64.3 (83/129) (55.8–72.1)	63.5 (47/74) (52.1–73.6)	65.5 (36/55) (52.3–76.6)
Depression	36.5 (31/85) (27.0–47.1)	34.3 (24/70) (24.3–46.0)	46.7 (7/15) (24.8–69.9)
Rigid/fixed	28.5 (33/116) (21.0–37.3)	20.3 (13/64) (12.3–31.7)	38.5 (20/52) (26.5–52.0)
Ulceration	61.1 (11/18) (38.6–79.7)	60.0 (6/10) (31.3–83.2)	62.5 (5/8) (30.6–86.3)
Kudo V pit pattern and ≥1 additional feature[a]	66.2 (45/68) (54.3–76.9)	69.6 (32/46) (55.2–80.9)	59.1 (13/22) (38.7–78.5)

NOTE. Values are % (n/n) (95% confidence interval) or % (95% confidence interval).
LNPCP, large nonpedunculated colorectal polyp.
[a]Additional feature(s) included depression, rigid/fixed, and ulceration.

Supplementary Table 3. Miss Rates for Submucosal Invasive Cancer Overall and Stratified by Lesion Morphology, Granularity, Lesion Size, and Location for Malignant LNPCPs

	All Malignant LNPCPs (n = 146)	Flat Malignant LNPCPs (n = 55)	Nodular Malignant LNPCPs (n = 91)	P value
All LNPCPs	32.9 (48/146)	9.1 (5/55)	47.3 (43/91)	<.001
Granularity				
Granular	48.5 (32/66)	0.0 (0/8)	55.2 (32/58)	<.001
Nongranular	16.9 (10/59)	11.1 (5/45)	35.7 (5/14)	.034
Mixed	28.6 (6/21)	0.0 (0/2)	31.6 (6/19)	.359
Size				
<40 mm	24.1 (14/58)	5.6 (2/36)	54.5 (12/22)	<.001
≥40 mm	38.6 (34/88)	15.8 (3/19)	44.9 (31/69)	.022
Location				
Proximal colon[a]	33.9 (19/56)	13.8 (4/29)	55.6 (15/27)	.001
Rectosigmoid	32.2 (29/90)	3.8 (1/26)	43.8 (28/64)	<.001

NOTE. Values are % (n/n).
LNPCP, large nonpedunculated colorectal polyp.
[a]Proximal colon includes cecum, ascending colon, transverse colon, and descending colon

Supplementary Table 4. Univariable Analysis of Association With Missed SMIC on Optical Evaluation

	n	SMIC Missed	Odds Ratio (95% CI)	*P* value
Sex				
Male	864	23 (2.7)	1	
Female	719	25 (3.5)	1.3 (0.7–2.3)	.348
Age				
>70 y	717	15 (2.1)	1	
≤70 y	866	33 (3.8)	1.9 (1.0–3.4)	.050
Location				
Proximal to rectosigmoid	1095	19 (1.7)	1	
Rectosigmoid	488	29 (5.9)	3.6 (2.0–6.5)	<.001
Morphology				
Flat	855	5 (0.6)	1	
Nodular	728	43 (5.9)	10.7 (4.2–27.1)	<.001
Granularity				
Nongranular	456	10 (2.2)	1	
Mixed	115	6 (5.2)	2.5 (0.9–6.9)	.089
Granular	1012	32 (3.2)	1.5 (0.7–3.0)	.305
Lesion size				
<40 mm	887	14 (1.6)	1	
≥40 mm	696	34 (4.9)	3.2 (1.7–6.0)	<.001
Previously attempted				
Yes	153	3 (2.0)	1	
No	1430	45 (3.1)	1.6 (0.5–5.3)	.421

NOTE. Values are n (%), unless otherwise indicated.
CI, confidence interval; SMIC, submucosal invasive cancer.