

Dr Oliver Cronin – MBBS (Hons.), FRACP

Innovations in endoscopic resection of laterally spreading non-pedunculated colorectal polyps to improve clinical outcomes.

Faculty of Medicine and Health

University of Sydney

A thesis submitted to fulfil requirements for the degree of Doctor of Philosophy.

24th March, 2025

Statement of originality

This thesis is submitted in fulfilment with requirements of the University of Sydney
The work presented in this thesis, to my knowledge, is original unless specified and appropriately referenced. I declare appropriate ethical approval was obtained for the work presented in the thesis and I have not submitted this work to any other institution.

Name: Dr Oliver Cronin

Date: 20th December 2024

Author attributions statement

A list of authorship statements are included with each chapter.

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Student Name: Dr Oliver Cronin

Date: 20th December 2024

As supervisor I can confirm the statement above regarding authorship is correct.

Supervisor Name: Professor Michael John Bourke

Date: 20th December 2024

Acknowledgements

I wish to express my deep gratitude to Professor Michael Bourke, whose guidance and mentorship have been a constant source of inspiration throughout and beyond my thesis journey.

I am also indebted to the experienced group of senior endoscopy staff at Westmead Hospital, including Associate Professor Nicholas Burgess, Dr Stephen Williams and Dr Eric Lee. Their valuable teachings greatly enriched my thesis.

Most importantly, I wish to extend my heartfelt appreciation to my wife, Katie, for her unwavering support throughout this thesis. Her sacrifices have allowed me to complete this submission, for which I will be forever grateful. I also wish to thank my 3 daughters, Georgia, Margot and Matilda, for sharing with me, their inquisitive view of life.

Abstract

Introduction/Aims

Over the past two decades, there have been significant advancements in endoscopic resection (ER). ER is now considered the first-line technique for resection of all benign and some malignant lesions. Compared to surgery, ER is cost-effective with lower morbidity and mortality. Cold snare polypectomy (CSP) is safer and equally efficacious compared to hot snare polypectomy (HSP) for the removal of colonic polyps <10mm. The superior safety profile of CSP holds promise for the resection of laterally spreading non-pedunculated colorectal polyps ≥ 20 mm (LNPCPs). However, large randomised controlled trials comparing Cold-Endoscopic Mucosal Resection (C-EMR) to conventional EMR are lacking. A deeper understanding of the unique technical demands of C-EMR is needed. Additionally, the technical demands for ER of lesions within distinct environments, such within the rectum, high-risk lesions, and neoplastic growth at surgical anastomoses, require improved understanding.

This thesis aims to address these knowledge deficiencies.

Methods

Multi-centre prospective trials were conducted to address the aims outlined above. All studies received ethics approval. Written, informed consent was obtained from each participant.

Results

C-EMR has a higher recurrence rate compared to EMR for LNPCPs (17.2% vs 1.1%, $p < 0.001$). Using mathematical modelling, polyp area was shown to increase quadratically with increasing polyp radius. This results in disproportionately more sequential snare resections, with each resection carrying a risk of leaving residual adenoma. Lesion size, location, and morphology are the most important factors when predicting lesion histology. We found that cancer is 2.5 times more common in the rectum compared to the rest of the colon (Odds ratio 1.77, Confidence interval 1.25–2.53, $p < 0.001$). Full-thickness resection of small tumours can be effectively achieved with durable long-term outcomes. With site-specific technique modifications and the use of adjunctive techniques, ER is also effective for resection of large adenomatous anastomotic polyps (LAAPs).

Conclusions

ER should be considered first-line for the removal of neoplastic gastrointestinal lesions, including early cancers. Results from this thesis improve our understanding of ER techniques and their role within the ER algorithm.

Table of Contents

Abstract	5
List of Publications in this Thesis	8
Table of Abbreviations	10
List of Figures.....	12
List of Tables	16
Chapter 1 - Introduction	18
Chapter 2 - Endoscopic management of large non-pedunculated colorectal polyps	22
Chapter 3 - Cold vs hot snare endoscopic mucosal resection for large ($\geq 15\text{mm}$) flat non-pedunculated colorectal polyps: a randomized controlled trial.....	41
Chapter 4 - The geometry of cold snare polypectomy	58
Chapter 5 - A Comparison of the Morphology and Histopathology of Large Non-Pedunculated Colorectal Polyps in the Rectum and Colon: Implications for Endoscopic Treatment.....	79
Chapter 6 - Endoscopic Full Thickness Resection is Curative for Small, High-risk Colorectal Lesions.....	100
Chapter 7 - Follow-up of 35 appendiceal orifice neoplasms resected by endoscopic full thickness resection.....	126
Chapter 8 - Endoscopic resection of large anastomotic polyps is safe and effective.....	143
Chapter 9 - Integrated Discussion.....	158
Chapter 10 - Selection of endoscopic resection technique for large colorectal lesion treatment	162
Chapter 11 - Conclusions	180
Appendix I – Awards During Candidacy.....	181
Appendix II – Other Publications During Candidacy	182
Appendix III: Printed publications related to PhD during candidacy.....	188

List of Publications in this Thesis

Chapter 2

Cronin O, Bourke MJ. Endoscopic resection of large non-pedunculated colorectal polyps (review). *Cancers*, 2023 Jul;15(15):3805.

Chapter 3

O'Sullivan T, **Cronin O**, Van Hattem A, Mandarino FV, Gauci J, Kerrison C, Whitfield A, Gupta S, Lee E, Williams SJ, Burgess NG, Bourke MJ. Cold vs hot snare endoscopic mucosal resection for large (15mm) flat non-pedunculated colorectal polyps: a randomized controlled trial. *Gut* 2024 Oct 7;73(11):1823-1830.

Chapter 4

Cronin O, Kirzenblat D, Forbes N, O'Sullivan T, Whitfield A, Gupta S, Burgess NG, Bourke MJ. The geometry of cold snare polypectomy. *Endoscopy* 2024 Mar;56(3):214-219.

Chapter 5

Cronin O, Sidhu M, Shahidi N, Gupta S, O'Sullivan T, Whitfield A, Wang H, Kumar P, Hourigan L, Byth K, Burgess NG, Bourke MJ. Comparison of Morphology and Histopathology of Polyps in the Rectum and Colon. *Gastrointestinal Endoscopy*, 2022 July; 96(1):118-24.

Chapter 6

Cronin O, Meys K, Hacking S, Alawad M, Yuen S, Cohen J, Gonda T, Bourke MJ, Haber GB. Endoscopic Full Thickness Resection is Curative for Small, High-risk Colorectal Lesions. *Endoscopy Internation Open* [Under review].

Chapter 7

Cronin O, Meys K, Yuen S, Vij A, Gonda T, Goodman AJ, Bourke MJ, Haber GB. Follow-up of 35 appendiceal orifice neoplasms resected by endoscopic full thickness resection. *Gastrointestinal Endoscopy* [Under review].

Chapter 8

Cronin O, Gupta S, Gauci J, Whitfield A, O'Sullivan T, Abuarisha M, Wang H, Lee EY, Williams SJ, Burgess NG, Bourke MJ. Endoscopic resection of large anastomotic polyps is safe and effective. *Endoscopy* 2024 Feb;56(2):125-130.

Chapter 10

Cronin O, Mandarino F, Bourke MJ. Selection of endoscopic resection technique for large colorectal lesion treatment. *Current Opinion in Gastroenterology* 2024 Sep1;40(5):355-62.

Table of Abbreviations

ACE	Australian Colonic Endoscopic Resection
AO	Appendiceal orifice
ASA	American Society of Anesthesiologists (ASA) classification
CAST	Cold-forceps avulsion with adjuvant snare tip soft coagulation
C-EMR	Cold-snare EMR
CI	Confidence interval
CRC	Colorectal cancer
CSP	Cold snare polypectomy
CSIPB	Clinically significant intraprocedural bleeding
DMI	Deep mural injury
EMR	Endoscopic mucosal resection
E-FTR	En bloc full thickness resection
ER	Endoscopic resection
ESD	Endoscopic submucosal dissection
FTR	Full thickness resection
FTRD	Full thickness resection device
GI	Gastrointestinal
HGD	High-grade dysplasia
HSP	Hot snare polypectomy
H-FTR	Hybrid full thickness resection
ICV	Ileocaecal valve
IRR	Incomplete resection rate
IQR	Interquartile range
LAAP	Large (≥ 20 mm) adenomatous anastomotic polyps

LGD	Low-grade dysplasia
LNPCP	Large non-pedunculated colorectal polyp
NBI	Narrow-band imaging
OR	Odds ratio
p-CSP	Piecemeal cold snare polypectomy
p-EMR	Piecemeal EMR
R0	Curative resection
RER	Resection error rate
RIR	Resection of incomplete resection
RRA	Residual or recurrent adenoma
SC1	First surveillance colonoscopy
SC2	Second surveillance colonoscopy
SMIC	Submucosal invasive cancer
STSC	Snare-tip soft coagulation
WSLHD HREC	Western Sydney Local Health District Human Research Ethics Committee

List of Figures

Chapter 1

Figure 1 – Thesis structure

Figure 2 – EMR procedure technique; EMR – endoscopic mucosal resection

Figure 3 – ESD procedure technique; ESD – endoscopic submucosal dissection

Chapter 2

Figure 1 - Endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and cold-snare EMR (C-EMR). **(a–c)** EMR of a 40 mm Paris 0-IIa+Is granular hepatic flexure lesion. **(d–f)** ESD of a hemi-circumferential 45 mm Paris 0-IIa+Is granular rectal lesion. **(g–i)** C-EMR of a 50 mm serrated lesion without dysplasia in a patient with serrated polyposis syndrome.

Figure 2 - A 35 mm granular Paris 0-IIa LNPCP in the mid-ascending colon. A 35 mm granular Paris 0-IIa LNPCP in the mid-ascending colon, assessed using **(a)** high-definition white light, **(b)** narrow band imaging (NBI) and **(c,d)** near-focus with NBI, demonstrating a homogenous pit pattern (Kudo pit pattern IV).

Figure 3 - A 20 mm sessile serrated Paris 0-IIa LNPCP in the proximal ascending colon, assessed using **(a,b)** near focus and **(c,d)** near focus with narrow band imaging (NBI). There is a central well-demarcated area with loss of homogeneity, neovascularization, dilated vessels and a non-structural pit pattern (Kudo pit pattern V_N), suggestive of a deeply invasive cancer.

Chapter 3

Figure 1 – Wide margin cold endoscopic mucosal resection technique for adenomatous large non-pedunculated colon polyps.

Figure 2 – Study enrolment flow diagram.

Chapter 4

Figure 1 - Risk of incomplete resection. A mathematical model demonstrating the risk of incomplete resection for cold snare polypectomy and hot snare polypectomy for increasing polyp size.

Figure 2 - Cold snare polypectomy for Paris 0-IIa polyp <10mm.

(A) 3mm Paris 0-IIa colorectal adenoma; (B) en bloc R0 excision with thin wire cold snare. Note wide margin of normal mucosa with snare placement; (C) the halo effect with blanching of the surrounding mucosa and hyperaemia of the adenoma; (D) post excision halo effect; (E) water expansion of the defect; (F) Careful inspection of margin.

Figure 3 - Piecemeal cold snare polypectomy for Paris 0-IIa lesion >20mm.

(A-C) >20mm lateral spreading lesion, examined with high-definition white light and narrow-band imaging; (D) lesion after submucosal injection; (E) piecemeal cold snare excision; (F) careful inspection of the post-resection defect margin.

Chapter 5

Figure 1 - Flow diagram of consecutive patients referred with LNPCPs for tissue resection

Chapter 6

Figure 1 - Endoscopic full thickness resection of a 20mm Paris 0-IIa+IIc ascending colon lesion. (A) A 20mm Paris 0-IIa+IIc ascending colon lesion assessed with white light endoscopy and (B) near focus, illustrating Kudo pit pattern Vi centrally. (C) Grasping forceps used to draw specimen into full thickness device. (D) Post-deployment with muscularis propria at periphery and serosa centrally. (E) Ex-vivo specimen with serosal view illustrating ink tattoo. (F) Pinned specimen with clear margins.

Figure 2 - Endoscopic hybrid full thickness resection of a 30mm Paris 0-IIa+IIc transverse colon lesion. (A) A 30mm Paris 0-IIa+IIc transverse colon lesion assessed with white light endoscopy, (B) narrow band imaging and (C-D) near focus, illustrating Kudo pit pattern Vi centrally. (E-G) Standard piecemeal EMR was performed around the periphery of the lesion.

(G) Piecemeal resection was continued until only the non-lifting portion of the lesion remained. (H-I) Endoscopic full thickness resection. (J-K) Ex-vivo lesion demonstrating sub-serosal fat. (L) Surveillance colonoscopy demonstrating a scar at resection site without evidence of recurrence.

Figure 3 - Flow diagram of consecutive lesions referred for consideration of endoscopic full thickness resection.

Figure 4 - Flow diagram of consecutive patients referred for endoscopic full thickness resection.

Figure 5 - Histogram illustrating the deepest resection layer for lesions resected by endoscopic full thickness resection device.

Chapter 7

Figure 1 - Endoscopic full thickness resection of a 20mm Paris 0-IIa appendiceal orifice lesion. (A) A 20mm Paris 0-IIa appendiceal orifice lesion assessed with white light endoscopy and (B) near focus, illustrating Kudo pit pattern Vi centrally. (C) Advancement of the colonoscope with the full thickness device. (D) Post-deployment with exposed serosa. (E) Pinned specimen viewed from serosal side. (F) Surveillance colonoscopy with biopsy-proven reactive hyperplastic tissue.

Figure 2 - Flow chart for 37 patients referred for consideration of endoscopic full thickness resection of an appendiceal orifice lesion.

Figure 3 - Entero-colonic fistula observed 6 months post endoscopic full thickness resection of a 20mm Paris0-IIa lesion at the appendiceal orifice. (A) View from the cecum with ileocecal valve located at 11 o'clock position. (B) Fistula at site of previous EFTR. (C-E) Appendectomy related surgical clip at superior margin of fistula. (F) View from within the fistula.

Figure 4A - Coronal CT Contrast Enhanced image of the abdomen: Yellow arrow denotes the ileo-cecal valve. Green Arrow denotes the terminal ileum. Blue arrow denotes the cecum.

Figure 4B - Yellow arrow annotates a surgical clip from a prior appendectomy. Green arrow annotates a fistula between the cecum and distal ileum, with fecalized cecal contents protruding through the defect into the distal ileum.

Chapter 8

Figure 1 - Endoscopic views of the resection of a 30-mm Paris 0-IIa large anastomotic polyp showing: **a** a lesion at the anastomosis under white light with near focus; **b** narrow-band imaging; **c** central non-lifting after submucosal injection with indigo carmine and Gelofusine; **d–f** sequential snare resection of areas with adequate submucosal lifting with interrogation of the defect for deep mural injury with topical chromoendoscopy after each snare resection.

Figure 2 - Endoscopic views of the resection of a 30-mm Paris 0-IIa large anastomotic polyp showing: **a–d** cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) applied to the central non-lifting segment that was resistant to snare capture; **e,f** through-the-scope clips applied to close a deep mural injury type II.

Figure 3 - Endoscopic views of the resection of a 40-mm Paris 0-IIa large anastomotic polyp showing: **a** the lesion at the anastomosis; **b** central non-lifting after submucosal injection with indigo carmine and Gelofusine; **c** sequential snare resection of areas with adequate submucosal lifting; **d** cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) applied to the central non-lifting segment that was resistant to snare capture, with thermal ablation to the defect margin by snare-tip soft coagulation; **e** through-the-scope clips applied to close a deep mural injury type II; **f** a bland scar seen on narrow-band imaging at 6-month surveillance.

Chapter 10

Figure 1: 40mm Granular Paris 0-IIa LNPCP in the mid-ascending colon resected by conventional Endoscopic Mucosal Resection.

Figure 2: 35mm Granular Paris 0-IIa LNPCP in the distal transverse colon resected by Cold Endoscopic Mucosal Resection.

Figure 3: 50mm Granular Paris 0-IIa+Is LNPCP in the rectum resected by Endoscopic Submucosal Dissection.

50mm Granular Paris 0-IIa+Is LNPCP assessed with (a) high-definition white light and (b) narrow band imaging (NBI). En bloc submucosal dissection and resection (c-e). Post-resection en bloc ex-vivo specimen (f).

List of Tables

Chapter 3

Table 1 - Baseline characteristics of study cohort

Table 2 - Lesion characteristics of C-EMR recurrences

Chapter 4

Table 1 -Polyp area, resection error rate and incomplete resection rate for hot and cold snare polypectomy.

Supplementary Table 1 - Literature search for residual or incomplete adenoma resection for piecemeal Cold Snare Polypectomy.

Chapter 5

Table 1 - Comparison of Rectal and Non-Rectal colonic LNPCPs.

Table 2: Multivariate analysis assessing variables independently associated with location, Rectum Vs Colon (excluding rectum).

Chapter 6

Table 1 - Patient characteristics with high-grade dysplasia and cancer resected by full-thickness resection

Table 2 - Cancer Histopathology (n=18)

Table 3 - Lesions with cancer referred for consideration of surgical resection post endoscopic full thickness resection.

Chapter 7

Table 1 - Patient characteristics for full thickness resections of the appendiceal orifice (n=35)

Chapter 8

Table 1- Characteristics of the 10 included patients and their large anastomotic polyps.

Table 2 - Procedure and follow-up details for the 10 large anastomotic polyps that were resected endoscopically.

Chapter 1 - Introduction

Colorectal cancer (CRC) was the third most commonly diagnosed cancer in Australia in 2017 with an estimated incidence of 67 per 100,000 in males and 49 per 100,000 in females.^{1,2} Globally, the burden of CRC is projected to increase by 60% by 2030.³ The majority of these tumours arise from colorectal polyps and colonoscopy exerts its beneficial effect by polypectomy.^{2,4}

Early detection of CRC has a mortality benefit.⁴ In an observational cohort study over 23 years, Zauber and colleagues (2012) reported a 53% reduction (Relative Risk [RR] 0.47; 95% Confidence Interval [CI] 0.26 to 0.80) in mortality among patients who had undergone polypectomy.⁵ Unfortunately, polypectomy technique is imperfect, typically taught heuristically from anecdotal experience. Zauber and colleagues reported that despite close follow-up, 12 out of 1226 patients (1%) died from CRC.⁶ With the increasing incidence of CRC, it is imperative that high-quality clinical research addresses what is currently a significant deficiency in our understanding of effective polypectomy technique.

Ideally polypectomy should be safe, efficient, cost-effective and curative. Recurrence and interval cancer (CRC diagnosed less than 3 years after colonoscopy) occur due to incomplete resection, which compromises clinical outcomes and increases healthcare costs.

The two modalities for polypectomy are: Cold Snare Polypectomy (CSP) which employs a thin wire to guillotine the polyp; and Hot Snare Polypectomy (HSP) which incorporates electrocautery. The overwhelming majority of colonic polyps measure less than 10mm and are safely and effectively managed by CSP.⁷ HSP has conventionally been used for resection of larger polyps greater than 20mm (large non-pedunculated colorectal polyp \geq 20mm, LNPCP). Compared to conventional surgery, ER is minimally invasive, cost-effective and organ-preserving with resultant lower morbidity and mortality. High quality evidence-based research as well as technical innovations has driven substantial advancements in over the last two decades.

CSP is safer and equally efficacious as HSP for the removal of small (<10mm) colorectal polyps. The absence of electrocautery virtually eliminates the risks of perforation and post-

polypectomy bleeding which can occur with HSP.^{7,8} This improved safety profile holds appeal for resection of larger lesions however to date, there have been no randomised controlled trials comparing cold endoscopic mucosal resection (C-EMR) to hot endoscopic mucosal resection (H-EMR).

Due to misconceived simplicity surrounding C-EMR, there has been an increasing shift toward resection of LNPCPs using this technique. CSP and C-EMR possibly demand greater technical skill than conventional H-EMR. Both techniques certainly rely on a deep understanding of the fundamentals of cold snare resection technique.

Several key aspects of CSP and C-EMR require further clarification and improved understanding. A head-to-head trial is required to appreciate the key differences in outcomes between C-EMR and H-EMR for resection of LNPCPs. An improved understanding of the fundamentals underpinning CSP and C-EMR is needed to better explain the higher risk of incomplete resection. This would better inform guidelines and may identify specific technical adaptations required to improve C-EMR related outcomes.

The risk of overt and covert submucosal invasive cancer (SMIC) should feed into any ER algorithm, to inform technique selection. For example, piecemeal EMR is not curative for lesions harbouring SMIC. These lesions need to be removed en bloc. Location in the colorectum greatly influences the risk of SMIC. Clarity of this association would provide confidence in the selection of ER technique and influence any ER algorithm.

Apart from rectal lesions, there are other lesions which require special consideration and technique adaptation, such as small, high-risk lesions in the colon, and lesions at the appendiceal orifice. Endoscopic full-thickness resection (EFTR) is a relatively new ER technique suited to these lesions. There is little long-term data evaluating its safety and efficacy. Adaptation of technique is also required for resection of large anastomotic adenomatous polyps (LAAPs) but there is little data on the success rate of ER for these lesions.

In this thesis, three key areas related to ER were identified for prospective research:

- 1) Comparison of C-EMR and H-EMR for resection of LNPCPs.

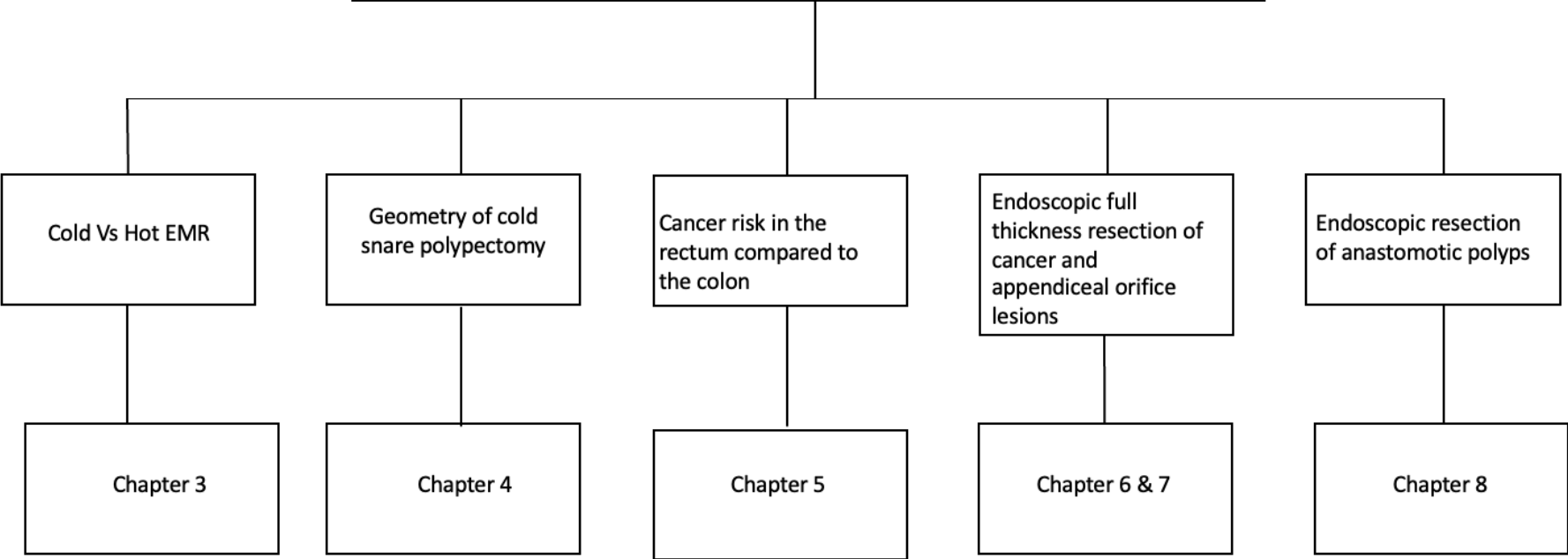
- 2) Understanding the fundamentals of C-EMR
- 3) The influence of location in the colo-rectum on the risk of covert and overt SMIC.
- 4) Long-term safety and efficacy of EFTR of high-risk colo-rectal lesions and lesions at the appendiceal orifice.
- 5) Safety and efficacy of ER of large anastomotic adenomatous polyps (LAAPs)

Based on the above, this thesis has the following aims:

- 1) Assess the long-term efficacy and safety of C-EMR compared to H-EMR for resection of LNPCPs.
- 2) Evaluate the risk of incomplete resection for C-EMR.
- 3) Compare the key differences between rectal lesions and lesions in the rest of the colon.
- 4) Assess the efficacy and safety of EFTR for high-risk colorectal lesions.
- 5) Assess the efficacy and safety of EFTR for appendiceal orifice lesions.
- 6) Assess the efficacy and safety of ER for the removal of large (≥ 20 mm) adenomatous anastomotic polyps (LAAPs).

To address the aims of this thesis, several prospective studies were conducted, with ethical approval from the Western Sydney Local Health District Human Research Ethics Committee (WSLHD-HREC).

Innovations in endoscopic resection of laterally spreading non-pedunculated colorectal polyps to improve clinical outcomes.



Chapter 2 - Endoscopic management of large non-pedunculated colorectal polyps

Publication:

Cronin O, Bourke MJ. Endoscopic management of large non-pedunculated colorectal polyps. *Cancers* 2023 Jul;15(15):3803.

In brief:

ER should be the first-line treatment for pre-malignant and early colorectal cancers. This review outlines endoscopic resection techniques for the removal of colorectal lesions.

Contribution:

- ER is organ-sparing, safe and effective. It has a lower morbidity and mortality compared to surgery.
- An ER algorithm should guide the resection modality and account for lesion size, site, morphology and predicted histology.

Endoscopic management of large non-pedunculated colorectal polyps.

Authors: Oliver Cronin MBBS FRACP^{1,2}, Michael J Bourke MBBS FRACP^{1,2}.

1. Westmead Hospital, Department of Gastroenterology and Hepatology, Sydney, New South Wales, Australia
2. Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia

Corresponding Author:

Michael J. Bourke MBBS FRACP
Clinical Professor of Medicine
Westmead Hospital, Department of Gastroenterology and Hepatology
University of Sydney, Westmead Clinical School
Suite 106a 151-155 Hawkesbury Road
Sydney, New South Wales, Australia 2145
Email: michael@citywestgastro.com.au

Conflict of interest statement/Disclosures:

Oliver Cronin No conflicts of interest
Michael J Bourke Olympus, Cook Medical, Boston Scientific – research support

Financial Support

The Cancer Institute of New South Wales provided funding for a research nurse to assist with the administration of the study in Sydney, New South Wales. They had no input regarding the review design, analysis, interpretation, preparation, review or approval of the manuscript.

Authorship statements:

Oliver Cronin Review design, literature search, analysis, interpretation, drafted and revisions of manuscript after review by the co-author.
Michael J Bourke Conceived, designed and lead the review. Critical revisions and approval of final manuscript.

Abbreviations

ARJ	Anorectal junction
CAST	Cold-forceps avulsion with adjuvant snare-tip soft coagulation
ER	Endoscopic resection
HSP	Hot snare polypectomy
LNPCP	Large non-pedunculated colorectal polyps ≥ 20 mm
EMR	Endoscopic mucosal resection
C-EMR	Cold-endoscopic mucosal resection
DMI	Deep mural injury
ESD	Endoscopic submucosal dissection
HSP	Hot snare polypectomy
JNET	Japan Narrow-Band Imaging Expert Team
KPP	Kudo pit pattern
ICV	ileocaecal valve
NPV	Negative predictive value
SRA	Selective resection algorithm
SMIC	Submucosal invasive cancer
URA	Universal resection algorithm

Simple summary: Endoscopic resection (ER) of large non-pedunculated colorectal polyps ≥ 20 mm (LNPCPs) is safe, effective and the preferred treatment compared to surgery.

Predicted histopathology of the LNPCP based on size, morphology, granularity, pit pattern and location in the colo-rectum is essential when deciding upon resection technique. Post resection defect inspection and adjuvant techniques such as thermal ablation of the margin have been demonstrated to reduce recurrence rates. Follow-up surveillance colonoscopy can accurately identify recurrence. Endoscopic treatment of recurrence is effective.

Abstract

Large non-pedunculated colorectal polyps ≥ 20 mm (LNPCPs) comprise about 1% of all colorectal polyps. LNPCPs more commonly contain high-grade dysplasia, covert and overt cancer. These lesions can be resected by several means including conventional Endoscopic Mucosal Resection (EMR), Cold-snare EMR (C-EMR) and Endoscopic Submucosal

Dissection (ESD). Evidence-based, selective resection algorithms should be used when choosing the most appropriate technique to ensure the safe and effective removal of LNPCPs. Due to its enhanced safety and comparable efficacy, there has been a paradigm shift towards cold snare polypectomy (CSP) for the removal of small polyps (<10mm). This technique is now being applied to the management of LNPCPs, however further research is required to define the optimal LNPCP subtypes to target and the viable upper size limit. Adjuvant techniques such as thermal ablation of the resection margin significantly reduce recurrence risk. Bleeding risk can be mitigated by use of through-the-scope clips to close defects in the right colon. Endoscopic surveillance is important to detect recurrence and synchronous lesions. Recurrence can be readily managed with an endoscopic approach.

Keywords: Colonoscopy; polyp; polypectomy; colorectal cancer; endoscopic mucosal resection; endoscopic submucosal dissection.

Introduction

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second most frequent cause of cancer-related death.^{1,2} The majority of CRC arises via the stepwise acquisition of molecular abnormalities in the adenoma-carcinoma and serrated pathways.³⁻⁵ This creates the opportunity for intervention to remove premalignant polyps. Endoscopic resection (ER) of pre-malignant polyps has been shown to reduce the incidence of CRC.⁶⁻⁸ Moreover, screening colonoscopy and polypectomy has been shown to reduce the risk of death from CRC at 10 years (risk ratio 0.82, 95% confidence interval [CI] 0.70-0.93).⁹ In a large study (n=2602) with follow-up over 23 years, a 53% reduction (Relative Risk [RR] 0.47; 95% CI 0.26 to 0.80) in mortality was demonstrated in those who had undergone polypectomy.⁷

The majority (90%) of colorectal polyps are <10mm in size, do not contain advanced pathology and can be removed either en bloc or piecemeal by cold snare polypectomy (CSP).¹⁰⁻¹² Large non-pedunculated colorectal polyps \geq 20mm (LNPCPs) comprise ~1% of all colorectal polyps. These lesions have varied risk of overt and covert submucosal invasive cancer (SMIC) and therefore require a detailed, methodical optical assessment before

deciding on the most suitable resection technique.¹³⁻¹⁶ This algorithm needs to account for LNPCP size, morphology, location, pit pattern in addition to any patient specific factors such as co-morbidities and anticoagulation or anti-platelet medications.¹⁷

Consensus recommendations favour an endoscopic approach as first line for the resection of LNPCPs (based on high-quality evidence).^{18,19} Compared to surgical resection, EMR has been demonstrated to have reduced morbidity, mortality and lower healthcare costs.^{20,21}

ER can be divided into three discrete phases: pre-resection, resection and post-resection. Technical success of ER requires a methodical, collaborative approach, ideally at a centre with access to the complete range of ER techniques including conventional Endoscopic Mucosal Resection (EMR), Cold-snare EMR (C-EMR) and Endoscopic Submucosal Dissection (ESD) (Figure 1). Herein, we outline an evidence-based approach to the ER of colorectal polyps.

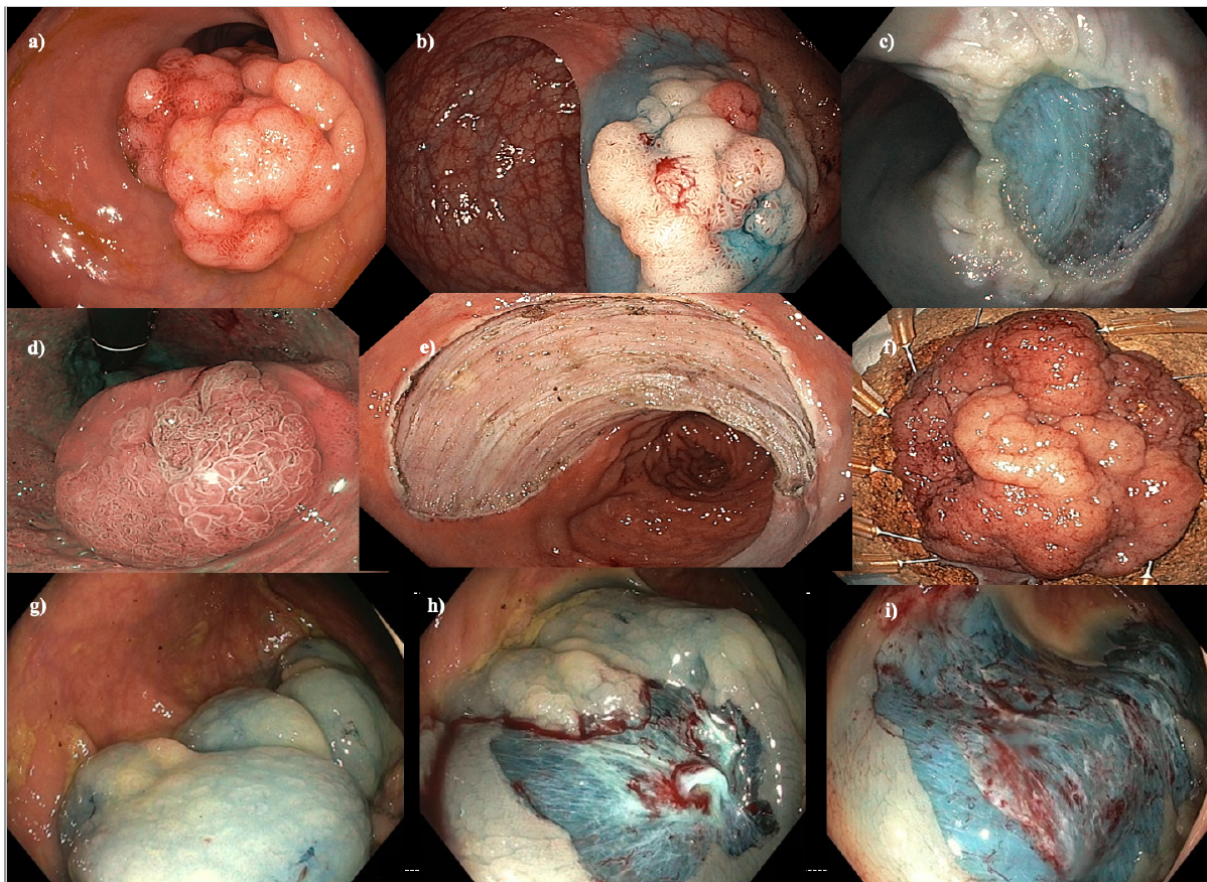


Figure 1. Endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and cold-snare EMR (C-EMR). (a–c) EMR of a 40 mm Paris 0-IIa+Is granular hepatic flexure lesion. (d–f) ESD of a hemi-circumferential 45 mm Paris 0-IIa+Is granular rectal lesion. (g–i) C-EMR of a 50 mm serrated lesion without dysplasia in a patient with serrated polyposis syndrome.

Pre-Resection

Planning is essential to ensure technical success. The planning phase can be sub-divided into pre-procedure and intra-procedure.

Pre-procedural planning starts with patient assessment, accounting for frailty, functional status, co-morbidities and medications. Consent must include the risks and benefits of ER and a discussion around alternative modalities such as surgery. Predicted lesion histopathology including the risk of SMIC should influence ER modality and any related imaging should be reviewed. Pre-procedural planning also includes an in-room discussion with the endoscopy team to ensure that nursing and anaesthetic staff are aware of the various stages of the procedure including any site-specific challenges such as those seen with ileocaecal valve (ICV) lesions.^{17, 22} The pre-procedure discussion with the endoscopy team should also include the expected procedure time, any required medications such as surgical antibiotic prophylaxis or local anaesthetic for anorectal junction (ARJ) lesions and a check to ensure appropriate snares and ESD knives are available.^{23, 24} ER should only be performed with carbon dioxide insufflation.²⁵ Required ancillary devices should be in the room pre-procedure including closure devices such as through-the-scope clips and those used to treat intra-procedural bleeding such as haemostatic forceps.

Intra-procedural planning starts with patient positioning. The optimal patient position is to have the fluid pool opposite the lesion to maximise the effect of gravity on lesion elevation and achieve a clear working field during tissue resection or for management of any complications. Therefore, a supine or right lateral position may be required. Position of the colonoscope to align the lesion at a 6 o'clock position is essential. Dependent on location, a retroflexed position may improve access and optical assessment.

Thorough optical assessment is key. The risk of overt (optical features of SMIC present) or covert (optical features of SMIC absent) can be predicted based on LNPCP size, location, morphology, granularity, microvascular and surface pit pattern.^{13, 26} Several classification systems exist including the Kudo pit pattern (KPP) and the Japan Narrow-Band Imaging Expert Team (JNET) classification.^{27, 28} An understanding of these systems is useful. A simple innovation to assist with familiarity and use is to place large posters of these classification systems in the endoscopy rooms and reporting areas. Benign lesions have surface homogeneity with a regular pit and microvascular pattern (Figure 2). High grade dysplasia or cancer within a benign lesion appears as a demarcated area of disruption within this regular pattern (Figure 3). Such areas need to be examined very carefully to ensure the correct optical diagnosis and treatment strategy.

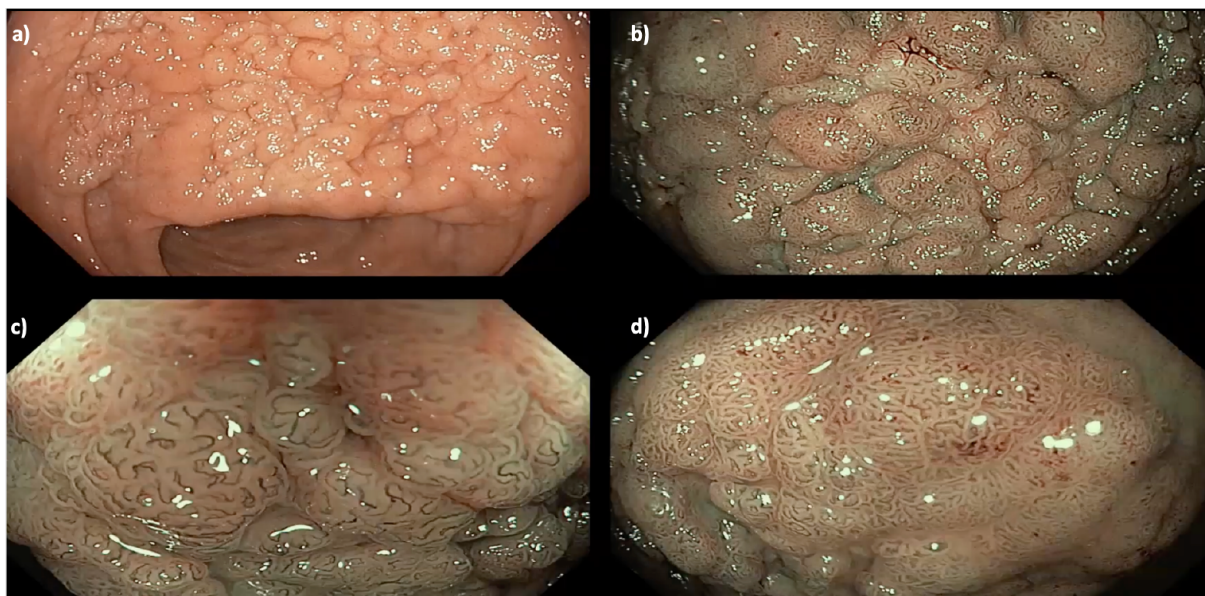


Figure 2. A 35 mm granular Paris 0-IIa LNPCP in the mid-ascending colon. A 35 mm granular Paris 0-IIa LNPCP in the mid-ascending colon, assessed using (a) high-definition white light, (b) narrow band imaging (NBI) and (c,d) near-focus with NBI, demonstrating a homogenous pit pattern (Kudo pit pattern IV).

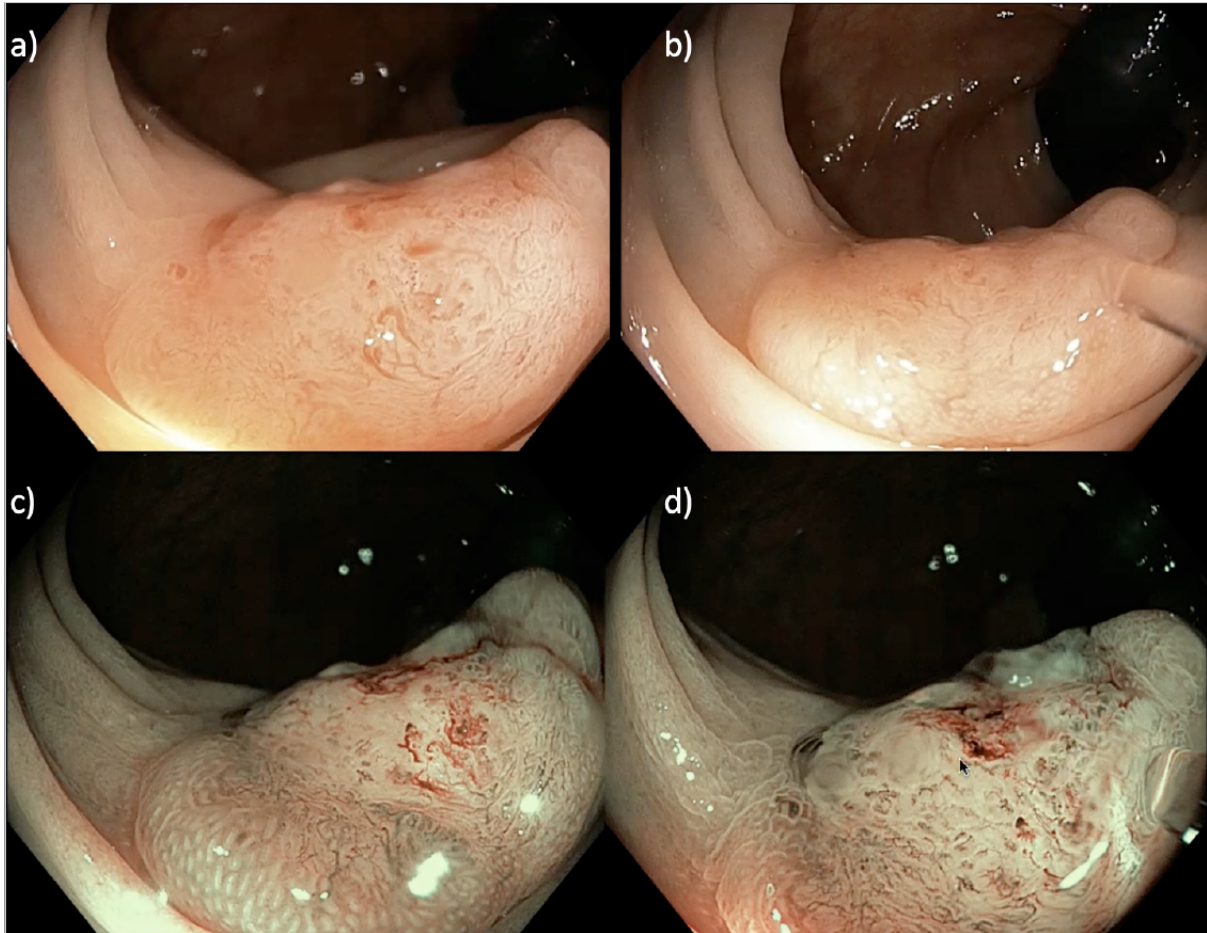


Figure 3. A 20 mm sessile serrated Paris 0-IIa LNPCP in the proximal ascending colon, assessed using (a,b) near focus and (c,d) near focus with narrow band imaging (NBI). There is a central well-demarcated area with loss of homogeneity, neovascularization, dilated vessels and a non-structural pit pattern (Kudo pit pattern V_N), suggestive of a deeply invasive cancer.

Traditionally the accuracy of optical diagnosis for SMIC was evaluated across the entire LNPCP spectrum and was found to have suboptimal utility. Recently, optical assessment of flat (Paris 0-IIa) LNPCPs is proven to be highly accurate.¹⁵ In a large, prospective, single-centre cohort study (n=1583), the sensitivity and specificity for predicting cancer in Paris 0-IIa LNPCPs was 91% and 96% respectively. The likelihood that cancer would be missed in this study was 6 in 1000 cases. Optical diagnosis for SMIC in nodular lesions is less accurate (sensitivity 53%, specificity 94%, missed SMIC 6%).¹⁵ Excluding those lesions with overt SMIC, a large multicentre, prospective study (n=2277) found that covert SMIC was associated with Paris 0-Is and Paris 0-IIa+Is morphology, non-granularity, size and distal location.¹³ Supporting this, a large, prospective cohort study (n=3405) demonstrated that

nodular rectal LNPCPs are more likely to contain SMIC than non-rectal colonic LNPCPs (15% vs 6%, $p < 0.001$).²⁶

Resection

In 2023, a selective resection algorithm should be employed when considering a therapeutic strategy for any colorectal polyp or neoplasm. This is based on optical diagnosis for predicted histology, lesion size, morphology and surface granularity and location in the colon.

Diminutive (<5mm) and small (5-9mm) colorectal polyps

The overwhelming majority of colonic polyps are diminutive (<5mm) or small (5-9mm). CSP is safer and equi-efficacious to hot snare polypectomy (HSP) for the removal of these colorectal polyps. The absence of electrocautery all but eliminates the risks of perforation and post-polypectomy bleeding.^{29,30} Based on high quality data, en bloc or oligo-piecemeal CSP should be used to resect these polyps.^{18,19}

Medium (10-19mm) colorectal polyps

There is a paradigm shift toward C-EMR given the superior safety profile. A large, prospective, multicentre cohort study (n=286 lesions) comparing conventional EMR to C-EMR for polyps 6-15mm, favoured the use of C-EMR over EMR.³¹ At present, US consensus guidelines recommend either EMR or C-EMR for resection of lesions 10-19mm.¹⁸

Large (>20mm) non-pedunculated colorectal polyps

Conventional EMR is the mainstay for ER of LNPCPs due to its superior safety, efficacy and cost effectiveness compared to surgery and ESD.^{17-19,22} High-quality studies over the past 10-15 years have led to improvements in safety and efficacy of EMR. These include the use of CO₂ for insufflation; addition of chromo-injectate into the submucosal space; use of a systematic inject and sequential snare resection technique; removing a 2-3mm margin of normal mucosa; water expansion of the defect to identify any residual adenoma and recognition and management of significant DMI.^{25,32,33} Once all visible adenoma has been

excised, thermal ablation of the margin should be completed by gently applying snare-tip soft coagulation (Effect 4, 80W: ERBE Electromedizin, Tübingen, Germany), aiming for a 3-5mm rim of ablated mucosa.³⁴ In a large, prospective cohort (n=390) comparing conventional EMR without and with thermal ablation, recurrence rates reduced from 21.0% (37/176) to 5.2% (10/192), p<0.001. No adverse events were attributed to margin thermal ablation. Since inception, application of this adjuvant technique has improved. In a recent, larger multi-centre cohort (n=1049), recurrence rates at 6-month follow-up colonoscopy (SC1) were 1.4% (10/707).³⁵

At present given the paucity of data, conventional EMR is recommended over C-EMR for LNPCP resection. The safety profile of C-EMR is appealing for the piecemeal resection of Paris 0-IIa (flat, sessile) LNPCPs however the upper size limit that can be effectively removed by C-EMR without excessive burden of recurrence is unknown. Several ongoing large randomised controlled trials comparing EMR and C-EMR for non-serrated LNPCPs (clinicaltrials.gov identifier: NCT04138030; NCT04418843) aim to provide clarity on this issue. The next important RCT will compare C-EMR to C-EMR with thermal ablation of the margin (clinicaltrials.gov identifier NCT05041478).

In contrast to adenomatous LNPCPs, C-EMR is always the primary modality for ER of serrated LNPCPs, irrespective of size.³⁶ This large study (n=562) of serrated lesions found no difference in technical success and recurrence rates between EMR and C-EMR groups however bleeding (0% vs 5.1%) and significant deep mural injury (DMI) (0% vs 2.8%) were more common in the EMR group.

Special considerations

Site specific considerations and technique modifications may be needed for LNPCPs located at the ICV, appendiceal orifice, at a surgical anastomosis, or ARJ or those which are circumferential.^{16, 37-39}

The rectum should be regarded as a complex high-risk site, with distinct challenges compared to the colon. This is not due to its technical limitations but due to its increased risk of covert SMIC.^{26, 40} Furthermore, the consequences of failed endoscopic cure include consideration of the most hazardous and complicated forms of colorectal surgery including permanent ostomy formation⁴¹. In a large, multicentre observational study (n=618) rectal LNPCPs were more likely to have nodular morphology (53% vs 17%, p<0.001) and contain cancer (15% vs 6%, p<0.001) compared to LNPCPs in the remainder of the colon.²⁶ Endoscopic en bloc resection for any LNPCP with a nodular component is critical with the aim of achieving an R0 (curative) resection. This requires meticulous planning.

ESD was developed as an ER technique for the curative treatment of early gastric cancer. ESD is now an established technique in the colo-rectum. It is typically performed with a generous submucosal injection, in a retroflexed position for improved scope stability and an improved more parallel angle of the cutting plane. Dissection is performed with an electro-surgical knife. Technique has improved over the past 10 years, aided by internal and external traction devices as well as techniques such as pocket creation ESD.

EMR and ESD are complementary techniques for resection of rectal LNPCPs. A selective resection algorithm (SRA) has demonstrated superior outcomes compared to a universal EMR algorithm (UEA). In a large study (n=480) comparing a SRA to a UEA, LNPCPs underwent ESD if they had features suggestive of superficial overt SMIC (1000µm, KPP Vi) or covert SMIC (Paris 0-Is or a dominant nodule). All (n=7, 100%) LNPCPs with SMIC amenable to R0 resection which underwent ESD, were cured.¹⁶ A rectum-specific SRA avoids the piecemeal resection of cancer.

Prevention of bleeding by prophylactic treatment of medium and large vessels with coagulating forceps is key. Bleeding stains the mucosa impeding views, leading to a higher risk of incomplete resection. Treatment of bleeding can char the mucosa, also obscuring views. Given its resource intensive, time-consuming nature, this technique is best reserved for lesions with superficial overt SMIC or high risk of covert SMIC. In clinical practice, this limits its use predominantly to the rectum.²⁴

Previously attempted LNPCPs are common and present a unique set of challenges. Due to the dense submucosal fibrosis, submucosal lift is often unsuccessful. A large observational study (n=1292) demonstrated that with the use of auxiliary these lesions can be effectively resected by EMR. CAST was used in 73 (46.2%) cases. No recurrence (n=0, 0%) was identified in any previously attempted LNPCPs which underwent margin thermal ablation demonstrating that EMR is effective for resection of these lesions.⁴²

Complications

Deep Mural Injury

Significant DMI (Deep Mural Injury Type III-V) was previously a feared intra-procedural complication, with a frequency of around 3%.⁴⁰ However, due to an improved understanding of risk factors, earlier recognition and advances in closure devices such as through-the scope clips, significant DMI can now be successfully managed.^{40, 43} In a large, prospective cohort (n=911) significant DMI was associated with attempted en bloc resection, advanced histopathology and transverse colon location.⁴³ In a large, prospective cohort (n=3717), significant DMI occurred in 2.7% (101/3717) of EMR resections (median lesion size 35mm, interquartile range 25mm-45mm). Successful defect closure occurred in 97.0% (98/101) of cases. There were no differences found between DMI and non-DMI cases in terms of technical success or recurrence.⁴⁰

Post-procedural bleeding

Prophylactic treatment of visible vessels within a defect post EMR, has been previously investigated. In a multi-centre RCT (n=347, 55.3% proximal colonic lesions) prophylactic endoscopic coagulation of all visible vessels within the post-EMR defect did not reduce clinically significant post-EMR bleeding compared to no treatment (5.2% vs 8.0%, p=0.30).⁴⁴ Post-resection defect closure for right sided lesions using through-the-scope clips has been shown to reduce clinically significant post-EMR bleeding from 10.6% (12/113) to 3.4% (4/118), p=0.031.⁴⁵

Post-ER bleeding has a frequency of 6-7% dependent on defect location and the selected ER modality. Bleeding typically does not require any intervention and these cases are managed conservatively in >50% of cases.⁴⁶

Post-Resection

Post-operative care

Post-resection instructions and communication with nursing staff, patients and their next-of-kin is important to ensure early recognition and management of any adverse events or complications. Recovery staff should receive a verbal handover and a written endoscopy report from the proceduralist including any complexities or nuances of the case. Dependent on the procedure type, patients should remain fasting for at least 2 hours or until they have been reviewed by the proceduralist. After clinical assessment, if the patient is well, they can commence a clear fluid diet.

The patient should receive a copy of their report. Dietary instructions should be highlighted and details of the best hospital contact should be clear, should the patient have any issues or questions overnight. Most patients can be discharged home the same day, but an endoscopy team member should contact the patient the following day for a telehealth assessment.

Surveillance

Guidelines recommend a follow-up surveillance colonoscopy 6 months post-ER.^{18, 19, 47} Surveillance post-ER is essential to evaluate the previous resection site and to exclude synchronous lesions.⁴⁸ Co-existent advanced pathology (polyps >10mm or with a villous component or high-grade dysplasia) is reported to occur at surveillance in 10-20% of cases.^{48,}

⁴⁹

The previous ER site can be identified by a bland pale area, sometimes with anatomic distortion of the mucosal folds.⁵⁰ A standardised imaging protocol for optical assessment of the scar should include high-definition white light and narrow band imaging (NBI, Olympus, Inc, Tokyo, Japan).⁵⁰ Optical scar assessment is accurate. A recent multicentre single-blind

cross-over trial (n=203) to compare NBI and high-definition white light for the assessment of recurrence or residual adenoma at a post-EMR scar, reported a negative predictive value (NPV) >90% (NPV 96% using NBI, NPV 93% using high-definition white light).⁵¹ Use of NBI was not superior to high-definition white light ($p=0.06$).⁵¹ Expert consensus is that a biopsy is not needed for a bland scar with uniform pit pattern.⁵⁰ Common mimics of recurrence include clip artefact and inflammatory nodules. If an abnormality is suspected, this area should be excised and ablated, as described in a proposed Westmead algorithm for evaluating recurrence.⁵² Techniques include cold snare resection or cold-forceps avulsion with adjunct snare-tip soft coagulation (CAST), margin ablation and clip closure if any DMI \geq Type 2.^{34, 43, 53}

Conclusion

ER is organ-sparing and minimally invasive. It is the recommended primary management strategy for the excision of LNPCPs, supported by high-quality studies. Referral to an expert endoscopist, rather than for surgery is the standard of care for all patients with an LNPCP. Predicted histopathology underpins the selective resection algorithm and accounts for lesion size, site, granularity, pit pattern and morphology. These resection decision strategies have revolutionised management of LNPCPs. Compared to surgery, they have a lower morbidity, mortality and are more cost-effective. Unnecessary surgery remains an important issue and can be overcome by greater awareness of the efficacy and superior risk profiles of ER.

References

1. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol* 2019;16:713-732.
2. Patel SG, Karlitz JJ, Yen T, et al. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol Hepatol* 2022;7:262-274.
3. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008;134:1570-95.

4. Kedrin D, Gala MK. Genetics of the serrated pathway to colorectal cancer. *Clin Transl Gastroenterol* 2015;6:e84.
5. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 2004;287:G7-17.
6. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993;329:1977-81.
7. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;366:687-96.
8. Kahi CJ, Imperiale TF, Juliar BE, et al. Effect of screening colonoscopy on colorectal cancer incidence and mortality. *Clin Gastroenterol Hepatol* 2009;7:770-5; quiz 711.
9. Bretthauer M, Løberg M, Wieszczy P, et al. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. *N Engl J Med* 2022;387:1547-1556.
10. Rex DK. Have we defined best colonoscopic polypectomy practice in the United States? *Clin Gastroenterol Hepatol* 2007;5:674-7.
11. Gupta N, Bansal A, Rao D, et al. Prevalence of advanced histological features in diminutive and small colon polyps. *Gastrointest Endosc* 2012;75:1022-30.
12. Repici A, Hassan C, Vitetta E, et al. Safety of cold polypectomy for <10mm polyps at colonoscopy: a prospective multicenter study. *Endoscopy* 2012;44:27-31.
13. Burgess NG, Hourigan LF, Zanati SA, et al. Risk Stratification for Covert Invasive Cancer Among Patients Referred for Colonic Endoscopic Mucosal Resection: A Large Multicenter Cohort. *Gastroenterology* 2017;153:732-742.e1.
14. Holt BA, Bourke MJ. Wide field endoscopic resection for advanced colonic mucosal neoplasia: current status and future directions. *Clin Gastroenterol Hepatol* 2012;10:969-79.
15. Vosko S, Shahidi N, Sidhu M, et al. Optical evaluation for predicting cancer in large non-pedunculated colorectal polyps is accurate for flat lesions. *Clin Gastroenterol Hepatol* 2021.
16. Shahidi N, Vosko S, Gupta S, et al. A Rectum-Specific Selective Resection Algorithm Optimizes Oncologic Outcomes for Large Nonpedunculated Rectal Polyps. *Clin Gastroenterol Hepatol* 2023;21:72-80.e2.
17. Shahidi N, Bourke MJ. How to Manage the Large Nonpedunculated Colorectal Polyp. *Gastroenterology* 2021;160:2239-2243.e1.

18. Kaltenbach T, Anderson JC, Burke CA, et al. Endoscopic Removal of Colorectal Lesions: Recommendations by the US Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2020;115:435-464.
19. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2017;49:270-297.
20. Jayanna M, Burgess NG, Singh R, et al. Cost Analysis of Endoscopic Mucosal Resection vs Surgery for Large Laterally Spreading Colorectal Lesions. *Clinical Gastroenterology and Hepatology* 2016;14:271-278.e2.
21. Ahlenstiel G, Hourigan LF, Brown G, et al. Actual endoscopic versus predicted surgical mortality for treatment of advanced mucosal neoplasia of the colon. *Gastrointest Endosc* 2014;80:668-676.
22. Jideh B, Bourke MJ. How to Perform Wide-Field Endoscopic Mucosal Resection and Follow-up Examinations. *Gastrointest Endosc Clin N Am* 2019;29:629-646.
23. Holt BA, Bassan MS, Sexton A, et al. Advanced mucosal neoplasia of the anorectal junction: endoscopic resection technique and outcomes (with videos). *Gastrointest Endosc* 2014;79:119-26.
24. Shahidi N, Sidhu M, Vosko S, et al. Endoscopic mucosal resection is effective for laterally spreading lesions at the anorectal junction. *Gut* 2020;69:673-680.
25. Bassan MS, Holt B, Moss A, et al. Carbon dioxide insufflation reduces number of postprocedure admissions after endoscopic resection of large colonic lesions: a prospective cohort study. *Gastrointest Endosc* 2013;77:90-5.
26. Cronin O, Sidhu M, Shahidi N, et al. Comparison of the morphology and histopathology of large nonpedunculated colorectal polyps in the rectum and colon: implications for endoscopic treatment. *Gastrointest Endosc* 2022;96:118-124.
27. Kudo S, Tamura S, Nakajima T, et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc* 1996;44:8-14.
28. Sano Y, Tanaka S, Kudo SE, et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. *Dig Endosc* 2016;28:526-33.
29. Chang LC, Shun CT, Hsu WF, et al. Risk of delayed bleeding before and after implementation of cold snare polypectomy in a screening colonoscopy setting. *Endosc Int Open* 2019;7:E232-e238.

30. Tolliver KA, Rex DK. Colonoscopic polypectomy. *Gastroenterol Clin North Am* 2008;37:229-51, ix.
31. Rex DK, Anderson JC, Pohl H, et al. Cold versus hot snare resection with or without submucosal injection of 6- to 15-mm colorectal polyps: a randomized controlled trial. *Gastrointest Endosc* 2022;96:330-338.
32. Bourke MJ, Bhandari P. How I remove polyps larger than 20 mm. *Gastrointest Endosc* 2019;90:877-880.
33. Moss A, Bourke MJ, Metz AJ. A randomized, double-blind trial of succinylated gelatin submucosal injection for endoscopic resection of large sessile polyps of the colon. *Am J Gastroenterol* 2010;105:2375-82.
34. Klein A, Tate DJ, Jayasekeran V, et al. Thermal Ablation of Mucosal Defect Margins Reduces Adenoma Recurrence After Colonic Endoscopic Mucosal Resection. *Gastroenterology* 2019;156:604-613.e3.
35. Sidhu M, Shahidi N, Gupta S, et al. Outcomes of Thermal Ablation of the Mucosal Defect Margin After Endoscopic Mucosal Resection: A Prospective, International, Multicenter Trial of 1000 Large Nonpedunculated Colorectal Polyps. *Gastroenterology* 2021;161:163-170.e3.
36. van Hattem WA, Shahidi N, Vosko S, et al. Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: a retrospective comparison across two successive periods. *Gut* 2021;70:1691-1697.
37. Nanda KS, Tutticci N, Burgess NG, et al. Endoscopic mucosal resection of laterally spreading lesions involving the ileocecal valve: technique, risk factors for failure, and outcomes. *Endoscopy* 2015;47:710-8.
38. Vosko S, Gupta S, Shahidi N, et al. Impact of technical innovations in EMR in the treatment of large nonpedunculated polyps involving the ileocecal valve (with video). *Gastrointest Endosc* 2021;94:959-968.e2.
39. Tate DJ, Desomer L, Awadie H, et al. EMR of laterally spreading lesions around or involving the appendiceal orifice: technique, risk factors for failure, and outcomes of a tertiary referral cohort (with video). *Gastrointest Endosc* 2018;87:1279-1288.e2.
40. Bar-Yishay I, Shahidi N, Gupta S, et al. Outcomes of Deep Mural Injury After Endoscopic Resection: An International Cohort of 3717 Large Non-Pedunculated Colorectal Polyps. *Clin Gastroenterol Hepatol* 2022;20:e139-e147.
41. Vennix S, Pelzers L, Bouvy N, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev* 2014:Cd005200.

42. Shahidi N, Vosko S, Gupta S, et al. Previously Attempted Large Nonpedunculated Colorectal Polyps Are Effectively Managed by Endoscopic Mucosal Resection. *Am J Gastroenterol* 2021;116:958-966.
43. Burgess NG, Bassan MS, McLeod D, et al. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. *Gut* 2017;66:1779-1789.
44. Bahin FF, Naidoo M, Williams SJ, et al. Prophylactic endoscopic coagulation to prevent bleeding after wide-field endoscopic mucosal resection of large sessile colon polyps. *Clin Gastroenterol Hepatol* 2015;13:724-30.e1-2.
45. Gupta S, Sidhu M, Shahidi N, et al. Effect of prophylactic endoscopic clip placement on clinically significant post-endoscopic mucosal resection bleeding in the right colon: a single-centre, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2022;7:152-160.
46. Burgess NG, Metz AJ, Williams SJ, et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. *Clin Gastroenterol Hepatol* 2014;12:651-61.e1-3.
47. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. *Gastrointest Endosc* 2020;91:463-485.e5.
48. Bick BL, Ponugoti PL, Rex DK. High yield of synchronous lesions in referred patients with large lateral spreading colorectal tumors. *Gastrointest Endosc* 2017;85:228-233.
49. O'Sullivan T, Tate D, Sidhu M, et al. The Surface Morphology of Large Nonpedunculated Colonic Polyps Predicts Synchronous Large Lesions. *Clin Gastroenterol Hepatol* 2023.
50. Desomer L, Tutticci N, Tate DJ, et al. A standardized imaging protocol is accurate in detecting recurrence after EMR. *Gastrointest Endosc* 2017;85:518-526.
51. João M, Areia M, Pinto-Pais T, et al. Can white-light endoscopy or narrow-band imaging avoid biopsy of colorectal endoscopic mucosal resection scars? A multicenter randomized single-blind crossover trial. *Endoscopy* 2023.
52. Burgess N, Bourke M. Can we stop routine biopsy of post-endoscopic mucosal resection scars? *Endoscopy* 2023.

53. Tate DJ, Bahin FF, Desomer L, et al. Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) is an effective and safe strategy for the management of non-lifting large laterally spreading colonic lesions. *Endoscopy* 2018;50:52-62.

Chapter 3 - Cold vs hot snare endoscopic mucosal resection for large (≥ 15 mm) flat non-pedunculated colorectal polyps: a randomized controlled trial

Publication:

O'Sullivan T, **Cronin O**, Van Hattem A, Mandarino FV, Gauci J, Kerrison C, Whitfield A, Gupta S, Lee E, Williams SJ, Burgess NG, Bourke MJ. Cold vs hot snare endoscopic mucosal resection for large (15mm) flat non-pedunculated colorectal polyps: a randomized controlled trial. Gut 2024 Oct 7;73(11):1823-1830.

In brief:

This randomised control trial (RCT) compared the recurrence rates of lesions removed by cold EMR and hot (conventional) EMR. Cold EMR had a higher recurrence rate compared to hot EMR.

Contribution:

This large RCT helps to advance our understanding of the advantages and limitations of cold EMR. Cold EMR has a significantly higher recurrence rate but with a lower rate of delayed bleeding.

****As the corresponding author, I certify that Dr Oliver Cronin made a significant contribution to this manuscript to justify inclusion of this manuscript as a thesis chapter.**

Sincerely,

Professor Michael Bourke

Cold vs hot snare endoscopic mucosal resection for large (≥ 15 mm) flat non-pedunculated colorectal polyps: a randomized controlled trial

O'Sullivan T^{1,2}, Cronin O^{1,2}, Van Hattem A³, Mandarino FV¹, Gauci J¹, Kerrison C¹, Whitfield A^{1,2}, Gupta S^{1,2}, Lee E¹, Williams SJ¹, Burgess NG^{1,2}, Bourke MJ^{1,2}

- 1 Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney, New South Wales, Australia
- 2 Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia

Corresponding author:

Michael J. Bourke, MBBS, FRACP

Westmead Hospital, Department of Gastroenterology and Hepatology

University of Sydney, Westmead Clinical School

Suite 106a 151–155 Hawkesbury Road

Sydney

New South Wales, 2145

Australia

Email: michael@citywestgastro.com.au

Abstract

Background and aims

Conventional hot snare Endoscopic Mucosal Resection (H-EMR) is effective for the management of large (≥ 20 mm) non-pedunculated colon polyps (LNPCPs) however, electrocautery-related complications may incur significant morbidity. With a superior safety profile, cold snare EMR (C-EMR) of LNPCPs is an attractive alternative however evidence is lacking. We conducted a randomized trial to compare the efficacy and safety of C-EMR to H-EMR.

Methods

Flat, 15-50mm adenomatous LNPCPs were prospectively enrolled and randomly assigned to C-EMR or H-EMR with margin thermal ablation at a single tertiary centre. The primary outcome was endoscopically visible and/or histologically confirmed recurrence at 6 months surveillance colonoscopy (SC1). Secondary outcomes were clinically significant post-EMR bleeding (CSPEB), delayed perforation and technical success.

Results

177 LNPCPs were randomized to C-EMR arm (n=87) or H-EMR (n=90). Treatment groups were equivalent for technical success 86/87 (98.9%) C-EMR vs H-EMR 90/90 (100%); p=0.31. Recurrence was significantly greater in C-EMR (16/87, 18.4% vs 1/90, 1.1%; RR 16.6, 95%CI 2.24-122; p<0.001. Delayed perforation (1/90 (1.1%) vs 0; p=0.32) only occurred in the H-EMR group. CSPEB was significantly greater in the H-EMR arm (7/90 (7.8%) vs 1/87 (1.1%); RR 6.77, 95% CI 0.85-53.87; p = 0.034).

Conclusion

Compared to H-EMR, C-EMR for flat, adenomatous LNPCPs, demonstrates superior safety with equivalent technical success. However, endoscopic recurrence is significantly greater for cold snare resection and is currently a limitation of the technique.

Background and aims:

Conventional hot snare Endoscopic Mucosal Resection (H-EMR) of large (≥ 20 mm) non-pedunculated colonic polyps (LNPCPs) is standard of care within international consensus guidelines.^{1,2} For benign lesions, H-EMR supersedes surgical resection due to superior safety and cost effectiveness.³⁻⁷ Historically, recurrence was frequently encountered in H-EMR.^{8,9} This was a significant limitation of the technique that necessitated multiple procedures to establish endoscopic cure. The development of margin thermal ablation (MTA) to the post-EMR defect has mitigated recurrence and dramatically changed the EMR landscape.¹⁰⁻¹² Despite this, electrocautery-related complications of delayed bleeding and perforation persist and may incur significant morbidity.¹³⁻²²

Cold snare polypectomy is effective and safe for the resection of small polyps.^{1,2} Perforation and delayed bleeding are a rare occurrence with complete resection rates comparable to hot snare techniques.²³⁻²⁵ Application of cold snare resection to large polyps is consequently an attractive alternative. When performed on large non-dysplastic serrated polyps, it is safe and efficacious.²⁶⁻²⁸ Whether similar outcomes are achievable for adenomatous LNPCPs remains unclear, with high-quality evidence comparing cold EMR (C-EMR) to conventional hot snare EMR (H-EMR) lacking.

The aim of this study was to conduct a randomized trial comparing the efficacy and safety of C-EMR against conventional H-EMR for the resection of adenomatous LNPCPs.

Methods

Study Design

This was a prospective single-centre randomized controlled trial conducted at an Australian tertiary referral centre. The scientific protocol, data collection sheets and patient consent form were reviewed and approved by the Human Research Ethics Committee and registration was obtained (NCT04138030). All authors had access to the study data and reviewed and approved the final manuscript. The manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT) recommendations.²⁹

Patient selection and randomization

Between November 2019 and September 2023, patients referred with flat LNPCPs between 15-50mm in size were enrolled in the study unless they declined. Written informed consent was obtained from each patient on the day of the procedure. Exclusion criteria included: antiplatelet (excluding aspirin) or anticoagulant use not appropriately interrupted according to current guidelines, bleeding disorder or coagulopathy, inflammatory bowel disease associated dysplasia, LNPCPs concerning for SMIC (Kudo V surface appearance), serrated lesions, LNPCPs directly involving the ileocaecal valve (ICV), anorectal junction (ARJ) or appendiceal orifice (AO) and sessile LNPCPs with a Paris 0-Is component greater than 10mm in size.

Following optical evaluation, eligible lesions from consenting patients were randomized in a 1:1 ratio to the active (C-EMR) or control (H-EMR) arm using a randomly generated number table which was stored in a locked cabinet outside the procedural room. To minimise bias, allocation was conducted by a trained research nurse/investigator with the proceduralist blinded to the allocation process. Randomization was performed per lesion with only one lesion randomised for each patient.

Procedure

All endoscopic procedures were performed by either a study investigator (accredited gastroenterologist with advanced training at a tertiary referral centre in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their supervision. Anti-platelet (thienopyridine derivatives) and anti-coagulation medications were withheld pre-procedure, in accordance with consensus recommendations. Standard split dose bowel preparation was administered 24 hours prior to procedure. Intravenous sedation was with a combination of fentanyl, midazolam and propofol.

High-definition Olympus 190 series variable-stiffness colonoscopes (HQ190 PCF/CF; Olympus, Tokyo, Japan) were used for all procedures with carbon dioxide for insufflation. Optical evaluation was performed under high-definition white-light and narrow-band imaging (NBI) to exclude features of submucosal invasive cancer (SMIC). Polyp size was measured against an open snare of known size. Once deemed appropriate for EMR, a submucosal

cushion was created with injection of succinylated gelatin (Gelofusine; B. Braun, Bella Vista, Australia) with 0.4% indigo carmine and 1:100,000 epinephrine.

For conventional H-EMR, a standardized, previously described, inject and resect EMR technique was used.³⁰⁻³³ A microprocessor-controlled electrosurgical generator (Endocut effect 3, VIO 300D; ERBE Elektromedizin, Tübingen, Germany) with fractionated current was used for electrocautery. Thermal ablation of the resection margin was performed using snare tip soft coagulation (STSC) (ERBE VIO 300D, SOFT COAG: 80W, Effect 4; ERBE, Tübingen, Germany). The resected tissue was retrieved by suctioning into a polyp trap or collection with a roth-net.

For C-EMR, following submucosal injection, snare excision was performed with a dedicated stiff thin-wired cold snare (Boston Captivator 10mm). A 3 mm rim of normal mucosa surrounding the polyp was excised and any residual adenoma re-resected to obtain complete resection of the lesion. Resected tissue was retrieved by suctioning into a polyp trap.

Defects were inspected to assess for deep mural injury (DMI).¹⁵ Areas of significant injury (DMI II-V) were treated with mechanical clip closure. Intraprocedural bleeding (IPB) was treated with STSC, haemostatic forceps or clip closure. Although evidence for defect closure in the right colon emerged following the study's inception, to minimise bias, this was not routinely conducted during H-EMR procedures for bleeding prophylaxis. As per standard practice at study commencement, lesions deemed high risk of CSPEB based on defined risk factors were prophylactically closed at endoscopist discretion.¹⁸

Resection specimens were evaluated by specialist gastrointestinal pathologists. After completion of the procedure, patients were observed for 4 hours. If well, they were discharged on a clear fluid diet overnight. For patients who had their anti-thrombotic therapy withheld prior to EMR, they were instructed to recommence after 48 hours. Post procedure care was identical for both treatment arms.

Clinical follow up and endoscopic surveillance

At 14 days, all patients irrespective of intervention received were contacted by a study coordinator and underwent a structured telephone interview to identify peri-procedural

adverse events. Medical records were also interrogated to identify readmission for adverse events and record subsequent management. Patients and investigators were not blinded to the intervention received as this was documented on procedural reports.

First surveillance colonoscopy (SC1) was performed 6 months following index resection and scars optically evaluated under high-definition white-light and narrow-band imaging (NBI) with meticulous photo documentation. Proceduralists were not blinded to the intervention received during scar examination. Biopsies were subsequently taken of bland scars to confirm the absence of recurrence. Residual or recurrent adenoma (RRA) when identified, was treated with either hot snare excision or cold biopsy forcep avulsion with adjuvant STSC (CAST).³⁴

Study definitions and endpoints

Baseline patient demographics were collected including age, gender, and American Society of Anaesthesiologists (ASA) classification. LNPCPs characteristics included Paris classification, surface granularity (granular vs non-granular), size, location, and histopathological diagnosis. Intra-procedural data was recorded including adverse events. IPB was defined as oozing or spurting blood loss for >60 seconds, not responding to water jet irrigation and requiring either STSC, coagulation forceps, or mechanical haemostasis. Significant DMI was defined as grade II-V.

The primary outcome was endoscopically visible and/or histologically confirmed RRA identified in the EMR scar at SC1. Secondary outcomes included technical success and adverse events of clinically significant post-EMR bleeding (CSPEB) and delayed perforation. CSPEB was defined as any bleeding that occurred after the procedure with either a haemoglobin drop, hospital admission, or re- intervention (endoscopy, angiography, surgery) within 14 days. Delayed perforation was defined as the clinical syndrome of pain after EMR with imaging or surgical evidence of full-thickness injury to the colorectal wall.

Statistical Analysis

Initial sample size calculations utilised recurrence rates of 7% in conventional EMR vs 14% for C-EMR. Using a 2-sided alpha of 0.05 and power of 80%, the sample size initially

required was 300 lesions each arm. Following study commencement, real-world recurrence data from our centre was published demonstrating RRA of 1.4%.¹¹ Sample size calculations were subsequently adjusted to reflect recurrence rates of 2% in conventional EMR. Using a 2-sided alpha of 0.05 and power of 80%, a reduced sample size of 79 lesions each arm was calculated. An additional ~10% of cases were added to account for patient dropout during the study period.

IBM SPSS Statistics 27.0 software (SPSS Inc, IBM Corp, New York, NY) was used for statistical analyses. Two tailed tests with a significance level of 5% were used throughout. Continuous variables are summarized as mean with standard deviation or median with interquartile range (IQR) depending on distribution. Categorical variables were described using frequencies. Primary analysis was performed based on intention-to-treat (ITT) principles. Subsequent per-protocol (PP) analysis considered whether the actual assigned treatment was performed.

Primary and secondary outcomes were expressed as absolute and relative risks with 95% confidence intervals and compared using chi-square or Fisher's exact tests as appropriate. Due to the low event rate, multivariate regression analysis was not sufficiently powered to identify predictors of RRA.

Results

Cohort characteristics

A total of 931 LNPCPs were referred for endoscopic resection over 46 months between November 2019-September 2023. 180 LNPCPs met eligibility criteria in accordance with the study protocol. Three patients were inappropriately randomized on two occasions and these lesions excluded. 87 lesions were randomized to the C-EMR arm and 90 to the H-EMR arm. Mean patient age was 68±9.98 with 53.1% male and 81.3% ASA Class II. Median lesion size was 30mm (IQR 25-35mm) with a predominant granular (55.4%) Paris 0-IIa morphology (94.4%). The majority (63.8%) of lesions were located in the ascending colon/caecum. Baseline characteristics between treatment arms are summarised in Table 1.

Technical success

Technical success was equivalent with no significant difference between treatment arms (C-EMR 86/87 (98.9%) vs H-EMR 90/90 (100%); $p=0.31$). A single C-EMR procedure performed on a 40mm, granular Paris 0-IIa, caecal lesion required conversion to H-EMR due to unexpected submucosal fibrosis.

Recurrence at first colonoscopy surveillance (SC1)

146 LNPCPs undertook SC1 (76 C-EMR, 70 H-EMR). In the C-EMR arm four patients were ineligible for surveillance colonoscopy (two due to synchronous cancers and two for significant comorbidities). In the H-EMR arm two patients were ineligible due to comorbidities, two patients underwent surgery for unexpected poor prognostic SMIC in the resected specimen and one patient required surgery for a delayed perforation. Two patients in the H-EMR cohort died prior to undertaking surveillance due to conditions unrelated to the EMR procedure (cerebral malignancy and neurodegenerative disease). Of those patients eligible for surveillance, 10 were lost to follow up (4 C-EMR arm, 6 H-EMR arm). Three patients declined/cancelled follow up surveillance procedures (1 C-EMR arm, 2 H-EMR arm).

On intention to treat analysis, recurrence was significantly greater in the C-EMR arm 16/87 (18.4%) compared to the H-EMR arm 1/90 (1.1%) RR 16.6, 95%CI 2.24-122; $p<0.001$). On per protocol analysis, crude rates were higher, with recurrence in C-EMR in 16/76 (21.1%) compared to 1/70 (1.4%) in the H-EMR arm ($p<0.001$). All recurrences were diminutive and successfully treated endoscopically with no complications.

C-EMR recurrences were predominately caecal location (7/16 (43.8%)) with a granular (11/16 68.8%) Paris 0-IIa (100%) morphology (Table 2). Median lesion size was 35mm (IQR 30-40mm). Only 3 lesions under 30mm in size demonstrated recurrence with cold EMR.

Clip closure, deep mural injury and bleeding complications

Clip closure was performed as per standard practice in 40 cases (1 C-EMR arm, 39 H-EMR arm). Indications for clipping included significant DMI (II-V), persistent intraprocedural bleeding or patients deemed high risk for CSPEB based on defined predictors.¹⁸

An isolated case of intraprocedural bleeding in the C-EMR arm was successfully treated with clip closure. Intraprocedural bleeding was significantly greater in the H-EMR arm (12/90

(13.3%) compared to the C-EMR arm 1/87 (1.1%); $p=0.002$. Haemostasis was achieved in the H-EMR arm with STSC (9/12, 75%), coagulation forceps (2/12, 16.7%) and clip closure (1/12, 8.3%).

Significant deep mural injury (DMI II-V) was only encountered in the H-EMR arm (27/90 (30%) vs 0; $p<0.001$). All 27 cases were appropriately closed with endoscopic clips. The majority were DMI Type II (23/27, 85.2%) with 1/27 (3.7%) Type III DMI and 3/27 (11.1%) type IV.¹⁵

CSPEB was greater in the H-EMR arm (7/90 (7.8%) vs 1/87 (1.1%); RR 6.77, 95% CI 0.85-53.87; $p = 0.034$. 11 cases of clip closure in the H-EMR arm were performed for bleeding prophylaxis based on individual patient risk. A further case required clipping due to adjacent mucosal trauma. 3/7 cases of CSPEB in the H-EMR arm were clipped intraprocedurally for DMI Type II (2/3) and IPB (1/3).

Delayed perforation only occurred in the H-EMR group with an isolated case managed with surgical resection (1/90 (1.1%) vs 0; $p=0.32$).

Discussion

H-EMR is effective for the management of LNPCPs with recurrence an infrequent finding since the introduction of MTA.¹⁰⁻¹² Electrocautery driven post procedural adverse events remain problematic and may incur significant morbidity. Cold snare polypectomy demonstrates superior safety for diminutive polyps and serrated lesions, however its application to LNPCPs lacks high-quality evidence. This randomized trial has evaluated the safety and effectiveness of C-EMR in the resection of adenomatous LNPCPs.

Post-procedural bleeding and perforation may incur significant morbidity and are a limitation of conventional H-EMR for LNPCPs. A prospective series of 1172 patients identified CSPEB in 6.2% of cases with proximal colon rates of 10-12%.¹⁸ >40% of CSPEB cases require repeat colonoscopy with 37% necessitating endoscopic haemostasis.¹³ Recently demonstrated, prophylactic defect closure in the right colon is an effective preventative measure for CSPEB. A meta-analysis of four randomized trials demonstrated CSPEB in 3.5% of clipped vs 9.0% of unclipped EMR defects.²² Whilst exceedingly rare, delayed perforation is a complication requiring emergent surgical treatment with significant post-

operative morbidity and mortality.^{9, 15,16,17,35} Recognition and closure of DMI however, has made delayed perforation a largely preventable complication.^{15,17} H-EMR adverse events are largely driven by electrocautery-induced deep thermal tissue injury.³⁶⁻³⁷ In a study of 193 polypectomy specimens, submucosal resection depth with hot snares was 338 μm . In contrast, cold snare resection was shallower (76 μm), with resection layers residing in the submucosa in 9% of cases compared to 92% for hot snare resection ($p < 0.001$).³⁸⁻³⁹

In the absence of electrocautery, for polyps <15mm in size, cold snare polypectomy (CSP) is highly effective with minimal adverse events. A non-inferiority trial examining complete resection rate (CRR) demonstrated 98.2% CRR for CSP compared to 97.4% for hot snare (non-inferiority $p < 0.0001$).²⁴ A meta-analysis of 4535 polyps reported similar findings with no significant difference in CRR between CSP and HSP (OR 0.86, 95% CI 0.60-1.24).²⁷ A single centre retrospective study reported no cases of delayed bleeding for CSP in 2-11mm polyps compared to hot snare polypectomy (HSP) ($P = 0.02$).²² A randomized trial comparing HSP and CSP for polyps $\leq 10\text{mm}$ reported no delayed bleeding with CSP compared to 14% requiring endoscopic haemostasis with HSP ($P = .027$).²⁵ CSP is consequently standard of care for small polyps with increasing application to larger lesions.

Large, non-dysplastic serrated polyps are safely and effectively resected with cold snare resection. A prospective series of C-EMR in 163 large SSLs demonstrated residual polyp in one case with no CSPEB.³⁰ Similar findings were reported in a prospective series of 41 SSLs with no reported cases of CSPEB or recurrence.³¹ A comparative study for 562 large, serrated lesions found no adverse events with C-EMR with significantly greater frequency of CSPEB and DMI with H-EMR (5.1% and 3.4% respectively). No significant difference was noted for recurrence (4.3% versus 4.6%).³²

In contrast to serrated lesions, C-EMR of adenomatous LNPCPs remains poorly investigated, with data limited to observational studies. A metanalysis of eight studies and 522 polyps reported postprocedural bleeding in 0.5% (95% CI, .1%-1.2%) with no perforations. However, pooled residual rates in adenomas were 11.1% (95% CI, 4.1%-18.1%) which increased to 22% in the subgroup of polyps over 20mm in size.⁴⁰ Other retrospective series have reported recurrence rates of 11-34% which increment with growing LNPCP size.⁴¹⁻⁴²

This randomized trial has confirmed C-EMR as a technically successful technique for adenomatous LNCPs with significantly reduced rates of delayed bleeding and perforation. Within the C-EMR arm, CSPEB was present in 1/87 (1.1%) patients compared to 7/90 (7.8%) in the H-EMR arm (RR 6.77, 95% CI 0.85-53.87; $p = 0.034$). Anticoagulation was withheld periprocedurally across both treatment arms with higher anticoagulant use in the C-EMR cohort (23% vs 16.5%). Of the seven cases in the H-EMR arm, four (57.1%) required repeat colonoscopy for endoscopic haemostasis and an additional case received angio-embolization. Three cases were on anticoagulation which was appropriately withheld perioperatively. The single case of CSPEB in the C-EMR arm was on aspirin monotherapy and was managed conservatively. We recognise that during the study period, prophylactic clip closure of right colon H-EMR defects became standard of care following multiple studies demonstrating a reduction in CSPEB. To minimise bias, this practice was not universally adopted, with clip closure performed for significant deep mural injury (II-V), intraprocedural bleeding or risk factors for delayed CSPEB (as was standard practice at trial inception). Clip closure was utilised for 40 cases (1/40 C-EMR arm, 39/40 H-EMR arm) with 12/39 H-EMR closures performed for bleeding prophylaxis. We recognise such practices may have lowered the prevalence of CSPEB in the H-EMR cohort and masked an even larger difference in delayed bleeding between treatment arms.

Delayed perforation was rare in this study with only one case in the H-EMR arm 1/90 (1.1% vs 0; $p=0.32$). This lesion demonstrated type II DMI which was prophylactically clipped. Within 24 hours post-procedure the patient re-presented with abdominal pain and radiological evidence of localised perforation. Following failure of conservative management, a laparotomy and right hemicolectomy was conducted. The patient was discharged after a 16-day admission.

Despite its superior safety, this study has demonstrated endoscopic recurrence to be significantly greater with C-EMR and a limitation of the technique. Historically conventional H-EMR was limited by recurrence rates exceeding 13% (13.8%, 95% CI 12.9% to 14.7%).⁹ Whilst endoscopically treatable, this was at the cost of an increased procedural burden.³⁴ MTA has been transformative to H-EMR practice, with recurrence in <5% of cases.^{10,11,12} Within this trial, one case of recurrence in the H-EMR arm reflects previous studies, with C-EMR demonstrating recurrence at a significantly greater rate on intention to treat analysis

16/87 (18.4%) compared to H-EMR 1/90 (1.1%) (RR 16.6, 95%CI 2.24-122; p<0.001). All cases were diminutive foci which were managed endoscopically.

Before the introduction of MTA in conventional EMR, LNPCP size ≥ 40 mm, IPB, and high-grade dysplasia were identified as independent predictors of recurrence.⁴³ Whilst there were not enough recurrence events to power a multivariate analysis in this study, there is indications that similar predictors are present in the C-EMR cohort. Recurrence was predominately observed in larger LNPCPs with 13/16 cases ≥ 30 mm in size. Furthermore, while C-EMR did not demonstrate significant IPB requiring adjuvant haemostasis techniques, compared to H-EMR, mild venous ooze is consistently observed which interferes with defect visualisation and accurate characterisation of resection margins.

The success of MTA in H-EMR suggests recurrence is a consequence of microscopic adenoma within peripheral margins. Previously, no significant difference has been demonstrated in specimen muscularis mucosa for both CSP and HSP (96% vs 92%; p=0.603).⁴⁴ CSP however, frequently demonstrates incomplete resection at defect margins within biopsy specimens.^{24-25,45} Whether MTA will be as effective in C-EMR is unknown and a focus for future studies.

The findings of this study emphasise that despite C-EMR demonstrating infrequent adverse events, recurrence is significantly greater compared to conventional H-EMR. C-EMR may be considered for individual cases where adverse events are unacceptable including, medical comorbidities, geographical isolation or anticoagulation use. Superior safety however does not justify universal implementation of the technique. A recent economic study comparing C-EMR vs H-EMR suggest the safety of C-EMR positions it as the more cost-effective modality. There were several limitations to this study, however. The cost difference was largely driven by the absence of routine prophylactic clip-closure with C-EMR. In contrast to recommended practice, all H-EMR procedures underwent defect closure for bleeding prophylaxis and surveillance colonoscopy was not increased if recurrence was detected. Furthermore, recurrence in H-EMR was 5% which exceeded real world figures of <2%. Further economic analyses with accurate C-EMR data are required to definitively understand the financial impact of this technique.

This study is not without limitations. Firstly, the trial was conducted at a tertiary centre with expert endoscopists trained in endoscopic resection. We recognise that the low recurrence rates experienced with H-EMR may not be reproducible in other centres. Secondly, Paris 0-Is lesions and locations of ICV, AO and ARJ are not represented in this cohort. Bulky lesions are less likely to be effectively transected without electrocautery and the ICV, AO and ARJ represent unique locations with individual technical challenges and recurrence rates. Finally, the single-centre study design and small numbers made identification of predictors of recurrence statistically challenging. Future larger studies are required to explore predictors of recurrence within C-EMR cohorts.

In conclusion, compared to H-EMR, C-EMR for flat, adenomatous LNPCPs, demonstrates superior safety with equivalent technical success. These advantages, however, are at the cost of significantly increased endoscopic recurrence for C-EMR. Currently this is a significant limitation of the technique requiring further investigation of both predictors and preventative measures.

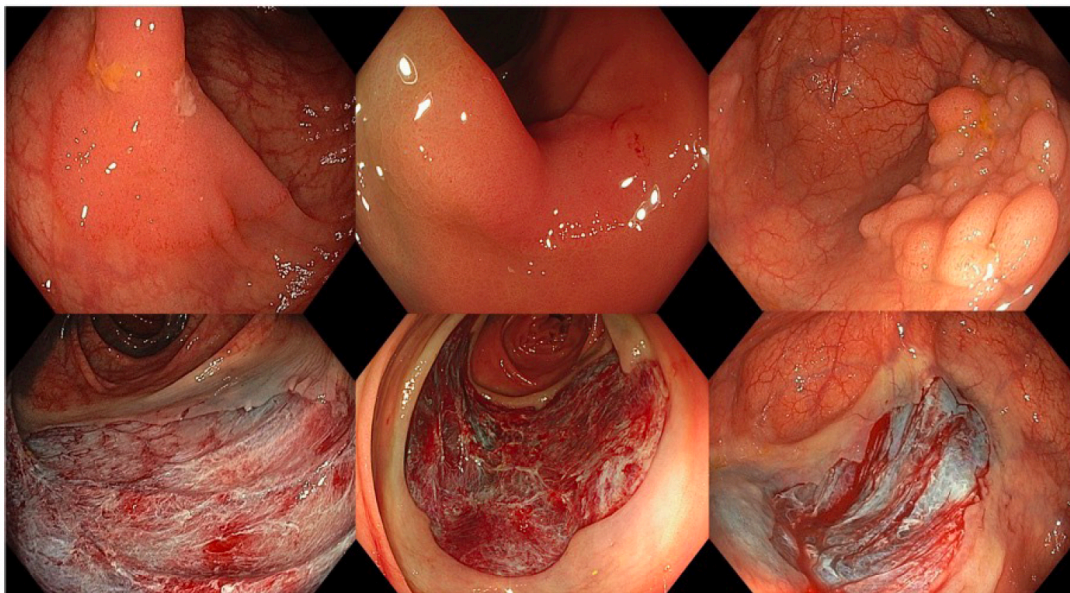
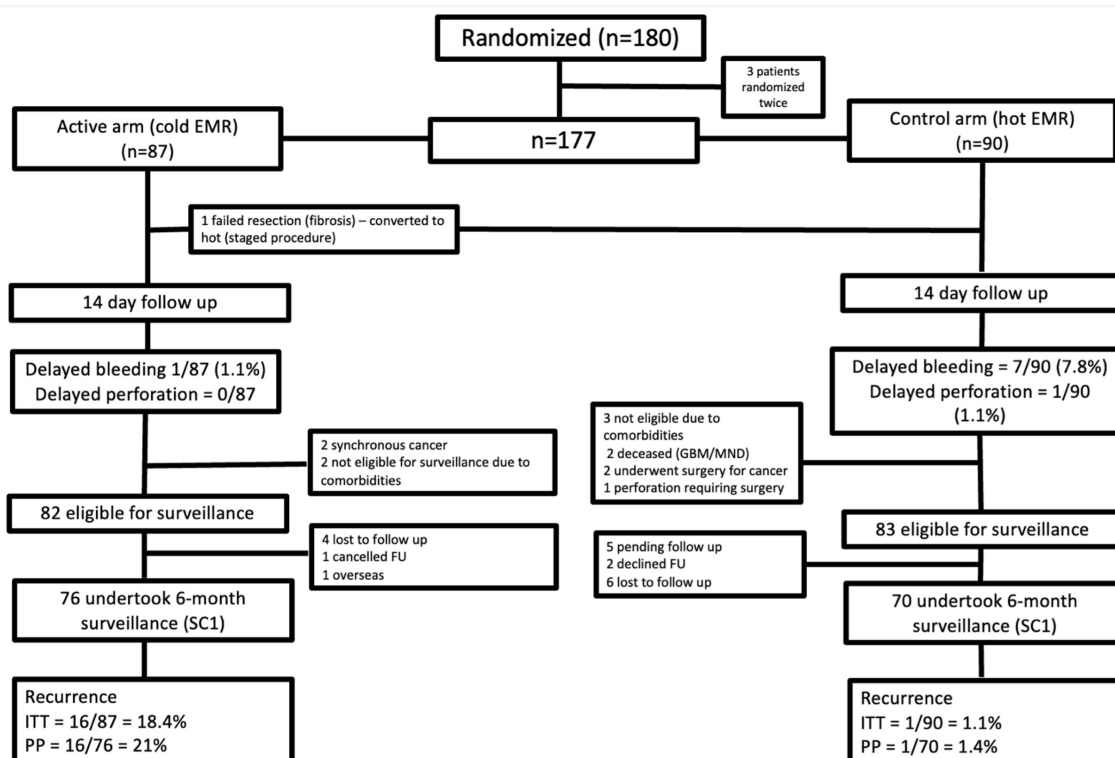


Figure 1 Wide margin cold endoscopic mucosal resection technique for adenomatous large non-pedunculated colon polyps.

Figure 2 Study enrolment flow diagram



EMR, endoscopic mucosal resection; ITT, Intention to treat; PP, per-protocol; SC1, first surveillance colonoscopy, FU, follow up.

Table 1: Baseline characteristics of study cohort

	Active arm (Cold) = 87	Control arm (Hot) = 90
Age (SD)	69.1 +/- 9.87	67.3 +/- 10.1
Gender		
Male	43 (49.4%)	52 (57.1%)
Female	44 (50.6%)	39 (42.9%)

ASA		
I	7 (8.1%)	9 (10%)
II	71 (82.6%)	72 (80%)
III	8 (9.3%)	9 (10%)
Size (mm) IQR	30 (25-40)	30 (25-35)
Location		
Rectum	3 (3.4%)	3 (3.3%)
Sigmoid	0	3 (3.3%)
Descending	0	6 (6.7%)
Transverse	26 (29.9%)	23 (25.6%)
Ascending	24 (27.6%)	24 (26.7%)
Caecum	34 (39.1%)	31 (34.4%)
Paris Classification		
0-Is	0	2 (2.2%)
0-IIa/IIb	82 (94.3%)	85 (94.4%)
0-IIa + Is	5 (5.7%)	3 (3.3%)
Morphology		
Granular	46 (52.9%)	52 (57.8%)
Nongranular	37 (42.5%)	36 (40%)
Mixed	4 (4.6%)	2 (2.2%)
Histology		
Low grade dysplasia	79 (90.8%)	79 (87.8%)
High grade dysplasia	8 (9.2%)	11 (12.2%)
SMIC	0	2 (2.2%)
Successful EMR	86 (98.9%)	90 (100%)
IPB	1 (1.1%)	12 (13.3%)
DMI		
I	0	2 (2.2%)
II	0	23 (25.6%)
III	0	1 (1.1%)
IV	0	3 (3.3%)

Clip closure	1 (1.1%)	39 (43.3%)
Anticoagulant use	20 (23%)	15 (16.7%)

Anaesthesiologists Classification; SMIC, submucosal invasive cancer;

Table 2 Lesion characteristics of C-EMR recurrences

Characteristics	N = 16 (%)
Size (median; IQR)	35mm (30-40mm)
Location	
Transverse	5 (31.3%)
Ascending	4 (25%)
Caecum	7 (43.8%)
Paris 0-IIa	16 (100%)
Morphology	
Granular	11 (68.8%)
Nongranular	5 (31.3%)
High grade dysplasia	1 (6.2%)
IPB	1 (6.3%)
DMI	0 (0%)

Chapter 4 - The geometry of cold snare polypectomy

Publication:

Cronin O, Kirzenblat D, Forbes N, O'Sullivan T, Whitfield A, Gupta S, Burgess NG, Bourke MJ. The geometry of cold snare polypectomy. Endoscopy 2024 Mar;56(3):214-219.

In brief:

- Polyp area increases quadratically with increasing polyp radius.
- Resection error rate (RER) is more important for piecemeal-cold snare polypectomy (P-CSP) than with hot snare polypectomy (HSP).
- Rate of incomplete resection (RIR) increases with the number of snare resections.

Contribution:

- This study highlights that RER is more important with p-CSP than with HSP.
- Incomplete resection rates are higher with P-CSP than HSP
- The benefits of p-CSP may begin to be outweighed by the risk of incomplete resection for polyps >30-40mm
- Techniques specific to P-CSP as well as innovations to endoscopic resection equipment need to be studied and developed.

The Geometry of Cold Snare Polypectomy.

Authors: Oliver Cronin MBBS^{1,2}, David Kirszenblat PhD³, Nauzer Forbes MD⁴, Sunil Gupta MD^{1,2}, Anthony Whitfield MBBS^{1,2}, Timothy O'Sullivan MBBS^{1,2}, Julia Gauci MD^{1,2}, Muhammad Abuarisha MD^{1,2}, Hunter Wang MBBS^{1,2}, Eric Lee MBBS^{1,2}, Stephen Williams MBBS^{1,2}, Nicholas G Burgess MBChB^{1,2}, Michael J Bourke MBBS^{1,2}.

1. Westmead Hospital, Department of Gastroenterology and Hepatology, Sydney, New South Wales, Australia
2. Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia
3. Department of Mathematics, University of Melbourne, Melbourne, Australia.
4. University of Calgary, Calgary, Canada.

Corresponding Author:

Michael J. Bourke MBBS FRACP

Clinical Professor of Medicine

Westmead Hospital, Department of Gastroenterology and Hepatology

University of Sydney, Westmead Clinical School

Suite 106a 151-155 Hawkesbury Road

Sydney, New South Wales, Australia 2145

Email: michael@citywestgastro.com.au

Conflict of interest statement/Disclosures:

- Michael Bourke Research Support: Olympus Medical, Cook Medical, Boston Scientific.
- Nauzer Forbes Speaker and consultant for Boston Scientific and Pentax Medical; research support from Pentax Medical.

Financial Support

The Cancer Institute of New South Wales provided funding for a research nurse to assist with the administration of the study in Sydney, New South Wales. They had no input regarding the review design, analysis, interpretation, preparation, review or approval of the manuscript.

Authorship statements:

- Oliver Cronin Study concept and design, acquisition of data, analysis and interpretation, drafting, critical revisions, statistical analysis, approval of final manuscript.
- David Kirszenblat Acquisition, analysis and interpretation of data, approval of final manuscript.
- Nauzer Forbes Acquisition of data, approval of final manuscript.
- Sunil Gupta Acquisition of data, approval of final manuscript.
- Anthony Whitfield Acquisition of data, approval of final manuscript.
- Timothy O’Sullivan Acquisition of data, approval of final manuscript.
- Julia Gauci Acquisition of data, approval of final manuscript.
- Muhammad Abuarisha Acquisition of data, approval of final manuscript.
- Hunter Wang Acquisition of data, approval of final manuscript.
- Eric Lee Critical revision of the manuscript for important intellectual content, approval of final manuscript.

Stephen Williams Critical revision of the manuscript for important intellectual content, approval of final manuscript.

Nicholas G Burgess Critical revision of the manuscript for important intellectual content, approval of final manuscript.

Michael J Bourke Critical revision of the manuscript for important intellectual content, study supervision, approval of final manuscript.

Funding: The Cancer Institute of New South Wales provided funding for a research nurse and data manager to assist with the administration of the study. There was no influence regarding study design or conduct, data collection, management, analysis, interpretation, preparation, review or approval of the manuscript.

Data transparency statement

All data relevant to the study are included in the article.

The abstract of this study was accepted as a poster presentation at the Australian Gastroenterology Week (AGW) conference in Sydney, Australia 2022 and at Digestive Diseases Week (DDW) in Chicago, United States of America 2022.

Abbreviations

CI	Confidence interval
CRC	Colorectal cancer
CSP	Cold snare polypectomy
DMI	Deep mural injury
EMR	Endoscopic mucosal resection
HR	Hazard ratio
HSP	Hot snare polypectomy
OR	Odds ratio
p-CSP	Piecemeal cold snare polypectomy
RCT	Randomised controlled trial
RER	Resection error rate
RIR	Rate of incomplete resection
SSL	Sessile serrated lesion

Abstract

Background and Aims

Cold snare polypectomy (CSP) is safer and equi-efficacious to hot snare polypectomy (HSP) for the removal of small (<10mm) colorectal polyps. The upper limit of polyp size that can be effectively managed by piecemeal CSP (p-CSP) without an excessive burden of recurrence is unknown.

Methods

Resection error rate (RER) for CSP and HSP were calculated based on the rate of incomplete resection in the literature. Polyp area, snare size, estimated number of resections and optimal resection defect area were modelled. The rate of incomplete resection (RIR) is defined as $RIR=1-(1-p)^n$, where p is the RER and n the number of resections.

Results

Polyp area increases quadratically as polyp radius increases. Comparing a 20mm vs 40mm polyp, area is four times greater (314.16mm² vs 1256.64mm²) and the number of required resections was 3 times greater (11 vs 33, assuming 8 mm piecemeal resection pieces for p-CSP respectively). The RIR of a 40mm polyp by HSP and p-CSP were 15.1%-23% and 40.74%-60.6% respectively.

Conclusion

RER is more important with p-CSP than with HSP. RER and consequent RIR increases with increasing polyp size. Given the overwhelming safety of CSP, specific techniques to minimise the RER should be studied and developed.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide. [1] The majority of these tumours arise from colorectal polyps and colonoscopy exerts its beneficial effect by polypectomy. [2] Ideally polypectomy should be safe, efficient, cost-effective and curative. Recurrence occurs due to incomplete resection which compromises clinical outcomes and increases cost.

The overwhelming majority of colonic polyps are less than 10mm and are safely and effectively managed with en bloc or oligo-piecemeal cold snare polypectomy. The absence of electrocautery all but eliminates the risks of perforation and post-polypectomy bleeding. [3] This safety and simplicity holds appeal for resection of larger lesions which have traditionally been removed by hot snare endoscopic mucosal resection (EMR). However, the use of diathermy carries with it a small but significant risk of perforation and delayed bleeding. [4, 5]

The upper limit of lesion size where piecemeal cold snare polypectomy (p-CSP) remains clinically effective, without excessive and burdensome rates of recurrence is currently unknown. We undertook a modelling study to address this important question.

Methods

Incomplete resection rates for hot snare polypectomy (HSP) and CSP were determined after a review of relevant literature. A formal systematic review with a comprehensive electronic search strategy was not employed. Rather, targeted literature searches were conducted for publications available up to 1st June 2022. The PubMed database was searched using the following terms: “cold snare” AND polypectomy AND incomplete (n=36); “cold snare” AND polypectomy AND residual (n=37).”

There were no restrictions on the type of publication and no restriction on study size. Language was limited to English. Data extracted included: Author, journal, year of publication, polyp size, injectate used, study size, rate of incomplete resection (Supplementary Table 1).

There is a paucity of data for RIR, particularly for piecemeal p-CSP. This data included a recent large multicentre trial (n=1393) which reported a RIR of 1.5% for polyps ≤10 mm. [6] However, there is little data reporting the RIR using p-CSP for polyps >20mm. With the scarcity of relevant studies, a reasonable surrogate measure was extrapolated from the CARE study (n=110, RIR 17.3% for polyps 10-20mm). This may underestimate the actual incomplete resection rate for p-CSP given this study used HSP. [7]

Snare size and shape

A 10mm snare is assumed for CSP modelling. Resection pieces vary between 6-8mm in diameter. [8] A 15mm snare was assumed for HSP, with a resection diameter of 15mm. The snare shape has been assumed to be circular, as a surrogate for the true slightly elliptical shape of a snare.

Resection Error Rate – a cumulative risk estimate

Resection error rate (RER) is defined as the likelihood of incomplete removal of adenomatous tissue per snare resection. This cumulative rate increases with sequential snare resections during piecemeal EMR. Based on a 20mm polyp area with 3mm margin of normal tissue (530.93mm²), the number of p-CSP resections with an 8mm snare (area 50.26mm²) is 10.56. This is supported by the ‘Disc covering problem’ which estimates the smallest number of smaller discs required to cover a larger disc. [9] Clinically, this equates to 10 to 11 sequential snare resections. Dividing 17.3%, the RIR from the literature, by the number of sequential snares (10-11) the p-CSP RER is estimated at 1.57%-1.73%.

Moreover, HSP has evolved with advances such as thermal ablation of the defect margin which have greatly reduced recurrence rates. [10, 11] RIR with HSP is also likely to be lower due to the tissue destruction from the thermal penumbra of the hot snare. However, conservatively, based on the Pohl study, it is reasonable to assume an incomplete resection rate of 17.3% for a 20mm polyp. [7] A 20mm polyp resected with a 15mm hot snare, with 15mm resection pieces would require 10 resections. RER for HSP is estimated at 1.73%.

Incomplete resection rate equation

$RIR = 1 - (1 - RER)^n$, where n is the total number of resections required. This dynamic equation, accounts for the cumulative risk of missed adenoma with each piecemeal snare resection.

Data analyses

Polyp area, snare area and defect area have been estimated using $\text{Area}=\pi r^2$ (r, radius). A 3mm edge of normal tissue was added to the resection size, irrespective of polyp size. Recurrence rates have been used as a surrogate for incomplete resection. Incomplete resection rate has been assumed to be cumulative with each resection. Data were computed and graphically illustrated using Mathematica 12.3.1 (Wolfram Research) by a mathematician with expertise in mathematical modelling.

Results

Polyp area

Polyp area increases quadratically with increasing polyp radius (Figure 1). For example, the area of a 5mm, 10mm and 20mm polyp is 19.6mm², 78.5mm² and 314.2mm² respectively (Table 1, Figures 2-3). This difference is further emphasised when comparing a 30mm and 40mm polyp which have areas of 706.9mm² and 1256.6mm² respectively. With the addition of a 3mm margin of normal tissue, the area difference between a 10mm and 20mm polyp is 329.9mm² (2.6 times larger).

Resection number

Resection number is influenced by polyp area and sequential resection area (Table 1). A 20mm polyp (with a 3mm margin of normal tissue) removed by p-CSP, requires 18.8 and 10.6 resections using an 6mm vs 8mm diameter piecemeal resection size.

Incomplete resection rate

RIR is directly proportional to the number of resections, influenced by polyp size and snare area. The predicted RIR for a 20mm vs 40mm polyp removed by p-CSP with a 6mm resection size is 25.7% and 60.6% respectively. The predicted rate of incomplete resection for a 20mm vs 40mm polyp removed by p-CSP with an 8mm resection size is 15.4% and 40.7% respectively.

Discussion

It has been shown that p-CSP is safer than HSP. However, anecdotally for adenomas recurrence seems to be excessive. We undertook a mathematical modelling study to better understand the size at which recurrence from p-CSP becomes particularly burdensome. There is a paucity of data for the RIR for piecemeal CSP and HSP. After extensive review of the literature, we used contemporary data from the highest quality publications to inform our model. RIR using p-CSP for polyps >20mm was 25.7% with 6mm pieces. Using p-CSP with 8mm pieces, the 20mm RIR was 15.4% and comparable to the pre-thermal ablation recurrence rates prior to thermal ablation of the margin. However, as size increased RIR for p-CSP became excessive at >40% for lesions ≥ 40 mm.

The risk profile of CSP is clearly advantageous. Delayed bleeding and perforation are extremely rare events. The mitigation of bleeding risk is also very appealing in an era where anticoagulant and antiplatelet agents are common. The safety profile of CSP has been demonstrated in a large retrospective study (n=562) that compared conventional EMR to p-CSP for resection of large ≥ 20 mm sessile serrated lesions (SSLs). [12] There were no adverse events reported in the p-CSP group compared to delayed bleeding and significant deep mural injury (Sydney classification type 3-5) [4] in the EMR group of 5.1% (n=18) and 3.4% (n=12) respectively. Technical success was 100% in both groups and recurrence at 18 months were similarly low at <2%. [13]

Paradoxically, despite the excellent safety profile of p-CSP, there is a hesitancy to resect wide margins of normal tissue potentially leading to higher recurrence rates. Without meticulous attention to ensure sequential snare overlap, there is a risk of incomplete resection with each snare resection. Each pass with the snare-wire carries a small but cumulative error rate. The RIR becomes unacceptably high when removing even larger lesions. In this study, RIR for a 40mm polyp was >40% when using an 8mm resection size and >60% when using a 6mm resection size.

Using modelling, we have demonstrated that as lesion size increases, recurrence rates disproportionately increase and become potentially unacceptably high at >40% for lesions

40mm. This indicates that current techniques or devices are inadequate to manage larger lesions in this way.

There is a lack of literature assessing the natural history of incompletely resected adenomas. Approximately one-third of post-colonoscopy CRCs are found within the same colorectal segment suggesting that these could be a result of incomplete resection [14]. Pohl and colleagues study (n=233) demonstrated a greater risk for neoplastic polyps in colon segments after incomplete polyp resection compared to segments with a prior complete resection [Odds Ratio (OR) 3.0, Confidence Interval (CI) 1.12 to 8.17]. [15] There is also no guarantee that these patients will comply with a surveillance program or that the polypectomy site will be found during surveillance procedures. For every 1% increase in adenoma detection rate, there is an associated 3% decrease in the risk of cancer (HR 0.97, 95%CI 0.96 to 0.98). [16] Moreover the financial burden of surveillance is significant.

In contrast to HSP, p-CSP relies purely on a wide resection margin and sequential snare resection overlap to prevent recurrence. Key factors in reducing recurrence rates include resecting a 2-3mm margin of normal tissue and meticulous post-resection examination of the p-CSP defect. [13, 17] Despite the development of thin wire snares (0.30mm) for CSP, in an international multicentre randomised controlled trial (RCT) (n=1393) incomplete polyp resection was similar compared to use of a thick-wire snare (0.47mm) with only a single case of post endoscopic bleeding seen in the thin-wire snare group. [6] Although high quality technique is critical to optimise outcomes, further reductions in RER are likely to be driven by advances in device design. Intraprocedural bleeding has also been identified as an independent risk factor for recurrence. [18, 19] In comparison to HSP, intraprocedural bleeding (IPB) is more frequent when using CSP therefore we suggest the use of dilute adrenaline 1:100000 added to the injectate to minimise bleeding when performing p-CSP for lesions >20mm.

Preventing recurrence is important for several reasons. Due to the fibrosis typically encountered around a recurrent polyp, resection is more challenging. [20] This increases the risk of complications and resultant morbidity. Additional health-care related costs are attributed to an often-prolonged procedure time to treat the recurrence, an increased risk of admission post-procedure as well as the need for additional procedures for ongoing

surveillance. All of this assumes that the patient is adherent to the management plan and is not lost to follow-up. Hence, techniques to reduce recurrence risk are essential.

The results of this study have several important clinical implications. Piecemeal-CSP almost eliminates the risk of post-procedural bleeding and perforation however recurrence is greatly increased in comparison to conventional EMR. Lesion location, patient frailty and co-morbidities, lesion morphology and predicted histology need to be factored into the process of selecting the appropriate resection technique which ideally would minimise complications, achieve successful lesion excision and avoid burdensome surveillance. For example, in the right colon, large non-pedunculated colonic polyps ≥ 20 mm have a 10-12% risk of post-procedural bleeding in the absence of defect closure, but many of these lesions are very large and defy current closure techniques. However, the risk of recurrence is also related to lesion size. These are some of the factors that need to be considered. These considerations usher in a new approach to colonic tissue resection which may become more individualised and bespoke.

This study has several limitations. Firstly, a targeted review of the literature rather than a systematic review was employed to estimate RER for our equation. We acknowledge this method could have biased our model. However, our modelled IRRs are consistent with recurrence rates reported in a recent systematic review. [21] Abdallah et al. reported a recurrence rate of 12.3% (3.4%-35.7%) for polyps ≥ 20 mm resected by piecemeal-cold snare polypectomy (P-CSP), derived from 4 studies. [13, 22-24] Unfortunately, recurrence rates for adenomas and sessile serrated lesions (SSLs) were not reported separately. SSLs are particularly suited to P-CSP due to their thin mucosal profile, and therefore have a lower recurrence rate, compared to adenomas. In particular, Van Hattem et al. included only SSLs (n=562, 4.3%). [13] The recurrence rate for adenomas is therefore likely higher than concluded by Abdallah et al. and more in-line with our model.

Secondly, this model assumes that each resection is an independent entity. In clinical practice however, each resection is related in varying degrees, to the previous resections. Based on current literature, accounting for this is not feasible. Thirdly, it was assumed that polyp and snare shape are circular which made calculation of area and number of resections more practical. This assumption likely underestimates the number of resections required to remove

large non-circular lesions. Fourthly, technical challenges such as difficult access and intra-procedural bleeding have not been accounted for but are likely to increase the number of resections for a lesion of any given size. Fifthly, the analysis was based on a very low incomplete resection rate which was conducted by experts who had received prior training and likely underestimates the true numerical value of RER. Other studies have reported a rate of incomplete resection of 8-10%. Finally, during p-CSP re-excision of suspicious areas may serve to reduce RIR. To what extent this occurs, and its efficacy is currently unknown and not feasible to model.

Conclusions

It is important for any endoscopist undertaking p-CSP to have a deep understanding of the fundamentals which underpin endoscopic resection technique. These include sound optical evaluation skills and a willingness to resect a wide margin with meticulous defect inspection and sequential snare overlap. This study demonstrates that the benefits of p-CSP may begin to be outweighed by the risk of incomplete resection for polyps >30-40mm. Further research is needed to develop better tools to minimise incomplete resection when using p-CSP and to understand the upper limit for p-CSP where its safety advantages become outweighed by the burden of recurrence and its sequelae.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30.
2. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet.* 1996;348(9040):1472-7.
3. Chang LC, Shun CT, Hsu WF, et al. Risk of delayed bleeding before and after implementation of cold snare polypectomy in a screening colonoscopy setting. *Endosc Int Open.* 2019;7(2):E232-e8.
4. Burgess NG, Bassan MS, McLeod D, et al. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. *Gut.* 2017;66(10):1779-89.

5. Burgess NG, Metz AJ, Williams SJ, et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. *Clin Gastroenterol Hepatol*. 2014;12(4):651-61.e1-3.
6. Sidhu M, Forbes N, Tate DJ, et al. 109 EFFICACY OF A THIN- VERSUS THICK-WIRE DIAMETER SNARE FOR COLD SNARE POLYPECTOMY – A MULTI-CENTER RANDOMIZED CONTROLLED TRIAL. *Gastrointestinal Endoscopy*. 2020;91(6):AB19-AB20.
7. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. *Gastroenterology*. 2013;144(1):74-80.e1.
8. Kudo T, Horiuchi A, Kyodo R, et al. Mucosal defect size predicts the adequacy of resection of ≤ 10 mm nonpedunculated colorectal polyps using a new cold snare polypectomy technique. *Eur J Gastroenterol Hepatol*. 2021;33(1S Suppl 1):e484-e9.
9. Weisstein E. MathWorld - A Wolfram Web Resource [Available from: <https://mathworld.wolfram.com/DiskCoveringProblem.html>].
10. Klein A, Tate DJ, Jayasekeran V, et al. Thermal Ablation of Mucosal Defect Margins Reduces Adenoma Recurrence After Colonic Endoscopic Mucosal Resection. *Gastroenterology*. 2019;156(3):604-13.e3.
11. Sidhu M, Shahidi N, Gupta S, et al. Outcomes of Thermal Ablation of the Mucosal Defect Margin After Endoscopic Mucosal Resection: A Prospective, International, Multicenter Trial of 1000 Large Nonpedunculated Colorectal Polyps. *Gastroenterology*. 2021;161(1):163-70.e3.
12. Backes Y, Schwartz MP, Ter Borg F, et al. Multicentre prospective evaluation of real-time optical diagnosis of T1 colorectal cancer in large non-pedunculated colorectal polyps using narrow band imaging (the OPTICAL study). *Gut*. 2019;68(2):271-9.
13. van Hattem WA, Shahidi N, Vosko S, et al. Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: a retrospective comparison across two successive periods. *Gut*. 2021;70(9):1691-7.
14. Belderbos TD, Pullens HJ, Leenders M, et al. Risk of post-colonoscopy colorectal cancer due to incomplete adenoma resection: A nationwide, population-based cohort study. *United European Gastroenterol J*. 2017;5(3):440-7.
15. Pohl H, Anderson JC, Aguilera-Fish A, et al. Recurrence of Colorectal Neoplastic Polyps After Incomplete Resection. *Ann Intern Med*. 2021.

16. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med*. 2014;370(14):1298-306.
17. Tutticci NJ, Kheir AO, Hewett DG. The Cold Revolution: How Far Can It Go? *Gastrointest Endosc Clin N Am*. 2019;29(4):721-36.
18. Tate DJ, Desomer L, Klein A, et al. Adenoma recurrence after piecemeal colonic EMR is predictable: the Sydney EMR recurrence tool. *Gastrointest Endosc*. 2017;85(3):647-56.e6.
19. Moss A, Williams SJ, Hourigan LF, et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut*. 2015;64(1):57-65.
20. Shahidi N, Vosko S, Gupta S, et al. Previously Attempted Large Nonpedunculated Colorectal Polyps Are Effectively Managed by Endoscopic Mucosal Resection. *Am J Gastroenterol*. 2021;116(5):958-66.
21. Abdallah M, Ahmed K, Abbas D, et al. Cold Snare Endoscopic Mucosal Resection for Colon Polyps: A Systematic Review and Meta-Analysis. *Endoscopy*. 2023.
22. Suresh S, Zhang J, Ahmed A, et al. Risk factors associated with adenoma recurrence following cold snare endoscopic mucosal resection of polyps ≥ 20 mm: a retrospective chart review. *Endosc Int Open*. 2021;9(6):E867-e73.
23. Mangira D, Cameron K, Simons K, et al. Cold snare piecemeal EMR of large sessile colonic polyps ≥ 20 mm (with video). *Gastrointest Endosc*. 2020;91(6):1343-52.
24. Piraka C, Saeed A, Waljee AK, et al. Cold snare polypectomy for non-pedunculated colon polyps greater than 1 cm. *Endosc Int Open*. 2017;5(3):E184-e9.

Figures

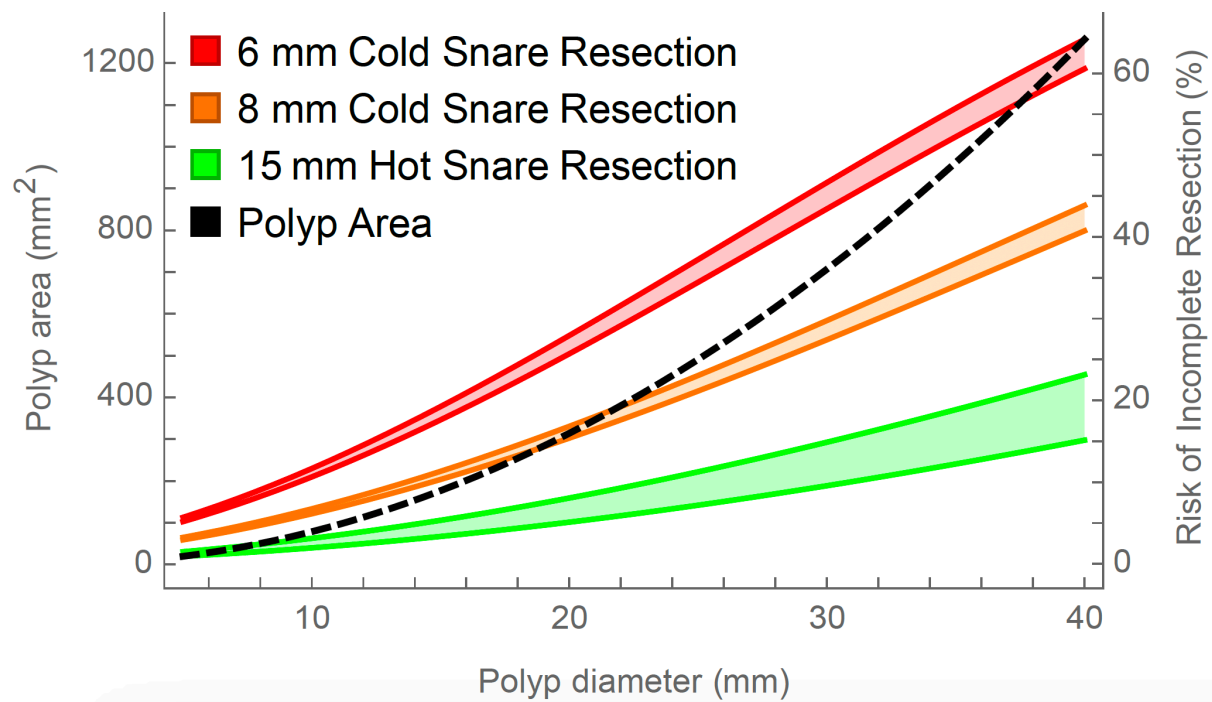


Figure 1. Risk of incomplete resection

A mathematical model demonstrating the risk of incomplete resection for cold snare polypectomy and hot snare polypectomy for increasing polyp size.

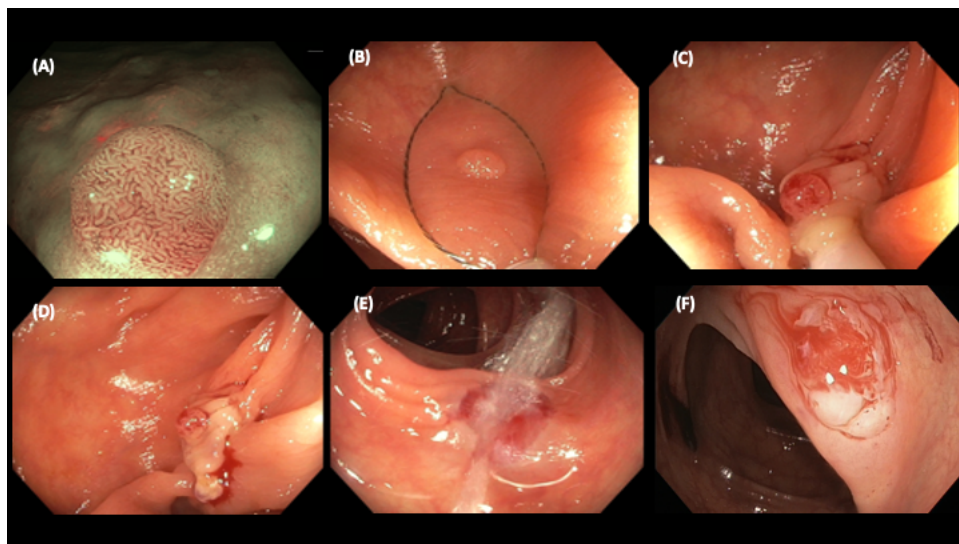


Figure 2. Cold snare polypectomy for Paris 0-IIa polyp <10mm.

(A) 3mm Paris 0-IIa colorectal adenoma; (B) en bloc R0 excision with thin wire cold snare. Note wide margin of normal mucosa with snare placement; (C) the halo effect with blanching of the surrounding mucosa and hyperaemia of the adenoma; (D) post excision halo effect; (E) water expansion of the defect; (F) Careful inspection of margin.

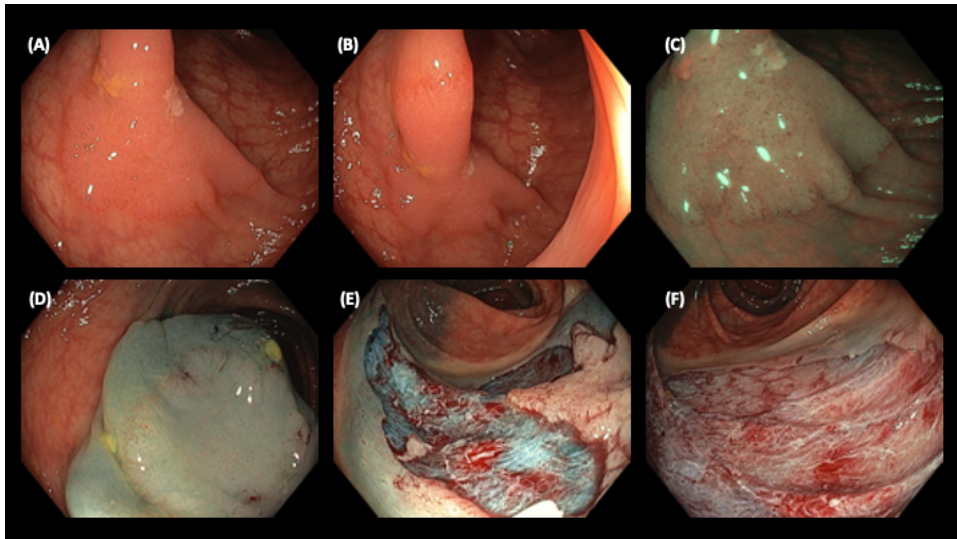


Figure 3. Piecemeal cold snare polypectomy for Paris 0-IIa lesion >20mm.

(A-C) >20mm lateral spreading lesion, examined with high-definition white light and narrow-band imaging; (D) lesion after submucosal injection; (E) piecemeal cold snare excision; (F) careful inspection of the post-resection defect margin.

Table 1. Polyp area, resection error rate and incomplete resection rate for hot and cold snare polypectomy.

<i>Polyp diameter (mm)</i>	5	10	15	20	25	30	35	40
Polyp area, mm ²	19.63	78.54	176.71	314.16	490.87	706.86	962.11	1256.64
Defect area, mm ²	95.03	201.06	346.36	530.93	754.77	1017.88	1320.25	1661.90
No. of 6mm resections	3.36	7.11	12.25	18.78	26.70	36.00	46.70	58.79
Risk of IR (RER 1.57%)	5.20%	10.60%	17.60%	25.70%	34.50%	43.40%	52.20%	60.60%
No. of 8mm resections	1.89	4.00	6.89	10.56	15.01	20.25	26.26	33.06
Risk of IR (RER 1.73%)	2.95%	6.13%	10.33%	15.39%	21.14%	27.42%	34.00%	40.74%
No. of resections with hot snare (15mm)	0.54	1.14	1.96	3.00	4.27	5.76	7.47	9.40
Risk of IR (RER 1.73%)	0.94%	1.97%	3.36%	5.10%	7.18%	9.56%	12.22%	15.13%
IR, Incomplete resection; RER, resection error rate.								

Supplementary Table 1: Literature search for residual or incomplete adenoma resection for piecemeal Cold Snare Polypectomy.

Publication	Size (mm)	pCSP (n)	IRR % (n)	RRA % (n)
Ma X, Clin Gastro Hep 2022 [1]	-	5	20.0 (1)	-
Kimoto Y, Clin Gastro Hep 2022 [2]	23 (range 18-40)	106	0.0 (0)	-
McWhinney CD, Gastrointest Endosc 2021 [3]	17.2 mean (6.5 SD)	225	-	8.0 (18)
Suresh S, EIO 2021 [4]	29.4 (range 20-80)	310	-	34.8 (108)
Augusto Barros, R EIO 2021 [5]	13.7 mean (5.2 SD)	293	-	7.8 (23)**
Li D, Scand J Gastro 2020 [6]	-	176	-	31.3 (55)***
van Hattem A, Gut 2020 [7]	25 (IQR 20-30)	92	-	4.3 (4)
Mangira D, Gastrointest Endosc 2020 [8]	20 (IQR 20-30)	164	-	5.5 (9)
Van Overbeke L, AGEB 2019 [9]	-	87	-	10.3 (9)****
Tate DJ, Endoscopy 2018 [10]	15.0 (IQR 14.5-20)	15	-	0.0 (0)
Tutticci NJ, Gastrointest Endosc 2018 [11]	17.5 mean 15.0 median	163	1.2 (2)	-

Tutticci NJ, Gastrointest Endosc 2018 [11]	17.5 mean 15.0 median	134	-	0.6 (1)
Rameshshanker R, Endoscopy 2018 [12]	15.7 mean	29	-	3.4 (1)
Piraka C, EIO 2017 [13]	20.0 (range 12-60)	72	-	9.7 (7)
Muniraj T, Gastro Res Prac 2015 [14]	19.0 (8.8 SD)	30	-	20.0 (6)

Literature search terms: "cold snare" AND polypectomy AND incomplete; "cold snare" AND polypectomy AND residual.

Size, mean diameter of lesions removed via pCSP; pCSP, piecemeal Cold Snare Polypectomy; IRR, Incomplete Resection Rate, measured according to biopsies of edges taken at the time of resection; RRA, Residual or Recurrent Adenoma rate, measured at first surveillance colonoscopy.

1. Ma X, Feng X, Li Y, Du Y, Wang J, Wu Y, et al. A Comparison of Incomplete Resection Rate of Large and Small Colorectal Polyps by Cold Snare Polypectomy. *Clin Gastroenterol Hepatol.* 2022;20(5):1163-70.
2. Kimoto Y, Sakai E, Inamoto R, Kurebayashi M, Takayanagi S, Hirata T, et al. Safety and Efficacy of Cold Snare Polypectomy Without Submucosal Injection for Large Sessile Serrated Lesions: A Prospective Study. *Clin Gastroenterol Hepatol.* 2022;20(2):e132-e8.
3. McWhinney CD, Vemulapalli KC, El Rahyel A, Abdullah N, Rex DK. Adverse events and residual lesion rate after cold endoscopic mucosal resection of serrated lesions ≥ 10 mm. *Gastrointest Endosc.* 2021;93(3):654-9.
4. Suresh S, Zhang J, Ahmed A, Abu Ghanimeh M, Elbanna A, Kaur R, et al. Risk factors associated with adenoma recurrence following cold snare endoscopic mucosal resection of polyps ≥ 20 mm: a retrospective chart review. *Endosc Int Open.* 2021;9(6):E867-e73.

5. Barros RA, Monteverde MJ, Dumonceau JM, Barros AS, Rainero GL, Barros RF, et al. Cold snare polypectomy without submucosal injection: safety and efficacy in 615 large serrated lesions. *Endosc Int Open*. 2021;9(9):E1421-e6.
6. Li D, Wang W, Xie J, Liu G, Wang R, Jiang C, et al. Efficacy and safety of three different endoscopic methods in treatment of 6-20 mm colorectal polyps. *Scand J Gastroenterol*. 2020;55(3):362-70.
7. van Hattem WA, Shahidi N, Vosko S, Hartley I, Britto K, Sidhu M, et al. Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: a retrospective comparison across two successive periods. *Gut*. 2021;70(9):1691-7.
8. Mangira D, Cameron K, Simons K, Zanati S, LaNauze R, Raftopoulos S, et al. Cold snare piecemeal EMR of large sessile colonic polyps ≥ 20 mm (with video). *Gastrointest Endosc*. 2020;91(6):1343-52.
9. Van Overbeke L, Ilegems S, Mertens G, Mortier L, van Dongen J, Verbeke L, et al. Cold snare endoscopic resection of nonpedunculated colorectal polyps larger than 10 mm. A retrospective series. *Acta Gastroenterol Belg*. 2019;82(4):475-8.
10. Tate DJ, Awadie H, Bahin FF, Desomer L, Lee R, Heitman SJ, et al. Wide-field piecemeal cold snare polypectomy of large sessile serrated polyps without a submucosal injection is safe. *Endoscopy*. 2018;50(3):248-52.
11. Tutticci NJ, Hewett DG. Cold EMR of large sessile serrated polyps at colonoscopy (with video). *Gastrointest Endosc*. 2018;87(3):837-42.
12. Rameshshanker R, Tsiamoulos Z, Latchford A, Moorghen M, Saunders BP. Resection of large sessile serrated polyps by cold piecemeal endoscopic mucosal resection: Serrated COld Piecemeal Endoscopic mucosal resection (SCOPE). *Endoscopy*. 2018;50(7):E165-e7.
13. Piraka C, Saeed A, Waljee AK, Pillai A, Stidham R, Elmunzer BJ. Cold snare polypectomy for non-pedunculated colon polyps greater than 1 cm. *Endosc Int Open*. 2017;5(3):E184-e9.
14. Muniraj T, Sahakian A, Ciarleglio MM, Deng Y, Aslanian HR. Cold snare polypectomy for large sessile colonic polyps: a single-center experience. *Gastroenterol Res Pract*. 2015;2015:175959.

Chapter 5 - A Comparison of the Morphology and Histopathology of Large Non-Pedunculated Colorectal Polyps in the Rectum and Colon: Implications for Endoscopic Treatment

Publication:

Cronin O, Sidhu M, Shahidi N, Gupta S, O'Sullivan T, Whitfield A, Wang H, Kumar P, Hourigan L, Byth K, Burgess NG, Bourke MJ. Comparison of Morphology and Histopathology of Polyps in the Rectum and Colon. *Gastrointestinal Endoscopy*, 2022 July; 96(1):118-24.

In brief:

- Large non-pedunculated colorectal polyps (LNPCPs) in the rectum are more likely to be larger, granular and have a nodular component compared to non-rectal LNPCPs. Rectal lesions are more likely to have tubulovillous histopathology and contain cancer.

Contribution:

- Lesion location predicts cancer risk and therefore should be included in any endoscopic resection algorithm, to inform resection technique.
- Larger, nodular LNPCPs within the rectum have the greatest risk of containing cancer.
- These lesions should be removed en bloc to achieve an R0 resection.

Title: A Comparison of the Morphology and Histopathology of Large Non-Pedunculated Colorectal Polyps in the Rectum and Colon: Implications for Endoscopic Treatment

Authors: Oliver Cronin MBBS(Hons)^{1,2}, Mayenaaz Sidhu MBBS^{1,2}, Neal Shahidi MD^{1,2,3}, Sunil Gupta MD^{1,2,4,5}, Timothy O’Sullivan MBBS^{1,2}, Anthony Whitfield MBBS^{1,2}, Hunter Wang MBBS^{1,2}, Puja Kumar MD^{1,2}, Luke F Hourigan MBBS^{4,5}, Karen Byth PhD², Nicholas G Burgess MBChB^{1,2}, Michael J Bourke MBBS^{1,2}.

1. Westmead Hospital, Department of Gastroenterology and Hepatology, Sydney, New South Wales, Australia
2. Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia
3. University of British Columbia, Department of Medicine, Vancouver, British Columbia, Canada
4. Princess Alexandra Hospital, Department of Gastroenterology and Hepatology, School of Medicine University of Queensland, Brisbane, Queensland, Australia
5. Gallipoli Medical Research Foundation, Greenslopes Private Hospital, Brisbane, Queensland, Australia.

Corresponding Author:

Michael J. Bourke MBBS FRACP

Clinical Professor of Medicine

Westmead Hospital, Department of Gastroenterology and Hepatology

University of Sydney, Westmead Clinical School

Suite 106a 151-155 Hawkesbury Road

Sydney, New South Wales, Australia 2145

Email: michael@citywestgastro.com.au

Fax: +61 2 9845 5637

Conflict of Interest

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

Neal Shahidi: Honorarium: Boston Scientific, Pendopharm

The remaining authors have no conflicts of interest to disclose

Financial support

The Cancer Institute of New South Wales provided funding for a research nurse and data manager to assist with the administration of the study. The Gallipoli Medical Research Foundation provided funding and support for research at Greenslopes Private Hospital. There was no influence from either institution regarding study design or conduct, data collection, management, analysis, interpretation, preparation, review or approval of the manuscript.

Data transparency statement

All data relevant to the study are included in the article.

Author Contributions

Oliver Cronin Study concept and design, acquisition of data, analysis and interpretation, drafting, critical revisions, statistical analysis, approval of final manuscript.

Mayenaaz Sidhu Analysis and interpretation of data, statistical analysis.

Neal Shahidi Drafting of the manuscript.

Sunil Gupta Acquisition of data.

Timothy O'Sullivan Acquisition of data.

Anthony Whitfield Acquisition of data.

Hunter Wang Acquisition of data.

Puja Kumar Acquisition of data.

Luke F Hourigan Acquisition of data.

Karen Byth Statistical analysis

Nicholas G Burgess Critical revision of the manuscript

Michael J Bourke Critical revision of the manuscript, study supervision.

The abstract of this study was accepted as an oral presentation at the Australian Gastroenterology Week (AGW) conference in Sydney, Australia 2021 and as a poster presentation at Digestive Diseases Week (DDW) in San Diego, United States of America 2021.

Clinicaltrials.gov identifiers: NCT01368289; NCT02000141.

Abbreviations

ACE	Australian Colonic Endoscopic Resection
ASA	American Society of Anesthesiologists
CI	Confidence interval
CRC	Colorectal cancer
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
IQR	Interquartile range
LNPCP	Large non-pedunculated colorectal polyp ≥ 20 mm
SMIC	Submucosal invasive cancer
STARD	Standards for Reporting of Diagnostic Accuracy Studies
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

Abstract

Background and Aims

The risk of cancer in Large Non-Pedunculated Colorectal Polyps $\geq 20\text{mm}$ (LNPCPs) in the rectum relative to the remainder of the colon is unknown. We aimed to describe differences between rectal and colonic LNPCPs to better inform treatment decisions.

Methods

LNPCPs referred to tertiary centers for endoscopic resection, within a prospective, multi-center, observational cohort were evaluated. Data recorded included participant demographics, LNPCP location, morphology, resection modality and histopathological data. Multiple logistic regression analysis was used to identify those variables independently associated with rectal versus non-rectal location in the colon.

Results

LNPCPs referred for endoscopic resection between July 2008 and July 2021 were included. Rectal LNPCPs ($n=618$) were larger (median size 40mm Vs. 30mm, $p<0.001$) and more likely to be granular (79% Vs. 50%, $p<0.001$) with a nodular component (53% Vs. 17%, $p<0.001$) compared to non-rectal LNPCPs ($n=2787$). Rectal LNPCPs were more likely to have tubulovillous histopathology (72% Vs 47%, $p<0.001$) and contain cancer (15% Vs 6%, $p<0.001$). After adjusting for the other features independently associated with location, cancer was more common in the rectum compared to the colon [Odds Ratio (OR) 1.77, 95%CI 1.25-2.53].

Conclusions

This study suggests that, compared to LNPCPs in the rest of the colon, rectal LNPCPs are more likely to be larger and contain more advanced pathology. These findings have implications for curative endoscopic resection techniques particularly where early cancer is present.

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

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the burden of disease is projected to increase by 60% by 2030 (1-3). This underscores the importance of colonoscopy in the early detection of CRC and its prevention through the removal of pre-malignant polyps (4, 5). Large ($\geq 20\text{mm}$) non-pedunculated colorectal polyps (LNPCPs) are an important polyp subgroup as they are more likely to harbour cancer and therefore require a multi-disciplinary approach between organ-sparing endoscopic resection techniques and surgery (6).

The primary objectives of endoscopic resection are to achieve cure, minimise recurrence, ensure safety, avoid surgery and its attendant comorbidity and minimise unnecessary costs. Endoscopic Mucosal Resection (EMR) is the favoured technique in the colon due to its excellent performance characteristics. With site-specific technical modifications, EMR is also the favoured technique in parts of the colon that have traditionally been more challenging for resection such as the appendiceal orifice and the ileocecal valve (ICV) (7-9). However, a universal EMR approach may not be appropriate, specifically in the rectum. This is due to the ramifications of piecemeal resection of malignant LNPCPs and the associated morbidity, mortality and risk of permanent ostomy formation associated with distal colorectal surgery; which in turn has stimulated the development and application of en bloc resection techniques such as endoscopic submucosal dissection (ESD) and trans-anal endoscopic microsurgery (TEM).

Little is known about the differences between rectal versus non-rectal LNPCPs. It is important to identify differences which may influence resection technique selection and thereby impact both clinical outcomes and resource utilization. This study quantifies the differences between rectal and colonic LNPCPs to better inform current practice.

Materials and Methods

This manuscript has been prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (10, 11). All authors had access to the study data and reviewed and approved the final manuscript.

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 ≥ 20 mm. Center-specific Institutional Review Board approval is maintained at each center. Written informed consent is obtained from each participant prior to enrolment.

Between July 2008 to July 2021, consecutive participants were enrolled from three high volume ACE sites (Westmead Hospital, Princess Alexandra Hospital, Greenslopes Hospital) in Australia. All sites have an established tissue resection program which includes EMR and ESD. All endoscopic procedures were performed by one of five study investigators (accredited Gastroenterologist with advanced training and an established tertiary referral practice in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their direct supervision. EMR was performed with a standardised technique which was modified over time as technical innovations emerged (12-17).

Histopathology Evaluation

After endoscopic resection, specimens were collected and processed for histopathology review, in accordance with the Australasian Gastrointestinal Pathology Society guidelines (18). Histopathology review was completed by expert gastrointestinal pathologists, at their respective site. Cancer was defined by neoplastic invasion into the submucosa (19).

Data Extraction and Analysis

Prospectively collected data included: 1) Patient characteristics: age, sex, American Society of Anesthesiologists (ASA) classification; 2) LNPCP characteristics: location,

size, Paris classification, surface granularity, Kudo pit pattern, Submucosal Invasive Cancer (SMIC); resection technique; 3) Histopathology evaluation.

Statistical Analysis

SPSS version 27.0 (IBM Corp, Armonk, NY, USA) was used for data analysis. The continuous variables age and lesion size were summarized as median [interquartile range (IQR)] following assessment of non-normality using Shapiro-Wilk's test. Categorical variables were summarised as frequencies (%). Mann-Whitney tests were used to test for differences in continuous distributions between groups. Chi-squared tests (or exact permutation tests if required) were used to test for association between categorical variables. All variables associated with lesion location (rectal versus non-rectal) at the $p < 0.1$ level were considered as candidate variables for inclusion in multivariable models. Multiple logistic regression with backward stepwise variable selection was used to identify those candidate variables independently associated with lesion location. Odds ratios (OR) with 95% confidence intervals (CI) were used to quantify the strength of association. All analyses were exploratory and two-tailed tests with a 5% significance level were used throughout.

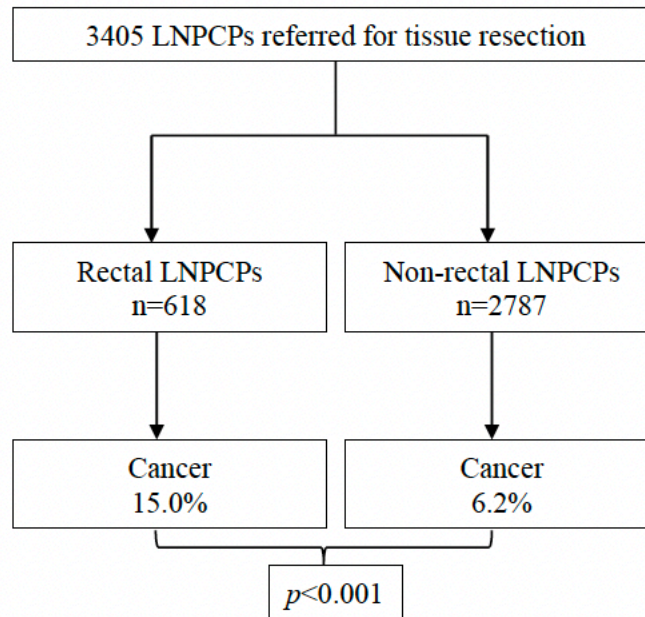
Patient and Public Involvement

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

Results

Between July 2008 and July 2021, 3405 LNPCPs in 2984 patients were referred for endoscopic resection (Figure 1). Resection was not attempted in 101 LNPCPs (3%) due to a suspicion of cancer, 7 (<1%) due to appendiceal orifice involvement; 11 (<1%) due to difficult access or position and 4 (<1%) due to ileocecal valve involvement. The majority of LNPCPs were removed by EMR (n=3258, 96%) of which 3118 (96%) had technical success, defined as complete excision of all visible adenomatous tissue.

Figure 1: Flow diagram of consecutive patients referred with LNPCPs for tissue resection.



Demographic and LNPCP Characteristics

The median age of the 2984 patients was 69 years (IQR 60-75mm) and 84% had an American Society of Anaesthesiologists score of 1 or 2. Overall, the median LNPCP size was 30mm (IQR 25-45mm). Most lesions were granular (1879, 55%) with tubulovillous histology being most common (1750, 51%).

Rectal LNPCPs were larger (median size 40mm Vs 30mm, $p<0.001$) and more likely to be granular (79% Vs. 50%, $p<0.001$) with a nodular component (53% Vs. 17%, $p<0.001$) compared to colonic LNPCPs (Table 1). They were more likely to have tubulovillous histopathology (72% Vs. 47%, $p<0.001$) As expected, rectal sessile serrated LNPCPs were infrequent totalling 6 (1%) of all rectal LNPCPs. Cancer was more common in rectal LNPCPs compared to LNPCPs in the colon (15% Vs 6%, $p<0.001$). The adjusted odds ratios and 95%CIs for those variables independently associated with rectal versus non-rectal location in the best fitting multiple logistic regression model are tabulated (Table 2). In summary, rectal LNPCPs are significantly larger, granular, nodular or mixed nodular and more frequently have advanced endoscopic pit pattern. Most importantly, they more often contain cancer (adjusting OR 1.77, 95%CI 1.25 – 2.53).

Discussion

The rectum and colon are in a digestive continuum and any contained pathology has been generally considered and managed uniformly. Accordingly, until very recent times all colorectal LNPCPs have been generally subjected to the same endoscopic treatment algorithm, regardless of location. The tendency for rectal LNPCPs to have more advanced characteristics has strong implications for therapeutic decision making.

Previously, many endoscopists from non-specialist tissue resection centers have felt comfortable with resection of rectal LNPCPs. Options for resection include EMR, ESD, transanal minimally invasive surgery (TAMIS) or transanal endoscopic surgery (TES) although EMR is the most commonly employed technique (20-24). Endoscopic resection has been demonstrated to have the lowest lifetime cost relative to the other resection modalities for removal of rectal LNPCPs. (25) Non-specialised Endoscopists seem more willing to tackle a rectal LNPCP than a LNPCP at a site perceived as traditionally more challenging such as the ICV. The perceived safety of extraperitoneal rectum and the reduced risk of serious sequelae from perforation may embolden the decision making. This logic is flawed. The risk of cancer within a rectal LNPCP is greater and the consequences of failed endoscopic cure include consideration of the most hazardous and complicated forms of colorectal surgery including permanent ostomy formation (26). The rectum should be regarded as a complex high-risk site, not due to its technical limitations but due to its increased risk of cancer and the implications for incomplete resection.

Our findings reflect significant differences of LNPCPs in the rectum compared to the remainder of the colon. Rectal LNPCPs are more likely to be larger and have villous or tubulovillous histology. Rectal LNPCPs are more likely to have a nodular component and contain High Grade Dysplasia (HGD) or cancer. These fundamental differences have strong implications for endoscopic management decisions (20).

This study found that rectal LNPCPs are more likely to have a nodular component compared to LNPCPs in the colon. By their nature, LNPCPs with a nodule are more likely to contain SMIC (14, 27). Supporting this notion, a prospective multi-center

observational study that assessed optical evaluation to predict cancer in LNPCPs found independent predictors for missed SMIC were size ≥ 40 mm, nodular morphology and distal location (28). In a systematic review and meta-analysis, LNPCPs with SMIC were more commonly located in the distal colon compared to the proximal colon [Odds Ratio (OR) 2.5, 95% Confidence Interval (CI) 1.2-5.0] (29). Therefore, rectal LNPCPs with a nodular (Paris 0-Is) component or optical features concerning for SMIC require en bloc resection.

It has previously been suggested that optical evaluation for SMIC in LNPCPs has limitations (30). This study (n=343) observed that during optical assessment of endoscopically unresectable LNPCPs ($\geq T1$ Stage CRC), specificity was good (94%) but sensitivity was lower (79%). More recently, the ACE consortium (n=1583) reported similar rates of specificity (95%) and sensitivity (67%) (28). However, they found significant differences when optical evaluation performance was stratified by morphology. There was a greater sensitivity (91% Vs 53%, $p < 0.027$) and specificity (96% Vs 94%, $p < 0.027$) when comparing flat to nodular LNPCPs. Optical evaluation performance is therefore dependent on LNPCP morphology. The inherent challenges of accurate optical assessment of bulky LNPCPs have previously been published (14). Nodular morphology and larger size were associated with SMIC (14). We have found that LNPCPs with these features are more common in the rectum. This knowledge is important when planning resection, in terms of allowing more time for assessment and is relevant for endoscopy list planning (31).

Advanced histology is more common in rectal LNPCPs. Villous histology and HGD are independent risk factors for LNPCP recurrence (32-34). Regardless of whether rectal LNPCPs are resected en bloc or piecemeal, best practice endoscopic resection techniques such as margin ablation by Snare Tip Soft Coagulation (STSC) should be used to reduce recurrence risk (17, 35, 36).

This study found that cancer was more common in rectal LNPCPs. The risk of local recurrence of early rectal cancer is higher than for early colon cancer when treated with endoscopic resection alone (37). EMR is the accepted first line technique for LNPCPs (20, 21) but this technique may not achieve cure for LNPCPs containing

SMIC. ESD offers inherent advantages over EMR including reliable en bloc resection which allows for improved histologic resection completeness and potential cure of LNPCPs containing SMIC (38). Previous studies have demonstrated that selective resection algorithms for LNPCPs should be applied given the significant costs and resource utilisation associated with ESD relative to EMR as well as the higher required skill level (39, 40). Specific rectal LNPCP resection algorithms are needed given the increased risk of SMIC containing LNPCPs.

The ramifications for a sub-optimally managed rectal LNPCP could be considered greater in the rectum compared to the colon. Generally, surgery in the distal colon and rectum is associated with greater risk relative of morbidity compared to a right hemicolectomy (26, 41, 42). Patients with rectal lesions removed by a low or ultra-low anterior resection have an increased risk of incontinence (12%) (43), sexual dysfunction (20-46%) (44) and a 10-20% risk of permanent stoma (45, 46). Low anterior resection has a 30 day morbidity and mortality of 25% and 6% respectively (47). Our data suggests there should be a difference in the resection algorithm for rectal LNPCPs given their higher risk of SMIC, which may lead to reduced rates of incomplete resection, and thus a reduced need for surgery. Improved knowledge of predicting cancer and SMIC risk allows for a greater likelihood of successful resection on the first occasion leading to improved outcomes for patients as well as significant cost savings (39, 48-50).

Interestingly, within the rectum, the Anorectal Junction (ARJ) is a unique environment in which the risk of SMIC is low. A recent prospective observational study found that cancer rate at the ARJ was low (3%, n= 100) (24). Of note, there was no recurrence at Surveillance Colonoscopy 1 (SC1) for LNPCPs that were treated with STSC post resection (17, 24, 35). EMR can therefore be considered as a first line technique for the majority of ARJ-LNPCPs.

A limitation of this study is that patients were not randomised and were from an expert group which may limit the generalizability of the results. However, to our knowledge, this is the only published dataset comparing LNPCPs in the rectum to the rest of colon.

In conclusion, amongst a large multi-center observational cohort, rectal LNPCPs were more likely to be larger, granular, nodular with a villous component; and more frequently contained HGD and cancer. This data adds critically important insights to inform endoscopic treatment selection and enhance clinical outcomes for rectal LNPCPs. Through scientific research, resection guidelines for LNPCPs of the colon have largely been established, EMR is justifiably the predominant strategy (51, 52). The rectum is a different organ and should be regarded as a specialised site due to its increased risk of SMIC as well as the potential for significant sequelae should the endoscopic treatment be incomplete. Our data indicate that given this complexity, rectal LNPCPs should be managed at specialised tissue resection sites. To achieve the best patient outcomes, the ability to undertake ESD would appear to be a necessary requirement for those endoscopists performing endoscopic resection in the rectum. ESD should be the favoured technique for rectal LNPCPs considered at any risk for harbouring SMIC. Further research is needed to develop rectum specific resection algorithms.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65(2):87-108.
3. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut.* 2017;66(4):683-91.
4. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology.* 2008;134(5):1570-95.
5. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet.* 1996;348(9040):1472-7.

6. Rotondano G, Bianco MA, Buffoli F, Gizzi G, Tessari F, Cipolletta L. The Cooperative Italian FLIN Study Group: prevalence and clinico-pathological features of colorectal laterally spreading tumors. *Endoscopy*. 2011;43(10):856-61.
7. Tate DJ, Desomer L, Awadie H, Goodrick K, Hourigan L, Singh R, et al. EMR of laterally spreading lesions around or involving the appendiceal orifice: technique, risk factors for failure, and outcomes of a tertiary referral cohort (with video). *Gastrointest Endosc*. 2018;87(5):1279-88.e2.
8. Nanda KS, Tutticci N, Burgess NG, Sonson R, Williams SJ, Bourke MJ. Endoscopic mucosal resection of laterally spreading lesions involving the ileocecal valve: technique, risk factors for failure, and outcomes. *Endoscopy*. 2015;47(8):710-8.
9. Ponugoti PL, Broadley HM, Garcia J, Rex DK. Endoscopic management of large ileocecal valve lesions over an 18-year interval. *Endosc Int Open*. 2019;7(12):E1646-e51.
10. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open*. 2016;6(11):e012799.
11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147(8):573-7.
12. Klein A, Bourke MJ. Advanced polypectomy and resection techniques. *Gastrointest Endosc Clin N Am*. 2015;25(2):303-33.
13. Jideh B, Bourke MJ. How to Perform Wide-Field Endoscopic Mucosal Resection and Follow-up Examinations. *Gastrointest Endosc Clin N Am*. 2019;29(4):629-46.
14. Burgess NG, Hourigan LF, Zanati SA, Brown GJ, Singh R, Williams SJ, et al. Risk Stratification for Covert Invasive Cancer Among Patients Referred for Colonic Endoscopic Mucosal Resection: A Large Multicenter Cohort. *Gastroenterology*. 2017;153(3):732-42.e1.
15. Fahrtash-Bahin F, Holt BA, Jayasekeran V, Williams SJ, Sonson R, Bourke MJ. Snare tip soft coagulation achieves effective and safe endoscopic hemostasis during wide-field endoscopic resection of large colonic lesions (with videos). *Gastrointest Endosc*. 2013;78(1):158-63.e1.

16. Tate DJ, Desomer L, Klein A, Brown G, Hourigan LF, Lee EY, et al. Adenoma recurrence after piecemeal colonic EMR is predictable: the Sydney EMR recurrence tool. *Gastrointest Endosc.* 2017;85(3):647-56.e6.
17. Sidhu M, Shahidi N, Gupta S, Desomer L, Vosko S, Arnout van Hattem W, et al. Outcomes of Thermal Ablation of the Mucosal Defect Margin After Endoscopic Mucosal Resection: A Prospective, International, Multicenter Trial of 1000 Large Nonpedunculated Colorectal Polyps. *Gastroenterology.* 2021;161(1):163-70.e3.
18. Kumarasinghe M, Bourke MJ, Brown I, Draganov P, McLeod D, Streutker C, et al. GIPS-AGPS Recommendations For Pathologic Assessment And Reporting Of EMR/ESD <http://www.agps.org.au/guidelines.php>2019 [
19. Rex DK, Hassan C, Bourke MJ. The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management. *Gastrointest Endosc.* 2017;86(2):253-63.
20. Kaltenbach T, Anderson JC, Burke CA, Dominitz JA, Gupta S, Lieberman D, et al. Endoscopic Removal of Colorectal Lesions 2014;Recommendations by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology.* 2020;158(4):1095-129.
21. Ferlitsch M, Moss A, Hassan C, Bhandari P, Dumonceau JM, Paspatis G, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy.* 2017;49(3):270-97.
22. Holt BA, Bassan MS, Sexton A, Williams SJ, Bourke MJ. Advanced mucosal neoplasia of the anorectal junction: endoscopic resection technique and outcomes (with videos). *Gastrointest Endosc.* 2014;79(1):119-26.
23. Morino M, Risio M, Bach S, Beets-Tan R, Bujko K, Panis Y, et al. Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference. *Surg Endosc.* 2015;29(4):755-73.
24. Shahidi N, Sidhu M, Vosko S, van Hattem WA, Bar-Yishay I, Schoeman S, et al. Endoscopic mucosal resection is effective for laterally spreading lesions at the anorectal junction. *Gut.* 2020;69(4):673-80.
25. Yu JX, Russell WA, Ching JH, Kim N, Bendavid E, Owens DK, et al. Cost Effectiveness of Endoscopic Resection vs Transanal Resection of Complex Benign Rectal Polyps. *Clin Gastroenterol Hepatol.* 2019;17(13):2740-8.e6.

26. Vennix S, Pelzers L, Bouvy N, Beets GL, Pierie JP, Wiggers T, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev*. 2014(4):Cd005200.
27. Yamada M, Saito Y, Sakamoto T, Nakajima T, Kushima R, Parra-Blanco A, et al. Endoscopic predictors of deep submucosal invasion in colorectal laterally spreading tumors. *Endoscopy*. 2016;48(5):456-64.
28. Vosko S, Shahidi N, Sidhu M, van Hattem WA, Bar-Yishay I, Schoeman S, et al. Optical evaluation for predicting cancer in large non-pedunculated colorectal polyps is accurate for flat lesions. *Clin Gastroenterol Hepatol*. 2021.
29. Bogie RMM, Veldman MHJ, Snijders L, Winkens B, Kaltenbach T, Masclee AAM, et al. Endoscopic subtypes of colorectal laterally spreading tumors (LSTs) and the risk of submucosal invasion: a meta-analysis. *Endoscopy*. 2018;50(3):263-82.
30. Backes Y, Schwartz MP, Ter Borg F, Wolfhagen FHJ, Groen JN, de Vos Tot Nederveen Cappel WH, et al. Multicentre prospective evaluation of real-time optical diagnosis of T1 colorectal cancer in large non-pedunculated colorectal polyps using narrow band imaging (the OPTICAL study). *Gut*. 2019;68(2):271-9.
31. Sidhu M, Tate DJ, Desomer L, Brown G, Hourigan LF, Lee EYT, et al. The size, morphology, site, and access score predicts critical outcomes of endoscopic mucosal resection in the colon. *Endoscopy*. 2018;50(7):684-92.
32. Chang J-J, Chien C-H, Chen S-W, Chen L-W, Liu C-J, Yen C-L. Long term outcomes of colon polyps with high grade dysplasia following endoscopic resection. *BMC Gastroenterology*. 2020;20(1):376.
33. Moss A, Bourke MJ, Williams SJ, Hourigan LF, Brown G, Tam W, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. *Gastroenterology*. 2011;140(7):1909-18.
34. Moss A, Williams SJ, Hourigan LF, Brown G, Tam W, Singh R, et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut*. 2015;64(1):57-65.
35. Klein A, Tate DJ, Jayasekeran V, Hourigan L, Singh R, Brown G, et al. Thermal Ablation of Mucosal Defect Margins Reduces Adenoma Recurrence After Colonic Endoscopic Mucosal Resection. *Gastroenterology*. 2019;156(3):604-13.e3.

36. Whitfield AM, Burgess NG, Bahin FF, Kabir S, Pellisé M, Sonson R, et al. Histopathological effects of electrosurgical interventions in an in vivo porcine model of colonic endoscopic mucosal resection. *Gut*. 2021.
37. Ikematsu H, Yoda Y, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. *Gastroenterology*. 2013;144(3):551-9; quiz e14.
38. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2015;47(9):829-54.
39. Bahin FF, Heitman SJ, Rasouli KN, Mahajan H, McLeod D, Lee EYT, et al. Wide-field endoscopic mucosal resection versus endoscopic submucosal dissection for laterally spreading colorectal lesions: a cost-effectiveness analysis. *Gut*. 2018;67(11):1965.
40. Fuccio L, Repici A, Hassan C, Ponchon T, Bhandari P, Jover R, et al. Why attempt en bloc resection of non-pedunculated colorectal adenomas? A systematic review of the prevalence of superficial submucosal invasive cancer after endoscopic submucosal dissection. *Gut*. 2018;67(8):1464-74.
41. Bokey EL, Chapuis PH, Fung C, Hughes WJ, Koorey SG, Brewer D, et al. Postoperative morbidity and mortality following resection of the colon and rectum for cancer. *Dis Colon Rectum*. 1995;38(5):480-6; discussion 6-7.
42. Peery AF, Shaheen NJ, Cools KS, Baron TH, Koruda M, Galanko JA, et al. Morbidity and mortality after surgery for nonmalignant colorectal polyps. *Gastrointest Endosc*. 2018;87(1):243-50.e2.
43. Duran E, Tannriseven M, Ersoz N, Oztas M, Ozerhan IH, Kilbas Z, et al. Urinary and sexual dysfunction rates and risk factors following rectal cancer surgery. *Int J Colorectal Dis*. 2015;30(11):1547-55.
44. Celentano V, Cohen R, Warusavitarne J, Faiz O, Chand M. Sexual dysfunction following rectal cancer surgery. *Int J Colorectal Dis*. 2017;32(11):1523-30.
45. Climent M, Martin ST. Complications of laparoscopic rectal cancer surgery. *Mini-invasive Surgery*. 2018;2:45.
46. Lindgren R, Hallböök O, Rutegård J, Sjødahl R, Matthiessen P. What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial. *Dis Colon Rectum*. 2011;54(1):41-7.

47. Cuccurullo D, Pirozzi F, Sciuto A, Bracale U, La Barbera C, Galante F, et al. Relaparoscopy for management of postoperative complications following colorectal surgery: ten years experience in a single center. *Surg Endosc.* 2015;29(7):1795-803.
48. Jayanna M, Burgess NG, Singh R, Hourigan LF, Brown GJ, Zanati SA, et al. Cost Analysis of Endoscopic Mucosal Resection vs Surgery for Large Laterally Spreading Colorectal Lesions. *Clinical Gastroenterology and Hepatology.* 2016;14(2):271-8.e2.
49. Russo P, Barbeiro S, Awadie H, Libânio D, Dinis-Ribeiro M, Bourke M. Management of colorectal laterally spreading tumors: a systematic review and meta-analysis. *Endosc Int Open.* 2019;7(2):E239-E59.
50. Bourke MJ, Neuhaus H. Colorectal endoscopic submucosal dissection: when and by whom? *Endoscopy.* 2014;46(8):677-9.
51. Hassan C, Repici A, Sharma P, Correale L, Zullo A, Bretthauer M, et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. *Gut.* 2016;65(5):806-20.
52. Heitman SJ, Bourke MJ. Endoscopic submucosal dissection and EMR for large colorectal polyps: "the perfect is the enemy of good". *Gastrointestinal Endoscopy.* 2017;86(1):87-9.

Table 1: Comparison of Rectal and Non-Rectal colonic LNPCPs.

LNPCPs	Rectum	Colon (non-rectum)	Total	<i>p</i>
	n=618	n=2787	n=3405	
Age, years, median (IQR)	67 (59-74)	69 (61-76)	67.0 (12.3)	0.001
Sex, n (%)				
M (%)	330 (53.4)	1332 (47.8)	1662 (48.9)	<0.011
F (%)	288 (46.6)	1455 (52.2)	1743 (51.2)	
ASA, n (%)				
≤2	551 (89.2)	2376 (85.3)	2927 (86)	0.923
>2	67 (10.8)	411 (14.7)	478 (14)	
Lesion				
Median Size, mm (IQR)	40 (30-60)	30 (25-40)	30 (25-40)	<0.001
Paris, n (%)				
Is	98 (15.9)	307 (11)	405 (11.9)	<0.001
IIa	154 (24.9)	1729 (62)	1883 (55.3)	
IIa+Is	330 (53.4)	480 (17.2)	810 (23.8)	
Any 'c' component	26 (4.2)	130 (4.7)	156 (4.6)	
Other	10 (1.6)	141 (5.1)	151 (4.4)	
Morphology				
Granular, n (%)	488 (79.0)	1391 (49.9)	1879 (55.2)	<0.001
Non-Granular, n (%)	72 (11.7)	759 (27.2)	831 (24.4)	
Mixed, n (%)	51 (8.3)	149 (5.3)	200 (5.9)	
Other, n (%)	7 (1.1)	488 (17.5)	495 (14.5)	
Kudo, n (%)				
III	87 (14.3)	701 (25.2)	788 (23.3)	

IV	443 (71.7)	1289 (46.2)	1732 (50.9)	<0.001
V	72 (11.7)	172 (6.2)	244 (7.2)	
Other	16 (2.6)	625 (22.4)	641 (18.9)	
Previously attempted, n (%)	70 (11.3)	297 (10.7)	367 (10.8)	0.56
Submucosal Fibrosis, n (%)	157 (25.4)	669 (24.0)	826 (24.2)	0.31
Histopathology, n (%)				
Tubular adenoma	63 (10.2)	741 (26.6)	804 (23.6)	<0.001
Tubulovillous adenoma	445 (72.0)	1305 (46.8)	1750 (51.4)	
Villous	17 (2.8)	17 (0.6)	34 (1.0)	
Sessile serrated lesion	6 (1.0)	636 (22.8)	642 (18.9)	
Other	87 (14.1)	88 (3.2)	175 (5.1)	
High-Grade dysplasia, n (%)	176 (28.4)	492 (17.7)	668 (19.6)	<0.001
Invasive Cancer, n (%)	93 (15.0)	172 (6.2)	265 (7.8)	<0.001

Table 2: Multivariate analysis assessing variables independently associated with location, Rectum Vs Colon (excluding rectum).

Variable	adjusted OR	95% C.I.for OR		p-value
		Lower	Upper	
Size (per 10mm)	1.22	1.15	1.29	<0.001
Paris 0-1s	1.88	1.40	2.52	<0.001
Paris 0-IIa+Is	3.07	2.42	3.90	<0.001
Granular	2.70	2.02	3.63	<0.001
Mixed granular	2.01	1.30	3.11	0.002
Kudo IV	1.67	1.28	2.18	<0.001
Kudo V	3.31	2.16	5.08	<0.001
Tubulovillous adenoma	1.35	1.07	1.71	0.011
Villous adenoma	3.56	1.64	7.73	0.001
Cancer	1.77	1.25	2.53	0.001

Chapter 6 - Endoscopic Full Thickness Resection is Curative for Small, High-risk Colorectal Lesions.

Publication:

Cronin O, Meys K, Hacking S, Alawad M, Yuen S, Cohen J, Gonda T, Bourke MJ, Haber GB. Endoscopic Full Thickness Resection is Curative for Small, High-risk Colorectal Lesions. Endoscopy Internation Open [Under review].

In brief:

- Endoscopic full thickness resection (EFTR) is a novel resection technique for the endoscopic resection of small, high risk colorectal lesions.
- There is limited data only evaluating its safety and efficacy

Contribution:

- EFTR offers a viable alternative for the endoscopic resection of small, high-risk colorectal lesions.

Endoscopic Full Thickness Resection is Curative for Small, High-risk Colorectal Lesions.

Authors: Oliver Cronin MBBS FRACP,¹⁻³ Kayla Meys APRN,³ Sean Hacking MD,⁴ Mouyed Alawad MD,⁴ Sofia Yuen,³ Jonathan Cohen MD,³ Tamas Gonda MD,³ Michael J Bourke MBBS FRACP,^{1,2} Gregory B. Haber MD FRCP.³

1. Westmead Hospital, Department of Gastroenterology and Hepatology, Sydney, New South Wales, Australia
2. Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia
3. Division of Gastroenterology and Hepatology, Department of Medicine, New York University Langone Health, New York, New York, USA
4. Department of Pathology, NYU Langone Health, NYU Grossman School of Medicine, New York, NY, USA.

Corresponding author:

Dr Gregory B. Haber MD FRCP (C)
Professor of Medicine
Chief of Endoscopy
Director of Advanced Therapeutics and Innovation
NYU Langone Health
New York, NY

Author contributions

Study concept and design: OC, GH

Acquisition of data: OC, KM, SH, MA, JC, TG, GH, JC, SY

Analysis and interpretation of data: OC, SH, MA, GH

Drafting of the manuscript: OC, GH

Critical revision of the manuscript for important intellectual content: OC, GH, MB

Statistical analysis: OC, GH

Study supervision: GH, MB

Conflict of Interest

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

Gregory Haber: Consultant: Olympus Medical, Boston Scientific, Medtronic, Exact Sciences, Creo Medical, Fujinon

The remaining authors have no conflicts of interest to disclose.

Data transparency statement

All data relevant to the study are included in the article.

Funding

This manuscript was not supported by any funding.

Abstract

Background and Aims

Endoscopic submucosal dissection (ESD) is the primary resection technique recommended for high-risk colonic lesions to ensure an R0 resection. Endoscopic full-thickness resection (EFTR) offers a viable alternative. We aimed to evaluate outcomes of patients with lesions containing high-grade dysplasia (HGD) and invasive cancer, resected by EFTR.

Patients and Methods

Consecutive non-lifting lesions referred to a single tertiary center with suspected localised advanced pathology for consideration of EFTR were prospectively studied. Multiple data points were recorded including technical success, EFTR histopathological data, complications, and follow-up surveillance data.

Results

Over a 4-year period to July 2023, 39 lesions were considered eligible for EFTR as an alternative to EMR or ESD, of which 33 (85%) underwent EFTR.

18/33 (55%) lesions contained cancer and 15/33 (45%) lesions contained HGD only. The median size of cancer was 7mm [Interquartile range (IQR) 4-10mm] contained within a median lesion size of 30mm (IQR 21-31mm). The median depth of invasion was 2550 μ m (IQR 1625-3075 μ m) and the deepest resected layer contained sub-serosal fat. Of the lesions containing cancer removed by FTR, 17/18 (94%) had an R0 resection.

At 6-month (IQR 5-7 months) surveillance colonoscopy, there was 1/23 (4%) case with recurrence, successfully re-resected with FTR. Of the patients with cancer who were referred for surgical resection post-FTR, no (0/7, 0%) cases had residual cancer within the surgical specimen.

Conclusions

EFTR offers a viable, safe and effective alternative for ER of high-risk lesions. Resection options need to be individualised and clearly outlined to the patient.

Key Words: colorectal cancer; full-thickness resection; endoscopy; adenoma; polyp.

Introduction

The introduction of screening programs for colorectal cancer (CRC) has increased the detection of early CRC (T1 and T2). [1] Early CRCs generally pose a low-risk of lymphatic spread necessitating a delicate balance in management to ensure cancer cure while minimising treatment-related morbidity, mortality and costs. [2, 3] Pursuit of this balance, has led to a trend towards minimally invasive endoscopic treatments for early CRC, replacing conventional surgery in those cases considered low-risk of metastatic disease. [4, 5]

The recommendation for lesions with a high suspicion of cancer, is en bloc ER (ER) for cure. The concern for cancer is based on prior biopsy with HGD, or topographic features with vascular and pit pattern changes suggestive of invasive cancer. Indeed, larger series of high-risk lesions show upgrading of the pathology in 26%-36% of lesions. [6-8]

Conventional endoscopic resection (ER) options include en bloc Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD) but both techniques have several downsides. [9, 10] EMR is less precise, and may struggle to achieve an R0 resection of the lateral and vertical margins, particularly in the setting of dense fibrosis which is often encountered in lesions with advanced histology or prior resection attempts . [11] ESD offers superior control of resection margins. However, it is technically challenging, resource intensive and has limited access, particularly in Western countries. [12-15] ESD may also struggle to achieve a curative vertical resection margin in the presence of deeper submucosal invasion.

To overcome some of these barriers, an integrated endoscopic full-thickness resection device (FTRD; Ovesco Endoscopy, Tübingen, Germany) was developed for select gastrointestinal lesions. The FTRD single-clip closure and resection device permits full thickness resection (FTR) without exposing the peritoneum to luminal contents during resection. [16-18] A limitation of the FTRD is lesion size, restricted to the volume of tissue that can be pulled into the over-the-scope cap. Lesion size is one of the strongest predictors of advanced histology. [19] Fortunately, most cancer-containing lesions have a small focus of cancer centrally located within a larger pre-malignant lesion. An observational study (n=69) demonstrated the

efficacy of resection of larger cancer containing lesions by hybrid EMR/FTR (H-FTR) (mean lesion size 39.2mm, standard deviation 13.6mm). [20]

Several large cohorts have reported FTR as a safe and effective technique, however long-term follow-up outcomes need to be evaluated. [21, 22] Moreover, the dimensions and depth of cancer in lesions considered potentially curable with ER are often overlooked when considering curative strategies. Most publications on ER of high-risk lesions >2cm, consider ESD as the preferred technique. [23, 24] This study aimed to assess the long-term outcomes of en bloc-FTR (E-FTR) and H-FTR for the resection of polyps with early colorectal cancer and high-grade dysplasia, as a viable alternative to ESD for curative resection.

Methods

The study was approved by the Institutional Review Board of New York University Langone Health. All authors had access to the study data and reviewed and approved the final manuscript.

Between July 2019 and July 2023, eligible consecutive participants were enrolled at a single high-volume endoscopic tissue resection center in the United States of America. All patients had undergone a complete colonoscopy before inclusion by either a referring endoscopist or by one of our participating advanced endoscopists. Eligibility criteria included the suspected or confirmed presence of a localized (T1 or T2) colorectal cancer or HGD. Patients were excluded from endoscopic FTR and referred to a multidisciplinary team if there was evidence of metastatic disease.

All endoscopic procedures were performed by one of four study investigators (accredited gastroenterologists with advanced training and an established tertiary referral practice in colorectal ER) or a senior interventional endoscopy fellow under the direct supervision of one of the investigators. Prior to resection, all lesions were re-assessed optically using high-definition white light, narrow-band imaging (NBI), and near focus. The decision to resect the lesion by FTR was determined by the presence of either overt or a high-risk of covert cancer, determined by lesion size, site, morphology and Kudo pit pattern (Vi or Vn). [25]

Resection was performed for all lesions using the FTRD system (Ovesco, Tübingen, Germany) using a standardized E-FTR or H-FTR technique. [9, 20] For lesions ≥ 20 mm, the initial step was to remove the surrounding non-malignant LNPCP by conventional EMR. The remaining non lifting, central portion of the polyp was then removed using the FTRD.

Indication for FTR included suspected T1 or T2 malignancy or high-grade dysplasia. Primary outcome measures were technical success and R0 resection rate. Technical success was defined as successful advancement of the FTRD to the lesion, entrapment of the lesion, successful clip deployment and snare resection, and en bloc resection without evidence of macroscopic residual pathology. [26] R0 resection was defined as a histologically complete resection (lateral and vertical margins clear of neoplastic tissue). For H-FTR, the lateral margin of the FTR specimen may have been contiguous with the EMR resection bed. The R0 resection definition for H-FTR was modified to reflect a vertical margin free of neoplasm and a lateral margin free of cancer.

Secondary outcomes were adverse events, and subsequent need for surgery. Intraprocedural bleeding was defined as bleeding that required the use of coagulation forceps for hemostasis. For patients referred for surgery, surgical histopathological results were recorded. Recurrence was defined as neoplastic tissue seen optically or histologically at surveillance colonoscopy, performed 3-6 months after resection. All polypectomy scars were biopsied even in the absence of visible residual neoplasm, to ensure microscopic recurrence would not be overlooked.

Patient and public involvement

Neither patients nor the public were involved in the design or execution of this study.

FTR procedure

All procedures were performed by experienced endoscopists, who underwent training in the use of the device in a live animal model before patient use. Procedures were performed with monitored anesthesia care with propofol intravenous sedation. Patients were instructed to continue aspirin use during the periprocedural period; all other anticoagulants and antiplatelet medications were temporarily held, consistent with guideline recommendations. Carbon dioxide gas was used for insufflation. Bowel cleansing was

achieved using a standard split-regimen bowel preparation. Standard colonoscopy was first performed with an adult colonoscope (CF-HQ190L/I; Olympus) with a distal cap attachment (D-201-14304; Olympus).

All lesions were carefully examined using magnification endoscopy under white-light and narrow-band imaging to clearly delineate areas suspicious for invasive carcinoma. After lesion assessment, a decision was made regarding the suitability of the lesion for EMR, ESD, E-FTR (Figure 1), or H-FTR (Figure 2). H-FTR was indicated for lesions ≥ 20 mm, although the proceduralist had final decision on resection technique. For H-FTR, the periphery of the lesion was lifted using a standard injection solution of either normal saline solution or 3% hydroxyethyl starch with 1 mg/L (1 part per million dilution) of epinephrine and methylene blue. Standard piecemeal EMR was performed around the periphery of the lesion (Figure 2, image E-G). Resection was continued until only the non-lifting portion of the lesion remained (Figure 2, image G).

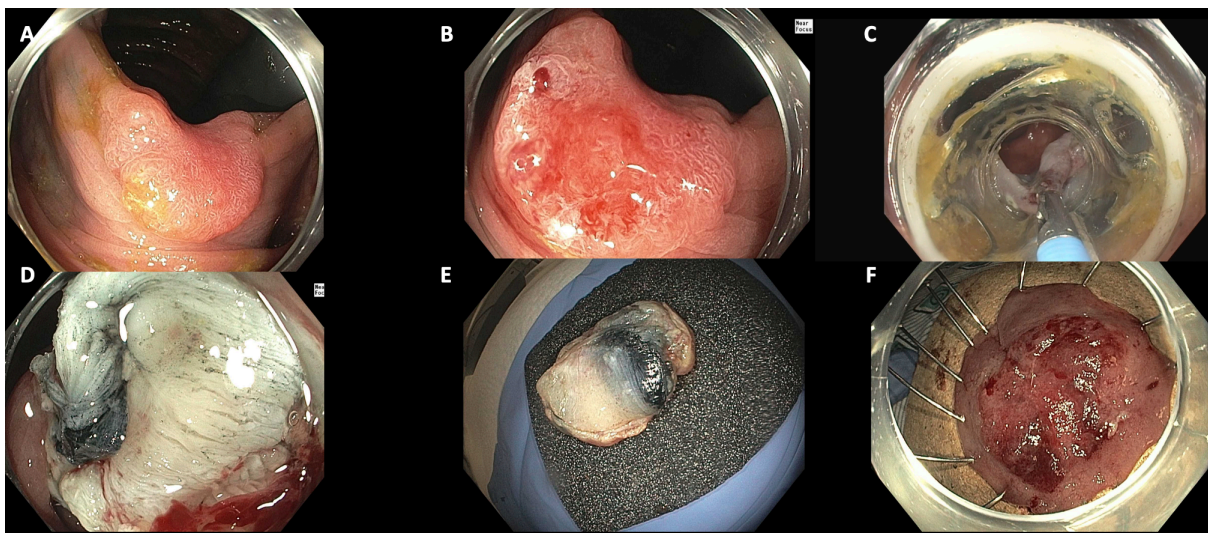


Figure 1. Endoscopic full thickness resection of a 20mm Paris 0-IIa+IIc ascending colon lesion. (A) A 20mm Paris 0-IIa+IIc ascending colon lesion assessed with white light endoscopy and **(B)** near focus, illustrating Kudo pit pattern Vi centrally. **(C)** Grasping forceps used to draw specimen into full thickness device. **(D)** Post-deployment with muscularis propria at periphery and serosa centrally. **(E)** Ex-vivo specimen with serosal view illustrating ink tattoo. **(F)** Pinned specimen with clear margins.

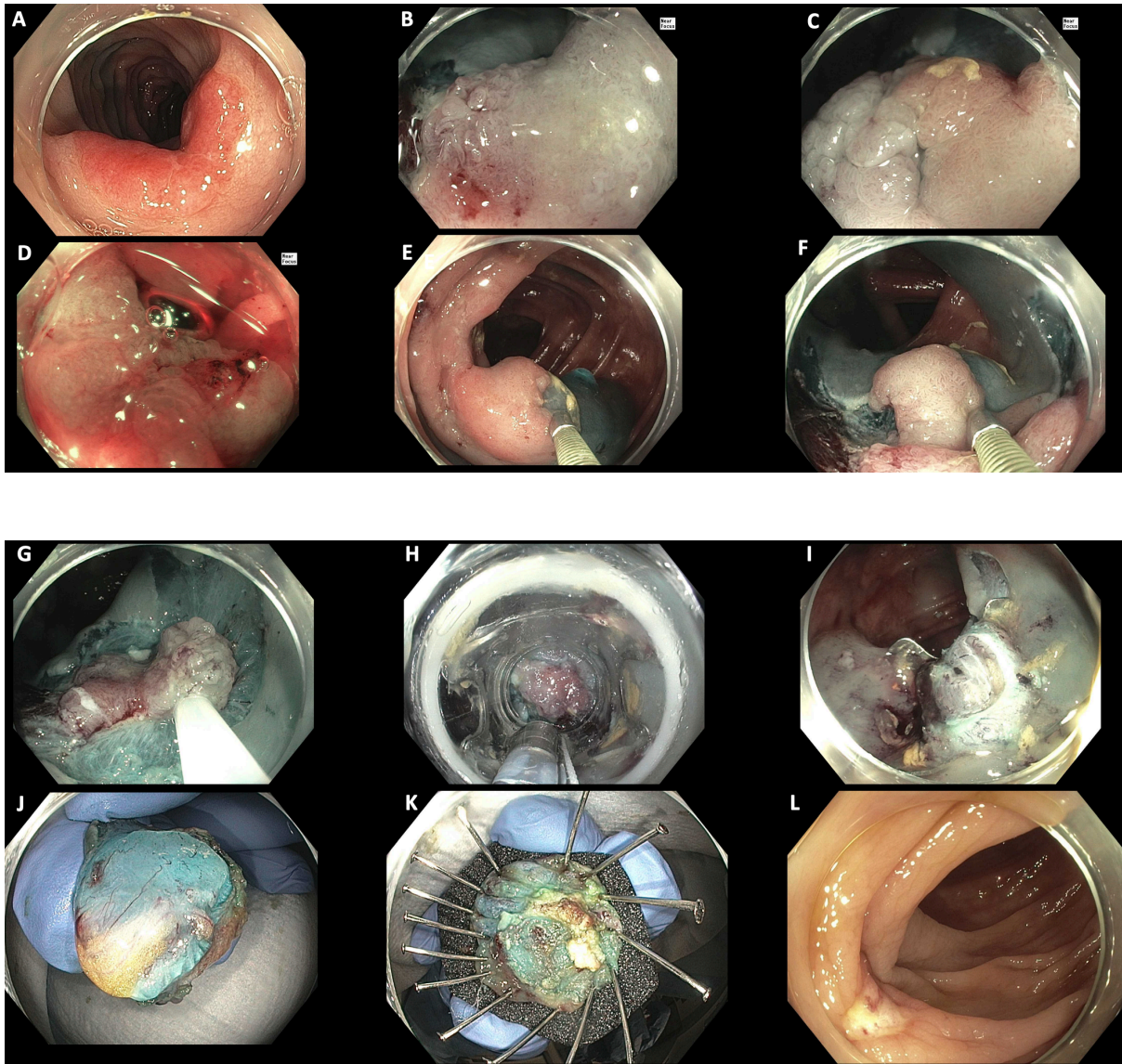


Figure 2. Endoscopic hybrid full thickness resection of a 30mm Paris 0-IIa+IIc transverse colon lesion. (A) A 30mm Paris 0-IIa+IIc transverse colon lesion assessed with white light endoscopy, (B) narrow band imaging and (C-D) near focus, illustrating Kudo pit pattern Vi centrally. (E-G) Standard piecemeal EMR was performed around the periphery of the lesion. (G) Piecemeal resection was continued until only the non-lifting portion of the lesion remained. (H-I) Endoscopic full thickness resection. (J-K) Ex-vivo lesion demonstrating sub-serosal fat. (L) Surveillance colonoscopy demonstrating a scar at resection site without evidence of recurrence.

The FTR procedure has been described in detail elsewhere. [26] The periphery of the lesion was first marked using a cautery probe. A second colonoscope preloaded with the FTRD was then advanced to the lesion. Although a dummy sizing cap is available (prOVE Cap; Ovesco), it was not routinely used. If difficulty traversing loops of the colon was encountered, the following manoeuvres were attempted: changing patient position, manual abdominal pressure, water immersion, administration of glucagon, and use of an 18- to 20-mm controlled radial expansion balloon.

A grasping forcep (Figure 1, image C) was used to grasp the lesion and gently pull it into the cap, with adjuvant use of suction where necessary. The FTRD clip was then deployed. This was immediately followed by snare closure by an assistant and electrosurgical excision of the entrapped tissue using pure cutting current. The endoscope with the tissue specimen was withdrawn, and the neoplastic tissue was pinned (Figure 1, image F), measured, and placed in formalin for histopathology. A standard adult colonoscope with a distal cap attachment was then reintroduced to assess the area of resection and to ensure secure clip placement and absence of bleeding.

Patients were observed in the recovery unit for approximately 1 hour and if pain-free were discharged home the same day on a clear fluid diet for 24 hours. Antibiotics were not routinely administered unless the lesion involved the appendiceal orifice, in which case ciprofloxacin 400 mg intravenously was administered intra-procedurally and continued orally at 500 mg twice a day for 1 week for prophylaxis of appendicitis.

Histopathology evaluation

After ER, specimens were collected and processed for histopathological review. Histopathological review of all specimens was completed by 2 expert gastrointestinal pathologists. Cancer was defined by neoplastic invasion into the submucosa, measured in microns. [27]

Data extraction and analysis

Prospectively collected data included: (i) patient characteristics (age, sex, American Society of Anesthesiologists [ASA] classification); (ii) Lesion characteristics (location, size, Paris classification, surface granularity, Kudo pit pattern, resection technique); (iii) procedure time (iv) histopathological evaluation.

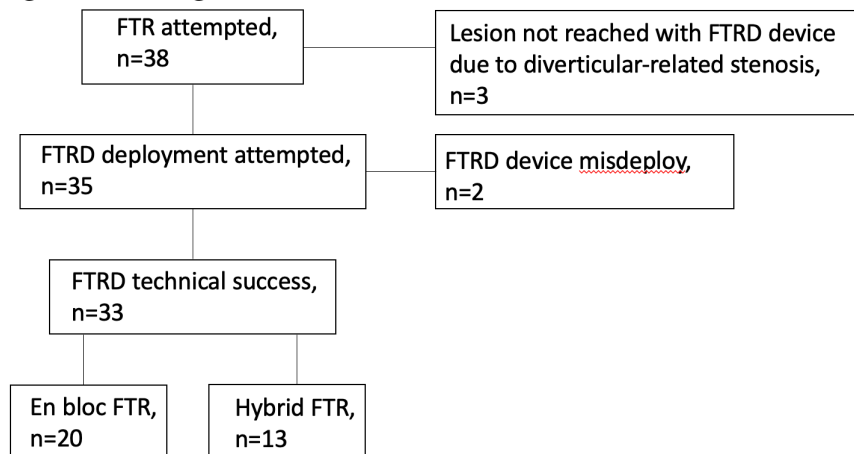
Statistical analysis

SPSS version 29.0 (IBM Corp., Armonk, New York, USA) was used for data analysis. The continuous variables age and lesion size were summarized as median (interquartile range [IQR]) following assessment of non-normality using Shapiro–Wilk’s test. Categorical variables were summarized as frequencies (%). Mann–Whitney tests were used to test for differences in continuous distributions between the groups. Chi-squared tests (or exact permutation tests if required) were used to test for association between the categorical variables.

Results

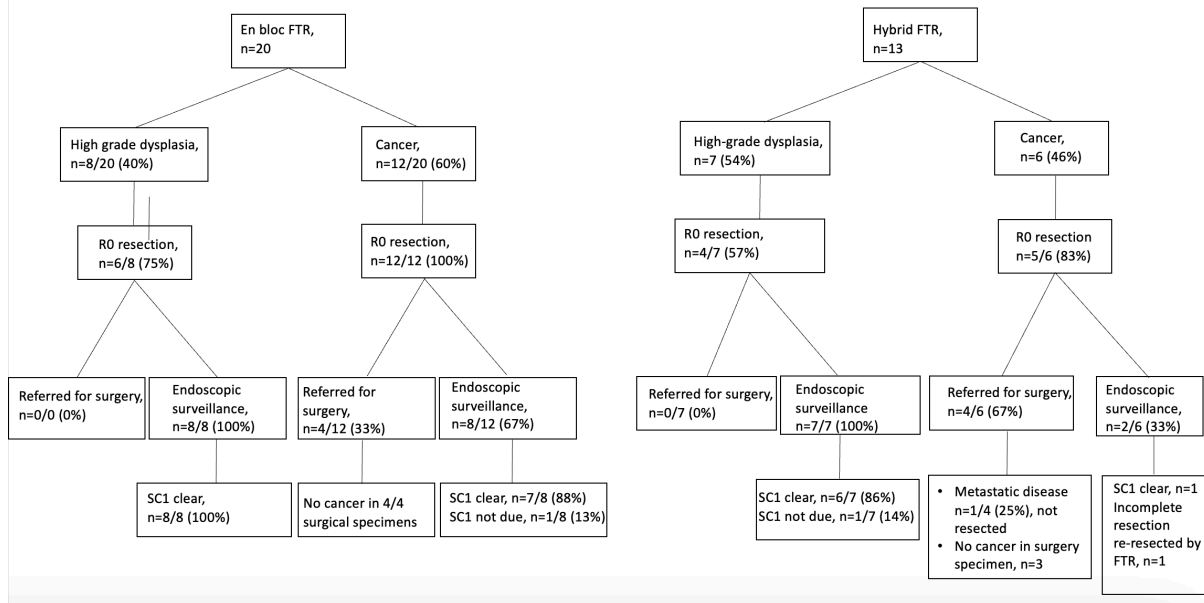
Over 48 months until July 2023, 38 patients were referred for consideration of colonic FTR (Figure 3). The median age was 77 years (IQR 64 - 81 years) (Table 1). Median lesion size was 23mm (IQR 18-35mm). Most lesions (n=20, 61%) were removed by E-FTR, and the remainder (n=13, 39%) were removed by H-FTR (Figure 4). 18 (55%) lesions contained cancer and 15 (45%) contained HGD only.

Figure 3. Flow diagram of consecutive lesions referred for consideration of endoscopic full thickness resection.



FTR, full thickness resection; FTRD, full thickness resection device.

Figure 4. Flow diagram of consecutive patients referred for endoscopic full thickness resection.



Demographic and lesion characteristics

Lesions removed by H-FTR were larger (40mm Vs 20mm, $p < 0.001$) (Table 1). All other characteristics including lesion location and morphology were similar. Technical success was achieved in all (100%) cases, in both groups and there were no significant complications in either group. Procedure duration was longer in the H-FTR cohort (46mins Vs 20mins, $p < 0.001$). The deepest layer resected was most commonly submucosa (12/33, 36%) or sub-serosal fat (10/33, 30%) (Figure 5). There were no significant differences between the H-FTR and E-FTR groups in terms of high-grade dysplasia (54% Vs 40%, $p = 0.435$) or cancer (46% vs 60%, $p = 0.435$).

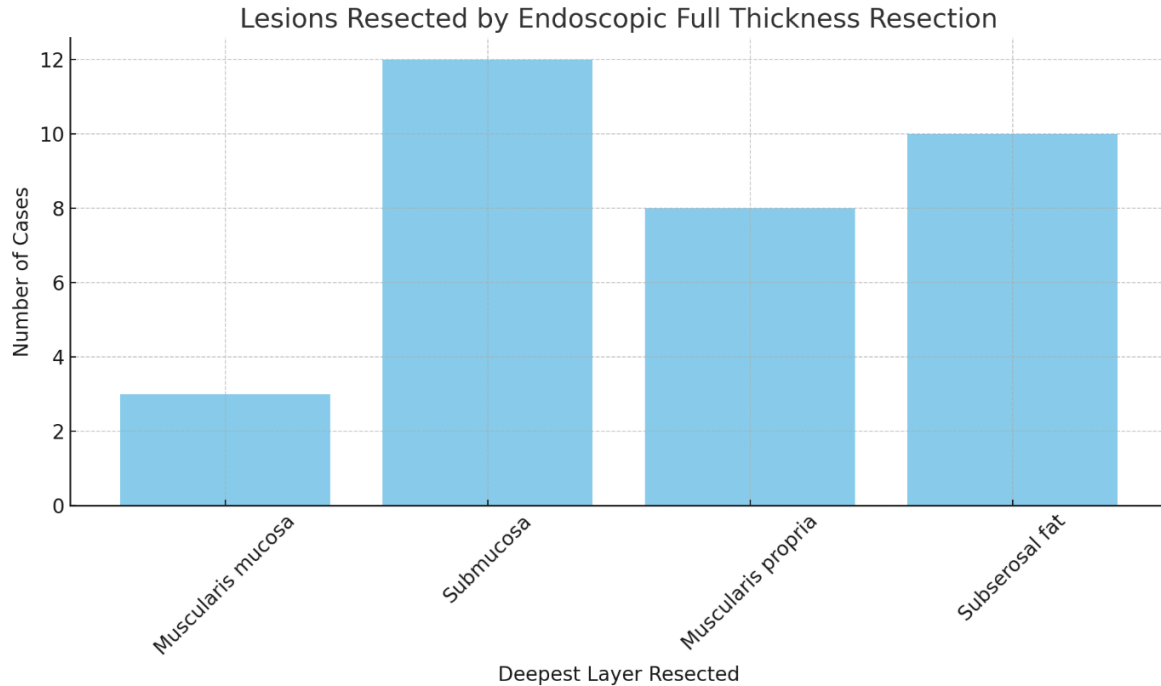


Figure 5. Histogram illustrating the deepest resection layer for lesions resected by endoscopic full thickness resection device.

Cancer results for 18 lesions

The median size of cancer was 7mm [Interquartile range (IQR) 4-10mm] contained within a median resected lesion size of 30mm (IQR 21-31mm). The median depth of invasion was 2550µm (IQR 1625-3075µm) and the deepest resected layer resected by the FTRD contained sub-serosal fat.

Lesions containing cancer resected by H-FTR were larger (40mm vs 20mm, $p < 0.001$) and had a greater invasion depth ($p < 0.001$), although the actual focus of cancer contained within the lesion remained small (median 5.3mm, IQR 4.3-7.5mm). R0 resection was achieved for most ($n=5$, 83%) lesions removed by H-FTR cases and for all ($n=12$, 100%) lesions removed by E-FTR. The only case with a positive vertical margin was resected to the sub-serosa (depth 4000µm) with lymphovascular invasion, perineural invasion, intermediate tumor budding and was poorly differentiated.

En-bloc FTR follow-up data for cancers

Eight (67%) and 4 (33%) patients with a resected cancer were referred for endoscopic surveillance and surgical resection respectively. 7/8 (88%) patients had completed a colonoscopy at 6 months (IQR 5-7 months) (Table 2). There were no (0%) patients with recurrence. Of the 4 patients with cancer removed by E-FTR referred for surgical resection, none (n=0, 0%) of the surgical specimens contained cancer (Table 3).

Hybrid FTR follow-up data for cancers

Two (33%) and 4 (67%) patients with a resected cancer were referred for endoscopic surveillance and surgical resection respectively. Of the patients referred for endoscopic surveillance, 1 patient had a lateral margin involved post H-FTR. A repeat FTR was performed, and subsequent surveillance colonoscopy was clear of recurrence. The second patient referred for endoscopic surveillance did not have recurrence. Of the 4 patients referred for consideration of surgical resection, 3 (75%) of whom did not have residual cancer at the resection site and 1 (25%) was found to have metastatic disease during surgical workup.

FTR of lesions with high-grade dysplasia

Of the 15 lesions containing HGD, 8 (53%) and 7 (47%) were removed by E-FTR and H-FTR respectively. There were no cases of recurrence at 6-month surveillance colonoscopy (IQR 5-7 months).

Discussion

Lesions with advanced histopathology present a unique set of challenges. Firstly, they often contain dense fibrosis which can make interpretation of dissection planes and margins more challenging. [11] Due to the fibrosis, submucosal injection is less effective posing additional challenges to ER. Secondly, the ramifications of a non-curative ER are greater, typically committing the patient to a surgical resection which is associated with greater rates of morbidity and mortality. [28] The results from this study demonstrate that EFTR is effective, safe and offers durable treatment for lesions containing HGD or cancer. There were no significant complications in our cohort, but larger cohorts have reported a complication rate of 9-12%. [21, 22]. This difference may be due to our relatively small cohort at a single center, with the majority of FTR procedures performed by one experienced proceduralist (GH), differing from larger national registries. [21, 22]

ER should be the first-line approach for the resection for lesions with HGD or suspected cancer. Prior to the development of the FTRD, ESD was the favoured approach due to its high rate of R0 resection. [29] Less precise alternatives include en bloc EMR and underwater EMR for smaller lesions. [30-32] A disadvantage of ESD is the steep and prolonged learning curve required to achieve proficiency. Gaining and then maintaining proficiency in ESD, particularly in Western countries is challenging due to a combination of lack of lesion volume and complexity. [33] Even in experienced hands, ESD is time-consuming and resource intensive. [12, 34] The development of the FTRD has offered a viable ER alternative in select cases. Compared to ESD, FTR has a shorter learning curve. The FTRD does not require prior learning of third space endoscopy or dissection planes. [9] FTR also has a shorter procedural duration, reducing patient exposure to other intra-procedural related morbidity such as anesthetic risk. [35] The use of FTR does have some limitations with respect to the location where it can be used. Low rectal lesions are not amenable given the risk of the device causing tenesmus or involving tissues around the anal verge. Similarly, lesions close to the ileo-cecal valve cannot be treated as the device may occlude the valve.

Removing some barriers of complex ER, such as those required to perform ESD, might result in FTR of lesions at lower-volume centers. Removal of any access barriers should be generally viewed as positive, although access should still be restricted to centers that can effectively manage any complications. In practice, most of these patients require multidisciplinary case discussions and are therefore referred to larger, higher volume centers with a streamlined multidisciplinary approach.

FTR is effective and demonstrates similar rates of cure compared to ESD for small lesions. Our R0 resection rate was 94% (n=17) for lesions with cancers. This is slightly higher than the reported R0 resection rates of 83% (n=159/192) and 89% (n=186/221) reported in the German colonic FTRD registry and the Dutch colorectal eFTR registry respectively. [21, 22] A large single centre study (n=361) assessing ESD efficacy and safety reported an R0 resection rate of 98.3% (355/361). [36] Our study also demonstrates that larger lesions can be effectively resected with H-FTR. While the median resected lesion size for H-FTR was 40mm, the median cancer size within the lesion was 9.5 mm. H-FTR is effective and offers an acceptable alternative to ESD for larger lesions as the focus of advanced histopathology is central and can be delineated and pulled into the FTRD cap. In this study, there was 1 cancer

with vertical margin involvement post FTR. This was a deeply invasive cancer, with an invasion depth 4000µm and sub-serosal fat contained within the specimen. The decision to include this patient for FTR was made by an endoscopist with less experience in assessing suitability of advanced lesions for FTR. Regardless, ESD would not have provided a better outcome in this case. A second cancer was incompletely resected with horizontal margin involvement. This was recognised on histopathological review, and the lesion was effectively re-treated at follow-up colonoscopy with a repeat FTR.

In this study, no cases that underwent surgical resection following FTR, contained cancer. One case had liver metastases. This is despite the presence of LVI, PNI and intermediate tumour found within some of the endoscopic specimens (Table 3). Positive predictors for curative CRC resection for ESD include a well differentiated lesion with the absence of LVI, low tumor budding score and submucosal invasion <1000µm (Sm1). [37] T1, SM1 CRCs resected by ESD which have met curative resection criteria have an estimated risk of lymph node metastasis of <2%. [37] Among the prognostic factors predictive of lymph node involvement, the depth of invasion has the least impact. More recent studies suggest that even with SM2 involvement, but with absence of other worrisome features, the risk of lymph node involvement remains acceptably low (<2%). Thus, FTR may be considered superior to ESD for curative resection given the deeper vertical resection margins achieved. The ability to achieve an R0 resection of an SM2 lesion with ESD would be more challenging. [38]

Our patient population is becoming increasingly complex, often with advancing age and other co-morbidities. This highlights the importance of improving our understanding of risk factors for non-curative ER and when surgical referral may or may not be needed. The delicate balance of over and under-treatment needs to be better understood, to improve the precision of management plans.

There are limitations to this study. Firstly, this is a small sample size. However, this is the largest study of cancers resected by FTR from a single centre. Secondly, given the small number of lesions, a multivariate analysis would not provide accurate or meaningful results. A direct comparison with ESD would strengthen the fundamental understanding of where the FTRD fits within the ER algorithm.

In conclusion, FTR provides an effective, viable alternative to ESD for resection of lesions containing HGD and cancer. FTR has less technical demands, offers resource and time efficiencies, and provides acceptable curative resection rates. FTR will not replace ESD which remains a fundamental resection tool, particularly for lesions with a larger focus of cancer. Instead, resection of advanced lesions is becoming more individualised and precise, accounting for lesion nuances and patient co-morbidities. Larger studies are needed to improve our understanding of the limitations of EFTR to better refine its place within any complex lesion ER algorithm.

References

1. Reggiani-Bonetti L, Di Gregorio C, Pedroni M, et al. Incidence trend of malignant polyps through the data of a specialized colorectal cancer registry: clinical features and effect of screening. *Scand J Gastroenterol.* 2013;48(11):1294-301.
2. Kim JB, Lee HS, Lee HJ, et al. Long-Term Outcomes of Endoscopic Versus Surgical Resection of Superficial Submucosal Colorectal Cancer. *Dig Dis Sci.* 2015;60(9):2785-92.
3. Vermeer NCA, Backes Y, Snijders HS, et al. National cohort study on postoperative risks after surgery for submucosal invasive colorectal cancer. *BJS Open.* 2019;3(2):210-7.
4. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy.* 2017;49(3):270-97.
5. Kaltenbach T, Anderson JC, Burke CA, et al. Endoscopic Removal of Colorectal Lesions: Recommendations by the US Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol.* 2020;115(3):435-64.
6. Ma MX, Tate DJ, Sidhu M, et al. Effect of pre-resection biopsy on detection of advanced dysplasia in large nonpedunculated colorectal polyps undergoing endoscopic mucosal resection. *Endoscopy.* 2023;55(3):267-73.
7. Kakushima N, Ono H, Takao T, et al. Method and timing of resection of superficial non-ampullary duodenal epithelial tumors. *Dig Endosc.* 2014;26 Suppl 2:35-40.

8. Klein A, Nayyar D, Bahin FF, et al. Endoscopic mucosal resection of large and giant lateral spreading lesions of the duodenum: success, adverse events, and long-term outcomes. *Gastrointest Endosc.* 2016;84(4):688-96.
9. Aslanian HR, Sethi A, Bhutani MS, et al. ASGE guideline for endoscopic full-thickness resection and submucosal tunnel endoscopic resection. *VideoGIE.* 2019;4(8):343-50.
10. Andrisani G, Hassan C, Pizzicannella M, et al. Endoscopic full-thickness resection versus endoscopic submucosal dissection for challenging colorectal lesions: a randomized trial. *Gastrointestinal Endoscopy.* 2023;98(6):987-97.e1.
11. Kuroha M, Shiga H, Kanazawa Y, et al. Factors Associated with Fibrosis during Colorectal Endoscopic Submucosal Dissection: Does Pretreatment Biopsy Potentially Elicit Submucosal Fibrosis and Affect Endoscopic Submucosal Dissection Outcomes? *Digestion.* 2021;102(4):590-8.
12. Bahin FF, Heitman SJ, Rasouli KN, et al. Wide-field endoscopic mucosal resection versus endoscopic submucosal dissection for laterally spreading colorectal lesions: a cost-effectiveness analysis. *Gut.* 2018;67(11):1965.
13. Arezzo A, Passera R, Marchese N, et al. Systematic review and meta-analysis of endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions. *United European Gastroenterol J.* 2016;4(1):18-29.
14. Saito Y, Uraoka T, Matsuda T, et al. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc.* 2007;66(5):966-73.
15. Maple JT, Abu Dayyeh BK, Chauhan SS, et al. Endoscopic submucosal dissection. *Gastrointest Endosc.* 2015;81(6):1311-25.
16. Schmidt A, Meier B, Caca K. Endoscopic full-thickness resection: Current status. *World J Gastroenterol.* 2015;21(31):9273-85.
17. Xu M, Wang XY, Zhou PH, et al. Endoscopic full-thickness resection of colonic submucosal tumors originating from the muscularis propria: an evolving therapeutic strategy. *Endoscopy.* 2013;45(9):770-3.
18. Sedarat A. Clips for closure of full-thickness defects. *Techniques and Innovations in Gastrointestinal Endoscopy.* 129-35.
19. Burgess NG, Hourigan LF, Zanati SA, et al. Risk Stratification for Covert Invasive Cancer Among Patients Referred for Colonic Endoscopic Mucosal Resection: A Large Multicenter Cohort. *Gastroenterology.* 2017;153(3):732-42.e1.

20. Mahadev S, Vareedayah AA, Yuen S, et al. Outcomes of a hybrid technique using EMR and endoscopic full-thickness resection for polyps not amenable to standard techniques (with video). *Gastrointest Endosc.* 2021;94(2):358-67.e1.
21. Zwager LW, Bastiaansen BAJ, van der Spek BW, et al. Endoscopic full-thickness resection of T1 colorectal cancers: a retrospective analysis from a multicenter Dutch eFTR registry. *Endoscopy.* 2022;54(5):475-85.
22. Meier B, Stritzke B, Kuellmer A, et al. Efficacy and Safety of Endoscopic Full-Thickness Resection in the Colorectum: Results From the German Colonic FTRD Registry. *Am J Gastroenterol.* 2020;115(12):1998-2006.
23. Jacques J, Schaefer M, Wallenhorst T, et al. Endoscopic En Bloc Versus Piecemeal Resection of Large Nonpedunculated Colonic Adenomas : A Randomized Comparative Trial. *Ann Intern Med.* 2024;177(1):29-38.
24. Saito Y, Otake Y, Sakamoto T, et al. Indications for and technical aspects of colorectal endoscopic submucosal dissection. *Gut Liver.* 2013;7(3):263-9.
25. Kudo S, Tamura S, Nakajima T, et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc.* 1996;44(1):8-14.
26. Schmidt A, Beyna T, Schumacher B, et al. Colonoscopic full-thickness resection using an over-the-scope device: a prospective multicentre study in various indications. *Gut.* 2018;67(7):1280-9.
27. Rex DK, Hassan C, Bourke MJ. The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management. *Gastrointest Endosc.* 2017;86(2):253-63.
28. Peery AF, Shaheen NJ, Cools KS, et al. Morbidity and mortality after surgery for nonmalignant colorectal polyps. *Gastrointest Endosc.* 2018;87(1):243-50.e2.
29. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2022. *Endoscopy.* 2022;54(6):591-622.
30. Tziatzios G, Gkolfakis P, Triantafyllou K, et al. Higher rate of en bloc resection with underwater than conventional endoscopic mucosal resection: A meta-analysis. *Dig Liver Dis.* 2021;53(8):958-64.
31. Tate DJ, Sidhu M, Bar-Yishay I, et al. Impact of en bloc resection on long-term outcomes after endoscopic mucosal resection: a matched cohort study. *Gastrointest Endosc.* 2020;91(5):1155-63.e1.

32. Maselli R, Spadaccini M, Belletrutti PJ, et al. Endoscopic submucosal dissection for colorectal neoplasia: outcomes and predictors of recurrence. *Endosc Int Open*. 2022;10(1):E127-e34.
33. Zhang X, Ly EK, Nithyanand S, et al. Learning Curve for Endoscopic Submucosal Dissection With an Untutored, Prevalence-Based Approach in the United States. *Clin Gastroenterol Hepatol*. 2020;18(3):580-8.e1.
34. Kim YJ, Kim ES, Cho KB, et al. Comparison of clinical outcomes among different endoscopic resection methods for treating colorectal neoplasia. *Dig Dis Sci*. 2013;58(6):1727-36.
35. Guo JT, Zhang JJ, Wu YF, et al. Endoscopic full-thickness resection using an over-the-scope device: A prospective study. *World J Gastroenterol*. 2021;27(8):725-36.
36. Toyonaga T, Man-i M, East JE, et al. 1,635 Endoscopic submucosal dissection cases in the esophagus, stomach, and colorectum: complication rates and long-term outcomes. *Surg Endosc*. 2013;27(3):1000-8.
37. Wang TT, He JJ, Zhou PH, et al. Endoscopic diagnosis and treatment of an appendiceal mucocele: A case report. *World J Clin Cases*. 2021;9(16):3936-42.
38. Gijsbers KM, van der Schee L, van Veen T, et al. Impact of ≥ 0.1 -mm free resection margins on local intramural residual cancer after local excision of T1 colorectal cancer. *Endosc Int Open*. 2022;10(4):E282-e90.

Table 1. Patient characteristics with high-grade dysplasia and cancer resected by full-thickness resection			
	En bloc (n=20)	Hybrid (n=13)	p value
Mean age, y (standard deviation)	77 (64-81)	77 (65-81)	0.143
Male patients	14 (78)	4 (22)	
Lesion characteristics			
Lesion size mm (IQR)*	20 (15-25)	40 (30-50)	<0.001
Morphology			
Ia	1 (5)	1 (8)	0.751
Ia+Ic	13 (65)	8 (62)	0.84
Is	4 (20)	1 (8)	0.335
Ia+Is	2 (10)	3 (23)	0.12
Location			
Rectum	1 (5)	3 (23)	0.12
Sigmoid	6 (30)	0 (0)	0.029
Descending Colon	1 (5)	1 (8)	0.751
Transverse Colon	3 (15)	2 (15)	0.976
Ascending Colon	4 (20)	5 (38)	0.245
Caecum	1 (5)	2 (15)	0.311
Ileocecal valve	1 (5)	0 (0)	0.413

Appendiceal Orifice	3 (15)	0 (0)	0.143
Technical Success	20 (100)	13 (100)	0.143
Procedure duration mins (IQR)	20 (18-25)	46 (45-50)	p<0.001
Length of Stay, days (IQR)	1 (1-1)	1 (1-1)	
Histopathology			
High-grade dysplasia	8 (40)	7 (54)	0.435
Cancer	12 (60)	6 (46)	0.435

*Intra-procedural estimate by Endoscopist.

Table 2. Cancer Histopathology (n=18)			
	En bloc (n=12)	Hybrid (n=6)	p value
Size of specimen resected by FTR, mm (IQR)	30 (23-31)	26 (19-30)	0.171
Size of cancer, mm (IQR)	9.5 (5-15)	5.3 (4.3-7.5)	0.171
Depth of invasion, μ m (IQR)	2000 (1150-2600)	3400 (3175-3750)	<0.001
Margin clear (R0)	12 (100)	5 (83)	0.034
Vertical margin, mm (IQR)	1.4 (0.7-2.3)	3.5 (1.5-5.5)	0.289
Horizontal margin, mm (IQR)	3 (2-4.3)	2.5 (0.5-3)	0.423
Lymphovascular invasion	3 (25)	6 (100)	0.003
Intermediate (5-9) tumour budding	1 (8)	1 (17)	0.596
Perineural invasion	1 (8)	2 (33)	0.034
Degree of differentiation			
Well/moderate	9 (75)	5 (83)	0.180
Poor	0 (0)	1 (17)	0.051
Stage			
T1NxMx	9 (75)	2 (33)	0.087
T2NxMx	3 (25)	4 (67)	0.087
Referred for surgery	4 (33)	4* (67)	0.18
Cancer in surgical specimen	0/4 (0)	0/3 (0)	0.596
Referred for endoscopic surveillance	8 (67)	2 (33)	0.49

Recurrence at colonoscopy	0 (0)	1/2 (50)	0.035
Endoscopic surveillance not due	1 (13)	0 (0)	0.197

*There were 3 surgical specimens. Case 4 was found to have metastatic disease during surgical work-up and did not undergo surgery.

	Histopathological data	Tumour depth, μm	Deepest layer resected	Vertical margin, mm	Horizontal margin, mm	Outcome
Patient 1	Poor differentiation, LVI+, Bd2, PNI+	4000	Subserosal fat	0	0	Metastatic disease, no surgical resection
Patient 2	Moderate differentiation, LVI+, Bd1, PNI+	2600	Subserosal fat	2	3	Transverse colon resection, no cancer
Patient 3	Moderate differentiation, LVI+, Bd2, PNI+	3400	Subserosal fat	6	2	Extended right hemicolectomy, no cancer
Patient 4	Moderate differentiation, LVI+, Bd1, PNI-	4500	Subserosal fat	6	8	Right hemicolectomy, no cancer
Patient 5	Moderate differentiation, LVI+, Bd1, PNI-	500	Submucosa	3	0.5	Right hemicolectomy, no cancer
Patient 6	Moderate differentiation, LVI+, Bd1, PNI-	1200	Muscularis propria	0.9	0.9	Total colectomy, no cancer
Patient 7	Moderate differentiation, LVI+, Bd1, PNI-	2000	Submucosa	0.7	5	Right hemicolectomy, no cancer
Lesion 8	Well differentiated, LVI-, Bd1, PNI-	0	Muscularis mucosa	1	3	Low anterior resection, no cancer

LVI, lymphovascular invasion; Bd1, tumour budding 1-4; Bd2, tumour budding 5-9; PNI, perineural invasion.

Chapter 7 - Follow-up of 35 appendiceal orifice neoplasms resected by endoscopic full thickness resection

Publication:

Cronin O, Meys K, Yuen S, Vij A, Gonda T, Goodman AJ, Bourke MJ, Haber GB. Follow-up of 35 appendiceal orifice neoplasms resected by endoscopic full thickness resection. *Gastrointestinal Endoscopy* [Under review].

In brief:

- Endoscopic resection of lesions at the appendiceal orifice offer a unique set of challenges.

Contribution:

- Endoscopic full thickness resection (EFTR) offers a viable alternative to conventional surgery for the en bloc resection of these lesions.

Follow-up of 35 appendiceal orifice neoplasms resected by endoscopic full thickness resection.

Authors: Oliver Cronin MBBS,^{1,4} Kayla Meys APRN,³ Sofia Yuen MD,³ Abhinav Vij MD,³ Tamas Gonda MD,³ Adam J Goodman MD,³ Michael Bourke MBBS,^{1,2} Gregory B. Haber MD.³

1. Westmead Hospital, Department of Gastroenterology and Hepatology, Sydney, New South Wales, Australia
2. Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia
3. Division of Gastroenterology and Hepatology, Department of Medicine, New York University Langone Health, New York, New York, USA
4. Northern Health, Melbourne, Australia.

Corresponding author:

Dr Gregory B. Haber MD FRCP (C)
Professor of Medicine
Chief of Endoscopy
Director of Advanced Therapeutics and Innovation
NYU Langone Health
New York, NY

Abstract

Background and Aims

Endoscopic full-thickness resection (EFTR) is an established, safe technique for the resection of appendiceal orifice (AO) neoplasms. Post-EFTR appendicitis is a recognised adverse event. There are no systematic reviews and a paucity of literature which has assessed outcomes especially with respect to delayed appendicitis, mucocele, or fistula formation. We aimed to evaluate efficacy of EFTR for AO lesions.

Patients and Methods

Consecutive AO lesions referred for consideration of EFTR were prospectively studied. Multiple data points were recorded including technical success, EFTR histopathological data, adverse events, and follow-up surveillance data by colonoscopy. Surveillance CT was performed due to concern of potential mucocele from the obstructed remnant appendix.

Results

Over a 4-year period to July 2023, 37 AO lesions were referred to a tertiary center for consideration of EFTR. EFTR was attempted in 35 (95%) lesions. Most lesions were small [median size 10mm, interquartile range (IQR) 10-15mm], Paris 0-IIa morphology (n=32, 91%) with serrated histopathology (n=17, 49%). R0 resection was achieved in all EFTR cases (n=30, 100%). Adverse events included appendicitis (n=4, 11%) and delayed bleeding (n=2, 6%).

At 6-month (IQR 4-6 months) surveillance colonoscopy, there was 1 (3%) case of residual lesion. This was successfully treated endoscopically, confirmed on a second surveillance colonoscopy. There was one case of appendicitis of the remnant at 7 months. At surveillance CT abdomen/pelvis (median 15 months, IQR 7-37 months), 2/17 (12%) fistulas were identified. Both patients had presumed adhesions due to abdominal surgery prior to EFTR.

Conclusions

EFTR is an effective technique for the curative resection of small, Paris 0-IIa (<20mm) AO lesions. Appendicitis is a relatively common adverse event but often managed conservatively.

The long-term significance post-EFTR fistulas remains unclear. Caution should be exercised when considering EFTR in a patient with prior regional surgery.

Key Words: appendiceal orifice; full-thickness resection; endoscopy; adenoma; polyp.

Introduction

Endoscopic Resection (ER) of lesions involving the peri-appendiceal orifice (AO) presents a unique set of challenges, mostly related to site-specific anatomy. The appendix is a narrow, blind-ended tube. The lumen is too narrow to be accessed endoscopically. Additionally, the colonic wall in the cecum is thinnest compared to the rest of the colon. AO lesions may also represent a more aggressive polyp sub-variant compared to the rest of the colon. [1] For these reasons, AO lesions have traditionally been managed with surgical resection.

Given the uncommon nature of AO lesions, technical data around the efficacy and safety of ER is limited. One large study from Japan (n=76) demonstrated successful endoscopic submucosal dissection (ESD) of AO lesions, although procedure time was long [mean 91minutes, standard deviation (SD) 52 minutes] and only 40% of these lesions actually involved the AO. [2] Another large (n=38) multi-center study described the efficacy and safety of EMR for resection of AO lesions. [3] EMR was attempted for 27 lesions (71%) and was successful in most cases (n=25/27, 93%). However, 11 (29%) AO lesions were unable to be attempted due to deep extension into the appendiceal lumen or due to suspected submucosal invasive cancer (SMIC). [3]

Given that extension of AO lesions into the narrow AO lumen appears common, an integrated Endoscopic full-thickness resection device (FTRD; Ovesco Endoscopy, Tübingen, Germany) was developed to overcome some of these barriers. The FTRD is a single-clip closure and resection device permits full thickness resection (FTR) without exposing the peritoneum to luminal contents during resection. [4-6] An accepted disadvantage of the FTRD is lesion size, limited to the volume of tissue that can be pulled into the over-the-scope cap. However, an observational study (n=69) has demonstrated efficacy of a hybrid EMR/FTR (H-FTR)

technique for resection of larger lesions (mean lesion size 39.2mm, standard deviation 13.6mm). [7]

Efficacy and safety of EFTR using the FTRD has been described in a large (n=66) retrospective, multicenter study. [8] Clinical success was achieved in most cases (n=53/66, 80%) and R0 resection was achieved in 52/56 (93%) cases, with a recurrence rate of 5/60 (12%). Recruitment at each center was low volume (18 centers over 45 months). Larger studies at higher volume centers, with long term follow-up data are needed to better evaluate efficacy and safety. No study to date has completed surveillance imaging in addition to a surveillance colonoscopy to assess for extra-luminal appendiceal stump recurrence or for mucocele presence. This study aimed to prospectively assess the efficacy of AO-EFTR at a high-volume single center.

Methods

The study was approved by the Institutional Review Board of New York University Langone Health. All authors had access to the study data and reviewed and approved the final manuscript.

Between July 2019 and July 2023, eligible consecutive participants were enrolled at a single high-volume endoscopic tissue resection center in the United States of America. All patients had undergone a complete colonoscopy prior to inclusion by either a referring endoscopist or by one of our participating advanced endoscopists. Eligibility criteria included confirmed presence of an AO lesion. Patients were excluded from endoscopic FTR and referred to a multidisciplinary team if there was evidence of a deeply invasive cancer.

All endoscopic procedures were performed by one of three study investigators (accredited gastroenterologists with advanced training and an established tertiary referral practice in colorectal endoscopic resection) or by a senior interventional endoscopy fellow under the direct supervision of one of the investigators. Prior to resection, all lesions were re-assessed optically using high-definition white light, narrow-band imaging (NBI), and near focus.

Resection was performed for all lesions using the FTRD system (Ovesco, Tübingen, Germany) using a standardized en bloc-FTR (E-FTR) or Hybrid EMR/FTR (H-FTR) technique. [7, 9] For lesions ≥ 20 mm, the initial step was to remove the surrounding peri-AO lesion by EMR. The remaining polyp at the AO was then removed using the FTRD.

Indication for FTR was an AO lesion with a distal margin unable to be visualised with an adult colonoscope due to extension into the AO lumen. Primary outcome measures were technical success and R0 resection rate. Technical success was defined as successful advancement of the FTRD to the lesion, entrapment of the lesion, successful clip deployment and snare resection, and en bloc resection without evidence of macroscopic residual pathology. [10] R0 resection was defined as a histologically complete resection (lateral and vertical margins clear of neoplastic tissue). For H-FTR, the lateral margins of the FTR specimen may have been contiguous with the EMR resection bed. For H-FTR, the definition of R0 resection was modified to only a vertical margin free of neoplasm as the lateral margin is always positive in the hybrid technique.

Secondary outcomes were adverse events including intraprocedural bleeding, post-operative pain, post-operative appendicitis, and delayed bleeding. Intraprocedural bleeding was defined as bleeding that required the use of coagulation forceps for hemostasis. Appendicitis diagnosis was made clinically and confirmed with imaging. A delayed bleed was recorded if the patient required re-admission within a 14-day period post EFTR with per-rectal bleeding. Recurrence was defined as neoplastic tissue seen optically or histologically at surveillance colonoscopy, performed 3-6 months after resection. All polypectomy scars were biopsied. Follow-up computed tomography abdomen/pelvis (CT A/P) with oral contrast was performed due to concern of potential mucocele from the obstructed remnant appendix.

FTR procedure

All procedures were performed by experienced endoscopists, who underwent training in the use of the device in a live animal model before patient use. Procedures were performed with monitored anesthesia care with propofol intravenous sedation. Patients were instructed to continue aspirin use during the periprocedural period; all other anticoagulants and antiplatelet medications were temporarily held, consistent with guideline

recommendations. Carbon dioxide gas was used for insufflation. Bowel cleansing was achieved using a standard split-regimen bowel preparation. Standard colonoscopy was first performed with an adult colonoscope (CF-HQ190L/I; Olympus) with a distal cap attachment (D-201-14304; Olympus).

All lesions were carefully examined using magnification endoscopy under white-light and narrow-band imaging to exclude clear evidence of deeply invasive carcinoma. After lesion assessment, a decision was made regarding the suitability of the lesion for standard EMR, E-FTR, or H-FTR. For H-FTR, the periphery of the lesion was lifted using a standard injection solution of either normal saline solution or 3% hydroxyethyl starch with 1 mg/L (1 part per million dilution) of epinephrine and methylene blue. Standard piecemeal EMR was performed around the periphery of the lesion. Resection was continued until only the non-lifting portion of the lesion remained.

The FTR procedure has been described in detail elsewhere. [10] Marking of the lesion margin was not necessary as the appendiceal location was always visible. A second colonoscope preloaded with the FTRD was then advanced to the lesion (Figure 1). Although a dummy sizing cap is available (prOVE Cap; Ovesco), it was not routinely used. If difficulty traversing loops of the colon was encountered, the following manoeuvres were attempted: changing patient position, manual abdominal pressure, water immersion, administration of glucagon, and use of an 18- to 20-mm controlled radial expansion balloon.

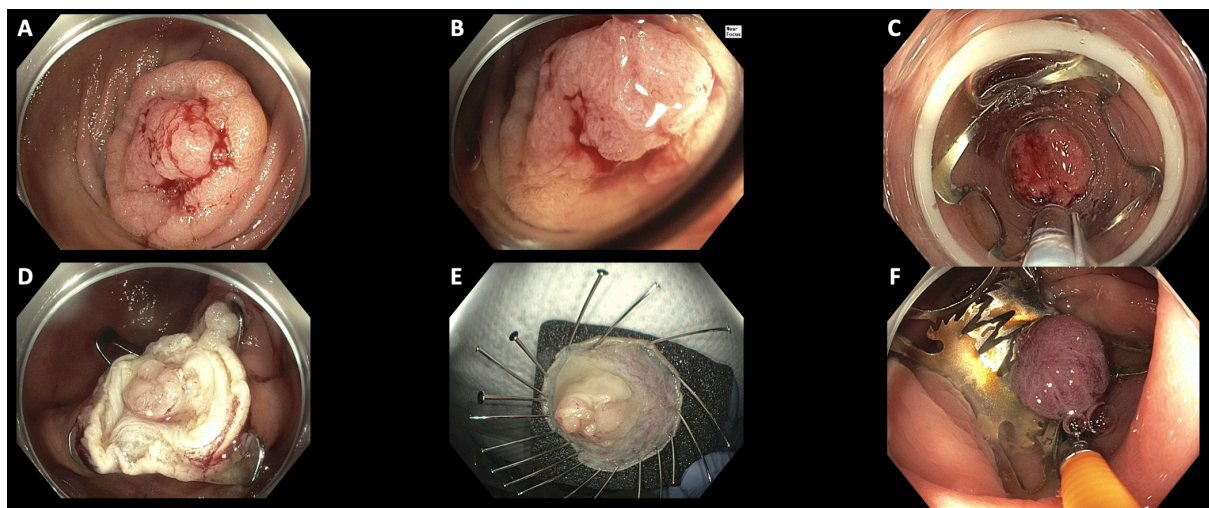


Figure 1. Endoscopic full thickness resection of a 20mm Paris 0-IIa appendiceal orifice lesion. (A) A 20mm Paris 0-IIa appendiceal orifice lesion assessed with white light endoscopy and (B) near focus, illustrating Kudo pit pattern Vi centrally. (C) Advancement of

the colonoscope with the full thickness device. (D) Post-deployment with exposed serosa. (E) Pinned specimen viewed from serosal side. (F) Surveillance colonoscopy with biopsy-proven reactive hyperplastic tissue.

A grasping forceps was used to grasp the lesion and gently pull it into the cap, with adjuvant use of suction where necessary. The FTRD clip was then deployed. This was immediately followed by snare closure by an assistant and electrosurgical excision of the entrapped tissue using pure cutting current. The endoscope with the tissue specimen was withdrawn, and the neoplastic tissue was pinned, measured, and placed in formalin for histopathology (Figure 1, image E). A standard adult colonoscope with a distal cap attachment was then reintroduced to assess the area of resection and to ensure secure clip placement.

Patients were observed in the recovery unit for approximately 1 hour and if pain-free were discharged home the same day on a clear fluid diet for 24 hours. Ciprofloxacin 400 mg intravenously was administered intraprocedural and continued orally at 500 mg twice a day for 1 week for appendicitis prophylaxis.

Histopathology evaluation

After ER, specimens were collected and processed for histopathology review. Histopathology review was completed by 2 expert gastrointestinal pathologists. [11]

Data extraction and analysis

Prospectively collected data included: (i) patient characteristics (age, sex, American Society of Anesthesiologists [ASA] classification); (ii) LNPCP characteristics (location, size, Paris classification, surface granularity, Kudo pit pattern, SMIC and resection technique; procedure time (iv) histopathological evaluation.

Statistical analysis

SPSS version 29.0 (IBM Corp., Armonk, New York, USA) was used for data analysis. The continuous variables age and lesion size were summarized as median (interquartile range [IQR]) following assessment of non-normality using Shapiro–Wilk’s test. Categorical variables were summarized as frequencies (%). Mann–Whitney tests were used to test for differences in continuous distributions between the groups. Chi-squared tests (or exact

permutation tests if required) were used to test for association between the categorical variables.

Patient and public involvement

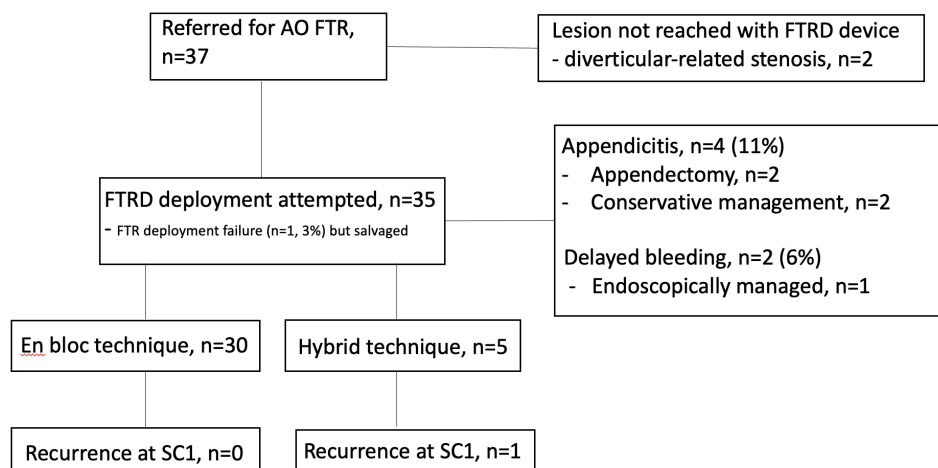
Neither patients nor the general public were involved in the design or execution of this study.

Results

Demographic and lesion characteristics

Over 48 months to July 2023, 37 consecutive appendiceal orifice lesions were referred to a tertiary center for consideration of EFTR (Figure 2).

Figure 2. Flow chart for 37 patients referred for consideration of endoscopic full thickness resection of an appendiceal orifice (AO) lesion.



2 (5%) lesions were unable to be accessed with the FTRD due to luminal stenosis of the sigmoid colon secondary to diverticulosis. EFTR was performed in 35 (95%) lesions of which 30 (86%) lesions were resected by E-FTR and 5 (14%) lesions were resected by H-FTR (Table 1). Most lesions were small [median size 10mm, interquartile range (IQR) 10-15mm], Paris 0-IIa morphology (n=32, 91%) and had serrated histopathology (n=17, 49%). R0 resection was achieved for all E-FTR cases (n=30, 100%). There was one adenocarcinoma, cured with an R0 resection.

Adverse Events

There were 4 (11%) cases with early post-procedural appendicitis, all of whom presented within 7 days post FTR. 2 required appendectomy and 2 were managed conservatively. There was a fifth patient with appendicitis, who presented 7 months post-FTR. It is unclear if the appendicitis was influenced by the OVESCO clip which remained in situ, the occluded remnant post FTR or was unrelated to the previous FTR.

2 (6%) patients presented with delayed bleeding, one of whom required a repeat colonoscopy and treatment of a bleeding vessel with haemostatic forceps.

Follow-up

At 6-month (IQR 4-6 months) surveillance colonoscopy, there was 1 (3%) lesion with residual lesion. The residual tissue was removed by EMR, but residual adenoma remained 4 months later at the second surveillance colonoscopy. This was successfully removed by EMR with a plan of ongoing endoscopic surveillance.

Surveillance CT A/P was completed in 17 (49%) cases (median time 15 months, IQR 7-37 months). 2/17 (12%) patients were identified with fistulas at the site of previous AO FTR, both of whom had prior abdominal surgery potentially resulting in adhesions of the appendix and cecum. (Figures 3-4). The first patient presented with hematuria 1 month post FTR. An entero-colonic fistula was diagnosed. The patient had a remote history of treated bladder cancer with a cystectomy and neobladder reconstructive surgery with ileal pouch 10 years prior. The fistula was managed with an appendectomy and fistula closure. The second had previously had an uncomplicated appendectomy 5 years prior to FTR (Figure 3). A post-appendectomy surgical clip was observed at the superior lip of the entero-colonic fistula on surveillance colonoscopy (Figure 3, image D-E). Given the patient was asymptomatic, the patient and clinician elected on conservative management. All other imaging for patients who underwent surveillance was unremarkable.

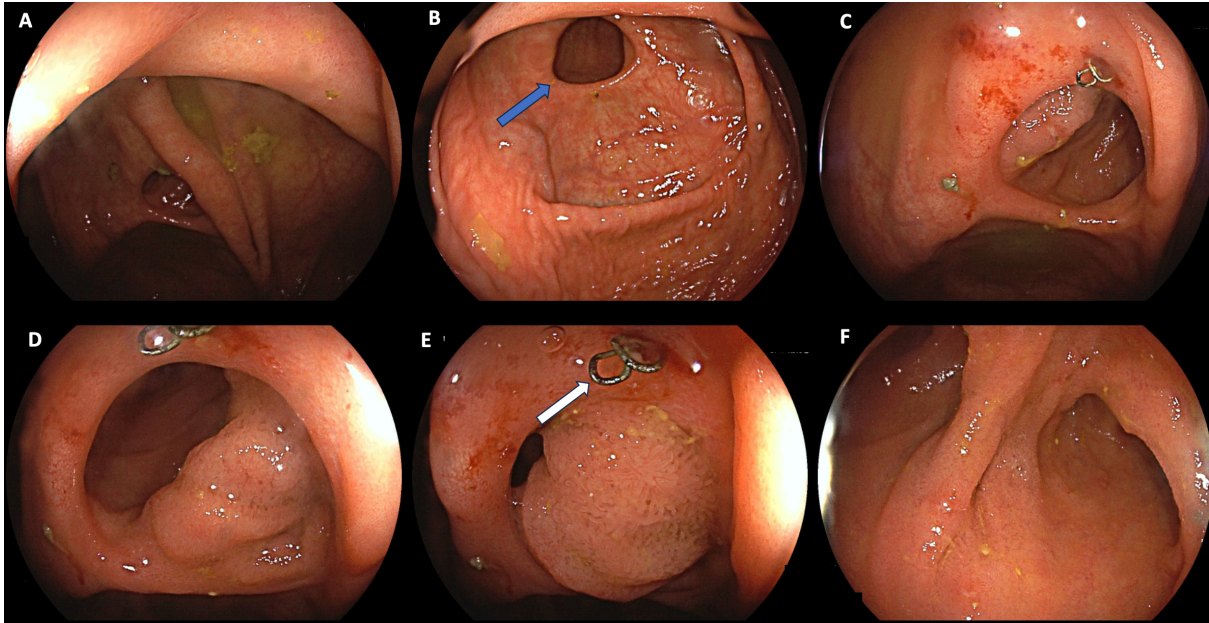


Figure 3. Entero-colonic fistula observed 6 months post endoscopic full thickness resection of a 20mm Paris0-IIa lesion at the appendiceal orifice. (A) View from the cecum with ileocecal valve located at 11 o'clock position. (B) Fistula at site of previous EFTR. (C-E) Appendectomy related surgical clip at superior margin of fistula. (F) View from within the fistula.

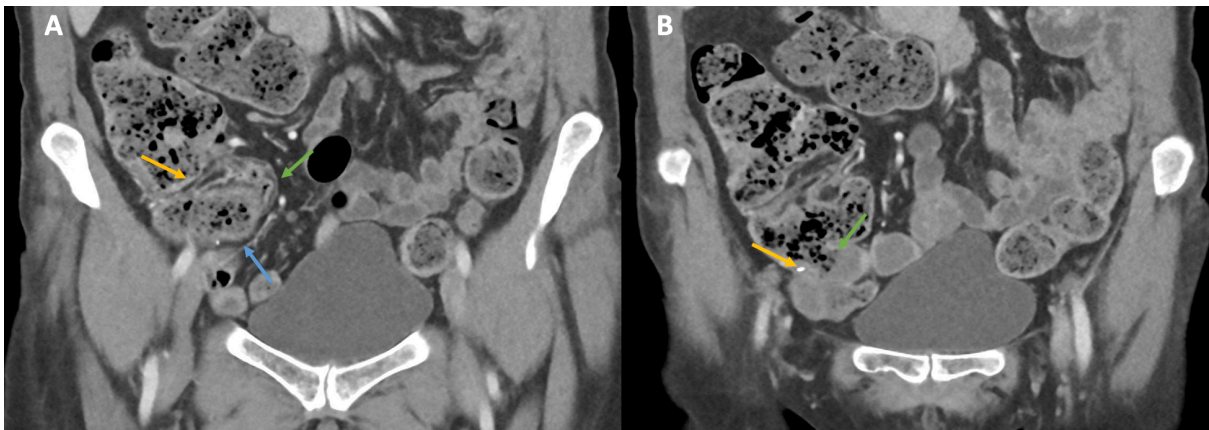


Figure 4A. Coronal CT Contrast Enhanced image of the abdomen: Yellow arrow denotes the ileo-cecal valve. Green Arrow denotes the terminal ileum. Blue arrow denotes the cecum.

Figure 4B. Yellow arrow annotates a surgical clip from a prior appendectomy. Green arrow annotates a fistula between the cecum and distal ileum, with fecalized cecal contents protruding through the defect into the distal ileum.

Discussion

ER of colorectal lesions has become the standard of care for most lesions. Historically there were several rare exceptions including AO lesions with deep extension, which was beyond the capability of endoscopic assessment and resection. The advent of the FTRD has made it possible for the complete resection of what was once an endoscopically unresectable lesion. To our knowledge, this is the largest single center study to evaluate the efficacy and safety of EFTR of AO lesions. We have demonstrated both safety and efficacy of this procedure. Post-procedural appendicitis is relatively common, but half of these cases were managed conservatively. This is also the only study to our knowledge which has systematically completed follow-up imaging, as a routine standard of care to exclude extraluminal complications.

EFTR is not the only option for ER of AO lesions. EMR is an effective, safe alternative to EFTR for AO lesions if the distal margins can be visualised. A large (n=38), multicenter observational study demonstrated EMR as a safe and effective technique. [3] There were no cases with post-procedural appendicitis or perforation. There were 5/22 (23%) cases with minor recurrence at the first surveillance colonoscopy and 3/5 (60%) were endoscopically treated. A major disadvantage of EMR is that it requires visualisation of the entire lesion. Underwater EMR (U-EMR) has also been described with the aim of floating the lesion into the lumen or gently teasing out the orifice with forceps to improve views. [12] There were 27 lesions (median size 15mm) included in the study of which 5 (19%) were on the AO rim and 22 (81%) extended into the AO. Successful U-EMR was achieved in 24 (89%) lesions and there were 2 (10%) lesions with residual adenoma at follow-up. [12] ESD is more time-consuming compared to EMR or EFTR without perceivable benefit for AO lesions, particularly for those lesions which are benign. A superior alternative to ESD for AO lesions is either EFTR or a surgical approach, if conventional EMR is not possible due to deep AO extension.

Parallel to advances in ER, there have been great innovations to laparoscopic surgical techniques for the partial removal of the cecum, with preservation of the ileocecal valve. [13] Other techniques such as a transcolonic endoscopic appendectomy may also be viable, although to date case numbers are small. [14] Given the simplicity and improved risk profile

of an appendectomy, an individualised decision approach should be undertaken, explaining the benefits and disadvantages of both surgery and EFTR. In our experience most patients prefer endoscopic removal even when quoted a risk of 15%. Surveillance is mandatory for all polyp patients whether resected surgically or endoscopically.

Appendicitis is a known complication of EFTR. In our cohort, 4/35 (11%) patients developed appendicitis. This is similar to that reported in the literature. A multicenter retrospective study reported 7/50 (14%) patients developed appendicitis, of whom 4/7 (57%) were managed conservatively. [15] Specific risk factors to predict patients at greater risk of developing appendicitis in the setting of EFTR have not been established. Endoscopists must make patients aware of this relatively common complication to facilitate early recognition and prompt treatment.

Fistula formation post EFTR is uncommon and has been limited to several case reports. [16, 17] To our knowledge, this is the first study to incorporate routine imaging as a standard of care, in addition to a surveillance colonoscopy, to identify extraluminal complications at the appendiceal stump. Importantly, results from this study may underestimate the true rate of fistula formation given that 18/35 (51%) of patients did not complete a follow-up CT. Both of our patients who developed fistulas had undergone prior abdominal surgery. It seems plausible that due to adhesive fibrosis of that area, previously discrete structures could become fused together and then be inadvertently pulled into the FTRD. Previous surgery may also result in low level chronic inflammation.

Surveillance data from this study demonstrates no cases of recurrence for lesions removed by E-FTR. There was one (1/5, 20%) case of recurrence for lesions removed by H-FTR. A hybrid technique has previously been shown as effective for resection of larger lesions. [7] The higher recurrence rate for H-FTR technique in this study is important to recognise. However further interpretation may be less meaningful given the small case number (n=5).

There are several limitations to this study. Firstly, this is a small sample size, but the largest study of AO lesions resected by FTR from a single center. Secondly, given the small patient numbers, it is not possible to identify potential risk factors for individual complications with

a multivariate analysis. Thirdly, a direct comparison with prospective appendectomy data for AO polyps was not possible at this center. Direct comparison would strengthen the fundamental understanding of where the FTRD fits within the AO lesion decision making pathway to better inform clinicians and patients. Also, a classification system of the degree of circumferential lesion involvement of the AO could have strengthened the findings. Finally, total procedure time was not recorded for all cases and would have provided another valuable comparator to ESD.

In conclusion, EFTR is an effective technique for the curative resection of select, small Paris 0-IIa (<20mm) AO lesions. Alternatives include EMR if the distal aspect of the lesion can be visualised. Appendectomy is also a reasonable approach, especially for lesions at high risk of malignancy. Clinicians should exert caution when performing EFTR for patients with risk of adhesions to the appendix or cecum. The moderate risk of appendicitis should be discussed with the patient prior to resection to facilitate prompt recognition and management.

References

1. Rubio CA. Serrated adenomas of the appendix. *J Clin Pathol*. 2004;57(9):946-9.
2. Jacob H, Toyonaga T, Ohara Y, et al. Endoscopic submucosal dissection of cecal lesions in proximity to the appendiceal orifice. *Endoscopy*. 2016;48(9):829-36.
3. Tate DJ, Desomer L, Awadie H, et al. EMR of laterally spreading lesions around or involving the appendiceal orifice: technique, risk factors for failure, and outcomes of a tertiary referral cohort (with video). *Gastrointest Endosc*. 2018;87(5):1279-88.e2.
4. Schmidt A, Meier B, Caca K. Endoscopic full-thickness resection: Current status. *World J Gastroenterol*. 2015;21(31):9273-85.
5. Xu M, Wang XY, Zhou PH, et al. Endoscopic full-thickness resection of colonic submucosal tumors originating from the muscularis propria: an evolving therapeutic strategy. *Endoscopy*. 2013;45(9):770-3.
6. Sedarat A. Clips for closure of full-thickness defects. *Techniques and Innovations in Gastrointestinal Endoscopy*.129-35.

7. Mahadev S, Vareedayah AA, Yuen S, et al. Outcomes of a hybrid technique using EMR and endoscopic full-thickness resection for polyps not amenable to standard techniques (with video). *Gastrointest Endosc.* 2021;94(2):358-67.e1.
8. Ichkhanian Y, Barawi M, Seoud T, et al. Endoscopic full-thickness resection of polyps involving the appendiceal orifice: a multicenter international experience. *Endoscopy.* 2022;54(1):16-24.
9. Aslanian HR, Sethi A, Bhutani MS, et al. ASGE guideline for endoscopic full-thickness resection and submucosal tunnel endoscopic resection. *VideoGIE.* 2019;4(8):343-50.
10. Schmidt A, Beyna T, Schumacher B, et al. Colonoscopic full-thickness resection using an over-the-scope device: a prospective multicentre study in various indications. *Gut.* 2018;67(7):1280-9.
11. Rex DK, Hassan C, Bourke MJ. The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management. *Gastrointest Endosc.* 2017;86(2):253-63.
12. Binmoeller KF, Hamerski CM, Shah JN, et al. Underwater EMR of adenomas of the appendiceal orifice (with video). *Gastrointest Endosc.* 2016;83(3):638-42.
13. Fujino S, Miyoshi N, Noura S, et al. Single-incision laparoscopic cecectomy for low-grade appendiceal mucinous neoplasm after laparoscopic rectectomy. *World journal of gastrointestinal surgery.* 2014;6(5):84.
14. Chen T, Xu A, Lian J, et al. Transcolonic endoscopic appendectomy: a novel natural orifice transluminal endoscopic surgery (NOTES) technique for the sessile serrated lesions involving the appendiceal orifice. *Gut.* 2021;70(10):1812-4.
15. Schmidbaur S, Wannhoff A, Walter B, et al. Risk of appendicitis after endoscopic full-thickness resection of lesions involving the appendiceal orifice: a retrospective analysis. *Endoscopy.* 2021;53(4):424-8.
16. Oliviero G, Gagliardi M, Napoli M, et al. Fatal Outcome Consequent to an Endoscopic Full Thickness Resection of a Colonic Lateral Spreading Tumor: A Case Report. *Am J Case Rep.* 2020;21:e922855.
17. Vargas JI, Rowsell C, Mosko JD. Enterocolonic fistula after endoscopic full-thickness resection of a peri-appendiceal orifice adenoma. *Gastrointest Endosc.* 2020;91(6):1405-6.

Table 1. Patient characteristics for full thickness resections of the appendiceal orifice (n=35)	
Mean age, years (IQR)	65 (59-74)
Male patients	16 (46)
American Society of Anesthesiologists (ASA) classification	
ASA 1	8 (23)
ASA 2	17 (49)
ASA 3	10 (29)
Lesion size, millimeters (IQR)	10 (10-15)
Morphology	
Paris 0-IIa	32 (91)
Paris 0-Is	3 (9)
Resection technique	
En bloc	30 (86)
Hybrid	5 (14)
Technical Success	35 (100)
Length of Stay, days	1 (1-1)
Histopathology	
Sessile serrated lesion	17 (49)
Tubular	9 (26)
Tubulovillous	6 (17)
Cancer	1 (3)
Other histology	2 (6)
R0 resection*	30 (100)
Complications	
Appendicitis	4 (11)
Delayed bleed	2 (6)
Surveillance	
Referred for surveillance colonoscopy (SC1)	33 (94)

Timing of SC1, months (IQR)	6 (4-6)
Residual lesion**	1 (3)
Completed surveillance imaging	17 (49)
Timing of imaging, months (IQR)	15 (7-37)
Abnormal imaging	2/17 (12)

*Includes all lesions removed by E-FTR.

** Recurrence rate 1/5 (20%) for hybrid technique and 0/30 (0%) for en bloc technique.

Chapter 8 - Endoscopic resection of large anastomotic polyps is safe and effective

Publication:

Cronin O, Gupta S, Gauci J, Whitfield A, O'Sullivan T, Abuarisha M, Wang H, Lee EY, Williams SJ, Burgess NG, Bourke MJ. Endoscopic resection of large anastomotic polyps is safe and effective. *Endoscopy* 2024 Feb;56(2):125-130.

In brief:

- Large adenomatous anastomotic polyps (LAAPs) are uncommon.
- Endoscopic resection can be challenging, mainly due to dense fibrosis.
- These challenges can be overcome with specific modification such as cold-biopsy forceps avulsion with adjuvant snare tip soft coagulation (CAST).

Contribution:

- LAAPs can be effectively and safely resected endoscopically, without the need for surgery.

Title: Endoscopic resection of large anastomotic polyps is safe and effective.

Short Title: Endoscopic resection of large anastomotic polyps

Oliver Cronin^{1,2}, Sunil Gupta^{1,2}, Julia Gauci^{1,2}, Anthony Whitfield^{1,2}, Timothy O'Sullivan^{1,2}, Muhammad Abuarisha^{1,2}, Hunter Wang^{1,2}, Eric Lee^{1,2}, Stephen Williams^{1,2}, Nicholas G Burgess^{1,2}, Michael J Bourke^{1,2}.

¹ Westmead Hospital, Department of Gastroenterology and Hepatology, Westmead, New South Wales, Australia

² University of Sydney Westmead Clinical School, Department of Medicine, Sydney, New South Wales, Australia

Corresponding author

Michael J. Bourke, MBBS, FRACP

Westmead Hospital, Department of Gastroenterology and Hepatology

University of Sydney, Westmead Clinical School

Suite 106a 151–155 Hawkesbury Road

Sydney

New South Wales, 2145

Australia

Email: michael@citywestgastro.com.au

Conflict of Interest

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

The remaining authors have no conflicts of interest to disclose

Financial support

The Cancer Institute of New South Wales provided funding for a research nurse and data manager to assist with the administration of the study. There was no influence from either institution regarding study design or conduct, data collection, management, analysis, interpretation, preparation, review or approval of the manuscript.

Data transparency statement

All data relevant to the study are included in the article.

Author Contributions

Oliver Cronin	Study concept and design, acquisition of data, analysis and interpretation, drafting, critical revisions, statistical analysis, approval of final manuscript.
Sunil Gupta	Acquisition of data.
Julia Gauci	Acquisition of data
Anthony Whitfield	Acquisition of data
Timothy O’Sullivan	Acquisition of data.
Muhammad Abuarisha	Acquisition of data
Hunter Wang	Acquisition of data.
Eric Lee	Acquisition of data
Stephen Williams	Acquisition of data
Nicholas G Burgess	Critical revision of the manuscript
Michael J Bourke	Critical revision of the manuscript, study supervision.

The abstract of this study was accepted as a poster presentation at the Australian Gastroenterology Week (AGW) conference in Sydney, Australia 2022 and as a poster presentation at Digestive Diseases Week (DDW) in Chicago, United States of America 2022.

Clinicaltrials.gov identifiers: NCT01368289; NCT02000141.

Abbreviations

ER	Endoscopic resection
EMR	Endoscopic mucosal resection

CAST	Cold-forceps avulsion with adjuvant snare-tip soft coagulation
CRC	Colorectal cancer
DMI	Deep mural injury
ESD	Endoscopic submucosal dissection
IQR	Interquartile range
LAAP	Large (≥ 20 mm) adenomatous anastomotic polyps
LNPCP	Large non-pedunculated colorectal polyp
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SMIC	Submucosal invasive cancer

Abstract

Background

Large (≥ 20 mm) adenomatous anastomotic polyps (LAAPs) are uncommon. Data pertaining to their prevalence, characteristics, and the efficacy of endoscopic resection (ER) are absent. A safe and effective strategy for ER would reduce morbidity and healthcare costs.

Methods

Large nonpedunculated colorectal polyps of ≥ 20 mm (LNPCPs) referred for ER were prospectively studied. Multiple data points were recorded including anastomotic location, polyp morphology, resection modality, complications, and technical success.

Results

Over 7 years until November 2022, 2629 lesions were referred. Of these, 10 (0.4%) were LAAPs (median size 35 mm [interquartile range (IQR) 30–40 mm]). All LAAPs were removed by piecemeal endoscopic mucosal resection (EMR), most ($n = 9$; 90%) in combination with cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST). On comparison of the LAAP group with the conventional LNPCP group, CAST was more commonly used (90% vs. 9%; $P < 0.001$) and deep mural injury (DMI) type II was more frequent (40% vs. 11%, $P = 0.003$); however, significant DMI (III–V) did not occur. At 6-month (IQR 5.25–6 months) surveillance, there was no recurrence in any of the 10 cases. There were no serious adverse events.

Conclusions

LAAPs present unique challenges owing to their location overlying an anastomosis. Despite these challenges they can be safely and effectively managed endoscopically without recurrence at endoscopic follow-up.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the burden of disease is projected to increase by 60% by 2030 [1–3]. Most CRCs develop from premalignant polyps. Most non-metastatic CRCs are treated by surgical excision. Postoperatively, regular surveillance colonoscopies are recommended to ensure that recurrence or synchronous lesions are detected and treated early [4].

Although uncommon, it is not surprising that there is a potential for large (≥ 20 mm) adenomatous anastomotic polyps (LAAPs) to develop at the site of a colonic anastomosis. These may be due to de novo polyp formation, recurrence related to inadequate margins at the initial resection, or a discrete polyp that was present but not identified at the time of surgery. LAAP removal is more likely to be challenging owing to the altered luminal anatomy and the underlying postsurgical fibrosis. It is probable that many such patients are managed by further surgery. Data are therefore limited and evidence for the efficacy of endoscopic resection (ER) is absent. An effective and safe strategy for the ER of LAAPs is required. The burden of CRC is expected to increase and further data on management of LAAPs would be valuable. We therefore evaluated our experience with LAAPs.

Methods

This manuscript has been prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [5,6]. All authors had access to the study data and reviewed and approved the final manuscript.

Between November 2015 and July 2022, eligible participants were enrolled at a single high volume endoscopic tissue resection center in Australia. Eligibility criteria included the

presence of a LAAP in the context of previous colorectal surgery. All endoscopic procedures were performed by one of four study investigators (accredited gastroenterologists with advanced training and an established tertiary referral practice in colorectal ER) or a senior interventional endoscopy fellow under the direct supervision of one of the investigators.

Resection was performed with a standardized technique [7–12]. The lesion was assessed optically using high-definition white light, narrow-band imaging (NBI), and near focus. Submucosal injection (indigo carmine and Gelofusine) was used before endoscopic mucosal resection (EMR) with a hot snare. The size of the snare was decided by the endoscopist at the time of the resection. Any poorly lifting areas were removed with cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST). Intraprocedural bleeding was defined as bleeding that required the use of coagulation forceps for hemostasis.

Recurrence post-anastomotic polypectomy was defined as neoplastic tissue seen optically or histologically at surveillance colonoscopy, performed 6 months after resection. All polypectomy scars were biopsied.

Histopathology evaluation

After ER, specimens were collected and processed for histopathology review, in accordance with the Australasian Gastrointestinal Pathology Society guidelines [13]. Histopathology review was completed by expert gastrointestinal pathologists. Cancer was defined by neoplastic invasion into the submucosa [14].

Data extraction and analysis

Prospectively collected data included: (i) patient characteristics (age, sex, American Society of Anesthesiologists [ASA] classification); (ii) LNPCP characteristics (location, size, Paris classification, surface granularity, Kudo pit pattern, submucosal invasive cancer [SMIC]) and resection technique; (iv) histopathologic evaluation.

Statistical analysis

SPSS version 27.0 (IBM Corp., Armonk, New York, USA) was used for data analysis. The continuous variables age and lesion size were summarized as median (interquartile range [IQR]) following assessment of non-normality using Shapiro–Wilk’s test. Categorical variables were summarized as frequencies (%). Mann–Whitney tests were used to test for differences in continuous distributions between the groups. Chi-squared tests (or exact permutation tests if required) were used to test for association between the categorical variables.

Patient and public involvement

Neither patients nor the general public were involved in the design or execution of this study.

Results

Over 84 months until November 2022, 2629 LNPCPs in 2350 patients were referred for ER. Of these, 10 lesions (0.4%) were classified as LAAPs.

Demographic and lesion characteristics

The median patient age was 75 years (IQR 70–80 years). Median lesion size was 35 mm (IQR 30–40 mm). The majority of lesions were granular ($n = 6$; 60%), Paris 0-IIa ($n = 5$; 50%), and had tubulovillous histology ($n = 6$; 60%) (**Table 1**).

Most anastomoses were colo–colonic ($n = 6$; 60%) and most LAAPs ($n = 9$; 90%) were removed by piecemeal EMR in combination with CAST (**Table 2; Figs. 1–3**). On comparison of the LAAP group with the conventional LNPCP group, CAST was more commonly used (90% vs. 9%; $P < 0.001$) and deep mural injury (DMI) type II was more frequent (40% vs. 11%; $P = 0.003$); however, significant DMI (III–V) did not occur. Clip closure was performed in 70% of LAAP cases. Technical success was 100% and at 6-month surveillance (IQR 5.25–6 months), there was no recurrence in any of the 10 cases. There were no serious adverse events, and no perforation or bleeding in the LAAP group. There was also no recurrence identified at second surveillance colonoscopy, which was completed in nine patients (90%) at 19 months (IQR 15–22.5 months) after the initial resection. One patient (10%) did not have a second surveillance colonoscopy owing to their frailty.

Discussion

LAAPs present unique challenges for ER for several reasons. Many anastomoses have inflammatory change, which can create difficulty for lesion and margin recognition. Because of the adherence of the mucosal layer to the scarred and potentially chronically ischemic anastomosis, the risk of DMI or incomplete snare resection is enhanced, which increases the need for adjuvant therapy and for clip closure of DMI type II [15]. Another challenge is the presence of surgical clips, which can impede assessment and resection. Finally, the scarred ridge line (**Fig. 1d**) of the anastomosis with depressed contours on either side can compromise the efficacy of conventional submucosal injection and resection techniques.

There are no published data on the efficacy or safety of ER for LAAPs. We have proposed techniques that can definitively treat LAAPs effectively and safely. Technical success was achieved in all cases without adverse events. At first surveillance colonoscopy at 6 months, there were no recurrences.

Most LAAPs (7/10; 70%) in this series occurred ≥ 5 years after initial surgical resection. These lesions were likely de novo lesions, given the duration from surgery [16]. Three LAAPs occurred within 5 years of surgery. Most likely these were due to a separate polyp not seen at the time of surgery that became involved in the anastomosis.

All LAAPs in this series were resected piecemeal after thorough optical assessment with white light and NBI, which should be used to guide the resection technique [17]. En bloc resection either by EMR or preferably endoscopic submucosal dissection (ESD) is important if there are morphological features consistent with SMIC. In this case series, all polyps were optically assessed as being benign. For scarred non-lifting lesions, some endoscopists may advocate using ESD or endoscopic full-thickness resection (EFTR). Such methods are resource intensive and potentially more hazardous [18]. Our data demonstrate that piecemeal EMR can effectively and safely remove LAAPs without the need for more complex resection techniques.

CAST (**Fig. 2a**) is a well validated, safe, and effective technique for the treatment of scarred non-lifting lesions [19]. Meticulous, precise, and methodical use of the biopsy forceps is

essential to ensure no adenomatous tissue remains. Controlled, purposeful closure of the biopsy forceps by an experienced assistant is equally important to prevent imprecision or slippage of the biopsy forceps. Adjuvant snare-tip soft coagulation of the avulsion bed and surrounding areas ensures thermal destruction of any remaining neoplastic cells [19,20].

Effective treatment of adenomatous tissue at an anastomosis is important for several reasons. Because of the fibrosis typically encountered at an anastomosis, resection is more challenging and time-consuming. Resection in this setting may also theoretically carry enhanced risks of bleeding and perforation owing to neovascularization and fibrosis. For these reasons it is essential that techniques are evoked to achieve complete resection at the first resection attempt.

There are limitations to this study. First, this is a small case series. It is however the only published case series. The data were derived prospectively from a high-volume tissue resection center. Larger case series or trials would be difficult owing to the infrequency of anastomotic polyps. This analysis provides meaningful outcome data for this clinically important problem.

In conclusion, this case series is the only published dataset that addresses the uncommon but clinically important question of how to effectively treat a LAAP. We have demonstrated that ER of LAAPs is effective and safe, without a high risk of bleeding or perforation. We have shown that the non-lifting areas at an anastomosis can be effectively treated with CAST. Significant DMI did not occur and none of the cases showed recurrence at 6-month endoscopic surveillance. Larger datasets are required to address any nuances that may be associated with the anastomotic location or histology of LAAPs.

References

- 1 Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; 67: 7–30
- 2 Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87–108

- 3 Arnold M, Sierra MF, Laversanne M et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017; 66: 683–691
- 4 Cancer Council Australia Clinical Guidelines. Clinical practice guidelines for surveillance colonoscopy Accessed: 14 September 2023. Available from: wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer/Colonoscopy_surveillance
- 5 Cohen JF, Korevaar DA, Altman DG et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* 2016; 6: e012799
- 6 von Elm E, Altman DG, Egger M et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577
- 7 Klein A, Bourke MJ. Advanced polypectomy and resection techniques. *Gastrointest Endosc Clin N Am* 2015; 25: 303–333
- 8 Jideh B, Bourke MJ. How to perform wide-field endoscopic mucosal resection and follow-up examinations. *Gastrointest Endosc Clin N Am* 2019; 29: 629–646
- 9 Burgess NG, Hourigan LF, Zanati SA et al. Risk stratification for covert invasive cancer among patients referred for colonic endoscopic mucosal resection: a large multicenter cohort. *Gastroenterology* 2017; 153: 732–742.e1
- 10 Fahrtash-Bahin F, Holt BA, Jayasekeran V et al. Snare tip soft coagulation achieves effective and safe endoscopic hemostasis during wide-field endoscopic resection of large colonic lesions (with videos). *Gastrointest Endosc* 2013; 78: 158–163.e1
- 11 Tate DJ, Desomer L, Klein A et al. Adenoma recurrence after piecemeal colonic EMR is predictable: the Sydney EMR recurrence tool. *Gastrointest Endosc* 2017; 85: 647–656.e6
- 12 Sidhu M, Shahidi N, Gupta S et al. Outcomes of thermal ablation of the mucosal defect margin after endoscopic mucosal resection: a prospective, international, multicenter trial of 1000 large nonpedunculated colorectal polyps. *Gastroenterology* 2021; 161: 163–170.e3

- 13 Kumarasinghe M, Bourke MP, Brown I et al. Pathological assessment of endoscopic resections of the gastrointestinal tract: a comprehensive clinicopathologic review. *Mod Pathol* 2020; 33: 986–1006
- 14 Rex DK, Hassan C, Bourke MJ. The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management. *Gastrointest Endosc* 2017; 86: 253–263
- 15 Burgess NG, Bassan MS, McLeod D et al. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. *Gut* 2017; 66: 1779–1789
- 16 Vleugels JLA, Hazewinkel Y, Fockens P et al. Natural history of diminutive and small colorectal polyps: a systematic literature review. *Gastrointest Endosc* 2017; 85: 1169–1176.e1
- 17 Vosko S, Shahidi N, Sidhu M et al. Optical evaluation for predicting cancer in large nonpedunculated colorectal polyps is accurate for flat lesions. *Clin Gastroenterol Hepatol* 2021; 19: 2425–2434.e4
- 18 Bahin FF, Heitman SJ, Rasouli KN et al. Wide-field endoscopic mucosal resection versus endoscopic submucosal dissection for laterally spreading colorectal lesions: a cost-effectiveness analysis. *Gut* 2018; 67: 1965–1973
- 19 Tate DJ, Bahin FF, Desomer L et al. Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) is an effective and safe strategy for the management of non-lifting large laterally spreading colonic lesions. *Endoscopy* 2018; 50: 52–62
- 20 Shahidi N, Vosko S, Gupta S et al. Previously attempted large nonpedunculated colorectal polyps are effectively managed by endoscopic mucosal resection. *Am J Gastroenterol* 2021; 116: 958–966

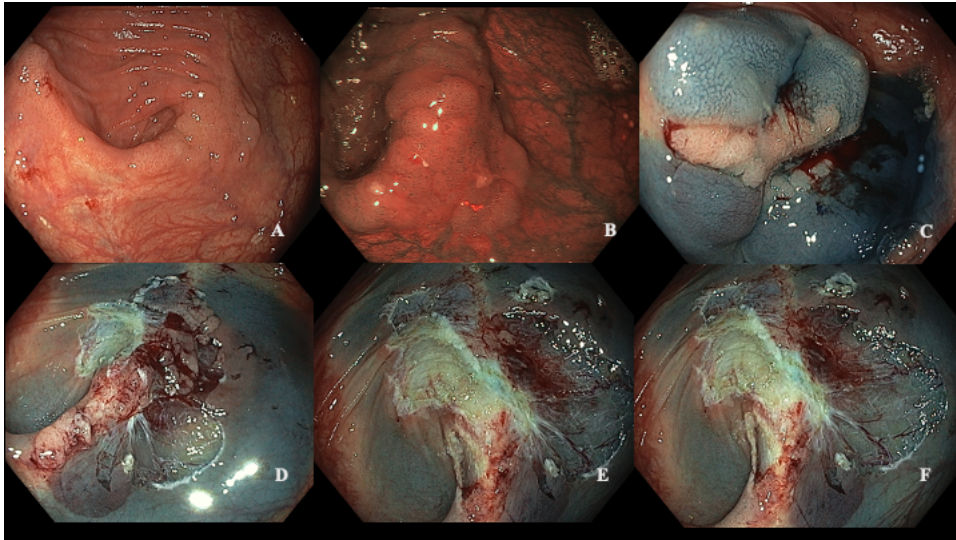


Fig. 1 Endoscopic views of the resection of a 30-mm Paris 0-IIa large anastomotic polyp showing: **a** a lesion at the anastomosis under white light with near focus; **b** narrow-band imaging; **c** central non-lifting after submucosal injection with indigo carmine and Gelofusine; **d–f** sequential snare resection of areas with adequate submucosal lifting with interrogation of the defect for deep mural injury with topical chromoendoscopy after each snare resection.

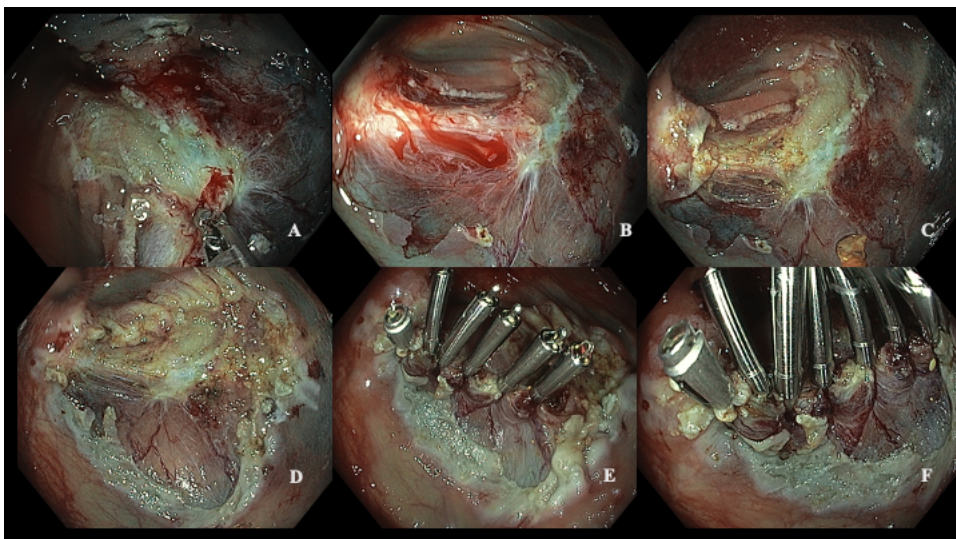


Fig. 2 Endoscopic views of the resection of a 30-mm Paris 0-IIa large anastomotic polyp showing: **a–d** cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST)

applied to the central non-lifting segment that was resistant to snare capture; **e,f** through-the-scope clips applied to close a deep mural injury type II.

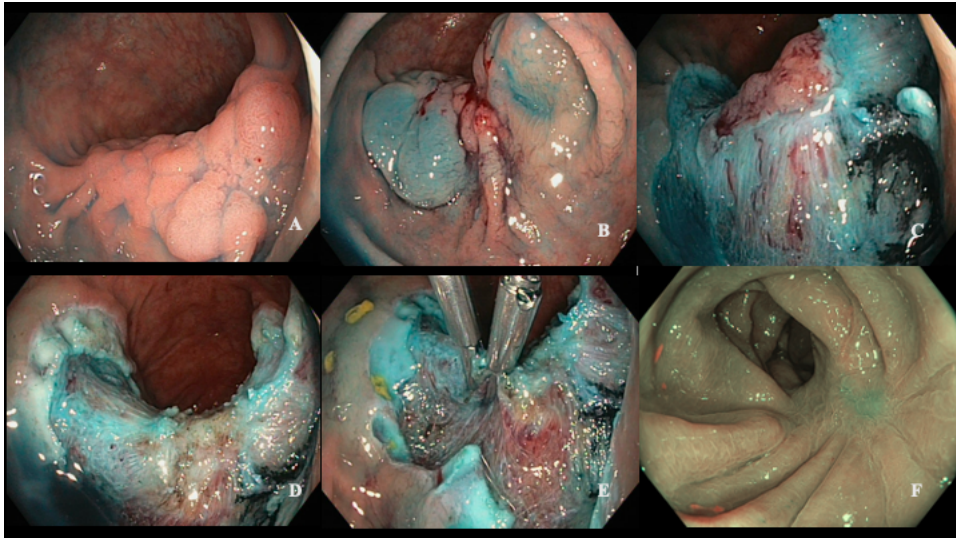


Fig. 3 Endoscopic views of the resection of a 40-mm Paris 0-IIa large anastomotic polyp showing: **a** the lesion at the anastomosis; **b** central non-lifting after submucosal injection with indigo carmine and Gelofusine; **c** sequential snare resection of areas with adequate submucosal lifting; **d** cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) applied to the central non-lifting segment that was resistant to snare capture, with thermal ablation to the defect margin by snare-tip soft coagulation; **e** through-the-scope clips applied to close a deep mural injury type II; **f** a bland scar seen on narrow-band imaging at 6-month surveillance.

Table 1 Characteristics of the 10 included patients and their large anastomotic polyps.

Patient	Age, years/ sex	Time interval, years*	Surgical histology	Anastomotic polyp size, mm	Paris type	Morphology	Histology
1	70/ Male	32	Adenocarcinoma	30	0-IIa	Granular	Tubular
2	52/ Female	15	Tubulovillous adenoma	35	0-IIb	Non- granular	Tubular
3	86/ Male	12	Adenocarcinoma	30	0-IIb	Non- granular	Tubulovillous
4	71/ Male	34	Familial adenomatous polyposis	35	0-IIb	Granular	Tubulovillous
5	78/ Female	10	Adenocarcinoma	20	0-IIa	Granular	Tubulovillous
6	84/ Male	5	Adenocarcinoma	40	0-IIa	Non- granular	Tubulovillous
7	65/ Male	1	Adenocarcinoma	12	0-IIc	Granular	Tubulovillous
8	76/ Male	29	Adenocarcinoma	40	0-IIa	Granular	Tubular
9	73/ Male	1	Tubulovillous adenoma	80	0- IIa+Is	Granular	Tubular
10	81/ Male	3	Adenocarcinoma	25	0-IIa	Non- granular	Tubulovillous

* Time in years from initial surgical resection to diagnosis of anastomotic polyp.

Table 2 Procedure and follow-up details for the 10 large anastomotic polyps that were resected endoscopically.

Patient	pEMR	CAST	Intra-procedural bleeding	DMI	Clipped	Surveillance colonoscopy, months post- resection	Recurrence at surveillance
1	Yes	Yes	No	No	Yes	6	No
2	Yes	Yes	No	No	Yes	6	No
3	Yes	Yes	No	II	Yes	6	No
4	Yes	Yes	No	No	Yes	4	No
5	Yes	No	No	No	No	6	No
6	Yes	Yes	Yes	II	Yes	6	No
7	Yes	Yes	Yes	No	No	6	No
8	Yes	Yes	No	II	Yes	7	No
9	Yes	Yes	No	II	Yes	5	No
10	Yes	Yes	No	No	No	6	No

pEMR, piecemeal endoscopy mucosal resection; CAST, cold-forceps avulsion with snare-tip soft coagulation; DMI, deep mural injury.

Chapter 9 - Integrated Discussion

There have been great advances in ER over the past decade. When compared to surgery, ER is organ-sparing and therefore minimally invasive, cost-effective and associated with less morbidity. [1] An ER algorithm should be used to decide upon the most appropriate resection technique, accounting for lesion size, site, morphology, and predicted histology. [2, 3]

For LNPCPs, ER resection options include conventional EMR, C-EMR and ESD. Full-thickness resection remains an option for select lesions and is mainly limited to lesions <20mm.

Cold-EMR in the Endoscopic Resection Algorithm

In recent years, there has been a paradigm shift toward C-EMR. Compared to HSP, C-EMR has a superior safety profile. C-EMR however, has the major limitation of a higher recurrence rate as outlined in Chapter 3. Recurrence rates were 18% vs 1% for C-EMR and EMR respectively. As expected, there was a lower rate of delayed bleeding in the C-EMR group compared to the EMR group (8% vs 1%). All other outcomes were similar.

Chapter 4 explained through mathematical modelling, the greater recurrence rate observed with C-EMR. The technique relies on meticulous resection technique. Without sufficient snare overlap during sequential snare resections, each snare resection is an opportunity for incomplete resection. Polyp area increases quadratically with every incremental increase in polyp radius. It is therefore appreciable that larger polyps require many more sequential snare resections and thus create more opportunities to inadvertently leave behind polyp. We demonstrated that as lesion size increases, recurrence rates disproportionately increase and become potentially unacceptably high. For example, a recurrence rate >40% for 40mm lesions.

Recurrence is burdensome for several reasons. The fibrosis encountered at sites of previous ER, increases the complexity of any resection. This increases the risk of complications and

resultant morbidity. Due to this added complexity, procedure time is often prolonged, which increases healthcare-related costs.

Polypectomy is becoming more nuanced and bespoke. Important patient factors such as frailty and co-morbidities feed into the interplay between safety and recurrence risk. For example, the risk of a delayed post-EMR bleed for LNPCP in the right colon, in the absence of clip closure is 10-12%. Additionally, many of these large defects defy current closure techniques. Conversely, the risk of a delayed bleed with p-CSP is negligible but the recurrence risk is greater. The weighting placed on delayed bleeding and recurrence risk differs in different patient groups. This fundamental understanding is particularly important to any endoscopist performing C-EMR.

Unique Environments in the Colo-rectum Should Influence Resection Technique

The rectum

Not all lesions should be removed by EMR. Lesions at high risk of containing SMIC should be removed en bloc to allow for accurate histological assessment. Chapter 5 compared lesions in the rectum to lesions in the remainder of the colon. 3405 LNPCPs were assessed. Rectal lesions (n=618) were more likely to be larger, nodular and granular compared to non-rectal LNPCPs (n=2787) and were 2.5 times more likely to contain cancer (15% vs 6%, $p<0.001$). The ramifications for non-curative ER are greater in the left colon compared to the right colon. Surgery in the distal colon carries a greater risk of morbidity compared to a right hemicolectomy. [4] Rectal LNPCPs should ideally be assessed at specialized tissue resection centres with the ability to undertake ESD if required. Any LNPCP suspected of harboring covert SMIC should be removed en bloc ideally with ESD to maximize the likelihood of curative resection.

Small, high-risk lesions

Chapters 6 and 7 assessed EFTR for lesions with high-risk features, early cancers or lesions at the appendiceal orifice. EFTR is safe, effective and does not require the prolonged learning

curve that is associated with learning ESD and third space endoscopy. This device may be well-suited to Western settings, where the case volume for ESD is low.

The recurrence rate was 3% and the most common adverse event was appendicitis (11%). In 2 patients, ileocolonic fistulas were identified on CT scans, performed routinely post-operatively. Both patients had previously had abdominal surgery and likely had adhesions or altered anatomy. Caution should be exercised when undertaking FTR in patients with a history of abdominal surgery.

Anastomotic polyps

Polyps encountered at a surgical anastomosis present a unique set of challenges. Site specific modification is required for effective ER. In Chapter 9, we examined the efficacy of ER of LAAPs. No previous studies have examined the efficacy of ER for these lesions. Over a 7-year period, 2629 lesions were resected, of which 10 (0.4%) were LAAPs. ER Technique modification is required for several reasons. Typically, many anastomoses have a degree of inflammatory change, which can impede optical evaluation. The densely fibrosed ridgeline results in adherence of the mucosal layer to the anastomosis, meaning that DMI is more common.

Of the 10 patients with LAAPs, 9 (90%) were resected with a combination of EMR and CAST. The technique is safe without any significant DMI (DMI Type III-V). Technical success was 100% and at 6-month follow-up colonoscopy, there was no recurrence in any case. This study demonstrates that LAAPs can be safely and effectively removed by ER.

Future directions

Underpinned by high-quality research as well as technical innovations, great advances have been made in our understanding and capabilities of ER. While this thesis has addressed some deficiencies in our understanding about ER technique, there are a number of important questions which remain:

- Thermal ablation of the margin as an adjuvant technique for C-EMR
- Other technical innovations to reduce recurrence rates with C-EMR

- Understanding the size cut-off at which the risk of recurrence for C-EMR becomes excessively burdensome
- Improving optical assessment of nodular rectal lesions to better predict SMIC risk
- Head-to-head trials of ESD vs Trans-anal Minimally Invasive Surgery (TAMIS) for resection of high-risk rectal lesions
- Long-term outcomes of EFTR compared to ESD for small, high-risk lesions

References

1. Bahin FF, Heitman SJ, Rasouli KN, et al. Wide-field endoscopic mucosal resection versus endoscopic submucosal dissection for laterally spreading colorectal lesions: a cost-effectiveness analysis. *Gut*. 2018;67(11):1965.
2. Cronin O, Bourke MJ. Endoscopic Management of Large Non-Pedunculated Colorectal Polyps. *Cancers (Basel)*. 2023;15(15).
3. Shahidi N, Vosko S, Gupta S, et al. A Rectum-Specific Selective Resection Algorithm Optimizes Oncologic Outcomes for Large Nonpedunculated Rectal Polyps. *Clin Gastroenterol Hepatol*. 2023;21(1):72-80.e2.
4. Cuccurullo D, Pirozzi F, Sciuto A, et al. Relaparoscopy for management of postoperative complications following colorectal surgery: ten years experience in a single center. *Surg Endosc*. 2015;29(7):1795-803.

Chapter 10 - Selection of endoscopic resection technique for large colorectal lesion treatment

Publication:

Cronin O, Mandarino F, Bourke MJ. Selection of endoscopic resection technique for large colorectal lesion treatment. *Current Opinion in Gastroenterology* 2024 Sep1;40(5):355-62.

In brief:

- Endoscopic resection should be considered as the first line option for the removal of all colorectal lesions.

Contribution:

- This review draws on contemporary data, to provide evidenced-based conclusions on the most appropriate use of the endoscopic resection algorithm.
- This chapter provides a summary of advances and techniques described in the earlier chapters of this thesis.

Selection of endoscopic resection technique for large colorectal lesion treatment

Authors: Oliver Cronin MBBS FRACP^{1,2}, Francesco Vito Mandarino MBBS^{1,2}, Michael J Bourke MBBS FRACP^{1,2}.

1. Westmead Hospital, Department of Gastroenterology and Hepatology, Sydney, New South Wales, Australia
2. Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia

Abstract: 177 words (limit 200 words); Manuscript 2640 words (limit 2500 words).

Corresponding Author:

Michael J. Bourke MBBS FRACP

Clinical Professor of Medicine

Westmead Hospital, Department of Gastroenterology and Hepatology

University of Sydney, Westmead Clinical School

Suite 106a 151-155 Hawkesbury Road

Sydney, New South Wales, Australia 2145

Email: michael@citywestgastro.com.au

Abstract

Purpose of review

Large non-pedunculated colorectal polyps ≥ 20 mm (LNPCPs) comprise one percent of all colorectal lesions. LNPCPs are more likely to contain advanced histology such as high-grade dysplasia and submucosal invasive cancer (SMIC). Endoscopic resection (ER) is the first-line approach for management of these lesions. ER options include endoscopic mucosal resection (EMR), cold-snare EMR (EMR), endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (EFTR). This review aimed to critically evaluate current ER techniques.

Recent findings

Evidence-based selective resection algorithms should inform the most appropriate ER technique. Most LNPCPs are removed by conventional EMR but there has been a trend toward C-EMR for ER of LNPCPs. More high-quality trials are required to better define the limitations of C-EMR. Advances in our understanding of ESD technique, have clarified its role within the colo-rectum. More recently, the development of a full thickness resection device (FTRD) has allowed the curative ER of select lesions.

Summary

ER should be regarded as the principal approach for all LNPCPs. Underpinned by high-quality research, ER has become more nuanced, leading to improved patient outcomes.

Keywords: Colonoscopy; polyp; polypectomy; colorectal cancer; endoscopic mucosal resection; endoscopic submucosal dissection, endoscopic full thickness resection.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality. [1] Most CRCs develop from the stepwise acquisition of molecular abnormalities along the adenoma-carcinoma and serrated pathways. [2-4] This pathogenic trajectory presents a strategic window for the potential prevention of CRC by the endoscopic resection (ER) of premalignant polyps. Compelling evidence underscores the efficacy of screening colonoscopy and polypectomy in diminishing the 10-year risk of CRC-related mortality [risk ratio 0.82, 95% confidence interval (CI) 0.70-0.93]. [5] The national polyp study (n=2602) in long-term follow-up revealed a 53% reduction in risk [relative risk (RR) 0.47, 95% CI 0.26-

0.80] among participants who underwent polypectomy. [6] Underpinned by high-quality research, improvements in our understanding of the fundamentals of ER, as well as concurrent technical innovations have allowed for the curative ER of advanced benign lesions and also lesions containing submucosal invasive cancer (SMIC).

Most colorectal lesions are <10mm in size, lack advanced histology and are amenable to en bloc or piecemeal removal with a cold snare. [7-9] Large non-pedunculated colorectal lesions ≥ 20 mm (LNPCPs) comprise ~1% of all polyps. They have a variable propensity to harbour overt and covert SMIC. [10] Currently, there are a range of effective techniques available for their endoscopic management.

Selection of the most appropriate technique is contingent upon multiple factors, including lesion size, morphology, location, and the perceived risk of SMIC. [10-12] In addition, patient specific factors must be considered including co-morbidities, anti-coagulant and anti-platelet medications. This nuanced approach ensures that the chosen management strategy is tailored to the unique characteristics of both the lesion and the patient.

ER is the recommended first-line modality for the management of LNPCPs. [13, 14] Compared to surgery, ER is equally effective and has a superior morbidity and healthcare cost profile. [15, 16] Technical success requires a collaborative, methodical approach. It starts with planning, comprehensive communication with endoscopy staff, patients and their families. It relies on a thorough optical assessment. Management should ideally be undertaken at a centre with access to all ER techniques including endoscopic mucosal resection (EMR), cold-snare EMR (C-EMR), endoscopic submucosal dissection (ESD) and endoscopic full thickness resection (EFTR) (Figures 1-3). This review aimed to critically analyse current ER techniques and to evaluate where each fit within a selective ER algorithm.

Pre-resection

Optimizing patient outcomes necessitates meticulous planning, particularly in the pre-procedural phase. This includes a comprehensive evaluation of the patient's medical history, functional status, co-morbidities, and current medications.

The pre-procedural planning phase extends to the endoscopy room where a collaborative discussion with nursing and anaesthetic staff provides great value. This collaborative approach ensures that all team members are well-informed about critical procedural steps, necessary equipment, and the anticipated duration of the procedure. Furthermore, it is advantageous to address any site-specific challenges that may arise during the procedure, such as expected fibrosis encountered in previously attempted lesions. [17]

Other important discussion points include any specific medications such as surgical antibiotic prophylaxis or local anaesthetic for lesions at the anorectal junction (ARJ). An equipment check should ensure the availability of all appropriate resection devices such as snares and ESD knives. [18, 19] It is imperative that ER is conducted exclusively with carbon dioxide insufflation. [20] Furthermore, essential ancillary devices, such as through-the-scope clips for closure and haemostatic forceps to address intra-procedural bleeding, should be pre-positioned in the procedure room.

Patient positioning is important and can improve efficiencies. The ideal orientation is with the patient positioned so that the fluid pool is opposite the lesion. Thus, leveraging gravity to optimize lesion elevation and ensure a clear working field for tissue resection or the management of any potential complications. Consequently, adopting a supine or right lateral position may be deemed necessary. Precise positioning of the colonoscope to align the lesion at a 6 o'clock position is imperative for optimal visualization and intervention. Depending on the lesion's location, the adoption of a retroflexed position may further enhance access and aide comprehensive optical assessment. Time spent early on patient positioning, promotes procedural efficacies, mitigates potential challenges, and optimises outcomes.

Pre-resection diagnosis is important to optimise decision making and patient outcomes. Thorough optical assessment stands as a cornerstone in diagnostic precision. The risk of overt (optical features of SMIC present) or covert (optical features of SMIC absent) cancer is contingent upon various parameters, including the size, location, morphology, granularity, and microvascular and surface pit patterns of the LNPCP. [10, 12] Classification systems, such as the Kudo pit pattern (KPP) and the Japan Narrow-Band Imaging Expert Team (JNET) classification, provide helpful frameworks for this multifaceted assessment. [21, 22] Proficiency in understanding these systems is helpful, however, quite simply benign lesions have surface homogeneity, loss of this homogeneity raises concern for SMIC. A pragmatic

approach to enhance familiarity and utilization could involve prominently displaying large posters of these classification systems in endoscopy rooms and reporting areas.

Flat benign lesions typically exhibit surface homogeneity characterized by a regular pit and microvascular pattern. In contrast, the presence of high-grade dysplasia or cancer manifests as a distinct demarcated area of disruption within this otherwise regular pattern. Rigorous examination of such areas is paramount to ensuring accurate optical diagnosis and guiding the formulation of an appropriate resection strategy. Bulky lesions may harbour SMIC within and risk is best stratified by surface morphology and location.

Traditionally, the “optical biopsy” was thought to be inaccurate. Recent advancements have highlighted the exceptional accuracy of optical assessment, particularly for flat (Paris 0-IIa) LNPCPs. [23] In a large, prospective, single-centre cohort study (n=1583), the sensitivity and specificity for predicting cancer in Paris 0-IIa LNPCPs were >90%. This study reported the chance of a missed cancer in a flat (Paris 0-IIa) lesion was 6 in 1000 cases.

Conversely, optical diagnosis for SMIC for nodular lesions is less accurate with a sensitivity of 53% and specificity of 94%, resulting in a 6% missed SMIC rate. [23] Excluding lesions with overt SMIC, a large multicentre, prospective study (n = 2277) revealed that covert SMIC was associated with Paris 0-Is and Paris 0-IIa+Is morphology, non-granularity, size, and distal location. [10] Corroborating this finding, a large prospective cohort study (n = 3405) reported that rectal LNPCPs have a higher likelihood of harbouring SMIC compared to their non-rectal colonic counterparts (15% vs. 6%, $p < 0.001$). [12] These advancements in understanding the optical diagnostic accuracy have refined our understanding of SMIC risk and influence the most appropriate ER technique.

A pre-resection biopsy has been traditionally used for pre-resection diagnosis however this is often inaccurate. In a large, retrospective study (n=586), compared to the post-resection specimen, pre-resection biopsy was inaccurate in 40% of lesions. [24]

Resection

A selective ER algorithm should guide therapeutic decisions for LNPCP management, integrating all known lesion parameters to predict histopathology and therefore maximise the chance of a curative resection.

Endoscopic Mucosal Resection

EMR remains the foundation for the effective removal of LNPCPs demonstrating superior safety, efficacy and cost-effectiveness compared to surgery. [25-27] Advancements over the past decade, informed by high-quality studies have enhanced EMR safety and efficacy. Key refinements include CO₂ insufflation, chromo-injectate utilisation in the submucosal space, systematic inject and sequential snare resection, incorporation of a 2-3mm margin of normal mucosa during ER, water jet expansion of the defect to identify residual adenoma and the early recognition of significant deep mural injury (DMI). [20, 28, 29] Following adenoma resection, thermal ablation (TA) of the margin is performed to achieve a 3-5mm rim of ablated mucosa. [30] With the addition of thermal ablation, recurrence rates have reduced from ~20% to below 2%. [30, 31]

In a recent large RCT (n=414), the efficacy of snare tip soft coagulation (STSC) was compared to argon plasma coagulation (APC) for TA of the margin. [32] Although not significantly different, recurrence rate at first surveillance colonoscopy was 4.6% vs 9.3% for the STSC and APC groups respectively. [32] The authors concluded that STSC is the favoured technique given it is more efficient to apply, less expensive and more carbon friendly than APC.

Cold-Endoscopic Mucosal Resection

Presently, due to limited data, conventional EMR is preferred over C-EMR for LNPCP resection. The safety profile of C-EMR is appealing for piecemeal resection of Paris 0-IIa LNPCPs however, the upper size limit for effective removal without excessive recurrence is unknown. A large, prospective, multicentre cohort study (n = 286 lesions) comparing conventional EMR to C-EMR for 6–15 mm polyps favoured the use of C-EMR over EMR. [33] At present, US consensus guidelines recommend either EMR or C-EMR for resection of lesions 10–19 mm. [13] Recently, the first large, prospective randomised controlled trial (RCT) compared C-EMR to conventional EMR for 15-50mm Paris 0-IIa lesions was

published. At 6-month surveillance colonoscopy, recurrence was significantly greater in the C-EMR group [(15/87, 17%) vs (1/93, 1%); $p < 0.001$]. Significant DMI [(0, 0%) vs (24/93, 26%); $p < 0.001$] and delayed perforation [(0,0%) vs (1/93, 1%); $p = 0.33$] only occurred in the EMR group. Clinically significant post procedural and intraprocedural bleeding were greater in the EMR arm [(1/87, 1.1%) vs (7/93, 7.5%); $p = 0.038$] and [(0/87, 0%) vs (10/93, 10.8%); $p = 0.002$] respectively. [34]

These findings suggest there is an upper limit to lesion size for C-EMR after which recurrence becomes overwhelming burdensome. This cut-off might differ between patients. For example, an elderly patient taking anticoagulation may not be bothered by recurrence, and any recurrence would be unlikely to shorten that patient's length or quality of life. Conversely, a delayed perforation or bleed post EMR could prove more challenging for that patient, swinging the ER pendulum in favour of C-EMR.

In contrast to adenomas, C-EMR is always recommended as the primary modality for ER of serrated lesions, irrespective of size. A large, prospective study (n=562) demonstrated comparable technical success and recurrence rates between C-EMR and EMR, while bleeding (0% Vs 5%) and significant DMI (0% Vs 3%) were more common in the EMR group. [35]

Endoscopic Submucosal Dissection

The rectum represents a highly intricate and high-risk anatomical site, characterised by unique challenges distinct from those encountered in the colon. The heightened risk of covert SMIC [12, 36] rather than technical limitations underscores its complexity. Additionally, the stakes are greater. Failed endoscopic cure necessitates the need for some of the most complex forms of colorectal surgery, associated with the risk of ostomy formation [37], increased risk of incontinence (12%) [38] and sexual dysfunction (20-46%) [39] along with a 10-20% risk of a permanent stoma. [40, 41] Low anterior resection, a common surgical approach, is associated with a 30-day morbidity and mortality of 25% and 6% respectively [42], emphasising the serious implications of surgery in the left colon. In this context, ER emerges as an organ sparing, minimally invasive alternative, mitigating the need for complex surgery in many cases. [43]

In a large multicentre observational study (n=618), rectal LNPCPs were more likely to contain cancer (15% vs 6%, p<0.001), 50% of which is covert, compared to the remainder of the colon. [12] To achieve R0 (curative) resection, en bloc resection is required.

Originally developed for treatment of early gastric cancer, ESD has evolved into an established technique in the colorectum. Using an electrosurgical knife for fine dissection, ESD allows precise en bloc resection of large lesions with more precision and control compared to EMR. A rectum-specific selective resection algorithm (SRA) has demonstrated superior outcomes compared to a Universal EMR algorithm (UEA). In a large study (n=480), LNPCPs underwent ESD if they had features suggestive of overt SMIC (1000µm, KPP V) or covert SMIC (Paris 0-1s, or a dominant nodule). All LNPCPs with SMIC amenable to R0 resection that underwent ESD achieved cure. [11] Implementing a rectum-specific SRA avoids the piecemeal resection of cancer.

In a recent large RCT (n=360), Jacques and colleagues compared EMR and ESD for LNPCPs ≥ 25 mm. Lesions within 15cm of the ARJ were excluded. [44] The rate of SMIC was 6% in keeping with previous studies. [12] While ESD had lower recurrence rate (0.6% vs 5.1%), adverse events were greater (36% vs 25%). The procedure time for ESD and EMR was 47 minutes vs 15 minutes respectively. Accounting for the opportunity and resource cost of ESD compared to EMR, as well as the low rate of covert SMIC outside of the rectum, this study underscored the importance of a selective ER approach. EMR is safe, efficient and less-expensive than ESD. ESD is an indispensable tool which should be reserved for lesions at high risk of superficial early overt SMIC or covert SMIC such as bulky rectal lesions. [45]

Endoscopic Full-Thickness Resection

High risk lesions require en bloc resection for cure. Until recently, the only ER options were en bloc EMR and ESD, but both have limitations. EMR is less precise and may struggle in achieving R0 resection of lateral and vertical margins, especially in fibrotic lesions with advanced histology. [46] While ESD offers superior margin control, it is technically challenging, resource intensive and has limited accessibility, particularly in Western countries. [47-50] Additionally, ESD may face challenges in achieving a curative vertical resection margin. To address these issues, an integrated endoscopic full-thickness resection

device (FTRD, Ovesco Endoscopy, Tübingen, Germany) was developed for select gastrointestinal lesions. The FTRD, featuring a single-clip closure and resection device enables EFTR without exposing the peritoneum to luminal contents during the procedure. [51-53] In contrast to ESD, EFTR does not have a lengthy learning curve and does not necessarily require knowledge of third-space endoscopy or resection planes. [54] Two large national registries have reported high curative results for select lesions with T1 cancer or high-grade dysplasia. [55, 56] However a limitation of the FTRD is the lesion size, determined by the volume of tissue that can be pulled into the distal over-the scope cap and the risk of delayed perforation which is 1%. [57] A study (n=69) has demonstrated efficacy of a hybrid EMR/EFTR technique for resection of larger lesions, but more data is required on long-term durability. [58] Due to the relative novelty of EFTR, long-term efficacy data is lacking.

Post-resection considerations

Regardless of the ER modality, it is vital that clear, written and verbal instructions are provided to the patient and their next of kin. Instructions should include when and how to contact medical staff should there be any issues. This ensures prompt recognition and effective management of any complications.

Post-resection surveillance is required for all resected lesions, the timing of which differs depending on the resected histology. Patients should ideally be scheduled for follow-up on the day of their index resection to ensure there are no errors in communication and they are not lost to follow-up.

The management of covert SMIC identified post-piecemeal ER has historically presented challenges. In a recent, large observational study (n=3372), 143 (4%) cases exhibited covert SMIC post-piecemeal resection. [59] Surgical resection was performed in 109 cases of which 62 (63%) contained no residual cancer. Among cases with residual intramucosal cancer (n=24), an R1 histological deep margin identified all instances. Poor differentiation and/or lymphovascular invasion conferred a high risk of lymph node metastasis (12/33) while cases lacking these features presented a very low risk (<1% < 0/35). Most patients with covert

SMIC resected piecemeal displayed no residual malignancy. Residual malignancy risk could be predicted by poor differentiation, lymphovascular invasion and an R1 deep margin.

In a large multicentre study (n=2255) of non-curative colorectal ESDs, none (0%) of the sm1 lesions had residual CRC after surgical resection and none of the >sm1 lesions had residual CRC if lymphovascular invasion (LVI) and poor differentiation were absent. LVI or poor differentiation warrant consideration of surgery due to the high risk of lymph node metastasis. [60]

Conclusion

This review compares various ER techniques and underscores the intricate balance of choosing the most appropriate technique for any given lesion and patient. EMR, C-EMR, ESD and EFTR all offer distinct value but each also have their weaknesses. Ultimately, ER is becoming more nuanced. Endoscopists should not only account for lesion sub-types, each with differing challenges and risks, but they also need to account for patient specific factors, embracing the paradigm of precision medicine. Current selective resection algorithms, based on high quality evidence, provide fundamental guidance to achieve the best outcomes for our patients. These are likely to be further refined in the immediate future.

Key points:

- Curative management of large non-pedunculated colorectal polyps requires comprehensive planning.
- Endoscopic mucosal resection (EMR), cold-EMR, endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection each have strengths and weaknesses.
- Selective endoscopic resection algorithms should guide selection of resection technique and account for lesion and patient specific factors.

Financial support:

The Cancer Institute of New South Wales provided funding for a research nurse and data manager to assist with the administration of our research. There was no influence regarding study design or conduct, data collection, management, analysis, interpretation, preparation, review or approval of the manuscript.

Conflicts of interest:

The authors report no conflicts of interest.

References

1. Patel SG, Karlitz JJ, Yen T, et al. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol Hepatol.* 2022;7(3):262-74.
2. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology.* 2008;134(5):1570-95.
3. Kedrin D, Gala MK. Genetics of the serrated pathway to colorectal cancer. *Clin Transl Gastroenterol.* 2015;6(4):e84.
4. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol.* 2004;287(1):G7-17.
5. Bretthauer M, Løberg M, Wieszczy P, et al. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. *N Engl J Med.* 2022;387(17):1547-56.
6. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med.* 2012;366(8):687-96.
7. Rex DK. Have we defined best colonoscopic polypectomy practice in the United States? *Clin Gastroenterol Hepatol.* 2007;5(6):674-7.
8. Gupta N, Bansal A, Rao D, et al. Prevalence of advanced histological features in diminutive and small colon polyps. *Gastrointest Endosc.* 2012;75(5):1022-30.

9. Repici A, Hassan C, Vitetta E, et al. Safety of cold polypectomy for <10mm polyps at colonoscopy: a prospective multicenter study. *Endoscopy*. 2012;44(1):27-31.
10. Burgess NG, Hourigan LF, Zanati SA, et al. Risk Stratification for Covert Invasive Cancer Among Patients Referred for Colonic Endoscopic Mucosal Resection: A Large Multicenter Cohort. *Gastroenterology*. 2017;153(3):732-42.e1.
11. Shahidi N, Vosko S, Gupta S, et al. A Rectum-Specific Selective Resection Algorithm Optimizes Oncologic Outcomes for Large Nonpedunculated Rectal Polyps. *Clin Gastroenterol Hepatol*. 2023;21(1):72-80.e2.
12. Cronin O, Sidhu M, Shahidi N, et al. Comparison of the morphology and histopathology of large nonpedunculated colorectal polyps in the rectum and colon: implications for endoscopic treatment. *Gastrointest Endosc*. 2022;96(1):118-24.*This study demonstrated that the risk of covert cancer in the rectum is 2.5 times that seen in rest of the colon.
13. Kaltenbach T, Anderson JC, Burke CA, et al. Endoscopic Removal of Colorectal Lesions: Recommendations by the US Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol*. 2020;115(3):435-64.
14. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy*. 2017;49(3):270-97.
15. Jayanna M, Burgess NG, Singh R, et al. Cost Analysis of Endoscopic Mucosal Resection vs Surgery for Large Laterally Spreading Colorectal Lesions. *Clinical Gastroenterology and Hepatology*. 2016;14(2):271-8.e2.
16. Ahlenstiel G, Hourigan LF, Brown G, et al. Actual endoscopic versus predicted surgical mortality for treatment of advanced mucosal neoplasia of the colon. *Gastrointest Endosc*. 2014;80(4):668-76.
17. Shahidi N, Vosko S, Gupta S, et al. Previously Attempted Large Nonpedunculated Colorectal Polyps Are Effectively Managed by Endoscopic Mucosal Resection. *Am J Gastroenterol*. 2021;116(5):958-66.
18. Holt BA, Bassan MS, Sexton A, et al. Advanced mucosal neoplasia of the anorectal junction: endoscopic resection technique and outcomes (with videos). *Gastrointest Endosc*. 2014;79(1):119-26.
19. Shahidi N, Sidhu M, Vosko S, et al. Endoscopic mucosal resection is effective for laterally spreading lesions at the anorectal junction. *Gut*. 2020;69(4):673-80.

20. Bassan MS, Holt B, Moss A, et al. Carbon dioxide insufflation reduces number of postprocedure admissions after endoscopic resection of large colonic lesions: a prospective cohort study. *Gastrointest Endosc.* 2013;77(1):90-5.
21. Kudo S, Tamura S, Nakajima T, et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc.* 1996;44(1):8-14.
22. Sano Y, Tanaka S, Kudo SE, et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. *Dig Endosc.* 2016;28(5):526-33.
23. Vosko S, Shahidi N, Sidhu M, et al. Optical evaluation for predicting cancer in large non-pedunculated colorectal polyps is accurate for flat lesions. *Clin Gastroenterol Hepatol.* 2021.
24. Ma MX, Tate DJ, Sidhu M, et al. Effect of pre-resection biopsy on detection of advanced dysplasia in large nonpedunculated colorectal polyps undergoing endoscopic mucosal resection. *Endoscopy.* 2023;55(3):267-73. *This study reported that a pre-resection biopsy is often inaccurate and is therefore less important compared to a thorough optical assessment.
25. Cronin O, Bourke MJ. Endoscopic Management of Large Non-Pedunculated Colorectal Polyps. *Cancers (Basel).* 2023;15(15).
26. Shahidi N, Bourke MJ. How to Manage the Large Nonpedunculated Colorectal Polyp. *Gastroenterology.* 2021;160(7):2239-43.e1.
27. Jideh B, Bourke MJ. How to Perform Wide-Field Endoscopic Mucosal Resection and Follow-up Examinations. *Gastrointest Endosc Clin N Am.* 2019;29(4):629-46.
28. Bourke MJ, Bhandari P. How I remove polyps larger than 20 mm. *Gastrointest Endosc.* 2019;90(6):877-80.
29. Moss A, Bourke MJ, Metz AJ. A randomized, double-blind trial of succinylated gelatin submucosal injection for endoscopic resection of large sessile polyps of the colon. *Am J Gastroenterol.* 2010;105(11):2375-82.
30. Klein A, Tate DJ, Jayasekeran V, et al. Thermal Ablation of Mucosal Defect Margins Reduces Adenoma Recurrence After Colonic Endoscopic Mucosal Resection. *Gastroenterology.* 2019;156(3):604-13.e3.
31. Sidhu M, Shahidi N, Gupta S, et al. Outcomes of Thermal Ablation of the Mucosal Defect Margin After Endoscopic Mucosal Resection: A Prospective, International, Multicenter Trial of 1000 Large Nonpedunculated Colorectal Polyps. *Gastroenterology.* 2021;161(1):163-70.e3.

32. Rex DK, Haber GB, Khashab M, et al. Snare Tip Soft Coagulation vs Argon Plasma Coagulation vs No Margin Treatment After Large Nonpedunculated Colorectal Polyp Resection: a Randomized Trial. *Clin Gastroenterol Hepatol*. 2024;22(3):552-61.e4.**This study underscored the importance of thermal ablation of the margin with snare-tip soft coagulation.
33. Rex DK, Anderson JC, Pohl H, et al. Cold versus hot snare resection with or without submucosal injection of 6- to 15-mm colorectal polyps: a randomized controlled trial. *Gastrointest Endosc*. 2022;96(2):330-8.*This study demonstrated that cold snare resection is effective for the resection of lesions 6mm-15mm.
34. O'Sullivan T, Cronin O, van Hattem W, et al. Cold vs hot snare endoscopic mucosal resection for large (≥ 15 mm) flat non-pedunculated colorectal polyps: a randomized controlled trial. *Gut*2024 [under review].**This study is the first large RCT to directly compare efficacy and long-term outcomes of cold-EMR to conventional EMR for the resection of LNPCPs.
35. van Hattem WA, Shahidi N, Vosko S, et al. Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: a retrospective comparison across two successive periods. *Gut*. 2021;70(9):1691-7.
36. Bar-Yishay I, Shahidi N, Gupta S, et al. Outcomes of Deep Mural Injury After Endoscopic Resection: An International Cohort of 3717 Large Non-Pedunculated Colorectal Polyps. *Clin Gastroenterol Hepatol*. 2022;20(2):e139-e47.
37. Vennix S, Pelzers L, Bouvy N, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev*. 2014(4):Cd005200.
38. Duran E, Tanriseven M, Ersoz N, et al. Urinary and sexual dysfunction rates and risk factors following rectal cancer surgery. *Int J Colorectal Dis*. 2015;30(11):1547-55.
39. Celentano V, Cohen R, Warusavitarne J, et al. Sexual dysfunction following rectal cancer surgery. *Int J Colorectal Dis*. 2017;32(11):1523-30.
40. Climent M, Martin ST. Complications of laparoscopic rectal cancer surgery. *Mini-invasive Surgery*. 2018;2:45.
41. Lindgren R, Hallböök O, Rutegård J, et al. What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial. *Dis Colon Rectum*. 2011;54(1):41-7.
42. Cuccurullo D, Pirozzi F, Sciuto A, et al. Relaparoscopy for management of postoperative complications following colorectal surgery: ten years experience in a single center. *Surg Endosc*. 2015;29(7):1795-803.

43. Mulita F, Liolis E, Akinosoglou K, et al. Postoperative sepsis after colorectal surgery: a prospective single-center observational study and review of the literature. *Prz Gastroenterol.* 2022;17(1):47-51.
44. Jacques J, Schaefer M, Wallenhorst T, et al. Endoscopic En Bloc Versus Piecemeal Resection of Large Nonpedunculated Colonic Adenomas : A Randomized Comparative Trial. *Ann Intern Med.* 2024;177(1):29-38.** This key study clarifies the role of ESD and EMR in the colorectum. As reflected in this study, a selective resection algorithm leads to improved outcomes.
45. Burgess NG, Bourke MJ. Endoscopic Submucosal Dissection Versus Endoscopic Mucosal Resection of Large Colon Polyps: Use Both for the Best Outcomes. *Ann Intern Med.* 2024;177(1):89-90.
46. Kuroha M, Shiga H, Kanazawa Y, et al. Factors Associated with Fibrosis during Colorectal Endoscopic Submucosal Dissection: Does Pretreatment Biopsy Potentially Elicit Submucosal Fibrosis and Affect Endoscopic Submucosal Dissection Outcomes? *Digestion.* 2021;102(4):590-8.
47. Bahin FF, Heitman SJ, Rasouli KN, et al. Wide-field endoscopic mucosal resection versus endoscopic submucosal dissection for laterally spreading colorectal lesions: a cost-effectiveness analysis. *Gut.* 2018;67(11):1965.
48. Arezzo A, Passera R, Marchese N, et al. Systematic review and meta-analysis of endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions. *United European Gastroenterol J.* 2016;4(1):18-29.
49. Saito Y, Uraoka T, Matsuda T, et al. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc.* 2007;66(5):966-73.
50. Maple JT, Abu Dayyeh BK, Chauhan SS, et al. Endoscopic submucosal dissection. *Gastrointest Endosc.* 2015;81(6):1311-25.
51. Schmidt A, Beyna T, Schumacher B, et al. Colonoscopic full-thickness resection using an over-the-scope device: a prospective multicentre study in various indications. *Gut.* 2018;67(7):1280-9.
52. Xu M, Wang XY, Zhou PH, et al. Endoscopic full-thickness resection of colonic submucosal tumors originating from the muscularis propria: an evolving therapeutic strategy. *Endoscopy.* 2013;45(9):770-3.
53. Sedarat A. Clips for closure of full-thickness defects. *Techniques and Innovations in Gastrointestinal Endoscopy.* 129-35.

54. Zhang X, Ly EK, Nithyanand S, et al. Learning Curve for Endoscopic Submucosal Dissection With an Untutored, Prevalence-Based Approach in the United States. *Clin Gastroenterol Hepatol*. 2020;18(3):580-8.e1.
55. Zwager LW, Bastiaansen BAJ, van der Spek BW, et al. Endoscopic full-thickness resection of T1 colorectal cancers: a retrospective analysis from a multicenter Dutch eFTR registry. *Endoscopy*. 2022;54(5):475-85.
56. Meier B, Stritzke B, Kuellmer A, et al. Efficacy and Safety of Endoscopic Full-Thickness Resection in the Colorectum: Results From the German Colonic FTRD Registry. *Am J Gastroenterol*. 2020;115(12):1998-2006.
57. Zwager LW, Mueller J, Stritzke B, et al. Adverse events of endoscopic full-thickness resection: results from the German and Dutch nationwide colorectal FTRD registry. *Gastrointest Endosc*. 2023;97(4):780-9.e4. *This is the largest registry reporting adverse events following full-thickness resection.
58. Mahadev S, Vareedayah AA, Yuen S, et al. Outcomes of a hybrid technique using EMR and endoscopic full-thickness resection for polyps not amenable to standard techniques (with video). *Gastrointest Endosc*. 2021;94(2):358-67.e1. *This is the first study to report the efficacy of a hybrid EMR/full thickness resection technique for resection of larger high risk lesions.
59. Gibson DJ, Sidhu M, Zanati S, et al. Oncological outcomes after piecemeal endoscopic mucosal resection of large non-pedunculated colorectal polyps with covert submucosal invasive cancer. *Gut*. 2022;71(12):2481-8. **This study reported that the risk of residual malignancy after the piecemeal resection of a LNPCP>20mm with covert SMIC is low. Residual malignancy can be ascertained with three key variables: poor differentiation, lymphovascular invasion and R1 deep margin.
60. Santos-Antunes J, Pioche M, Ramos-Zabala F, et al. Risk of Residual Neoplasia after a Local-Risk Resection of Colorectal Lesions by Endoscopic Submucosal Dissection: A Multinational Study. *J Clin Med*. 2023;12(16).**This key study reported that for lesions removed by ESD with a non-curative margin, the risk of residual cancer is low unless there are high risk features (lymphovascular invasion, poor differentiation).

Images

Figure 1: 40mm Granular Paris 0-IIa LNPCP in the mid-ascending colon resected by conventional Endoscopic Mucosal Resection.

40mm granular Paris 0-IIa LNPCP assessed with high-definition white light (a). Sequential submucosal injection and piecemeal resection (b-d) followed by thermal ablation of the margin (e). Surveillance colonoscopy demonstrating a bland scar at the site of resection (f).

Figure 2: 35mm Granular Paris 0-IIa LNPCP in the distal transverse colon resected by Cold Endoscopic Mucosal Resection.

35mm granular Paris 0-IIa LNPCP assessed with (a) high-definition white light and (b) narrow band imaging (NBI). Piecemeal cold snare resection with sequential snare overlap (c), resected with a wide margin (d-e). Surveillance colonoscopy demonstrating a bland scar at the site of resection (f).

Figure 3: 50mm Granular Paris 0-IIa+Is LNPCP in the rectum resected by Endoscopic Submucosal Dissection.

50mm Granular Paris 0-IIa+Is LNPCP assessed with (a) high-definition white light and (b) narrow band imaging (NBI). En bloc submucosal dissection and resection (c-e). Post-resection en bloc ex-vivo specimen (f).

Chapter 11 - Conclusions

ER is considered the first-line treatment for all pre-malignant gastrointestinal lesions. It should also be considered the first-line treatment for early cancers. Through high-quality research, our understanding of specific ER techniques and their associated strengths and deficiencies has improved. Innovations in both technique and equipment have led to improved understanding and efficacy of ER. There remain many unanswered questions in what is an ongoing task of continuous improvement with the constant over-arching goal of improved patient outcomes.

Appendix I – Awards During Candidacy

National and international oral and poster presentations/Awards related to thesis.

Awards

1. Fulbright Future Scholarship.
2. Postgraduate National Health and Medical Research Council (NHMRC) Scholarship.
3. Westmead Hospital Endoscopy Research Grant.
4. American Society of Gastrointestinal Endoscopy ‘Golden Scope’ Finalist.
5. Poster of Merit, Australian Gastroenterology Week, Sydney, Australia.

Presentations

- 1) **Cronin O**, Gupta S, O’Sullivan T, Gauci J, Burgess N, Bourke MJ. Endoscopic resection of large anastomotic polyps is safe and effective. Poster presentation. Digestive Diseases Week, May 8, 2023, Chicago, United States of America.
- 2) **Cronin O**, Kirszenblat D, O’Sullivan T, Whitfield A, Gupta S, Wang H, Lee E, Burgess NG, Bourke MJ. The geometry of cold snare polypectomy. Poster presentation. Australian Gastroenterology Week, Sep 10, 202, Sydney, Australia.
- 3) **Cronin O**, Sidhu M, Shahidi N, Gupta S, O’Sullivan T, Whitfield A, Wang H, Kumar P, Hourigan LF, Byth K, Burgess NG, Bourke MJ. Comparison of the morphology and histopathology of large non-pedunculated colorectal polyps in the rectum and colon: implications for endoscopic treatment. Poster presentation, Australian Gastroenterology Week, Sep 10, 202, Sydney, Australia.
- 4) **Cronin O**, Kirszenblat D, O’Sullivan T, Whitfield A, Kumar P, Lee E, Burgess NG, Bourke MJ. The Geometry of Cold Snare Polypectomy. Poster presentation. Digestive Diseases Week, May 22, San Diego, United States of America.
- 5) **Cronin O**, O’Sullivan T, Sidhu M, Shahidi N, Gupta S, Whitfield A, Wang H, Kumar P, Lee E, Williams S, Byth K, Burgess NG, Bourke MJ. Comparison of Morphology and Histopathology of Polyps in the Rectum and Colon. Poster presentation. May 21, San Diego, United States of America.

Appendix II – Other Publications During Candidacy

OTHER PUBLICATIONS DURING CANDIDACY (not included in final thesis)

- 1) O’Sullivan T, Mandarino F, Gauci J, Whitfield A, Kerrison C, Elhindi J, Nascimento C, Gupta S, **Cronin O** et al. Impact of margin ablation after endoscopic mucosal resection of large non-pedunculated colonic polyps on long-term recurrence. *Gut*, 2024 Aug.
- 2) Gauci J, Whitfield A, Medas R, Kerrison C, Mandarino F, Gibson D, O’Sullivan T, **Cronin O** et al. Prevalence of endoscopically curable low-risk cancer among large non-pedunculated polyps in the right colon. *Clinical Gastroenterology and Hepatology*. 2024, July.
- 3) Wang H, Nguyen M, Gupta S, Sidhu M, **Cronin O**, O’Sullivan T, Lee E, Burgess N, Bourke MJ. Long-term outcomes after endoscopic submucosal dissection for relative indication early gastric cancer in non-surgical candidates. *Gastrointestinal Endoscopy*. 2024, April.
- 4) O’Sullivan T, Craciun A, Gupta S, Byth K, Gauci J, **Cronin O**, Whitfield A, Abuarisha M, Williams S, Lee E, Burgess NG, Bourke MJ. A simple algorithm to evaluate the risk of submucosal invasive cancer in large (≥ 20 mm) non-pedunculated colonic polyps. *Endoscopy* 2024, August 56(8):596-604.
- 5) Gupta S, Craciun A, Wang H, Whitfield A, Gauci J, O’Sullivan T, **Cronin O**, Abuarisha M, Lee E, Burgess NG, Bourke MJ. Hybrid resection versus conventional resection for laterally spreading lesions of the papilla. *Gastrointestinal Endoscopy* 2024, March 99(3):428-436.

- 6) Perananthan V, Gupta S, Whitfield A, Craciun A, **Cronin O**, O'Sullivan T, Sidhu M, Hourigan L, Raftopoulos S, Burgess NG, Bourke MJ. When less is more: Lower oesophageal sphincter preserving per oral myotomy (LES-POEM) is effective for non-achalasia oesophageal motility disorders (NAEMD). *Endoscopy* 2024, June 56(6):431-436.
- 7) Gupta S, Gauci J, O'Sullivan T, **Cronin O**, Whitfield A, Craciun A, Awadie H, Yang J, Kwan V, Lee E, Burgess NG, Bourke MJ. A sub-epithelial lesion algorithm for endoscopic (SAFE) resection in the upper gastrointestinal tract. *Endoscopy* 2024, Oct, epub ahead of print.
- 8) Gauci J, Gupta S, Abuarisha M, Tang A, Whitfield A, O'Sullivan T, **Cronin O**, Kerrison C, Lee E, Burgess NG, Bourke MJ. Direct diverticular peroral endoscopic myotomy for the treatment of thoracic oesophageal diverticula: techniques and outcomes. *Endoscopy* 2024, January 56(1):41-46.
- 9) Gupta S, Vosko S, Shahidi N, O'Sullivan T, **Cronin O** et al. Endoscopic resection related colorectal strictures: risk factors, management and long-term outcomes. *Endoscopy* 2023, November 55(11):1010-18.
- 10) O'Sullivan T, Sidhu M, Gupta S, Byth K, Elhindi J, **Cronin O**, Whitfield A et al. A novel tool for case selection in endoscopic resection training. *Endoscopy* 2023, December 55(12):1095-1102.
- 11) O'Sullivan T, Tate D, Sidhu M, Gupta S, Elhindi J, Byth K, **Cronin O**, Whitfield A, Bourke MJ. The surface morphology of large non-pedunculated colonic polyps predicts synchronous large lesions. *Clinical Gastroenterology and Hepatology*, 2023 August 21(9):2270-2277.
- 12) Shahidi N, Vosko S, Gupta S, Whitfield A, **Cronin O**, Bourke MJ. A rectum-specific selection resection algorithm optimises oncologic outcomes for large non-pedunculated rectal polyps. *Clinical Gastroenterology and Hepatology*, 2023 January: 21(1):72-80.

- 13) Wang H, Sidhu M, Gupta S, **Cronin O**, O'Sullivan T, Whitfield A, Burgess NG, Bourke MJ. Cold snare EMR for the removal of large duodenal adenomas. *Gastrointestinal Endoscopy*, 2023 June: 97(6):1100-1108.
- 14) **Cronin O**, Burgess N, Bourke MJ. A call to arms for further randomised controlled trials in polypectomy. *Gastroenterology*, 2022 May;162(6):1775-76.
- 15) Book chapter: Shahidi N, Vosko S, **Cronin O**, Bourke MJ. Difficult endoscopic resections. In: Vivek K, Gross SA, eds. *Endoscopy Impossible: Solutions from the Experts!* SLACK Incorporated, 2022 [in press].
- 16) Shahidi N, Gupta S, Whitfield A, Vosko S, McKay O, **Cronin O**, Zahid S, Burgess N, Bourke M. Simple optical evaluation criteria reliably identify the post endoscopic mucosal resection scar for benign large non-pedunculated colorectal polyps without tattoo placement. *Endoscopy*, 2022 Feb;54(2):173-77.

OTHER ABSTRACTS DURING CANDIDACY (not included in final thesis)

- 1) O'Sullivan T, Gupta S, Gauci J, Whitfield A, **Cronin O**, Lee E, Burgess NG, Bourke MJ. A Simple Algorithm To Evaluate The Risk Of Submucosal Invasive Cancer In Large (>20mm) Non-Pedunculated Colonic Polyps. Oral presentation. Australian Gastroenterology Week, September 3, 2023, Brisbane, Australia.
- 2) Gupta S, O'Sullivan T, Gauci J, Whitfield A, **Cronin O**, Lee E, Burgess NG, Bourke MJ. Outcomes Of A Selective Resection Algorithm For The Endoscopic Treatment Of Barrett's Adenocarcinoma. Oral presentation. Australian Gastroenterology Week, September 3, 2023, Brisbane, Australia.
- 3) Gupta S, O'Sullivan T, Gauci J, Whitfield A, **Cronin O**, Lee E, Burgess NG, Bourke MJ. Outcomes Of Endoscopic Submucosal Dissection For The Treatment Of Oesophageal Squamous Dysplasia And Squamous Cell Carcinoma In The West. Oral presentation. Australian Gastroenterology Week, September 3, 2023, Brisbane, Australia.

- 4) O'Sullivan T, Tate DJ, Sidhu M, Gupta S, **Cronin O**, Whitfield A, Bourke MJ. Non-granular large non-pedunculated colonic polyps containing submucosal invasive cancer demonstrate unique characteristics. Oral presentation. Digestive Diseases Week, May 8, 2023, Chicago, United States of America.
- 5) Perananthan V, Gupta S, Craciun A, Whitfield A, O'Sullivan T, **Cronin O** et al. Peroral endoscopic myotomy with lower oesophageal sphincter preservation for non-achalasia motility disorders. Oral presentation. Digestive Diseases Week, May 8, 2023, Chicago, United States of America.
- 6) Whitfield A, **Cronin O** et al. Underutilisation of endoscopic resection for early rectal cancer is associated with avoidable morbidity and mortality. Poster presentation. May 6, 2023, Chicago, United States of America.
- 7) Gupta S, Gauci J, O'Sullivan T, **Cronin O** et al. An algorithm for the endoscopic resection of upper gastrointestinal subepithelial lesions. Poster presentation. Digestive Diseases Week, May 8, 2023, Chicago, United States of America.
- 8) Craciun A, Gupta S, Gauci J, O'Sullivan T, **Cronin O** et al. Intermuscular separation myotomy improves novice endoscopist outcomes in per-oral endoscopic myotomy (POEM) for achalasia. Poster presentation. Digestive Diseases Week, May 7, 2023, Chicago, United States of America.
- 9) Craciun A, Gupta S, Wang H, Whitfield A, Gauci J, O'Sullivan T, **Cronin O** et al. Hybrid hot plus cold snare endoscopic resection for laterally spreading papillary adenomas. Poster presentation. Digestive Diseases Week, May 7, 2023, Chicago, United States of America.
- 10) O'Sullivan T, Sidhu M, **Cronin O**, Whitfield A, Wang H, Byth K, Bourke MJ. The journey to colonic endoscopic mucosal resection independence: performance analysis of twelve tissue resection fellows. Oral presentation. Digestive Diseases Week, May 20, 2022, San Diego, United States of America.

- 11) Wang H, Nguyen M, Gupta S, Sidhu M, Kumar P, **Cronin O**, Whitfield A, O'Sullivan T, Lee E, Burgess NG, Bourke MJ. Gastric endoscopic submucosal dissection for early gastric cancer; outside criteria outcomes are comparable to inside criteria in a large Western cohort. Poster presentation. Digestive Diseases Week, May 8, 2022, Chicago, United States of America.
- 12) Perananthan V, Gupta S, Whitfield A, O'Sullivan T, **Cronin O**, Sidhu M, Banh X, Bradbear J, Hourigan LF, Raftopoulos S, Burgess NG, Bourke MJ. Peroral endoscopic myotomy is an effective treatment for hypercontractile oesophageal disorders. Oral presentation. Australian Gastroenterology Week, Sep 11, 2022, Sydney, Australia.
- 13) O'Sullivan T, Sidhu M, Gupta S, Elhindi J, **Cronin O**, Whitfield A, Wang H, Burgess NG, Bourke MJ. SMSA-EMR score: a novel risk assessment tool for predicting the "complex" lesion in colonic endoscopic mucosal resection. Poster presentation, Australian Gastroenterology Week, Sep 11, 2022, Sydney, Australia.
- 14) O'Sullivan T, Sidhu M, Cronin O, Whitfield A, Wang H, Byth K, Bourke MJ. The journey to colonic endoscopic mucosal resection independence: performance analysis of 12 tissue resection fellows. Poster presentation, Australian Gastroenterology Week, Sep 11, 2022, Sydney, Australia.
- 15) O'Sullivan T, Tate DJ, Sidhu M, Gupta S, **Cronin O**, Whitfield A, Bourke MJ. Nongranular large non-pedunculated colonic polyps harbour a increased risk of synchronous large lesions: implications of a "colonic mucosal phenotype" for practitioners of endoscopic resection. Poster presentation, Australian Gastroenterology Week, Sep 11, 2022, Sydney, Australia.
- 16) **Cronin O**, Kirszenblat D, O'Sullivan T, Whitfield A, Gupta S, Wang H, Lee E, Burgess NG, Bourke MJ. The geometry of cold snare polypectomy. Oral presentation. Australian Gastroenterology Week, Sep 11, 2022, Sydney, Australia.
- 17) **Cronin O**, Sidhu M, Shahidi N, Gupta S, O'Sullivan T, Whitfield A, Wang H, Kumar P, Hourigan LF, Byth K, Burgess NG, Bourke MJ. Comparison of the morphology

and histopathology of large non-pedunculated colorectal polyps in the rectum and colon: implications for endoscopic treatment. Poster presentation. Australian Gastroenterology Week, Sep 11, 2022, Sydney, Australia.

- 18) Gupta S, Tang A, Sidhu M, Tate D, Whitfield A, O'Sullivan T, **Cronin O**, Peranathan V, Burgess NG, Bourke MJ. Direct diverticular peroral endoscopy myotomy for the treatment of thoracic oesophageal diverticula: a prospective single-centre study. Poster presentation. Australian Gastroenterology Week, Sep 11, 2022, Sydney, Australia.
- 19) Gupta S, Kumar P, O'Sullivan T, Whitfield A, **Cronin O**, Wang H, Chacchi R, Murino A, Despott EJ, Lemmers A, Pioche M, Bourke MJ. Duodenal neuroendocrine tumours: short and long-term outcomes of endoscopic submucosal dissection performed in the Western setting. Poster presentation. Australian Gastroenterology Week, Sep 11, 2022, Sydney, Australia.

Appendix III: Printed publications related to PhD during candidacy

Review

Endoscopic Management of Large Non-Pedunculated Colorectal Polyps

Oliver Cronin ^{1,2} and Michael J. Bourke ^{1,2,*}¹ Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney, NSW 2145, Australia² Westmead Clinical School, University of Sydney, Sydney, NSW 2145, Australia

* Correspondence: michael@citywestgastro.com.au

Simple Summary: Endoscopic resection (ER) of large non-pedunculated colorectal polyps ≥ 20 mm (LNPCPs) is safe, effective and the preferred treatment compared to surgery. Predicted histopathology of an LNPCP based on size, morphology, granularity, pit pattern and location in the colo-rectum is essential when deciding upon resection technique. Post resection defect inspection and adjuvant techniques, such as thermal ablation of the margin, have been demonstrated to reduce recurrence rates. Follow-up surveillance colonoscopy can accurately identify recurrence. Endoscopic treatment of recurrence is effective.

Abstract: Large non-pedunculated colorectal polyps ≥ 20 mm (LNPCPs) comprise approximately 1% of all colorectal polyps. LNPCPs more commonly contain high-grade dysplasia, covert and overt cancer. These lesions can be resected using several means, including conventional endoscopic mucosal resection (EMR), cold-snare EMR (C-EMR) and endoscopic submucosal dissection (ESD). This review aimed to provide a comprehensive, critical and objective analysis of ER techniques. Evidence-based, selective resection algorithms should be used when choosing the most appropriate technique to ensure the safe and effective removal of LNPCPs. Due to its enhanced safety and comparable efficacy, there has been a paradigm shift towards cold-snare polypectomy (CSP) for the removal of small polyps (<10 mm). This technique is now being applied to the management of LNPCPs; however, further research is required to define the optimal LNPCP subtypes to target and the viable upper size limit. Adjuvant techniques, such as thermal ablation of the resection margin, significantly reduce recurrence risk. Bleeding risk can be mitigated using through-the-scope clips to close defects in the right colon. Endoscopic surveillance is important to detect recurrence and synchronous lesions. Recurrence can be readily managed using an endoscopic approach.

Keywords: colonoscopy; polyp; polypectomy; colorectal cancer; endoscopic mucosal resection; endoscopic submucosal dissection



Citation: Cronin, O.; Bourke, M.J. Endoscopic Management of Large Non-Pedunculated Colorectal Polyps. *Cancers* **2023**, *15*, 3805. <https://doi.org/10.3390/cancers15153805>

Academic Editor: Hajime Isomoto

Received: 13 June 2023

Revised: 14 July 2023

Accepted: 20 July 2023

Published: 27 July 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second most frequent cause of cancer-related death [1,2]. The majority of CRCs arise via the stepwise acquisition of molecular abnormalities in the adenoma–carcinoma and serrated pathways [3–5]. This creates the opportunity for intervention to remove premalignant polyps. Endoscopic resection (ER) of pre-malignant polyps has been shown to reduce the incidence of CRC [6–8]. Moreover, screening colonoscopy and polypectomy have been shown to reduce the risk of death from CRC at 10 years (risk ratio 0.82, 95% confidence interval (CI) 0.70–0.93) [9]. In a large study ($n = 2602$) with follow-up over 23 years, a 53% reduction (relative risk (RR) 0.47; 95% CI 0.26–0.80) in mortality was demonstrated in those who had undergone polypectomy [7].

The majority (90%) of colorectal polyps are <10 mm in size, do not contain advanced pathology and can be removed either en bloc or piecemeal using cold-snare polypectomy (CSP) [10–12]. Large non-pedunculated colorectal polyps ≥ 20 mm (LNPCPs) comprise

~1% of all colorectal polyps. These lesions have varied risk of overt and covert submucosal invasive cancer (SMIC), and therefore require a detailed, methodical optical assessment before deciding on the most suitable resection technique [13–16]. This algorithm needs to account for LNPCP size, morphology, location and pit pattern in addition to any patient-specific factors, such as co-morbidities and anticoagulation or anti-platelet medications [17].

Consensus recommendations favour an endoscopic approach as first line for the resection of LNPCPs (based on high-quality evidence) [18,19]. Compared to surgical resection, EMR has been demonstrated to have reduced morbidity and mortality and lower healthcare costs [20,21].

ER can be divided into three discrete phases: pre-resection, resection and post-resection. The technical success of ER requires a methodical, collaborative approach, ideally at a centre with access to the complete range of ER techniques, including conventional endoscopic mucosal resection (EMR), cold-snare EMR (C-EMR) and endoscopic submucosal dissection (ESD) (Figure 1). This review aimed to provide a comprehensive, critical and objective analysis of ER techniques. Herein, we outline an evidence-based approach to the ER of colorectal polyps.

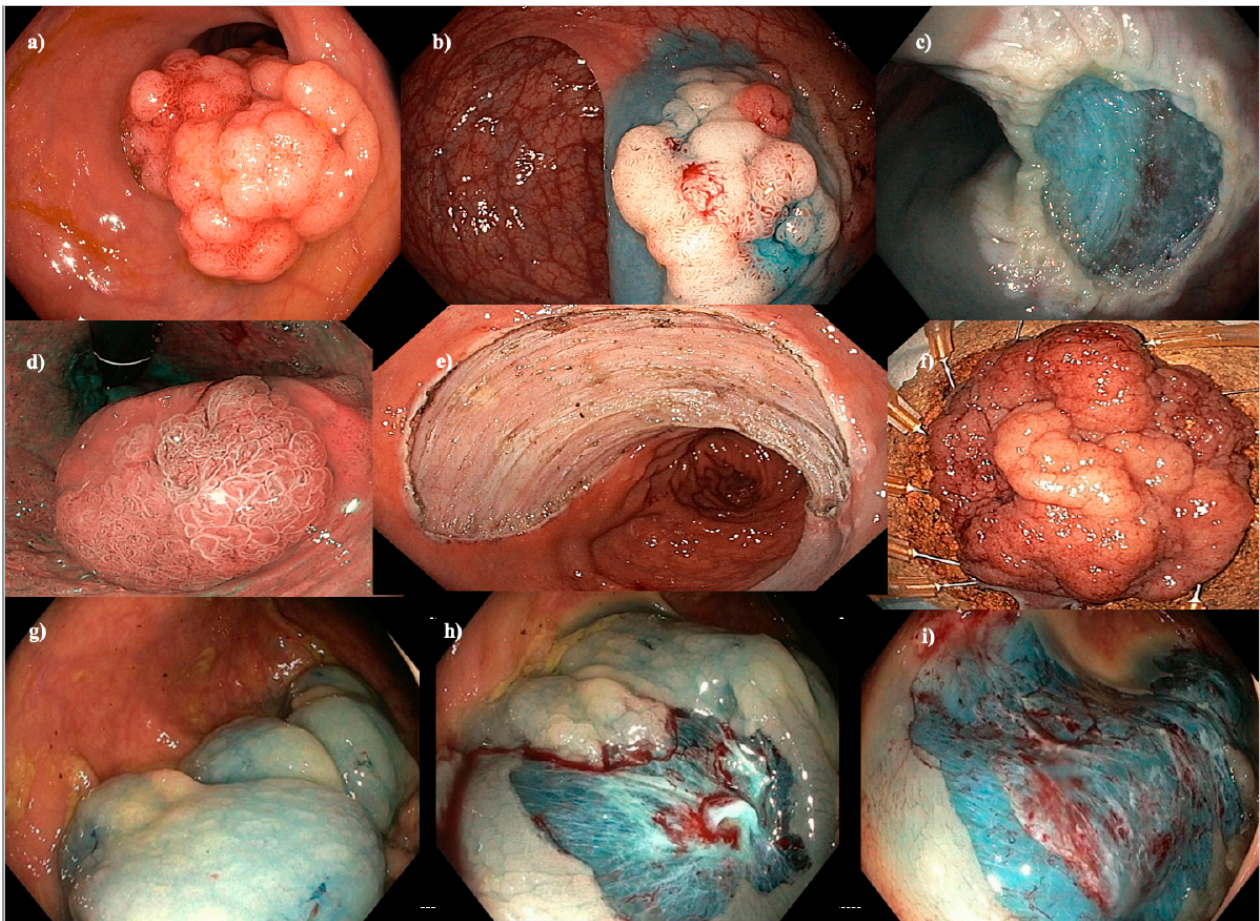


Figure 1. Endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and cold-snare EMR (C-EMR). (a–c) EMR of a 40 mm Paris 0-IIa+Is granular hepatic flexure lesion. (d–f) ESD of a hemi-circumferential 45 mm Paris 0-IIa+Is granular rectal lesion. (g–i) C-EMR of a 50 mm serrated lesion without dysplasia in a patient with serrated polyposis syndrome.

2. Pre-Resection

Planning is essential to ensure technical success. The planning phase can be subdivided into pre-procedure and intra-procedure.

Pre-procedural planning starts with patient assessment, accounting for frailty, functional status, co-morbidities and medications. Consent must include the risks and benefits of ER and a discussion around alternative modalities, such as surgery. Predicted lesion histopathology, including the risk of SMIC, should influence ER modality, and any related imaging should be reviewed. Pre-procedural planning also includes an in-room discussion with the endoscopy team to ensure that nursing and anaesthetic staff are aware of the various stages of the procedure, including any site-specific challenges, such as those seen with ileocaecal valve (ICV) lesions [17,22]. The pre-procedure discussion with the endoscopy team should also include the expected procedure time, any required medications, such as surgical antibiotic prophylaxis or local anaesthetic for anorectal junction (ARJ) lesions, and a check to ensure appropriate snares and ESD knives are available [23,24]. ER should only be performed using carbon dioxide insufflation [25]. Required ancillary devices should be in the room pre-procedure, including closure devices, such as through-the-scope clips, and those used to treat intra-procedural bleeding, such as haemostatic forceps.

Intra-procedural planning starts with patient positioning. The optimal patient position is to have the fluid pool opposite the lesion to maximise the effect of gravity on lesion elevation and achieve a clear working field during tissue resection or for management of any complications. Therefore, a supine or right lateral position may be required. Position of the colonoscope to align the lesion at a 6 o'clock position is essential. Dependent on location, a retroflexed position may improve access and optical assessment.

Thorough optical assessment is key. The risk of overt (optical features of SMIC present) or covert (optical features of SMIC absent) cancer can be predicted based on LNPCP size, location, morphology, granularity, and microvascular and surface pit patterns [13,26]. Several classification systems exist, including the Kudo pit pattern (KPP) and the Japan Narrow-Band Imaging Expert Team (JNET) classification [27,28]. An understanding of these systems is useful. A simple innovation to assist with familiarity and use is to place large posters of these classification systems in endoscopy rooms and reporting areas. Benign lesions have surface homogeneity with a regular pit and microvascular pattern (Figure 2). High grade dysplasia or cancer within a benign lesion appears as a demarcated area of disruption within this regular pattern (Figure 3). Such areas need to be very carefully examined to ensure the correct optical diagnosis and treatment strategy.

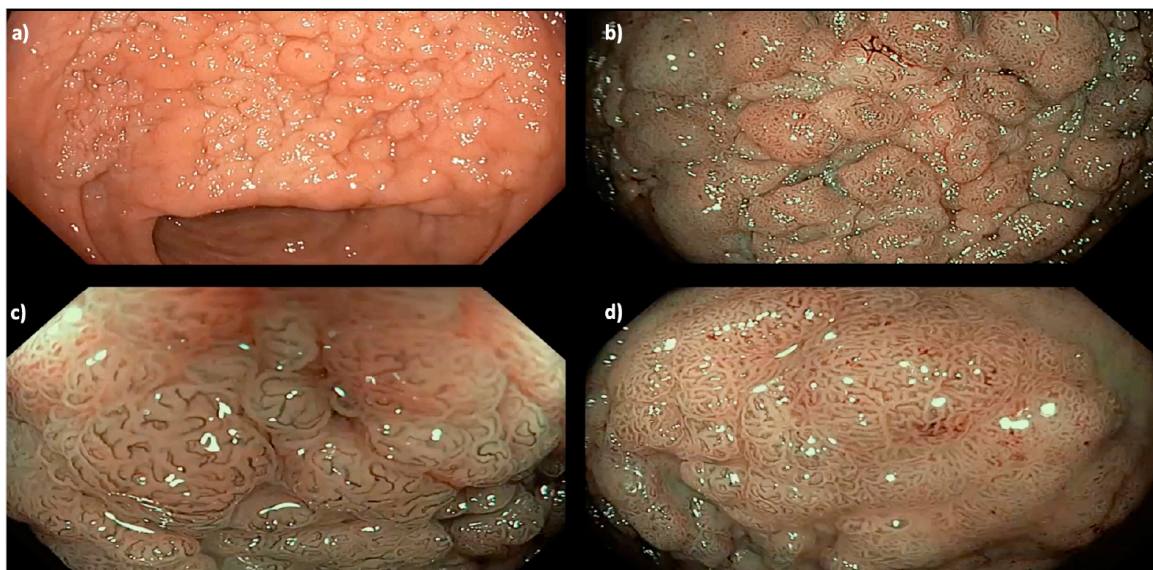


Figure 2. A 35 mm granular Paris 0-IIa LNPCP in the mid-ascending colon, assessed using (a) high definition white light, (b) narrow band imaging (NBI) and (c,d) near-focus with NBI, demonstrating a homogenous pit pattern (Kudo pit pattern IV).

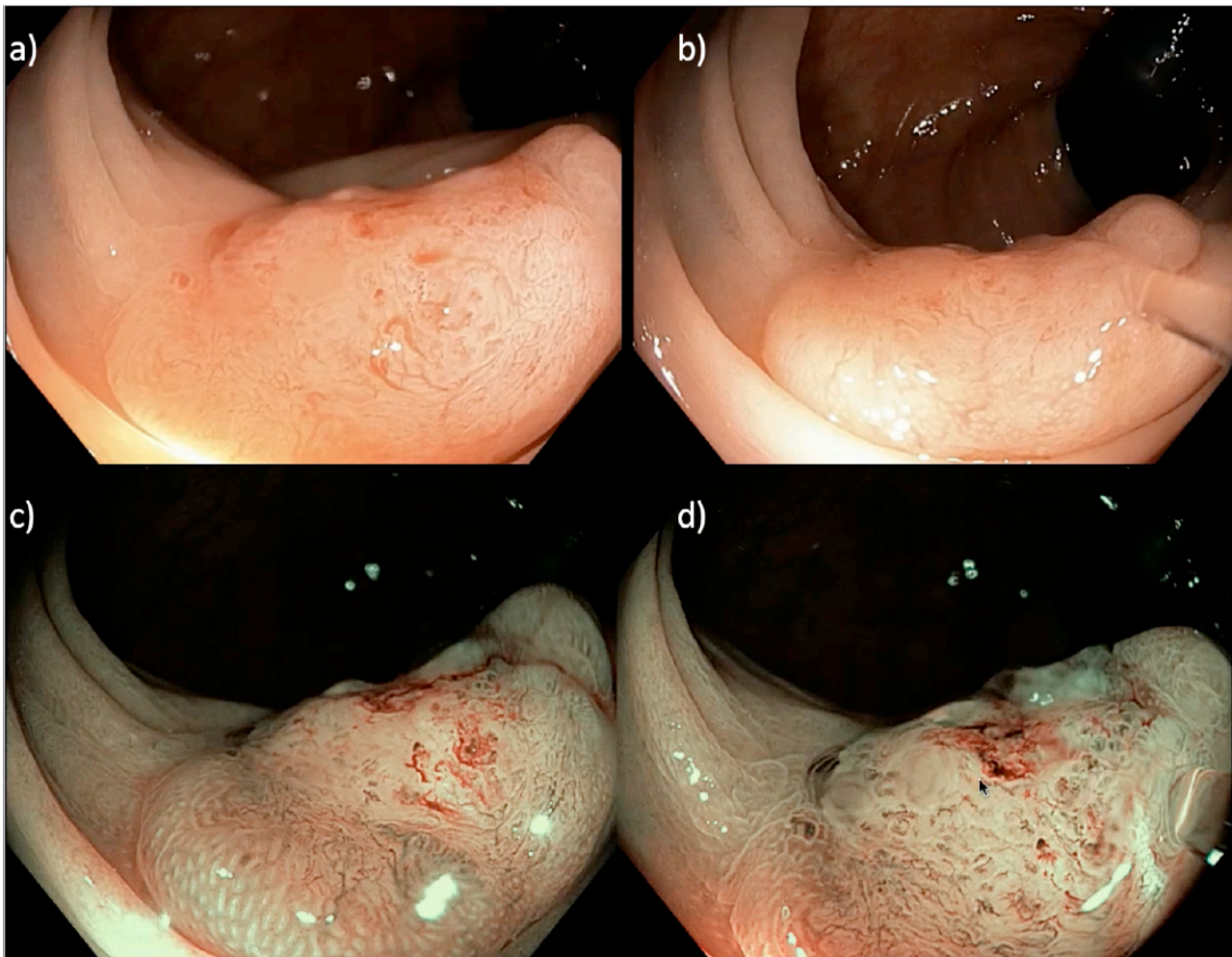


Figure 3. A 20 mm sessile serrated Paris 0-IIa LNPCP in the proximal ascending colon, assessed using (a,b) near focus and (c,d) near focus with narrow band imaging (NBI). There is a central well-demarcated area with loss of homogeneity, neovascularization, dilated vessels and a non-structural pit pattern (Kudo pit pattern V_N), suggestive of a deeply invasive cancer.

Traditionally, the accuracy of optical diagnosis for SMIC was evaluated across the entire LNPCP spectrum and was found to have suboptimal utility. Recently, optical assessment of flat (Paris 0-IIa) LNPCPs has been proven to be highly accurate [15]. In a large, prospective, single-centre cohort study ($n = 1583$), the sensitivity and specificity for predicting cancer in Paris 0-IIa LNPCPs was 91% and 96%, respectively. The likelihood that cancer would be missed in this study was 6 in 1000 cases. Optical diagnosis for SMIC in nodular lesions is less accurate (sensitivity 53%, specificity 94%, missed SMIC 6%) [15]. Excluding those lesions with overt SMIC, a large multicentre, prospective study ($n = 2277$) found that covert SMIC was associated with Paris 0-Is and Paris 0-IIa+Is morphology, non-granularity, size and distal location [13]. Supporting this, a large prospective cohort study ($n = 3405$) demonstrated that nodular rectal LNPCPs are more likely to contain SMIC than non-rectal colonic LNPCPs (15% vs. 6%, $p < 0.001$) [26].

3. Resection

In 2023, a selective resection algorithm should be employed when considering a therapeutic strategy for any colorectal polyp or neoplasm. This is based on optical diagnosis for predicted histology, lesion size, morphology, surface granularity and location in the colon.

3.1. Diminutive (<5 mm) and Small (5–9 mm) Colorectal Polyps

The overwhelming majority of colonic polyps are diminutive (<5 mm) or small (5–9 mm). CSP is safer and equi-efficacious compared to hot-snare polypectomy (HSP) for the removal of these colorectal polyps. The absence of electrocautery all but eliminates the risks of perforation and post-polypectomy bleeding [29,30]. Based on high quality data, en bloc or oligo-piecemeal CSP should be used to resect these polyps [18,19].

3.2. Medium (10–19 mm) Colorectal Polyps

There is a paradigm shift toward C-EMR given its superior safety profile. A large, prospective, multicentre cohort study ($n = 286$ lesions) comparing conventional EMR to C-EMR for 6–15 mm polyps favoured the use of C-EMR over EMR [31]. At present, US consensus guidelines recommend either EMR or C-EMR for resection of lesions 10–19 mm [18].

3.3. Large (>20 mm) Non-Pedunculated Colorectal Polyps

Conventional EMR is the mainstay for ER of LNPCPs due to its superior safety, efficacy and cost effectiveness compared to surgery and ESD [17–19,22]. High-quality studies over the past 10–15 years have led to improvements in the safety and efficacy of EMR. These include the use of CO₂ for insufflation; addition of chromo-injectate into the submucosal space; use of a systematic inject and sequential snare resection technique; removing a 2–3 mm margin of normal mucosa; water expansion of the defect to identify any residual adenoma; and recognition and management of significant DMI [25,32,33]. When all visible adenoma has been excised, thermal ablation of the margin should be completed by gently applying snare-tip soft coagulation (Effect 4, 80 W: ERBE Electromedizin, Tubingen, Germany), aiming for a 3–5 mm rim of ablated mucosa [34]. In a large, prospective cohort ($n = 390$) comparing conventional EMR without and with thermal ablation, recurrence rates reduced from 21.0% (37/176) to 5.2% (10/192), $p < 0.001$. No adverse events were attributed to margin thermal ablation. Since its inception, application of this adjuvant technique has improved. In a recent, larger multicentre cohort ($n = 1049$), recurrence rates at 6-month follow-up colonoscopy (SC1) were 1.4% (10/707) [35].

At present, given the paucity of data, conventional EMR is recommended over C-EMR for LNPCP resection. The safety profile of C-EMR is appealing for the piecemeal resection of Paris 0-IIa (flat, sessile) LNPCPs; however, the upper size limit that can be effectively removed using C-EMR without excessive burden of recurrence is unknown. Several ongoing large randomised controlled trials comparing EMR and C-EMR for non-serrated LNPCPs (clinicaltrials.gov identifier: NCT04138030; NCT04418843) aim to provide clarity on this issue. The next important RCT will compare C-EMR to C-EMR with thermal ablation of the margin (clinicaltrials.gov identifier NCT05041478).

In contrast to adenomatous LNPCPs, C-EMR is always the primary modality for ER of serrated LNPCPs, irrespective of size [36]. A large study ($n = 562$) of serrated lesions found no difference in technical success and recurrence rates between EMR and C-EMR groups; however, bleeding (0% vs. 5.1%) and significant deep mural injury (DMI) (0% vs. 2.8%) were more common in the EMR group.

3.4. Special Considerations

Site specific considerations and technique modifications may be needed for LNPCPs located at the ICV, appendiceal orifice, surgical anastomosis, or an ARJ or those which are circumferential [16,37–39].

The rectum should be regarded as a complex high-risk site, with distinct challenges compared to the colon. This is not due to its technical limitations, but due to its increased risk of covert SMIC [26,40]. Furthermore, the consequences of failed endoscopic cure include consideration of the most hazardous and complicated forms of colorectal surgery, including permanent ostomy formation [41]. Patients with rectal lesions removed using a low or ultra-low anterior resection have an increased risk of incontinence (12%) [42] and sexual dysfunction (20–46%) [43], and a 10–20% risk of permanent stoma [44,45]. Low

anterior resection has a 30-day morbidity and mortality of 25% and 6%, respectively [46]. Postoperative complications have been associated with negative economic impact, increased morbidity, extended postoperative hospital stay, readmission, sepsis and death. ER is organ-sparing and minimally invasive, which enables avoiding wound infections as well as other postoperative complications after open surgery, which cause pain and suffering to patients [47].

In a large, multicentre observational study ($n = 618$), rectal LNPCPs were more likely to have nodular morphology (53% vs. 17%, $p < 0.001$) and contain cancer (15% vs. 6%, $p < 0.001$) compared to LNPCPs in the remainder of the colon [26]. Endoscopic en bloc resection for any LNPCP with a nodular component is critical with the aim of achieving an R0 (curative) resection. This requires meticulous planning.

ESD was developed as an ER technique for the curative treatment of early gastric cancer. ESD is now an established technique in the colo-rectum. It is typically performed with a generous submucosal injection, in a retroflexed position for improved scope stability, and using an improved more parallel angle of the cutting plane. Dissection is performed using an electrosurgical knife. Technique has improved over the past 10 years, aided by internal and external traction devices as well as techniques such as pocket creation ESD.

EMR and ESD are complementary techniques for resection of rectal LNPCPs. A selective resection algorithm (SRA) has demonstrated superior outcomes compared to a universal EMR algorithm (UEA). In a large study ($n = 480$) comparing an SRA to a UEA, LNPCPs underwent ESD if they had features suggestive of superficial overt SMIC (1000 μm , KPP V₁) or covert SMIC (Paris 0-Is or a dominant nodule). All ($n = 7$, 100%) LNPCPs with SMIC amenable to R0 resection that underwent ESD were cured [16]. A rectum-specific SRA avoids the piecemeal resection of cancer.

Until recently, the management of covert SMIC discovered after piecemeal ER has been challenging. A recent observational study ($n = 3372$) identified 143 (4.2%) cases with covert SMIC post piecemeal resection [48]; 109 cases underwent surgical resection, and 62 (63%) cases had no residual cancer. All cases with residual intramucosal cancer ($n = 24$) could be identified by a R1 histological deep margin. Cases with poor differentiation and/or lymphovascular invasion had a high risk of lymph node metastases (12/33); there was a very low risk without these features (<1%, 0/35). The majority of patients with covert SMIC resected piecemeal had no residual malignancy. The risk of malignancy can be predicted by poor differentiation, lymphovascular invasion and an R1 deep margin.

Prevention of bleeding by prophylactic treatment of medium and large vessels with coagulating forceps is key. Bleeding stains the mucosa, impeding views, and leading to a higher risk of incomplete resection. Treatment of bleeding can char the mucosa, also obscuring views. Given its resource intensive, time consuming nature, this technique is best reserved for lesions with superficial overt SMIC or a high risk of covert SMIC. In clinical practice, this limits its use predominantly to the rectum [24].

Previously attempted LNPCPs are common and present a unique set of challenges. Due to the dense submucosal fibrosis, submucosal lift is often unsuccessful. A large observational study ($n = 1292$) demonstrated that with the use of auxiliary these lesions can be effectively resected by EMR. CAST was used in 73 (46.2%) cases. No recurrence ($n = 0$, 0%) was identified in any previously attempted LNPCPs that underwent margin thermal ablation, demonstrating that EMR is effective for resection of these lesions [49].

3.5. Complications

3.5.1. Deep Mural Injury

Significant DMI (Deep Mural Injury Types III–V) was previously a feared intra-procedural complication, with a frequency of approximately 3% [40]. However, due to an improved understanding of risk factors, earlier recognition and advances in closure devices, such as through-the-scope clips, significant DMIs can now be successfully managed [40,50]. In a large, prospective cohort ($n = 911$), significant DMI was associated with attempted en bloc resection, advanced histopathology and transverse colon location [50]. In

a large, prospective cohort ($n = 3717$), significant DMI occurred in 2.7% (101/3717) of EMR resections (median lesion size 35 mm, interquartile range 25–45 mm). Successful defect closure occurred in 97.0% (98/101) of cases. There were no differences found between DMI and non-DMI cases in terms of technical success or recurrence [40].

3.5.2. Post-Procedural Bleeding

Prophylactic treatment of visible vessels within a defect post EMR has been previously investigated. In a multicentre RCT ($n = 347$, 55.3% proximal colonic lesions), prophylactic endoscopic coagulation of all visible vessels within the post-EMR defect did not reduce clinically significant post-EMR bleeding compared to no treatment (5.2% vs. 8.0%; $p = 0.30$) [51]. Post-resection defect closure for right-sided lesions using through-the-scope clips has been shown to reduce clinically significant post-EMR bleeding from 10.6% (12/113) to 3.4% (4/118), $p = 0.031$ [52].

Post-ER bleeding has a frequency of 6–7%, dependent on defect location and the selected ER modality. Bleeding typically does not require intervention, and these cases are managed conservatively in >50% of cases [53].

4. Post-Resection

4.1. Post-Operative Care

Post-resection instructions and communication with nursing staff, patients and their next-of-kin are important to ensure early recognition and management of any adverse events or complications. Recovery staff should receive a verbal handover and a written endoscopy report from the proceduralist, including any complexities or nuances of the case. Dependent on the procedure type, patients should remain fasting for at least 2 h or until they have been examined by the proceduralist. After clinical assessment, if the patient is well, they can commence a clear fluid diet.

The patient should receive a copy of their report. Dietary instructions should be highlighted and details of the best hospital contact should be clear, should the patient have any issues or questions overnight. Most patients can be discharged home the same day, but an endoscopy team member should contact the patient the following day for a telehealth assessment.

4.2. Surveillance

Guidelines recommend a follow-up surveillance colonoscopy 6 months post-ER [18,19,54]. Surveillance post-ER is essential to evaluate the previous resection site and to exclude synchronous lesions [55]. Co-existent advanced pathology (polyps > 10 mm or with a villous component or high-grade dysplasia) is reported to occur at surveillance in 10–20% of cases [55,56].

The previous ER site can be identified by a bland pale area, sometimes with anatomic distortion of the mucosal folds [57]. A standardised imaging protocol for optical assessment of the scar should include high definition white light and narrow band imaging (NBI, Olympus, Inc, Tokyo, Japan) [57]. Optical scar assessment is accurate. A recent multicentre single-blind cross-over trial ($n = 203$) to compare NBI and high definition white light for the assessment of recurrence or residual adenoma at a post-EMR scar reported a negative predictive value (NPV) > 90% (NPV 96% using NBI, NPV 93% using high definition white light) [58]. Use of NBI was not superior to high definition white light ($p = 0.06$) [58]. Expert consensus is that a biopsy is not needed for a bland scar with a uniform pit pattern [57]. Common mimics of recurrence include clip artefact and inflammatory nodules. If an abnormality is suspected, this area should be excised and ablated, as described in a proposed Westmead algorithm for evaluating recurrence [59]. Techniques include cold-snare resection or cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST), margin ablation and clip closure if any DMI \geq Type 2 [34,50,60].

5. Conclusions

ER is organ-sparing and minimally invasive. It is the recommended primary management strategy for the excision of LNPCPs, supported by high-quality studies. Referral to an expert endoscopist, rather than for surgery, is the standard of care for all patients with an LNPCP. Predicted histopathology underpins the selective resection algorithm and accounts for lesion size, site, granularity, pit pattern and morphology. These resection decision strategies have revolutionised management of LNPCPs. Compared to surgery, they have a lower morbidity and mortality, and are more cost-effective. Unnecessary surgery remains an important issue, and can be overcome by greater awareness of the efficacy and superior risk profiles of ER.

Author Contributions: Conceptualization, M.J.B.; methodology, O.C. and M.J.B.; software, O.C.; validation, O.C. and M.J.B.; formal analysis, O.C. and M.J.B.; data curation, O.C.; writing—original draft preparation, O.C.; writing—review and editing, O.C. and M.J.B.; supervision, M.J.B.; project administration, M.J.B.; funding acquisition, M.J.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Keum, N.; Giovannucci, E. Global burden of colorectal cancer: Emerging trends, risk factors and prevention strategies. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 713–732. [[CrossRef](#)]
2. Patel, S.G.; Karlitz, J.J.; Yen, T.; Lieu, C.H.; Boland, C.R. The rising tide of early-onset colorectal cancer: A comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol. Hepatol.* **2022**, *7*, 262–274. [[CrossRef](#)]
3. Levin, B.; Lieberman, D.A.; McFarland, B.; Andrews, K.S.; Brooks, D.; Bond, J.; Dash, C.; Giardiello, F.M.; Glick, S.; Johnson, D.; et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* **2008**, *134*, 1570–1595. [[CrossRef](#)] [[PubMed](#)]
4. Kedrin, D.; Gala, M.K. Genetics of the serrated pathway to colorectal cancer. *Clin. Transl. Gastroenterol.* **2015**, *6*, e84. [[CrossRef](#)] [[PubMed](#)]
5. Itzkowitz, S.H.; Yio, X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: The role of inflammation. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2004**, *287*, G7–G17. [[CrossRef](#)] [[PubMed](#)]
6. Winawer, S.J.; Zauber, A.G.; Ho, M.N.; O'Brien, M.J.; Gottlieb, L.S.; Sternberg, S.S.; Wayne, J.D.; Schapiro, M.; Bond, J.H.; Panish, J.F.; et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N. Engl. J. Med.* **1993**, *329*, 1977–1981. [[CrossRef](#)]
7. Zauber, A.G.; Winawer, S.J.; O'Brien, M.J.; Lansdorf-Vogelaar, I.; van Ballegooijen, M.; Hankey, B.F.; Shi, W.; Bond, J.H.; Schapiro, M.; Panish, J.F.; et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N. Engl. J. Med.* **2012**, *366*, 687–696. [[CrossRef](#)]
8. Kahi, C.J.; Imperiale, T.F.; Juliar, B.E.; Rex, D.K. Effect of screening colonoscopy on colorectal cancer incidence and mortality. *Clin. Gastroenterol. Hepatol.* **2009**, *7*, 770–775, quiz 711. [[CrossRef](#)]
9. Bretthauer, M.; Løberg, M.; Wieszczyn, P.; Kalager, M.; Emilsson, L.; Garborg, K.; Rupinski, M.; Dekker, E.; Spaander, M.; Bugajski, M.; et al. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. *N. Engl. J. Med.* **2022**, *387*, 1547–1556. [[CrossRef](#)]
10. Rex, D.K. Have we defined best colonoscopic polypectomy practice in the United States? *Clin. Gastroenterol. Hepatol.* **2007**, *5*, 674–677. [[CrossRef](#)]
11. Gupta, N.; Bansal, A.; Rao, D.; Early, D.S.; Jonnalagadda, S.; Wani, S.B.; Edmundowicz, S.A.; Sharma, P.; Rastogi, A. Prevalence of advanced histological features in diminutive and small colon polyps. *Gastrointest. Endosc.* **2012**, *75*, 1022–1030. [[CrossRef](#)]
12. Repici, A.; Hassan, C.; Vitetta, E.; Ferrara, E.; Manes, G.; Gullotti, G.; Princiotta, A.; Dulbecco, P.; Gaffuri, N.; Bettoni, E.; et al. Safety of cold polypectomy for <10 mm polyps at colonoscopy: A prospective multicenter study. *Endoscopy* **2012**, *44*, 27–31. [[PubMed](#)]
13. Burgess, N.G.; Hourigan, L.F.; Zanati, S.A.; Brown, G.J.; Singh, R.; Williams, S.J.; Raftopoulos, S.C.; Ormonde, D.; Moss, A.; Byth, K.; et al. Risk Stratification for Covert Invasive Cancer Among Patients Referred for Colonic Endoscopic Mucosal Resection: A Large Multicenter Cohort. *Gastroenterology* **2017**, *153*, 732–742.e1. [[CrossRef](#)]

14. Holt, B.A.; Bourke, M.J. Wide field endoscopic resection for advanced colonic mucosal neoplasia: Current status and future directions. *Clin. Gastroenterol. Hepatol.* **2012**, *10*, 969–979. [[CrossRef](#)]
15. Vosko, S.; Shahidi, N.; Sidhu, M.; van Hattem, W.A.; Bar-Yishay, I.; Schoeman, S.; Tate, D.J.; Hourigan, L.F.; Singh, R.; Moss, A.; et al. Optical evaluation for predicting cancer in large non-pedunculated colorectal polyps is accurate for flat lesions. *Clin. Gastroenterol. Hepatol.* **2021**, *19*, 2425–2434. [[CrossRef](#)]
16. Shahidi, N.; Vosko, S.; Gupta, S.; Whitfield, A.; Cronin, O.; O’Sullivan, T.; van Hattem, W.A.; Sidhu, M.; Tate, D.J.; Lee, E.Y.T.; et al. A Rectum-Specific Selective Resection Algorithm Optimizes Oncologic Outcomes for Large Nonpedunculated Rectal Polyps. *Clin. Gastroenterol. Hepatol.* **2023**, *21*, 72–80.e2. [[CrossRef](#)]
17. Shahidi, N.; Bourke, M.J. How to Manage the Large Nonpedunculated Colorectal Polyp. *Gastroenterology* **2021**, *160*, 2239–2243.e2231. [[CrossRef](#)] [[PubMed](#)]
18. Kaltenbach, T.; Anderson, J.C.; Burke, C.A.; Dominitz, J.A.; Gupta, S.; Lieberman, D.; Robertson, D.J.; Shaikat, A.; Syngal, S.; Rex, D.K. Endoscopic Removal of Colorectal Lesions: Recommendations by the US Multi-Society Task Force on Colorectal Cancer. *Am. J. Gastroenterol.* **2020**, *115*, 435–464. [[CrossRef](#)]
19. Ferlitsch, M.; Moss, A.; Hassan, C.; Bhandari, P.; Dumonceau, J.M.; Paspatis, G.; Jover, R.; Langner, C.; Bronzwaer, M.; Nalankilli, K.; et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* **2017**, *49*, 270–297. [[CrossRef](#)] [[PubMed](#)]
20. Jayanna, M.; Burgess, N.G.; Singh, R.; Hourigan, L.F.; Brown, G.J.; Zanati, S.A.; Moss, A.; Lim, J.; Sonson, R.; Williams, S.J.; et al. Cost Analysis of Endoscopic Mucosal Resection vs Surgery for Large Laterally Spreading Colorectal Lesions. *Clin. Gastroenterol. Hepatol.* **2016**, *14*, 271–278.e2. [[CrossRef](#)]
21. Ahlenstiel, G.; Hourigan, L.F.; Brown, G.; Zanati, S.; Williams, S.J.; Singh, R.; Moss, A.; Sonson, R.; Bourke, M.J. Actual endoscopic versus predicted surgical mortality for treatment of advanced mucosal neoplasia of the colon. *Gastrointest. Endosc.* **2014**, *80*, 668–676. [[CrossRef](#)] [[PubMed](#)]
22. Jideh, B.; Bourke, M.J. How to Perform Wide-Field Endoscopic Mucosal Resection and Follow-up Examinations. *Gastrointest. Endosc. Clin. N. Am.* **2019**, *29*, 629–646. [[CrossRef](#)] [[PubMed](#)]
23. Holt, B.A.; Bassan, M.S.; Sexton, A.; Williams, S.J.; Bourke, M.J. Advanced mucosal neoplasia of the anorectal junction: Endoscopic resection technique and outcomes (with videos). *Gastrointest. Endosc.* **2014**, *79*, 119–126. [[CrossRef](#)] [[PubMed](#)]
24. Shahidi, N.; Sidhu, M.; Vosko, S.; van Hattem, W.A.; Bar-Yishay, I.; Schoeman, S.; Tate, D.J.; Holt, B.; Hourigan, L.F.; Lee, E.Y.; et al. Endoscopic mucosal resection is effective for laterally spreading lesions at the anorectal junction. *Gut* **2020**, *69*, 673–680. [[CrossRef](#)]
25. Bassan, M.S.; Holt, B.; Moss, A.; Williams, S.J.; Sonson, R.; Bourke, M.J. Carbon dioxide insufflation reduces number of postprocedure admissions after endoscopic resection of large colonic lesions: A prospective cohort study. *Gastrointest. Endosc.* **2013**, *77*, 90–95. [[CrossRef](#)] [[PubMed](#)]
26. Cronin, O.; Sidhu, M.; Shahidi, N.; Gupta, S.; O’Sullivan, T.; Whitfield, A.; Wang, H.; Kumar, P.; Hourigan, L.F.; Byth, K.; et al. Comparison of the morphology and histopathology of large nonpedunculated colorectal polyps in the rectum and colon: Implications for endoscopic treatment. *Gastrointest. Endosc.* **2022**, *96*, 118–124.
27. Kudo, S.; Tamura, S.; Nakajima, T.; Yamano, H.; Kusaka, H.; Watanabe, H. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest. Endosc.* **1996**, *44*, 8–14. [[CrossRef](#)]
28. Sano, Y.; Tanaka, S.; Kudo, S.E.; Saito, S.; Matsuda, T.; Wada, Y.; Fujii, T.; Ikematsu, H.; Uraoka, T.; Kobayashi, N.; et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. *Dig. Endosc.* **2016**, *28*, 526–533. [[CrossRef](#)]
29. Chang, L.C.; Shun, C.T.; Hsu, W.F.; Tu, C.H.; Chen, C.C.; Wu, M.S.; Chiu, H.M. Risk of delayed bleeding before and after implementation of cold snare polypectomy in a screening colonoscopy setting. *Endosc. Int. Open* **2019**, *7*, E232–E238. [[CrossRef](#)]
30. Tolliver, K.A.; Rex, D.K. Colonoscopic polypectomy. *Gastroenterol. Clin. N. Am.* **2008**, *37*, 229–251+ix. [[CrossRef](#)]
31. Rex, D.K.; Anderson, J.C.; Pohl, H.; Lahr, R.E.; Judd, S.; Antaki, F.; Lilley, K.; Castelluccio, P.F.; Vemulapalli, K.C. Cold versus hot snare resection with or without submucosal injection of 6- to 15-mm colorectal polyps: A randomized controlled trial. *Gastrointest. Endosc.* **2022**, *96*, 330–338. [[PubMed](#)]
32. Bourke, M.J.; Bhandari, P. How I remove polyps larger than 20 mm. *Gastrointest. Endosc.* **2019**, *90*, 877–880. [[CrossRef](#)] [[PubMed](#)]
33. Moss, A.; Bourke, M.J.; Metz, A.J. A randomized, double-blind trial of succinylated gelatin submucosal injection for endoscopic resection of large sessile polyps of the colon. *Am. J. Gastroenterol.* **2010**, *105*, 2375–2382. [[CrossRef](#)]
34. Klein, A.; Tate, D.J.; Jayasekeran, V.; Hourigan, L.; Singh, R.; Brown, G.; Bahin, F.F.; Burgess, N.; Williams, S.J.; Lee, E.; et al. Thermal Ablation of Mucosal Defect Margins Reduces Adenoma Recurrence After Colonic Endoscopic Mucosal Resection. *Gastroenterology* **2019**, *156*, 604–613.e3. [[CrossRef](#)]
35. Sidhu, M.; Shahidi, N.; Gupta, S.; Desomer, L.; Vosko, S.; Arnout van Hattem, W.; Hourigan, L.F.; Lee, E.Y.T.; Moss, A.; Raftopoulos, S.; et al. Outcomes of Thermal Ablation of the Mucosal Defect Margin After Endoscopic Mucosal Resection: A Prospective, International, Multicenter Trial of 1000 Large Nonpedunculated Colorectal Polyps. *Gastroenterology* **2021**, *161*, 163–170.e163.



36. van Hattem, W.A.; Shahidi, N.; Vosko, S.; Hartley, I.; Britto, K.; Sidhu, M.; Bar-Yishay, I.; Schoeman, S.; Tate, D.J.; Byth, K.; et al. Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: A retrospective comparison across two successive periods. *Gut* **2021**, *70*, 1691–1697.
37. Nanda, K.S.; Tutticci, N.; Burgess, N.G.; Sonson, R.; Williams, S.J.; Bourke, M.J. Endoscopic mucosal resection of laterally spreading lesions involving the ileocecal valve: Technique, risk factors for failure, and outcomes. *Endoscopy* **2015**, *47*, 710–718. [[PubMed](#)]
38. Vosko, S.; Gupta, S.; Shahidi, N.; van Hattem, W.A.; Zahid, S.; McKay, O.; Whitfield, A.; Sidhu, M.; Tate, D.J.; Lee, E.Y.T.; et al. Impact of technical innovations in EMR in the treatment of large nonpedunculated polyps involving the ileocecal valve (with video). *Gastrointest. Endosc.* **2021**, *94*, 959–968.e2. [[CrossRef](#)]
39. Tate, D.J.; Desomer, L.; Awadie, H.; Goodrick, K.; Hourigan, L.; Singh, R.; Williams, S.J.; Bourke, M.J. EMR of laterally spreading lesions around or involving the appendiceal orifice: Technique, risk factors for failure, and outcomes of a tertiary referral cohort (with video). *Gastrointest. Endosc.* **2018**, *87*, 1279–1288.e2. [[CrossRef](#)]
40. Bar-Yishay, I.; Shahidi, N.; Gupta, S.; Vosko, S.; van Hattem, W.A.; Schoeman, S.; Sidhu, M.; Tate, D.J.; Hourigan, L.F.; Singh, R.; et al. Outcomes of Deep Mural Injury After Endoscopic Resection: An International Cohort of 3717 Large Non-Pedunculated Colorectal Polyps. *Clin. Gastroenterol. Hepatol.* **2022**, *20*, e139–e147.
41. Vennix, S.; Pelzers, L.; Bouvy, N.; Beets, G.L.; Pierie, J.P.; Wiggers, T.; Breukink, S. Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst. Rev.* **2014**, Cd005200. [[CrossRef](#)]
42. Duran, E.; Tanriseven, M.; Ersoz, N.; Oztas, M.; Ozerhan, I.H.; Kilbas, Z.; Demirbas, S. Urinary and sexual dysfunction rates and risk factors following rectal cancer surgery. *Int. J. Color. Dis.* **2015**, *30*, 1547–1555. [[CrossRef](#)] [[PubMed](#)]
43. Celentano, V.; Cohen, R.; Warusavitarne, J.; Faiz, O.; Chand, M. Sexual dysfunction following rectal cancer surgery. *Int. J. Color. Dis.* **2017**, *32*, 1523–1530. [[CrossRef](#)]
44. Climent, M.; Martin, S.T. Complications of laparoscopic rectal cancer surgery. *Mini-Invasive Surg.* **2018**, *2*, 45. [[CrossRef](#)]
45. Lindgren, R.; Hallböök, O.; Rutegård, J.; Sjö Dahl, R.; Matthiessen, P. What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial. *Dis. Colon. Rectum* **2011**, *54*, 41–47. [[CrossRef](#)]
46. Cuccurullo, D.; Pirozzi, F.; Sciuto, A.; Bracale, U.; La Barbera, C.; Galante, F.; Corcione, F. Relaparoscopy for management of postoperative complications following colorectal surgery: Ten years experience in a single center. *Surg. Endosc.* **2015**, *29*, 1795–1803. [[CrossRef](#)]
47. Mulita, F.; Liolis, E.; Akinosoglou, K.; Tchabashvili, L.; Maroulis, I.; Kaplanis, C.; Vailas, M.; Panos, G. Postoperative sepsis after colorectal surgery: A prospective single-center observational study and review of the literature. *Prz. Gastroenterol.* **2022**, *17*, 47–51. [[PubMed](#)]
48. Gibson, D.J.; Sidhu, M.; Zanati, S.; Tate, D.J.; Mangira, D.; Moss, A.; Singh, R.; Hourigan, L.F.; Raftopoulos, S.; Pham, A.; et al. Oncological outcomes after piecemeal endoscopic mucosal resection of large non-pedunculated colorectal polyps with covert submucosal invasive cancer. *Gut* **2022**, *71*, 2481–2488. [[CrossRef](#)]
49. Shahidi, N.; Vosko, S.; Gupta, S.; van Hattem, W.A.; Sidhu, M.; Tate, D.J.; Williams, S.J.; Lee, E.Y.T.; Burgess, N.; Bourke, M.J. Previously Attempted Large Nonpedunculated Colorectal Polyps Are Effectively Managed by Endoscopic Mucosal Resection. *Am. J. Gastroenterol.* **2021**, *116*, 958–966. [[CrossRef](#)]
50. Burgess, N.G.; Bassan, M.S.; McLeod, D.; Williams, S.J.; Byth, K.; Bourke, M.J. Deep mural injury and perforation after colonic endoscopic mucosal resection: A new classification and analysis of risk factors. *Gut* **2017**, *66*, 1779–1789. [[CrossRef](#)]
51. Bahin, F.F.; Naidoo, M.; Williams, S.J.; Hourigan, L.F.; Ormonde, D.G.; Raftopoulos, S.C.; Holt, B.A.; Sonson, R.; Bourke, M.J. Prophylactic endoscopic coagulation to prevent bleeding after wide-field endoscopic mucosal resection of large sessile colon polyps. *Clin. Gastroenterol. Hepatol.* **2015**, *13*, e721–e722. [[CrossRef](#)] [[PubMed](#)]
52. Gupta, S.; Sidhu, M.; Shahidi, N.; Vosko, S.; McKay, O.; Bahin, F.F.; Zahid, S.; Whitfield, A.; Byth, K.; Brown, G.; et al. Effect of prophylactic endoscopic clip placement on clinically significant post-endoscopic mucosal resection bleeding in the right colon: A single-centre, randomised controlled trial. *Lancet Gastroenterol. Hepatol.* **2022**, *7*, 152–160. [[PubMed](#)]
53. Burgess, N.G.; Metz, A.J.; Williams, S.J.; Singh, R.; Tam, W.; Hourigan, L.F.; Zanati, S.A.; Brown, G.J.; Sonson, R.; Bourke, M.J. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. *Clin. Gastroenterol. Hepatol.* **2014**, *12*, 651–661.e3. [[CrossRef](#)]
54. Gupta, S.; Lieberman, D.; Anderson, J.C.; Burke, C.A.; Dominitz, J.A.; Kaltenbach, T.; Robertson, D.J.; Shaukat, A.; Syngal, S.; Rex, D.K. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. *Gastrointest. Endosc.* **2020**, *91*, 463–485.e5.
55. Bick, B.L.; Ponugoti, P.L.; Rex, D.K. High yield of synchronous lesions in referred patients with large lateral spreading colorectal tumors. *Gastrointest. Endosc.* **2017**, *85*, 228–233. [[CrossRef](#)]
56. O’Sullivan, T.; Tate, D.; Sidhu, M.; Gupta, S.; Elhindi, J.; Byth, K.; Cronin, O.; Whitfield, A.; Craciun, A.; Singh, R.; et al. The Surface Morphology of Large Nonpedunculated Colonic Polyps Predicts Synchronous Large Lesions. *Clin. Gastroenterol. Hepatol.* **2023**, in press. [[CrossRef](#)]
57. Desomer, L.; Tutticci, N.; Tate, D.J.; Williams, S.J.; McLeod, D.; Bourke, M.J. A standardized imaging protocol is accurate in detecting recurrence after EMR. *Gastrointest. Endosc.* **2017**, *85*, 518–526. [[CrossRef](#)] [[PubMed](#)]

58. João, M.; Areia, M.; Pinto-Pais, T.; Gomes, L.C.; Saraiva, S.; Alves, S.; Elvas, L.; Brito, D.; Saraiva, S.; Teixeira-Pinto, A.; et al. Can white-light endoscopy or narrow-band imaging avoid biopsy of colorectal endoscopic mucosal resection scars? A multicenter randomized single-blind crossover trial. *Endoscopy* **2023**, *55*, 601–607. [[CrossRef](#)] [[PubMed](#)]
59. Burgess, N.; Bourke, M. Can we stop routine biopsy of post-endoscopic mucosal resection scars? *Endoscopy* **2023**, *55*, 608–610. [[CrossRef](#)]
60. Tate, D.J.; Bahin, F.F.; Desomer, L.; Sidhu, M.; Gupta, V.; Bourke, M.J. Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) is an effective and safe strategy for the management of non-lifting large laterally spreading colonic lesions. *Endoscopy* **2018**, *50*, 52–62. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

Original research

Cold versus hot snare endoscopic mucosal resection for large (≥ 15 mm) flat non-pedunculated colorectal polyps: a randomised controlled trial

Timothy O'Sullivan,^{1,2} Oliver Cronin,^{1,2} W Arnout van Hattem ³,
 Francesco Vito Mandarino,¹ Julia L Gauci,¹ Clarence Kerrison,¹ Anthony Whitfield,^{1,2}
 Sunil Gupta,^{1,2} Eric Lee,¹ Stephen J Williams,¹ Nicholas Burgess,^{1,2}
 Michael J Bourke ^{1,2}

¹Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney, New South Wales, Australia

²Westmead Clinical School, The University of Sydney, Sydney, New South Wales, Australia

³Department of Gastroenterology and Hepatology, Netherlands Cancer Institute, Amsterdam, The Netherlands

Correspondence to

Dr Michael J Bourke;
 michael@citywestgastro.com.au

Received 5 May 2024
 Accepted 31 May 2024
 Published Online First
 4 July 2024

ABSTRACT

Background and aims Conventional hot snare endoscopic mucosal resection (H-EMR) is effective for the management of large (≥ 20 mm) non-pedunculated colon polyps (LNPCPs) however, electrocautery-related complications may incur significant morbidity. With a superior safety profile, cold snare EMR (C-EMR) of LNPCPs is an attractive alternative however evidence is lacking. We conducted a randomised trial to compare the efficacy and safety of C-EMR to H-EMR.

Methods Flat, 15–50 mm adenomatous LNPCPs were prospectively enrolled and randomly assigned to C-EMR or H-EMR with margin thermal ablation at a single tertiary centre. The primary outcome was endoscopically visible and/or histologically confirmed recurrence at 6 months surveillance colonoscopy. Secondary outcomes were clinically significant post-EMR bleeding (CSPEB), delayed perforation and technical success.

Results 177 LNPCPs in 177 patients were randomised to C-EMR arm (n=87) or H-EMR (n=90). Treatment groups were equivalent for technical success 86/87 (98.9%) C-EMR versus H-EMR 90/90 (100%); p=0.31. Recurrence was significantly greater in C-EMR (16/87, 18.4% vs 1/90, 1.1%; relative risk (RR) 16.6, 95% CI 2.24 to 122; p<0.001).

Delayed perforation (1/90 (1.1%) vs 0; p=0.32) only occurred in the H-EMR group. CSPEB was significantly greater in the H-EMR arm (7/90 (7.8%) vs 1/87 (1.1%); RR 6.77, 95% CI 0.85 to 53.9; p=0.034).

Conclusion Compared with H-EMR, C-EMR for flat, adenomatous LNPCPs, demonstrates superior safety with equivalent technical success. However, endoscopic recurrence is significantly greater for cold snare resection and is currently a limitation of the technique.

Trial registration number NCT04138030

BACKGROUND AND AIMS

Conventional hot snare endoscopic mucosal resection (H-EMR) of large (≥ 20 mm) non-pedunculated colonic polyps (LNPCPs) is the standard of care within international consensus guidelines.^{1,2} For benign lesions, H-EMR supersedes surgical resection due to superior safety and cost effectiveness.^{3–7}

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hot snare endoscopic mucosal resection (EMR) is effective for the management of large (≥ 20 mm) non-pedunculated colon polyps (LNPCPs), however, electrocautery-related complications may incur significant morbidity. Cold snare resection is a safe and effective technique when performed on small polyps and serrated lesions of all sizes. High-quality evidence evaluating the safety and efficacy of cold EMR of adenomatous LNPCPs is lacking.

WHAT THIS STUDY ADDS

⇒ This randomised trial compared the safety and efficacy of cold snare EMR for flat, adenomatous LNPCPs to conventional hot snare EMR. While cold EMR demonstrates superior safety and equivalent technical success, endoscopic recurrence is significantly greater and a limitation of the technique.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Despite superior safety, recurrence is a significant limitation of cold snare EMR of adenomatous LNPCPs. Refinements in cold EMR are required to reduce the risk of recurrence and gain a better understanding of lesions most amenable to the technique.

Historically, recurrence was frequently encountered in H-EMR.^{8,9} This was a significant limitation of the technique that necessitated multiple procedures to establish an endoscopic cure. The development of margin thermal ablation (MTA) to the post-EMR defect has mitigated recurrence and dramatically changed the EMR landscape.^{10–12} Despite this, electrocautery-related complications of delayed bleeding and perforation persist and may incur significant morbidity.^{13–22}

Cold snare polypectomy (CSP) is effective and safe for the resection of small polyps.^{1,2} Perforation and delayed bleeding are a rare occurrence with complete resection rates comparable to hot snare techniques.^{23–25} The application of cold snare



© Author(s) (or their employer(s)) 2024. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: O'Sullivan T, Cronin O, van Hattem WA, et al. *Gut* 2024;**73**:1823–1830.

resection to large polyps is consequently an attractive alternative. When performed on large non-dysplastic serrated polyps, it is safe and efficacious.^{26–28} Whether similar outcomes are achievable for adenomatous LNPCPs remains unclear, with high-quality evidence comparing cold EMR (C-EMR) to H-EMR lacking.

The aim of this study was to conduct a randomised trial comparing the efficacy and safety of C-EMR against conventional H-EMR for the resection of adenomatous LNPCPs.

METHODS

Study design

This was a prospective single-centre randomised controlled trial conducted at an Australian tertiary referral centre. The scientific protocol, data collection sheets and patient consent form were reviewed and registration was obtained. All authors had access to the study data and reviewed and approved the final manuscript. The manuscript adheres to the Consolidated Standards of Reporting Trials recommendations.²⁹

Patient selection and randomisation

Between November 2019 and September 2023, patients referred with flat LNPCPs between 15 and 50 mm in size were enrolled in the study unless they declined. Written informed consent was obtained from each patient on the day of the procedure. Exclusion criteria included: antiplatelet (excluding aspirin) or anticoagulant use not appropriately interrupted according to current guidelines, bleeding disorder or coagulopathy, inflammatory bowel disease associated dysplasia, LNPCPs concerning for submucosal invasive cancer (SMIC) (Kudo V surface appearance), serrated lesions, LNPCPs directly involving the ileocaecal valve (ICV), anorectal junction (ARJ) or appendiceal orifice (AO) and sessile LNPCPs with a Paris 0-Is component greater than 10 mm in size.

Following optical evaluation, eligible lesions from consenting patients were randomised in a 1:1 ratio to the active (C-EMR) or control (H-EMR) arm using a randomly generated number table which was stored in a locked cabinet outside the procedural room. To minimise bias, the allocation was conducted by a trained research nurse/investigator with the proceduralist blinded to the allocation process. Only one lesion was randomised per patient. In the presence of synchronous LNPCPs, multiple resections within the same procedure were performed if considered medically appropriate by the proceduralist. These remaining lesions were resected with conventional H-EMR as per best practice guidelines.

Procedure

All endoscopic procedures were performed by either a study investigator (accredited gastroenterologist with advanced training at a tertiary referral centre in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their supervision. Antiplatelet (thienopyridine derivatives) and anticoagulation medications were withheld preprocedure, in accordance with consensus recommendations. Standard split-dose bowel preparation was administered 24 hours prior to the procedure. Intravenous sedation was with a combination of fentanyl, midazolam and propofol.

High-definition Olympus 190 series variable-stiffness colonoscopes (HQ190 PCF/CF; Olympus, Tokyo, Japan) were used for all procedures with carbon dioxide for insufflation. Optical evaluation was performed under high-definition white-light and narrow-band imaging (NBI) to exclude features of SMIC. Polyp size was measured against an open snare of known size. Once

deemed appropriate for EMR, a submucosal cushion was created with an injection of succinylated gelatin (Gelifusine; B. Braun, Bella Vista, Australia) with 0.4% indigo carmine and 1:100 000 epinephrine.

For conventional H-EMR, a standardised, previously described, inject and resect EMR technique was used.^{30–33} A microprocessor-controlled electrosurgical generator (Endocut effect 3, VIO 300D; ERBE Elektromedizin, Tübingen, Germany) with fractionated current was used for electrocautery. Thermal ablation of the resection margin was performed using snare tip soft coagulation (STSC) (ERBE VIO 300D, SOFT COAG: 80W, Effect 4; ERBE, Tübingen, Germany). The resected tissue was retrieved by suctioning into a polyp trap or collection with a Roth Net.

For C-EMR, following submucosal injection, snare excision was performed with a dedicated stiff thin-wired cold snare (Boston Captivator 10 mm). In keeping with contemporary cold snare practice and recent guidelines, wide margins were deliberately taken during C-EMR.² We generally aimed for a 50% overlap between polyp tissue and surrounding normal mucosa to achieve a 5 mm resection margin in most cases. Any suspicion of residual adenoma was excised by cold snare once more to ensure complete resection of the lesion (figure 1). Resected tissue was retrieved by suctioning into a polyp trap.

Defects were inspected to assess for deep mural injury (DMI).¹⁵ Areas of significant injury (DMI II–V) were treated with mechanical clip closure. Intraprocedural bleeding (IPB) was treated with STSC, haemostatic forceps or clip closure. Although evidence for defect closure in the right colon emerged following the study's inception, to minimise bias, this was not routinely conducted during H-EMR procedures for bleeding prophylaxis. As per standard practice at study commencement, lesions at high risk of clinically significant post-EMR bleeding (CSPEB), based on defined risk factors, were prophylactically closed.¹⁸

Resection specimens were evaluated by specialist gastrointestinal pathologists. After completion of the procedure, patients were observed for 4 hours. If well, they were discharged on a clear fluid diet overnight. For patients who had their antithrombotic therapy withheld prior to EMR, they were instructed to recommence after 48 hours. Post-procedure care was identical for both treatment arms.

Clinical follow-up and endoscopic surveillance

At 14 days, all patients irrespective of intervention received were contacted by a study coordinator and underwent a structured telephone interview to identify periprocedural adverse events. Medical records were also interrogated to identify readmission for adverse events and record subsequent management. Patients and investigators were not blinded to the intervention received as this was documented on procedural reports.

The first surveillance colonoscopy (SC1) was performed 6 months following index resection and scars optically evaluated under high-definition white-light and NBI with meticulous photo documentation. Proceduralists were not blinded to the intervention received during scar examination. Biopsies were subsequently taken of bland scars to confirm the absence of recurrence. Residual or recurrent adenoma (RRA) when identified, was treated with either hot snare excision or cold biopsy forcep avulsion with adjuvant STSC (CAST).³⁴ Bland scar biopsies and resected recurrence specimens were reviewed by pathologists blinded to the intervention received.

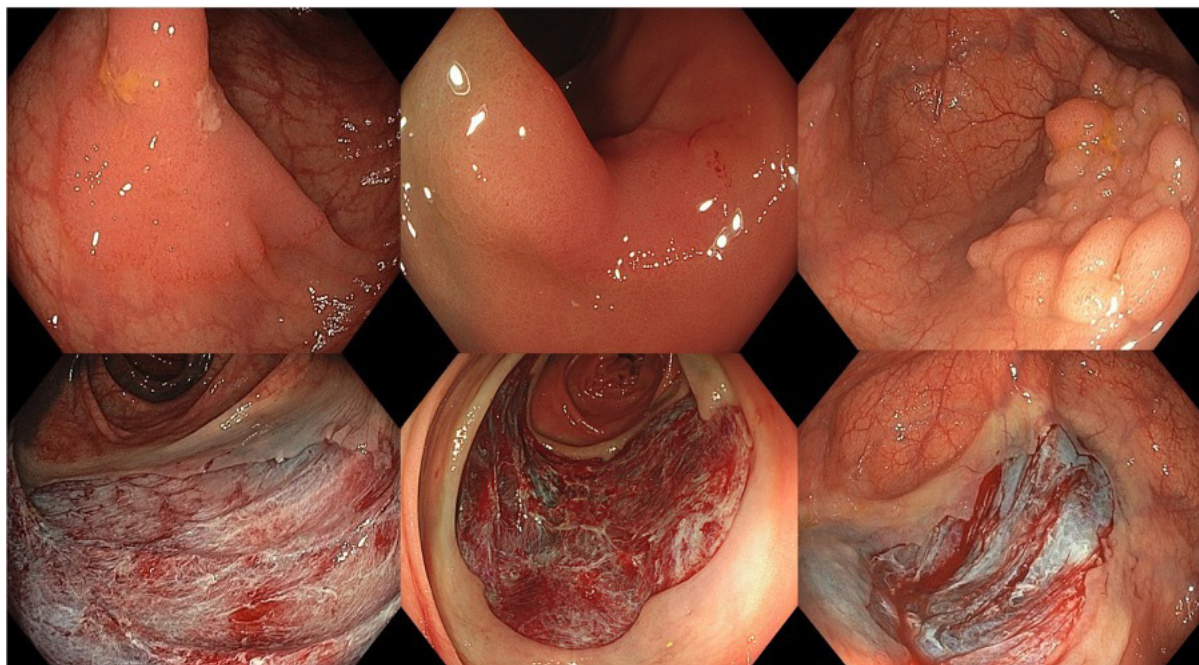


Figure 1 Wide margin cold endoscopic mucosal resection technique for adenomatous large non-pedunculated colon polyps.

Study definitions and endpoints

Baseline patient demographics were collected including age, gender and American Society of Anaesthesiologists (ASA) classification. LNPCPs characteristics included Paris classification, surface granularity (granular vs non-granular), size, location and histopathological diagnosis. Intraprocedural data was recorded including adverse events. IPB was defined as oozing or spurting blood loss for >60s, not responding to water jet irrigation and requiring either STSC, coagulation forceps or mechanical haemostasis. Significant DMI was defined as grade II–V.

The primary outcome was endoscopically visible and/or histologically confirmed RRA identified in the EMR scar at SC1. Secondary outcomes included technical success and adverse events of CSPEB and delayed perforation. CSPEB was defined as any bleeding that occurred after the procedure with either a haemoglobin drop ≥ 2 g/dL, hospital admission or re-intervention (endoscopy, angiography, surgery) within 14 days. Delayed perforation was defined as the clinical syndrome of pain after EMR with imaging or surgical evidence of full-thickness injury to the colorectal wall.

Statistical analysis

Initial sample size calculations used recurrence rates of 7% in conventional EMR versus 14% for C-EMR. Using a two-sided alpha of 0.05 and power of 80%, the sample size initially required was 300 lesions in each arm. Following the study commencement, real-world recurrence data from our centre was published demonstrating an RRA of 1.4%.¹¹ Sample size calculations were subsequently adjusted to reflect recurrence rates of 2% in conventional EMR. Using a two-sided alpha of 0.05 and power of 80%, a reduced sample size of 79 lesions in each arm was calculated. An additional ~10% of cases were added to account for patient dropout during the study period.

Jamovi V.2.3.19 statistics software was used for statistical analyses. Two-tailed tests with a significance level of 5% were used throughout. Continuous variables were summarised as mean with SD or median with IQR of 25–75%. Categorical variables were described using frequencies. The primary analysis

used intention-to-treat (ITT) principles with outcomes analysed for all patients based on the treatment arm to which they were randomised. Per-protocol (PP) analysis was also conducted which considered patients who adhered to the study protocol. Patients who failed to complete surveillance procedures or underwent crossover were excluded from recurrence analysis. Crossover cases were excluded from adverse event analysis where applicable.

Primary and secondary outcomes were expressed as absolute and relative risks with 95% CIs and compared using χ^2 tests as appropriate. Due to the low event rate, multivariate regression analysis was not sufficiently powered to identify predictors of RRA.

RESULTS

Cohort characteristics

A total of 920 LNPCPs were referred for endoscopic resection over 46 months between November 2019 and September 2023. The COVID-19 pandemic impacted LNPCP referral and recruitment from March 2020 to October 2021. In 23 cases endoscopic resection was not attempted due to suspected deep submucosal invasive cancer or technical reasons. 94 cases underwent Endoscopic Submucosal Dissection (ESD) as part of a selective colorectal ESD algorithm and 122 serrated lesions were excluded. Patients with multiple eligible lesions had a single lesion randomised with additional LNPCP resections excluded from the study. In the remaining cohort of LNPCPs the majority were excluded based on morphology or due to size and location criteria. 180 LNPCPs met eligibility criteria in accordance with the study protocol. Three patients were inappropriately randomised on two occasions and these lesions were excluded. 87 lesions were randomised to the C-EMR arm and 90 to the H-EMR arm in 177 patients (figure 2). The mean patient age was 68 ± 9.99 with 53.1% men and 81.3% ASA Class II. The median lesion size was 30 mm (IQR 25–35 mm) with a predominant granular (55.4%) Paris 0-IIa morphology (94.9%). The majority (64.4%) of the lesions were located in the ascending

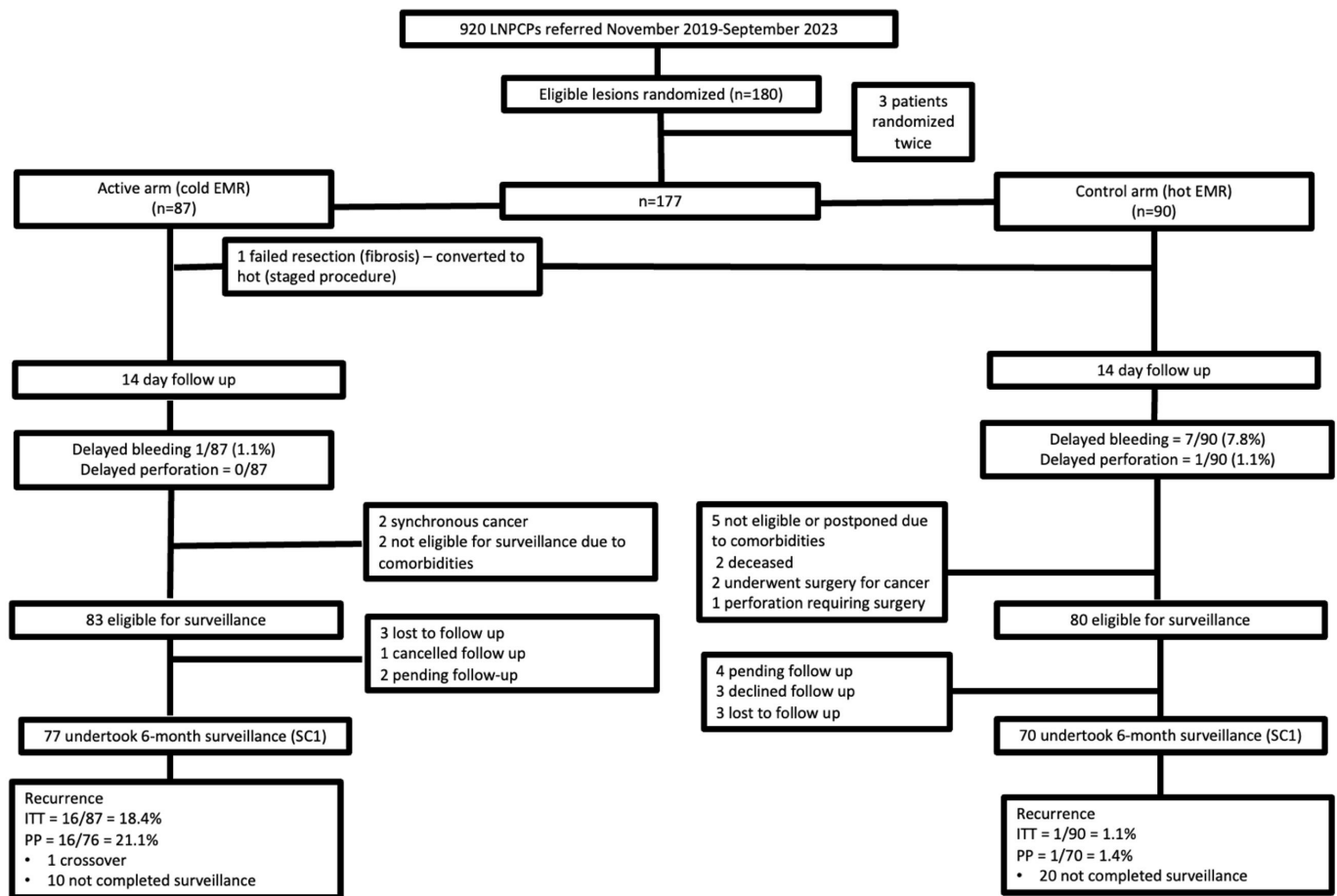


Figure 2 Study enrolment flow diagram. EMR, endoscopic mucosal resection; ITT, intention to treat; LNPCP, large non-pedunculated colorectal polyp; PP, per-protocol; SC1, first surveillance colonoscopy.

colon/caecum. Baseline characteristics between treatment arms are summarised in [table 1](#).

TECHNICAL SUCCESS

Technical success was equivalent with no significant difference between treatment arms (C-EMR 86/87 (98.9%) vs H-EMR 90/90 (100%); $p=0.31$) ([table 2](#)). A single C-EMR procedure performed on a 40 mm, granular Paris 0-IIa, caecal lesion required crossover to H-EMR due to unexpected submucosal fibrosis.

Recurrence at first surveillance colonoscopy

147 LNPCPs undertook SC1 (77 C-EMR, 70 H-EMR). In the C-EMR arm, four patients were ineligible for surveillance colonoscopy, two due to unexpected synchronous cancers and two for new significant comorbidities. In the H-EMR arm five patients were ineligible for surveillance or follow-up postponed due to comorbidities, two patients underwent surgery for unexpected early but non-curative submucosal invasive cancer in the resected specimen and one patient required surgery for a delayed perforation. Two patients in the H-EMR cohort died prior to undertaking surveillance due to conditions unrelated to the EMR procedure (cerebral malignancy and neurodegenerative disease). Of those patients eligible for surveillance, six were lost to follow-up (three C-EMR arm, three H-EMR arm). Four patients declined/cancelled follow-up surveillance procedures (one C-EMR arm, three H-EMR arm).

On ITT analysis, recurrence was significantly greater in the C-EMR arm 16/87 (18.4%) compared with the H-EMR arm 1/90 (1.1%) relative risk (RR) 16.6, 95% CI 2.24 to 122; $p<0.001$) ([table 2](#)). PP analysis was also conducted to analyse patients with completed surveillance and exclusion of crossover cases. Rates were higher, with recurrence in C-EMR in 16/76 (21.1%) compared with 1/70 (1.4%) in the H-EMR arm ($p<0.001$). All recurrences were diminutive and successfully treated endoscopically with no complications.

C-EMR recurrences occurred in lesions that were predominantly caecal location (7/16 (43.7%)) with a granular (11/16 (68.7%)) Paris 0-IIa (100%) morphology ([table 3](#)). The median lesion size was 35 mm (IQR 30–40 mm).

Clip closure, DMI and bleeding

Clip closure was performed as per standard practice in 40 cases (1 C-EMR arm, 39 H-EMR arm). Indications for clipping included significant DMI (II–V), persistent intraprocedural bleeding or patients deemed high risk for CSPEB based on defined predictors.¹⁸

An isolated case of persistent intraprocedural bleeding in the C-EMR arm was successfully treated with clip closure. Intraprocedural bleeding was significantly greater in the H-EMR arm (12/90 (13.3%)) compared with the C-EMR arm (1/87 (1.1%); $p=0.002$). Haemostasis was achieved in the H-EMR arm with STSC (9/12, 75%), coagulation forceps (2/12, 16.7%) and clip closure (1/12, 8.3%).

Table 1 Baseline characteristics of the study cohort

	Active arm (cold)=87	Control arm (hot)=90
Age (SD)	69.1±9.88	67.3±10.1
Gender		
Male	43 (49.4%)	51 (56.7%)
Female	44 (50.6%)	39 (43.3%)
ASA*		
I	7 (8.1%)	9 (10%)
II	71 (82.6%)	72 (80%)
III	8 (9.3%)	9 (10%)
Size (mm) IQR	30 (25–38)	30 (25–35)
Location		
Rectum	3 (3.4%)	3 (3.3%)
Sigmoid	0	3 (3.3%)
Descending	0	6 (6.7%)
Transverse	25 (28.7%)	23 (25.6%)
Ascending	24 (27.6%)	24 (26.7%)
Caecum	35 (40.2%)	31 (34.4%)
Paris classification		
0-Is	0	2 (2.2%)
0-IIa/IIb	83 (95.4%)	85 (94.4%)
0-IIa+Is	4 (4.6%)	3 (3.3%)
Morphology		
Granular	46 (52.9%)	52 (57.8%)
Non-granular	37 (42.5%)	36 (40%)
Mixed	4 (4.6%)	2 (2.2%)
Histology*		
Low-grade dysplasia	78 (91.8%)	77 (85.6%)
High-grade dysplasia	7 (8.2%)	11 (12.2%)
SMIC	0	2 (2.2%)
Successful EMR	86 (98.9%)	90 (100%)
IPB	1 (1.1%)	12 (13.3%)
DMI		
I	0	2 (2.2%)
II	0	23 (25.6%)
III	0	1 (1.1%)
IV	0	3 (3.3%)
Clip closure	1 (1.1%)	39 (43.3%)
Anticoagulant use*	19 (22.1%)	15 (16.7%)

*Missing data: 1 ASA, 1 anticoagulation, 2 inadequate histology sample. ASA, American Society of Anaesthesiologists Classification; DMI, deep mural injury; EMR, endoscopic mucosal resection; IPB, intraprocedural bleeding; SMIC, submucosal invasive cancer.

Significant DMI (II–V) was only encountered in the H-EMR arm (27/90 (30%) vs 0; $p<0.001$). All 27 cases were appropriately closed with endoscopic clips. The majority were DMI

Table 2 Primary and secondary outcome measures with intention to treat analysis

	Active arm (cold)=87	Control arm (hot)=90	P value
Recurrence	16 (18.4%)	1 (1.1%)	$p<0.001$
Clinically significant post-EMR bleeding	1 (1.1%)	7 (7.8%)	$p=0.034$
Delayed perforation	0%	1 (1.1%)	$p=0.32$
Technical success	86 (98.9%)	90 (100%)	$p=0.31$

EMR, endoscopic mucosal resection.

Table 3 Lesion characteristics of cold snare endoscopic mucosal resection recurrences

Characteristics	N=16 (%)
Size (median; IQR)	35 mm (30–40 mm)
Location	
Transverse	5 (31.3%)
Ascending	4 (25%)
Caecum	7 (43.7%)
Paris 0-IIa	16 (100%)
Morphology	
Granular	11 (68.7%)
Non-granular	5 (31.3%)
High-grade dysplasia	1 (6.3%)
IPB	1 (6.3%)
DMI	0 (0%)

DMI, deep mural injury; IPB, intraprocedural bleeding.

Type II (23/27, 85.2%) with 1/27 (3.7%) Type III DMI and 3/27 (11.1%) Type IV.¹⁵

CSPEB was greater in the H-EMR arm on ITT analysis (7/90 (7.8%) vs 1/87 (1.1%); RR 6.77, 95% CI 0.85 to 53.9; $p=0.034$ (table 2). 11 cases of clip closure in the H-EMR arm were performed for bleeding prophylaxis based on individual patient risk. 3/7 cases of CSPEB in the H-EMR arm were clipped intraprocedurally for DMI Type II (2/3) and IPB (1/3). One case of CSPEB occurred in a patient who had multiple lesions resected within a single clinical encounter. Both C-EMR as part of the study as well as a standard H-EMR for a synchronous LNPCP was conducted. A repeat colonoscopy was not required in this case and as such the culprit defect was not identifiable. Exclusion of this case was performed in the PP analysis which remained significant (7/90 (7.8%) H-EMR vs 1/85 (1.2%) C-EMR; $p=0.037$).

Delayed perforation only occurred in the H-EMR group with an isolated case managed with surgical resection. No significant difference was identified in ITT analysis (1/90 (1.1%) vs 0; $p=0.32$ (table 2).

DISCUSSION

H-EMR is effective for the management of LNPCPs with recurrence an infrequent finding since the introduction of MTA.^{10–12} Electrocautery-driven post-procedural adverse events remain problematic and may incur significant morbidity. CSP demonstrates superior safety for diminutive polyps and serrated lesions, however its application to LNPCPs lacks high-quality evidence. This randomised trial has evaluated the safety and effectiveness of C-EMR in the resection of adenomatous LNPCPs.

Post-procedural bleeding and perforation may incur significant morbidity and are a limitation of conventional H-EMR for LNPCPs. A prospective series of 1172 patients identified CSPEB in 6.2% of cases with proximal colon rates of 10–12%.¹⁸ More than 40% of CSPEB cases require repeat colonoscopy with 37% necessitating endoscopic haemostasis.¹³ Prophylactic defect closure in the right colon has recently been demonstrated to be an effective measure for the prevention of CSPEB. A meta-analysis of four randomised trials demonstrated CSPEB in 3.5% of clipped versus 9.0% of unclipped EMR defects.²² While uncommon, delayed perforation is a complication requiring emergent surgical treatment with significant postoperative morbidity and potential mortality.^{9 15–17 35} Recognition and closure of DMI, however, has made delayed perforation a largely

preventable complication.^{15 17} H-EMR adverse events are largely driven by electrocautery-induced deep thermal tissue injury.^{36 37} In a study of 193 polypectomy specimens, the submucosal resection depth with hot snares was 338 μm . In contrast, cold snare resection was shallower (76 μm), with resection layers residing in the submucosa in 9% of cases compared with 92% for hot snare resection ($p < 0.001$).^{38 39}

In the absence of electrocautery, for polyps < 15 mm in size, CSP is highly effective with minimal adverse events. A non-inferiority trial examining complete resection rate (CRR) demonstrated 98.2% CRR for CSP compared with 97.4% for hot snare (non-inferiority $p < 0.0001$).²⁴ With optimal cold snare technique, incomplete resection rates are 1.5% with no adverse event rates. This was demonstrated in an international multi-centre randomised trial of 660 patients.²³ CSP is consequently the standard of care for small polyps with increasing application to larger lesions.

Large, non-dysplastic serrated polyps are safely and effectively resected with cold snare resection. A prospective series of C-EMR in 163 large SSLs demonstrated residual polyp in one case with no CSPEB.²⁶ Similar findings were reported in a prospective series of 41 SSLs with no reported cases of CSPEB or recurrence.²⁷ A comparative study for 562 large, serrated lesions found no adverse events with C-EMR with significantly greater frequency of CSPEB and DMI with H-EMR (5.1% and 3.4% respectively). No significant difference was noted for recurrence (4.3% vs 4.6%).²⁸

In contrast to serrated lesions, C-EMR of adenomatous LNPCPs remains under investigation, with data limited to observational studies. A meta-analysis of eight studies and 522 polyps reported postprocedural bleeding in 0.5% (95% CI 0.1% to 1.2%) with no perforations. However, pooled residual rates in adenomas were 11.1% (95% CI 4.1% to 18.1%) which increased to 22% in the subgroup of polyps over 20 mm in size.⁴⁰ Other retrospective series have reported recurrence rates of 11–34% which increment with growing LNPCP size.^{41 42}

This randomised trial has confirmed C-EMR as a technically successful technique for flat adenomatous LNPCPs with significantly reduced rates of delayed bleeding. Within the C-EMR arm, CSPEB was present in 1/87 (1.1%) patients compared with 7/90 (7.8%) in the H-EMR arm (RR 6.77, 95% CI 0.85 to 53.9; $p = 0.034$). Anticoagulation was withheld periprocedurally across both treatment arms with higher anticoagulant use in the C-EMR cohort (22.1% vs 16.7%). Of the seven cases in the H-EMR arm, four (57.1%) required repeat colonoscopy for endoscopic haemostasis and an additional case received angioembolisation. Three cases were on anticoagulation which was appropriately withheld perioperatively. The single case of CSPEB in the C-EMR arm was on aspirin monotherapy and was managed conservatively. We recognise that during the study period, prophylactic clip closure of right colon H-EMR defects became standard of care following multiple studies demonstrating a reduction in CSPEB.^{19–21} To minimise bias, this practice was not universally adopted, with clip closure performed for significant DMI (II–V), intraprocedural bleeding or risk factors for delayed CSPEB (as was standard practice at trial inception). Clip closure was used for 40 cases (1/40 C-EMR arm, 39/40 H-EMR arm) with 11/39 H-EMR closures performed for bleeding prophylaxis. We recognise such practices may have lowered the prevalence of CSPEB in the H-EMR cohort and masked an even larger difference in delayed bleeding between treatment arms.

Delayed perforation was rare in this study with only one case in the H-EMR arm 1/90 (1.1%) vs 0; $p = 0.32$). This lesion demonstrated type II DMI which was prophylactically clipped.

Within 24 hours postprocedure the patient re-presented with abdominal pain and radiological evidence of localised perforation. Following the failure of conservative management, a laparotomy and right hemicolectomy were conducted. The patient was discharged after a 16-day admission.

Adverse events were a secondary outcome of this study and therefore lacked sufficient power to draw strong conclusions. However, it is established that adverse events in H-EMR are largely preventable and occur in $< 5\%$ of cases.^{17 19–22} For delayed perforation, prevalence is already known to be $< 1\%$ for both hot and cold snare resection.^{17 23 28} Therefore to establish whether cold EMR protects against delayed perforation would require sample sizes of greater than 1000 lesions in each arm which is logistically impossible. In contrast, recurrence imposes a heavy procedural burden on patients and health services to facilitate endoscopic treatment. Occurring at rates exceeding 20% in observational studies, we identified recurrence as the major limitation of the cold EMR technique and consequently made this our primary outcome measure.^{40–42}

Despite its safety, this study has demonstrated endoscopic recurrence to be significantly greater with C-EMR and a limitation of the technique. Historically conventional H-EMR was limited by recurrence rates exceeding 13% (13.8%, 95% CI 12.9% to 14.7%).⁹ While endoscopically treatable, this was at the cost of an increased procedural burden.³⁴ MTA has been transformative to H-EMR practice, with recurrence in $< 5\%$ of cases.^{10–12} This trial had only one case of recurrence in the H-EMR arm, in keeping with previous studies. On ITT analysis C-EMR had substantially more recurrence, 16/87 (18.4%) compared with H-EMR 1/90 (1.1%) (RR 16.6, 95% CI 2.24 to 122; $p < 0.001$). All recurrence was diminutive and managed readily endoscopically.

Before the introduction of MTA in conventional EMR, LNPCP size ≥ 40 mm, IPB and high-grade dysplasia were identified as independent predictors of recurrence.⁴³ While there were not enough recurrence events to power a multivariate analysis in this study, there is indications that similar predictors are present in the C-EMR cohort. Recurrence was predominately observed in larger LNPCPs with 13/16 cases ≥ 30 mm in size. Furthermore, while C-EMR did not demonstrate significant IPB requiring adjuvant haemostasis techniques, compared with H-EMR, mild venous ooze is consistently observed which interferes with defect visualisation and accurate characterisation of resection margins.

The success of MTA in H-EMR suggests recurrence is a consequence of microscopic adenoma within peripheral margins. Previously, no significant difference has been demonstrated in specimen muscularis mucosa for both CSP and hot snare polypectomy (96% vs 92%; $p = 0.603$).⁴⁴ CSP however, frequently demonstrates incomplete resection at defect margins within biopsy specimens.^{24 25 45} Whether MTA will be as effective in C-EMR is unknown and a focus for future studies.

The findings of this study emphasise that despite C-EMR demonstrating infrequent adverse events, recurrence is significantly greater compared with conventional H-EMR. C-EMR may be considered for individual cases where adverse events are unacceptable including, medical comorbidities, geographical isolation or anticoagulation use. Superior safety however does not justify universal implementation of the technique. A recent economic study comparing C-EMR versus H-EMR suggests the safety of C-EMR positions it as the more cost-effective modality.⁴⁶ However there were several limitations to this study, the cost difference was largely driven by the absence of routine prophylactic clip-closure with C-EMR. In contrast to the recommended

practice, all H-EMR procedures underwent defect closure for bleeding prophylaxis and surveillance colonoscopy was not increased if recurrence was detected. Further economic analyses with accurate C-EMR data are required to definitively understand the financial impact of this technique.

This study is not without limitations. First, the trial was conducted at a tertiary centre with expert endoscopists trained in endoscopic resection. Our recurrence rates for H-EMR may not be reproducible within other Western centres, with recent rates of 3–5% reported in large multi-centre studies.^{12–17} These findings bear consideration when powering comparable trials outside of our centre. Second, routine biopsy of recurrence-free scars was conducted in under 80% of cases. However, contemporary data demonstrates the negative predictive value of optical evaluation of a bland scar exceeds 95%, and consequently, the 2024 European Society of Gastrointestinal Endoscopy guideline recommends against scar biopsy.² Proceduralists were not blinded to original therapy and this is a limitation, however, histopathologists were blinded. Finally, the single-centre study design and small numbers made subgroup analysis challenging. Future large multicentre studies examining predictors of recurrence and long-term surveillance outcomes are required to guide lesion selection and appropriate surveillance intervals for C-EMR.

LNPCPs with a large Paris 0-Is component and locations of ICV, AO and ARJ were excluded from this study. Bulky lesions are less likely to be effectively transected without electrocautery and the ICV, AO and ARJ represent unique locations with individual technical challenges and recurrence rates.

In conclusion, compared with H-EMR, C-EMR for flat, adenomatous LNPCPs of 15–50 mm, demonstrates superior safety with equivalent technical success. However, endoscopic recurrence for C-EMR is of the order of 18% and this remains a significant limitation of the technique. Refinements in the C-EMR technique are required to reduce the risk of recurrence and gain a better understanding of lesions most amenable to C-EMR.

Contributors All authors for this manuscript contributed to the study. TO—acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis. OC—acquisition of data. WAvH—study concept and design, acquisition of data. FVM—acquisition of data, analysis and interpretation of data. JLG—acquisition of data. CK—acquisition of data. AMW—acquisition of data. SG—acquisition of data. EL—acquisition of data. SJW—acquisition of data. NB—acquisition of data. MJB—acquisition of data, analysis and interpretation of data, drafting of the manuscript, study concept and design and study supervision/guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests MJB: Research Support: Olympus Medical, Cook Medical, Boston Scientific. The remaining authors have no financial, professional or personal conflicts of interest to disclose.

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.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Western Sydney Local Health District Human Research Ethics Committee 2019/ETH11826. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iDs

W Arnout van Hattem <http://orcid.org/0000-0002-6651-4384>

Michael J Bourke <http://orcid.org/0000-0001-5047-312X>

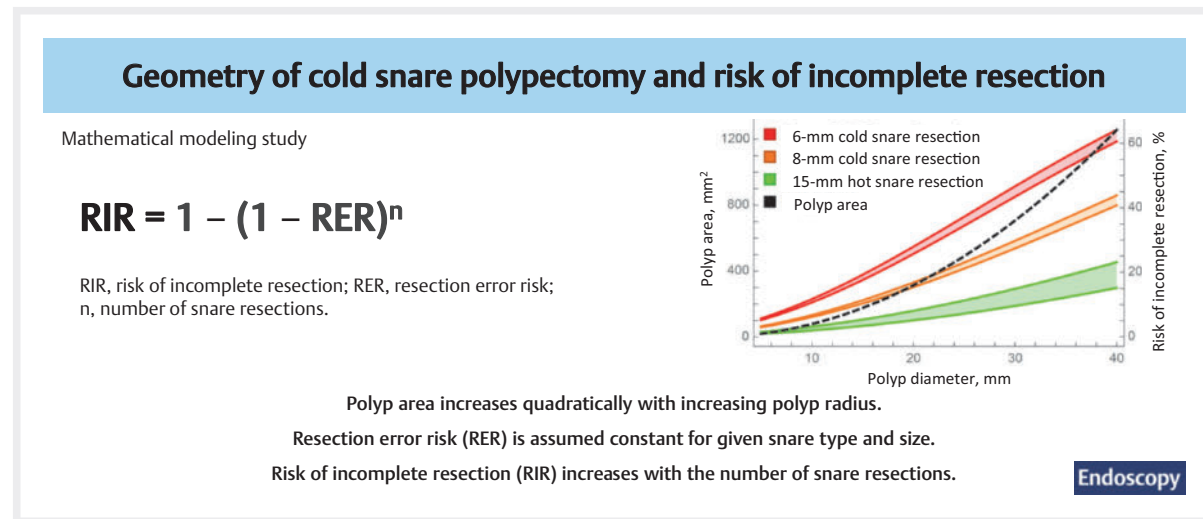
REFERENCES

- Kaltenbach T, Anderson JC, Burke CA, *et al.* Endoscopic removal of colorectal lesions: recommendations by the US multi-society task force on colorectal cancer. *Am J Gastroenterol* 2020;115:435–64.
- Ferlitsch M, Hassan C, Bisschops R, *et al.* Colorectal Polypectomy and endoscopic Mucosal resection: European society of gastrointestinal Endoscopy (ESGE) guideline - update 2024. *Endoscopy* 2024.;38670139.
- Keswani RN, Law R, Ciolino JD, *et al.* Adverse events after surgery for Nonmalignant colon polyps are common and associated with increased length of stay and costs. *Gastrointest Endosc* 2016;84:296–303.
- Peery AF, Shaheen NJ, Cools KS, *et al.* Morbidity and mortality after surgery for Nonmalignant colorectal polyps. *Gastrointest Endosc* 2018;87:243–50.
- Ahlenstiel G, Hourigan LF, Brown G, *et al.* Actual endoscopic versus predicted surgical mortality for treatment of advanced Mucosal Neoplasia of the colon. *Gastrointest Endosc* 2014;80:668–76.
- Swan MP, Bourke MJ, Alexander S, *et al.* Large refractory Colonic polyps: is it time to change our practice? A prospective study of the clinical and economic impact of a tertiary referral Colonic Mucosal resection and Polypectomy service (with videos). *Gastrointest Endosc* 2009;70:1128–36.
- Jayanna M, Burgess NG, Singh R, *et al.* Cost analysis of endoscopic Mucosal resection vs surgery for large Laterally spreading colorectal lesions. *Clin Gastroenterol Hepatol* 2016;14:271–8.
- Moss A, Williams SJ, Hourigan LF, *et al.* Long-term adenoma recurrence following wide-field endoscopic Mucosal resection (WF-EMR) for advanced Colonic Mucosal Neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut* 2015;64:57–65.
- Hassan C, Repici A, Sharma P, *et al.* Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. *Gut* 2016;65:806–20.
- Klein A, Tate DJ, Jayasekaran V, *et al.* Thermal ablation of Mucosal defect margins reduces adenoma recurrence after Colonic endoscopic Mucosal resection. *Gastroenterology* 2019;156:604–13.
- Sidhu M, Shahidi N, Gupta S, *et al.* Outcomes of thermal ablation of the Mucosal defect margin after endoscopic Mucosal resection: A prospective, International, multicenter trial of 1000 large Nonpedunculated colorectal polyps. *Gastroenterology* 2021;161:163–70.
- Abu Arisha M, Scapa E, Wishahi E, *et al.* Impact of margin ablation after EMR of large Nonpedunculated Colonic polyps in routine clinical practice. *Gastrointest Endosc* 2023;97:559–67.
- Burgess NG, Williams SJ, Hourigan LF, *et al.* A management algorithm based on delayed bleeding after wide-field endoscopic Mucosal resection of large Colonic lesions. *Clin Gastroenterol Hepatol* 2014;12:1525–33.
- Verlaan T, Voermans RP, van Berge Henegouwen MI, *et al.* Endoscopic closure of acute perforations of the GI tract: a systematic review of the literature. *Gastrointest Endosc* 2015;82:618–28.
- Burgess NG, Bassan MS, McLeod D, *et al.* Deep mural injury and Perforation after Colonic endoscopic Mucosal resection: a new classification and analysis of risk factors. *Gut* 2017;66:1779–89.
- Swan MP, Bourke MJ, Moss A, *et al.* The target sign: an endoscopic marker for the resection of the Muscularis Propria and potential Perforation during Colonic endoscopic Mucosal resection. *Gastrointest Endosc* 2011;73:79–85.
- Bar-Yishay I, Shahidi N, Gupta S, *et al.* Outcomes of deep mural injury after endoscopic resection: an international cohort of 3717 large non-Pedunculated colorectal polyps. *Clin Gastroenterol Hepatol* 2022;20:e139–47.
- Burgess NG, Metz AJ, Williams SJ, *et al.* Risk factors for Intraoperative and clinically significant delayed bleeding after wide-field endoscopic Mucosal resection of large Colonic lesions. *Clin Gastroenterol Hepatol* 2014;12:651–61.
- Gupta S, Sidhu M, Shahidi N, *et al.* Effect of prophylactic endoscopic clip placement on clinically significant post-endoscopic Mucosal resection bleeding in the right colon: a single-centre, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2022;7:152–60.
- Pohl H, Grimm IS, Moyer MT, *et al.* Clip closure prevents bleeding after endoscopic resection of large colon polyps in a randomized trial. *Gastroenterology* 2019;157:977–84.
- Albéniz E, Álvarez MA, Espinós JC, *et al.* Clip closure after resection of large colorectal lesions with substantial risk of bleeding. *Gastroenterology* 2019;157:1213–21.
- Forbes N, Gupta S, Frehlich L, *et al.* Clip closure to prevent adverse events after EMR of proximal large Nonpedunculated colorectal polyps: meta-analysis of individual patient data from randomized controlled trials. *Gastrointest Endosc* 2022;96:721–31.
- Sidhu M, Forbes N, Tate DJ, *et al.* A randomized controlled trial of cold snare Polypectomy technique: technique matters more than snare wire diameter. *Am J Gastroenterol* 2022;117:100.
- Kawamura T, Takeuchi Y, Asai S, *et al.* A comparison of the resection rate for cold and hot snare Polypectomy for 4–9 mm colorectal polyps: a Multicentre randomised controlled trial (CRESCENT study). *Gut* 2018;67:1950–7.

- 25 Rex DK, Anderson JC, Pohl H, *et al.* Cold versus hot snare resection with or without submucosal injection of 6- to 15-mm colorectal polyps: a randomized controlled trial. *Gastrointestinal Endoscopy* 2022;96:330–8.
- 26 Tutticci NJ, Hewett DG. Cold EMR of large Sessile Serrated polyps at colonoscopy (with Video). *Gastrointest Endosc* 2018;87:837–42.
- 27 Tate D, Awadie H, Bahin F, *et al.* Wide-field piecemeal cold snare Polypectomy of large Sessile Serrated polyps without a submucosal injection is safe. *Endoscopy* 2018;50:248–52.
- 28 van Hattem WA, Shahidi N, Vosko S, *et al.* Piecemeal cold snare Polypectomy versus conventional endoscopic Mucosal resection for large Sessile Serrated lesions: a retrospective comparison across two successive periods. *Gut* 2021;70:1691–7.
- 29 Schulz KF, Altman DG, Moher D, *et al.* CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Trials* 2010;11:1–8.
- 30 Klein A, Bourke MJ. How to perform high-quality endoscopic Mucosal resection during colonoscopy. *Gastroenterology* 2017;152:466–71.
- 31 Jideh B, Bourke MJ. How to perform wide-field endoscopic Mucosal resection and follow-up examinations. *Gastrointest Endosc Clin N Am* 2019;29:629–46.
- 32 Klein A, Bourke MJ. Advanced Polypectomy and resection techniques. *Gastrointest Endosc Clin N Am* 2015;25:303–33.
- 33 Bourke MJ, Bhandari P. How I remove polyps larger than 20 mm. *Gastrointest Endosc* 2019;90:877–80.
- 34 Tate DJ, Desomer L, Argenziano ME, *et al.* Treatment of adenoma recurrence after endoscopic Mucosal resection. *Gut* 2023;72:1875–86.
- 35 van der Sluis FJ, Loffeld RJ, Engel AF. Outcome of surgery for Colonoscopic Perforation. *Colorectal Dis* 2012;14:e187–90.
- 36 Chino A, Karasawa T, Uragami N, *et al.* A comparison of depth of tissue injury caused by different modes of Electrosurgical current in a pig colon model. *Gastrointest Endosc* 2004;59:374–9.
- 37 Tokar JL, Barth BA, Banerjee S, *et al.* Electrosurgical generators. *Gastrointestinal Endoscopy* 2013;78:197–208.
- 38 Takayanagi D, Nemoto D, Isohata N, *et al.* Histological comparison of cold versus hot snare Resections of the colorectal mucosa. *Dis Colon Rectum* 2018;61:964–70.
- 39 Ito A, Suga T, Ota H, *et al.* Resection depth and layer of cold snare Polypectomy versus endoscopic Mucosal resection. *J Gastroenterol* 2018;53:1171–8.
- 40 Thoguluva Chandrasekar V, Spadaccini M, Aziz M, *et al.* Cold snare endoscopic resection of Nonpedunculated colorectal polyps larger than 10 mm: a systematic review and pooled-analysis. *Gastrointest Endosc* 2019;89:929–36.
- 41 Mangira D, Cameron K, Simons K, *et al.* Cold snare piecemeal EMR of large Sessile Colonic polyps ≥ 20 mm (with Video). *Gastrointest Endosc* 2020;91:1343–52.
- 42 Suresh S, Zhang J, Ahmed A, *et al.* Risk factors associated with adenoma recurrence following cold snare endoscopic Mucosal resection of polyps ≥ 20 mm: a retrospective chart review. *Endosc Int Open* 2021;9:E867–73.
- 43 Tate DJ, Desomer L, Klein A, *et al.* Adenoma recurrence after piecemeal Colonic EMR is predictable: the Sydney EMR recurrence tool. *Gastrointest Endosc* 2017;85:647–56.
- 44 Suzuki S, Gotoda T, Kusano C, *et al.* Width and depth of resection for small colorectal polyps: hot versus cold snare Polypectomy. *Gastrointest Endosc* 2018;87:1095–103.
- 45 Pohl H, Srivastava A, Bensen SP, *et al.* Incomplete Polyp resection during colonoscopy—results of the Completeadenoma resection (CARE) study. *Gastroenterology* 2013;144:74–80.
- 46 Mehta D, Loutfy AH, Kushnir VM, *et al.* Cold versus hot endoscopic Mucosal resection for large Sessile colon polyps: a cost-effectiveness analysis. *Endoscopy* 2022;54:367–75.
- 47 Rex DK, Haber GB, Khashab M, *et al.* Snare tip soft coagulation vs argon plasma coagulation vs no margin treatment after large Nonpedunculated colorectal Polyp resection: a randomized trial. *Clin Gastroenterol Hepatol* 2024;22:552–61.
- 48 João M, Areia M, Pinto-Pais T, *et al.* Can white-light Endoscopy or narrow-band imaging avoid biopsy of colorectal endoscopic Mucosal resection scars? A multicenter randomized single-blind crossover trial. *Endoscopy* 2023;55:601–7.
- 49 Desomer L, Tutticci N, Tate DJ, *et al.* A standardized imaging protocol is accurate in detecting recurrence after EMR. *Gastrointest Endosc* 2017;85:518–26.
- 50 Burgess NG, Bourke MJ. Can we stop routine biopsy of post-endoscopic Mucosal resection scars *Endoscopy* 2023;55:608–10.

Geometry of cold snare polypectomy and risk of incomplete resection

GRAPHICAL ABSTRACT



Authors

Oliver Cronin^{1,2}, David Kirszenblat³, Nauzer Forbes⁴, Sunil Gupta^{1,2}, Anthony Whitfield^{1,2}, Timothy O'Sullivan^{1,2}, Julia Gauci^{1,2}, Muhammad Abuarisha^{1,2}, Hunter Wang^{1,2}, Nicholas G. Burgess^{1,2}, Eric Y.T. Lee^{1,2}, Stephen J. Williams^{1,2}, Michael J. Bourke^{1,2}

Institutions

- 1 Gastroenterology and Hepatology, Westmead Hospital, Sydney, Australia
- 2 Medicine, University of Sydney Westmead Clinical School, Sydney, Australia
- 3 Department of Mathematics and Statistics, University of Melbourne, Parkville, Australia
- 4 Medicine, University of Calgary, Calgary, Canada

received 28.3.2023

accepted after revision 29.9.2023

accepted manuscript online 29.9.2023

published online 17.1.2024

Bibliography

Endoscopy 2024; 56: 214–219

DOI 10.1055/a-2184-1609

ISSN 0013-726X

© 2024, Thieme. All rights reserved.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Supplementary material

Supplementary material is available under
<https://doi.org/10.1055/a-2184-1609>

Corresponding author

Michael J. Bourke, MBBS FRACP, Gastroenterology and Hepatology, Westmead Hospital, 151 Hawkesbury Rd, Sydney, Australia
michael@citywestgastro.com.au

ABSTRACT

Background Cold snare polypectomy (CSP) is safer than and equally efficacious as hot snare polypectomy (HSP) for the removal of small (<10 mm) colorectal polyps. The maximum polyp size that can be effectively managed by piecemeal CSP (p-CSP) without an excessive burden of recurrence is unknown.

Methods Resection error risks (RERs), defined as the estimated likelihood of incomplete removal of adenomatous tissue for a single snare resection pass, for CSP and HSP were calculated, based on an incomplete resection rate. Polyp area, snare size, estimated number of resections, and optimal resection defect area were modeled. Overall

risk of incomplete resection (RIR) was defined as $RIR = 1 - (1-p)^n$, where p is the RER and n the number of resections.

Results A 40-mm polyp has a four times greater area than a 20-mm polyp (314.16mm^2 vs. 1256.64mm^2), and requires three times more resections (11 vs. 33, respectively, assuming 8-mm piecemeal resection pieces for p-CSP). RIRs for a 40-mm polyp by HSP and p-CSP were 15.1%–23% and 40.74%–60.60% respectively.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide [1]. The majority of tumors arise from colorectal polyps and colonoscopy exerts its beneficial effect by polypectomy [2]. Ideally polypectomy should be safe, efficient, cost-effective and curative. Recurrence occurs due to incomplete resection which compromises clinical outcomes and increases cost.

The overwhelming majority of colonic polyps are less than 10 mm and are safely and effectively managed with en bloc or oligo-piecemeal cold snare polypectomy. The absence of electrocautery all but eliminates the risks of perforation and post-polypectomy bleeding [3]. This safety and simplicity holds appeal for resection of larger lesions. While these have traditionally been removed by hot snare endoscopic mucosal resection (EMR), the use of diathermy carries with it a small but significant risk of perforation and delayed bleeding [4, 5].

The upper limit of lesion size where piecemeal cold snare polypectomy (p-CSP) remains clinically effective, without excessive and burdensome recurrence rates, is currently unknown. We undertook a modelling study to address this important question.

Methods

Incomplete resection rates for hot snare polypectomy (HSP) and CSP were determined after a review of relevant literature. A formal systematic review with a comprehensive electronic search strategy was not employed. Rather, targeted literature searches were conducted for publications available up to 1st June 2022. The PubMed database was searched using the following terms: “cold snare” AND polypectomy AND incomplete ($n = 36$); “cold snare” AND polypectomy AND residual ($n = 37$).

There were no restrictions on the type of publication and no restriction on study size. Language was limited to English. Data extracted included: author, journal, year of publication, polyp size, injectate used, study size, and rate of incomplete resection (**Table 1s**, available online-only in Supplementary material).

There is a paucity of data for incomplete resection rates, particularly for piecemeal p-CSP. The data does include a recent large multicenter trial ($n = 1393$) which reported an incomplete resection rate of 1.5% for polyps ≤ 10 mm [6]. However, there is little data reporting the incomplete resection rate using p-CSP for polyps > 20 mm. Given the scarcity of relevant studies, a reasonable surrogate measure was taken from the CARE study [7]; this reported an incomplete resection rate of 17.3% for polyps

Conclusion RER is more important with p-CSP than with HSP. The number of resections, n , and consequently RIR increases with increasing polyp size. Given the overwhelming safety of CSP, specific techniques to minimize the RER should be studied and developed.

10–20 mm ($n = 110$). This may underestimate the actual incomplete resection rate for p-CSP given that this study used HSP [7].

Snare size and shape

A 10-mm snare was assumed for CSP modelling. Resection pieces vary between 6 and 8 mm in diameter [8]. A 15-mm snare was assumed for HSP, with a resection diameter of 15 mm. The snare shape has been assumed to be circular, as a surrogate for the true slightly elliptical shape of a snare.

Resection error risk

Resection error risk (RER) is defined as the likelihood of incomplete removal of adenomatous tissue per snare resection. This constant risk applies to each individual snare resection during piecemeal EMR and thus the overall risk accumulates with each sequential resection. Based on a 20-mm polyp area with a 3-mm margin of normal tissue (530.93mm^2), the number of p-CSP resections assuming 8-mm resection pieces (area 50.26mm^2) is 10.56. This is supported by the “disc covering problem” which estimates the smallest number of smaller discs required to cover a larger disc [9]. Clinically, this equates to 10 or 11 sequential snare resections. Dividing 17.3%, the incomplete resection rate from the literature, by the number of sequential snares (10 or 11) the p-CSP RER is estimated at 1.57%–1.73%.

HSP has evolved with advances such as thermal ablation of the defect margin which have greatly reduced recurrence rates [10, 11]. The incomplete resection rate with HSP is also likely to be lower due to the tissue destruction from the thermal penumbra of the hot snare. However, conservatively, based on the study by Pohl et al., it is reasonable to assume an incomplete resection rate of 17.3% for 20-mm polyps [7]. A 20-mm polyp resected with a 15-mm hot snare, with 15-mm resection pieces would require 10 resections. RER for HSP is estimated at 1.73%.

Incomplete resection risk equation

The overall risk of incomplete resection ($RIR = 1 - (1 - RER)^n$, where n is the total number of resections required. This dynamic equation estimates the cumulative risk of missed adenoma with each piecemeal snare resection.

Data analyses

Polyp area, snare area, and defect area were estimated using $\text{area} = \pi r^2$, where r was the radius. A 3-mm edge of normal tissue was added to the resection size, irrespective of polyp size.

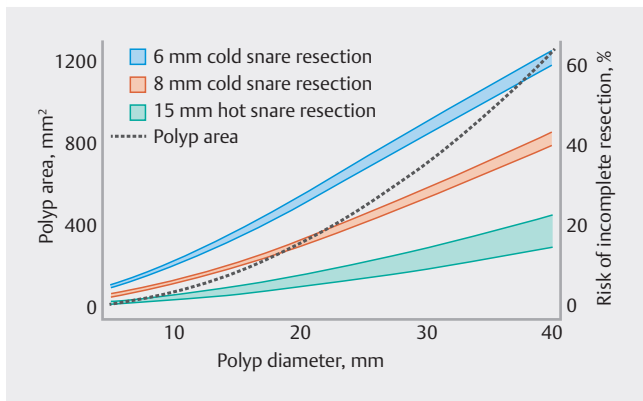


Fig. 1 Risk of incomplete resection (RIR). A mathematical model demonstrating the RIR with cold snare polypectomy and hot snare polypectomy for increasing polyp size.

RER has been assumed as constant with each resection. Data were computed and graphically illustrated using Mathematica 12.3.1 (Wolfram Research) by a mathematician with expertise in mathematical modeling.

Results

Polyp area

Polyp area increases quadratically with increasing polyp radius (► **Fig. 1**). For example, the areas of a 5-mm, 10-mm, and 20-mm polyp are 19.6mm², 78.5mm², and 314.2mm², respectively (► **Table 1, Fig. 2, ► Fig. 3**). This difference is further emphasized when comparing a 30-mm and 40-mm polyp which have areas of 706.9mm² and 1256.6mm² respectively. With the ad-

dition of a 3-mm margin of normal tissue, the area difference between a 10-mm and 20-mm polyp is 329.9mm² (2.6 times larger).

Resection number

Resection number is influenced by polyp area and sequential resection area (► **Table 1**). A 20-mm polyp (with a 3-mm margin of normal tissue) removed by p-CSP, would require 18.8 or 10.6 resections, using piecemeal resection sizes of 6-mm or 8-mm diameter, respectively.

Risk of incomplete resection (RIR)

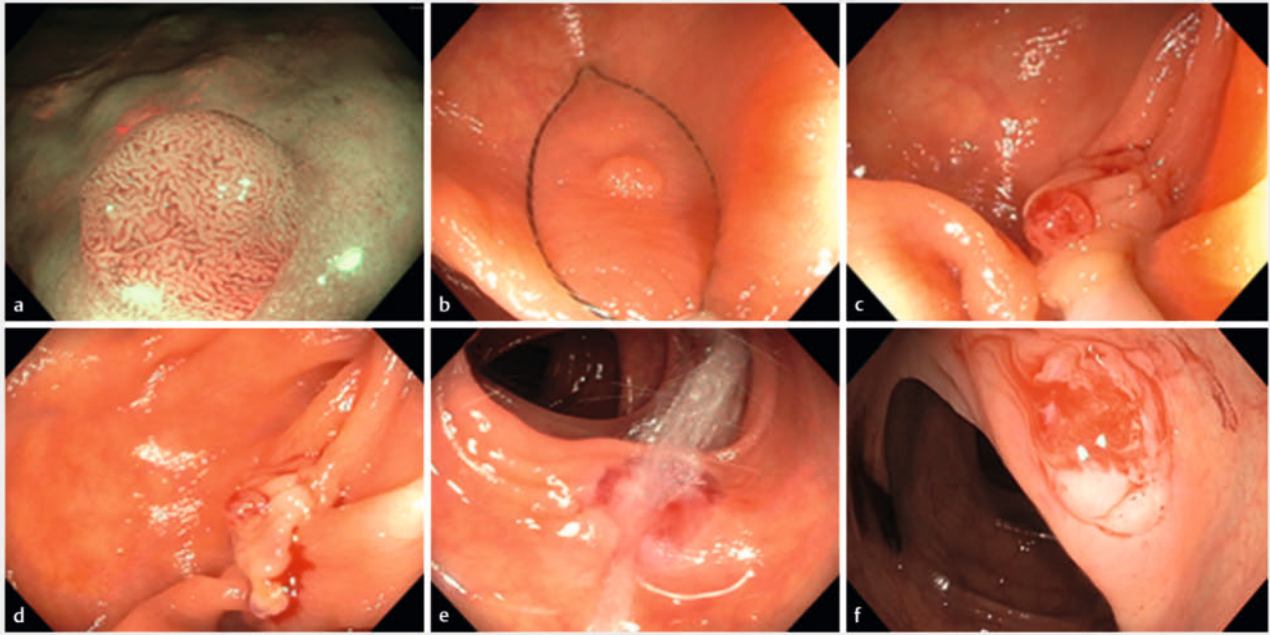
RIR is directly proportional to the number of resections, influenced by polyp size and snare area. The predicted RIRs for a 20-mm versus 40-mm polyp removed by p-CSP with a 6-mm resection piece size are 25.7% and 60.6% respectively. The predicted risks of incomplete resection for a 20-mm versus 40-mm polyp removed by p-CSP with an 8-mm resection piece size are 15.4% and 40.7%, respectively (► **Table 1, Fig. 1**).

Discussion

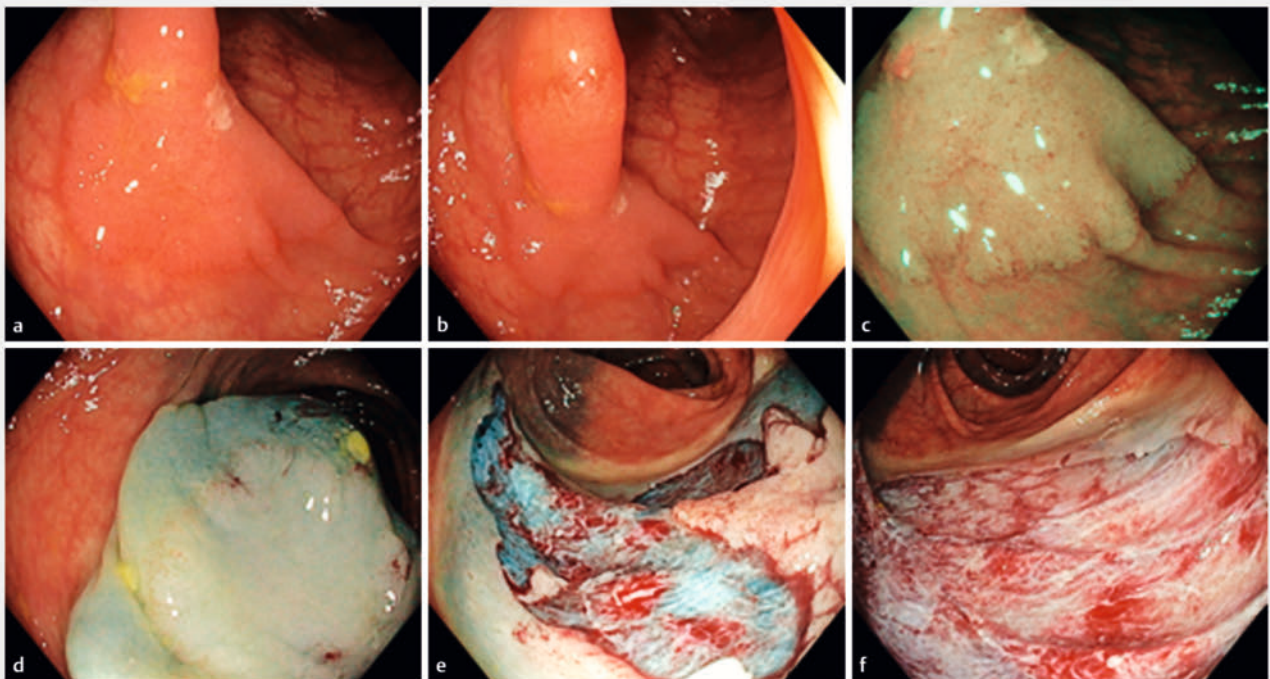
It has been shown that p-CSP is safer than HSP. However, anecdotally for adenomas recurrence seems to be excessive. We undertook a mathematical modeling study to better understand the size at which recurrence from p-CSP might become particularly burdensome. Data are scarce for the rates of incomplete resection for piecemeal CSP and HSP. After extensive review of the literature, we used contemporary data from the highest quality publications to inform our model. The RIR using p-CSP for polyps >20mm in size and 6-mm resection pieces was 25.7%. The corresponding value with 8-mm resection pieces

Table 1 Mathematical modelling of risk of incomplete resection (RIR) for hot and cold and hot snare polypectomy. Polyp area, based on polyp and defect area, resection error risk (RER), and number and size of resections.

	Polyp diameter,mm							
	5	10	15	20	25	30	35	40
Polyp area,mm ²	19.63	78.54	176.71	314.16	490.87	706.86	962.11	1256.64
Defect area,mm ²	95.03	201.06	346.36	530.93	754.77	1017.88	1320.25	1661.90
<i>6-mm resections</i>								
Number of resections	3.36	7.11	12.25	18.78	26.70	36.00	46.70	58.79
Risk of incomplete resection (RER 1.57%)	5.20%	10.60%	17.60%	25.70%	34.50%	43.40%	52.20%	60.60%
<i>8-mm resections</i>								
Number of resections	1.89	4.00	6.89	10.56	15.01	20.25	26.26	33.06
Risk of incomplete resection (RER 1.73%)	2.95%	6.13%	10.33%	15.39%	21.14%	27.42%	34.00%	40.74%
<i>Hot snare resections (15-mm)</i>								
Number of resections	0.54	1.14	1.96	3.00	4.27	5.76	7.47	9.40
Risk of incomplete resection (RER 1.73%)	0.94%	1.97%	3.36%	5.10%	7.18%	9.56%	12.22%	15.13%



► **Fig. 2** Cold snare polypectomy for Paris 0-IIa polyp <10 mm. **a** 3-mm Paris 0-IIa colorectal adenoma. **b** En bloc R0 excision with thin-wire cold snare. Note wide margin of normal mucosa with snare placement. **c** The halo effect with blanching of the surrounding mucosa and hyperemia of the adenoma. **d** Post-excision halo effect. **e** Water expansion of the defect. **f** Careful inspection of margin.



► **Fig. 3** Piecemeal cold snare polypectomy for Paris 0-IIa lesion >20 mm. **a–c** Laterally spreading lesion, >20 mm, examined with high definition white-light and narrow-band imaging. **d** Lesion after submucosal injection. **e** Piecemeal cold snare excision. **f** Careful inspection of the post-resection defect margin.

was 15.4% and comparable to the pre-thermal ablation recurrence rates prior to thermal ablation of the margin. However, as size increased RIR for p-CSP became excessive at >40% for lesions ≥ 40 mm.

The risk profile of CSP is clearly advantageous. Delayed bleeding and perforation are extremely rare events. The mitigation of bleeding risk is also very appealing in an era where anticoagulant and antiplatelet agents are common. The safety profile of CSP has been demonstrated in a large retrospective study ($n = 562$) that compared conventional EMR to p-CSP for resection of large ≥ 20 -mm sessile serrated lesions [12]. There were no adverse events reported in the p-CSP group compared to delayed bleeding and significant deep mural injury (Sydney classification type 3–5) [4] in the EMR group of 5.1% ($n = 18$) and 3.4% ($n = 12$) respectively. In both groups technical success was 100% and recurrence at 18 months was similarly low at <2% [12].

Paradoxically, despite the excellent safety profile of p-CSP, there is a hesitancy to resect wide margins of normal tissue and this potentially leads to higher recurrence rates. Without meticulous attention to ensure overlapping of sequential snares, there is a risk of incomplete resection with each snare resection. Each pass with the snare wire carries a small but cumulative error risk. The risk becomes unacceptably high when removing ever-larger lesions. In this study, the RIR for a 40-mm polyp was >40% with an 8-mm resection piece size and >60% with a 6-mm resection size.

Using modeling we have demonstrated that as lesion size increases, the risk of incomplete resection disproportionately increases and becomes potentially unacceptably high at >40% for lesions 40 mm. This indicates that current techniques or devices are inadequate to manage larger lesions in this way.

There is a lack of literature that assesses the natural history of incompletely resected adenomas. Approximately one-third of post-colonoscopy CRCs are found within the same colorectal segment where the adenoma was resected suggesting that these could be a result of incomplete resection [13]. Pohl et al.'s 2021 study ($n = 233$) demonstrated a greater risk for neoplastic polyps in colon segments after incomplete polyp resection compared to segments with a prior complete resection (odds ratio 3.0, 95%CI 1.12–8.17) [14]. There is also no guarantee that these patients will comply with a surveillance program or that the polypectomy site will be found during surveillance procedures. Moreover the financial burden of surveillance is significant.

In contrast to HSP, p-CSP relies purely on a wide resection margin and sequential snare resection overlap to prevent recurrence. Key factors in reducing recurrence rates include resecting a 2–3-mm margin of normal tissue and meticulous post-resection examination of the p-CSP defect [12, 15]. Although thin-wire snares (0.30 mm) have been developed for CSP, in an international multicenter randomized controlled trial ($n = 1393$) the rate of incomplete polyp resection was similar to that with use of a thick-wire snare (0.47 mm). There was only a single case of post-endoscopy bleeding; this was seen in the thin-wire snare group [6]. Although high quality technique is critical for optimizing outcomes, further reductions in RER are likely to

be driven by advances in device design. Intraprocedural bleeding has also been identified as an independent risk factor for recurrence [16, 17]. In comparison to HSP, intraprocedural bleeding is more frequent when using CSP. Therefore we suggest the use of dilute adrenaline 1:100 000 added to the injectate to minimize bleeding when performing p-CSP for lesions >20 mm.

Preventing recurrence is important for several reasons. Due to the fibrosis typically encountered around a recurrent polyp, resection is more challenging [18]. This increases the risk of complications and resultant morbidity. Additional healthcare-related costs are attributed to an often prolonged procedure time to treat the recurrence, an increased risk of admission post-procedure and the need for additional procedures for ongoing surveillance. All of this assumes that the patient is adherent to the management plan and is not lost to follow-up. Hence, techniques to reduce recurrence risk are essential.

The results of this study have several important clinical implications. Piecemeal-CSP almost completely eliminates the risk of post-procedural bleeding and perforation; however recurrence is greatly increased in comparison to conventional EMR. Lesion location, morphology, and predicted histology, and patient frailty and comorbidities need to be factored into the process of selecting the appropriate resection technique; this ideally would minimize complications, achieve successful lesion excision, and avoid burdensome surveillance. For example, in the right colon, large nonpedunculated colonic polyps ≥ 20 mm have a 10%–12% risk of post-procedural bleeding in the absence of defect closure, but many of these lesions are very large and defy current closure techniques. However the risk of recurrence is also related to lesion size. These are some of the factors that need to be borne in mind. These considerations usher in a new approach to colonic tissue resection which may become more individualized and bespoke.

This study has several limitations. Firstly, a targeted review of the literature rather than a systematic review was employed to estimate RER for our equation. We acknowledge this method could have biased our model. However, our modelled RIRs are consistent with recurrence rates reported in a recent systematic review [19]. Abdallah et al. reported a recurrence rate of 12.3% (3.4%–35.7%) for polyps ≥ 20 mm resected by p-CSP, derived from 4 studies [12, 20, 21, 22]. Unfortunately, recurrence rates for adenomas and SSLs were not reported separately. SSLs are particularly suited to p-CSP due to their thin mucosal profile, and therefore have a lower recurrence rate, compared to adenomas. In particular, Van Hattem et al. included only SSLs ($n = 562$, 4.3%) [12]. The recurrence rate for adenomas ≥ 20 mm is therefore likely higher than concluded by Abdallah et al. and more in line with our model.

Secondly, this model assumes that each resection is an independent entity. In clinical practice however, each resection is related in varying degrees, to the previous resections. This model also does not account for snare overlap. Based on current literature, accounting for this is not feasible. Thirdly, it was assumed that polyp and snare shape are circular to make calculation of area and number of resections more practicable. This assumption probably underestimates the number of resections required to remove large noncircular lesions. Fourthly,

technical challenges such as difficult access and intraprocedural bleeding have not been accounted for but are likely to increase the number of resections for a lesion of any given size. Fifthly, the analysis was based on a very low incomplete resection rate, in procedures conducted by experts who had received prior training, and it probably underestimates the true numerical value of RER. Other studies have reported a rate of incomplete resection of 8%–10%. Finally, during p-CSP re-excision of suspicious areas may serve to reduce the rate of incomplete resection; to what extent this occurs and its efficacy is currently unknown and not feasible to model.

Conclusions

It is important for any endoscopist undertaking p-CSP to have a deep understanding of the fundamentals which underpin endoscopic resection technique. These include sound optical evaluation skills and a willingness to resect a wide margin with meticulous defect inspection and sequential snare overlap. This study demonstrates that the benefits of p-CSP may begin to be outweighed by the risk of incomplete resection for polyps >30–40 mm. Further research is needed to develop better tools to minimize incomplete resection when using p-CSP, and to understand the upper limit for p-CSP where its safety advantages become outweighed by the burden of recurrence and its sequelae.

Conflict of Interest

Michael Bourke: Research Support: Olympus Medical, Cook Medical, Boston Scientific. Nauzer Forbes: Speaker and consultant for Boston Scientific and Pentax Medical; research support from Pentax Medical. There are no other potential conflicts of interest to report.

Funding

The Cancer Institute of New South Wales

References

- [1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; 67: 7–30 doi:10.3322/caac.21387
- [2] Hardcastle JD, Chamberlain JO, Robinson MH et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996; 348: 1472–1477 doi:10.1016/S0140-6736(96)03386-7
- [3] Chang LC, Shun CT, Hsu WF et al. Risk of delayed bleeding before and after implementation of cold snare polypectomy in a screening colonoscopy setting. *Endosc Int Open* 2019; 7: E232–E238
- [4] Burgess NG, Bassan MS, McLeod D et al. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. *Gut* 2017; 66: 1779–1789 doi:10.1136/gutjnl-2015-309848
- [5] Burgess NG, Metz AJ, Williams SJ et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. *Clin Gastroenterol Hepatol* 2014; 12: 651–661.e1–3
- [6] Sidhu M, Forbes N, Tate DJ et al. A randomized controlled trial of cold snare polypectomy technique: technique matters more than snare wire diameter. *Am J Gastroenterol* 2022; 117: 100
- [7] Pohl H, Srivastava A, Bensen SP et al. Incomplete polyp resection during colonoscopy—results of the complete adenoma resection (CARE) study. *Gastroenterology* 2013; 144: 74–80.e1
- [8] Kudo T, Horiuchi A, Kyodo R et al. Mucosal defect size predicts the adequacy of resection of ≤10 mm nonpedunculated colorectal polyps using a new cold snare polypectomy technique. *Eur J Gastroenterol Hepatol* 2021; 33: (Suppl. 01): e484–e489
- [9] Weisstein E. MathWorld - A Wolfram web resource. <https://mathworld.wolfram.com/DiskCoveringProblem.html>
- [10] Klein A, Tate DJ, Jayasekaran V et al. Thermal ablation of mucosal defect margins reduces adenoma recurrence after colonic endoscopic mucosal resection. *Gastroenterology* 2019; 156: 604–613.e3
- [11] Sidhu M, Shahidi N, Gupta S et al. Outcomes of thermal ablation of the mucosal defect margin after endoscopic mucosal resection: a prospective, international, multicenter trial of 1000 large nonpedunculated colorectal polyps. *Gastroenterology* 2021; 161: 163–170.e3
- [12] van Hattem WA, Shahidi N, Vosko S et al. Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: a retrospective comparison across two successive periods. *Gut* 2021; 70: 1691–1697 doi:10.1136/gutjnl-2020-321753
- [13] Belderbos TD, Pullens HJ, Leenders M et al. Risk of post-colonoscopy colorectal cancer due to incomplete adenoma resection: A nationwide, population-based cohort study. *United European Gastroenterol J* 2017; 5: 440–447 doi:10.1177/2050640616662428
- [14] Pohl H, Anderson JC, Aguilera-Fish A et al. Recurrence of colorectal neoplastic polyps after incomplete resection. *Ann Intern Med* 2021; 174: 1377–1384 doi:10.7326/M20-6689
- [15] Tutticci NJ, Kheir AO, Hewett DG. The cold revolution: How far can it go? *Gastrointest Endosc Clin N Am* 2019; 29: 721–736 doi:10.1016/j.giec.2019.06.003
- [16] Tate DJ, Desomer L, Klein A et al. Adenoma recurrence after piecemeal colonic EMR is predictable: the Sydney EMR recurrence tool. *Gastrointest Endosc* 2017; 85: 647–656.e6
- [17] Moss A, Williams SJ, Hourigan LF et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut* 2015; 64: 57–65
- [18] Shahidi N, Vosko S, Gupta S et al. Previously attempted large nonpedunculated colorectal polyps are effectively managed by endoscopic mucosal resection. *Am J Gastroenterol* 2021; 116: 958–966 doi:10.14309/ajg.000000000001096
- [19] Abdallah M, Ahmed K, Abbas D et al. Cold snare endoscopic mucosal resection for colon polyps: a systematic review and meta-analysis. *Endoscopy* 2023; doi:10.1055/a-2129-5752.
- [20] Suresh S, Zhang J, Ahmed A et al. Risk factors associated with adenoma recurrence following cold snare endoscopic mucosal resection of polyps ≥20 mm: a retrospective chart review. *Endosc Int Open* 2021; 9: E867–E873
- [21] Mangira D, Cameron K, Simons K et al. Cold snare piecemeal EMR of large sessile colonic polyps ≥20 mm (with video). *Gastrointest Endosc* 2020; 91: 1343–1343.e52
- [22] Piraka C, Saeed A, Waljee AK et al. Cold snare polypectomy for non-pedunculated colon polyps greater than 1 cm. *Endosc Int Open* 2017; 5: E184–E189



Comparison of the morphology and histopathology of large nonpedunculated colorectal polyps in the rectum and colon: implications for endoscopic treatment

Oliver Cronin, MBBS(Hons),^{1,2} Mayenaaz Sidhu, MBBS,^{1,2} Neal Shahidi, MD,^{1,2,3} Sunil Gupta, MD,^{1,2,4,5} Timothy O'Sullivan, MBBS,^{1,2} Anthony Whitfield, MBBS,^{1,2} Hunter Wang, MBBS,^{1,2} Puja Kumar, MD,^{1,2} Luke F. Hourigan, MBBS,^{4,5} Karen Byth, PhD,² Nicholas G. Burgess, MChB,^{1,2} Michael J. Bourke, MBBS^{1,2}

Sydney, New South Wales; Brisbane, Queensland, Australia; Vancouver, British Columbia, Canada

Background and Aims: The risk of cancer in large nonpedunculated colorectal polyps ≥ 20 mm (LNPCPs) in the rectum relative to the remainder of the colon is unknown. We aimed to describe differences between rectal and colonic LNPCPs to better inform treatment decisions.

Methods: Patients with LNPCPs referred to tertiary centers for endoscopic resection within a prospective, multi-center, observational cohort were evaluated. Data recorded were participant demographics, LNPCP location, morphology, resection modality, and histopathologic data. Multiple logistic regression analysis was used to identify those variables independently associated with rectal versus nonrectal location in the colon.

Results: Patients with LNPCPs referred for endoscopic resection between July 2008 and July 2021 were included. Rectal LNPCPs (n = 618) were larger (median size, 40 mm vs 30 mm; $P < .001$) and more likely to be granular (79% vs 50%, $P < .001$) with a nodular component (53% vs 17%, $P < .001$) compared with nonrectal LNPCPs (n = 2787). Rectal LNPCPs were more likely to have tubulovillous histopathology (72% vs 47%, $P < .001$) and contain cancer (15% vs 6%, $P < .001$). After adjusting for the other features independently associated with location, cancer was more common in the rectum compared with the colon (odds ratio, 1.77; 95% confidence interval, 1.25-2.53).

Conclusions: This study suggests that compared with LNPCPs in the rest of the colon, rectal LNPCPs are more likely to be larger and contain more advanced pathology. These findings have implications for curative endoscopic resection techniques particularly where early cancer is present. (Clinical trial registration numbers: NCT01368289 and NCT02000141.) (Gastrointest Endosc 2022;96:118-24.)

Colorectal cancer is the third most common cancer worldwide, and the burden of disease is projected to increase by 60% by 2030.¹⁻³ This underscores the importance of colonoscopy in the early detection of colorectal cancer and its preven-

tion through the removal of premalignant polyps.^{4,5} Large nonpedunculated colorectal polyps ≥ 20 mm (LNPCPs) are an important polyp subgroup because they are more likely to harbor cancer and therefore require a multidisciplinary

Abbreviations: CI, confidence interval; ESD, endoscopic submucosal dissection; LNPCP, large nonpedunculated colorectal polyp ≥ 20 mm; SMIC, submucosal invasive cancer.

DISCLOSURE: The following authors disclosed financial relationships: N. Shahidi: Honorarium from Boston Scientific and Pendopharm. M. J. Bourke: Research support from Olympus Medical, Cook Medical, and Boston Scientific. All other authors disclosed no financial relationships. Research support for this study was provided by the Cancer Institute of New South Wales for a research nurse and data manager to assist with study administration and the Gallipoli Medical Research Foundation for research at Greenslopes Private Hospital.

Copyright © 2022 by the American Society for Gastrointestinal Endoscopy 0016-5107/\$36.00
<https://doi.org/10.1016/j.gie.2022.02.022>

Received October 1, 2021. Accepted February 15, 2022.

Current affiliations: Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney, New South Wales, Australia (1), Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia (2), Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada (3), Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, School of Medicine, University of Queensland, Brisbane, Queensland, Australia (4), Gallipoli Medical Research Foundation, Greenslopes Private Hospital, Brisbane, Queensland, Australia (5).

Reprint requests: Michael J. Bourke, MBBS FRACP, Westmead Hospital, Department of Gastroenterology and Hepatology, University of Sydney, Westmead Clinical School, Ste 106a, 151-155 Hawkesbury Rd, Sydney, New South Wales, Australia 2145.

approach between organ-sparing endoscopic resection techniques and surgery.⁶

The primary objectives of endoscopic resection are to achieve cure, minimize recurrence, ensure safety, avoid surgery and its attendant comorbidity, and minimize unnecessary costs. EMR is the favored technique in the colon because of its excellent performance characteristics. With site-specific technical modifications, EMR is also the favored technique in parts of the colon that have traditionally been more challenging for resection such as the appendiceal orifice and the ileocecal valve.⁷⁻⁹ However, a universal EMR approach may not be appropriate, specifically in the rectum. This is because of the ramifications of piecemeal resection of malignant LNPCPs and the associated morbidity, mortality, and risk of permanent ostomy formation associated with distal colorectal surgery, which in turn has stimulated the development and application of en-bloc resection techniques such as endoscopic submucosal dissection (ESD) and transanal endoscopic microsurgery.

Little is known about the differences between rectal versus nonrectal LNPCPs. It is important to identify differences that may influence resection technique selection and thereby impact both clinical outcomes and resource utilization. This study quantifies the differences between rectal and colonic LNPCPs to better inform current practice.

METHODS

This article has been prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology initiative.^{10,11} All authors had access to the study data and reviewed and approved the final manuscript.

Australian Colonic Endoscopic Resection cohort

The Australian Colonic Endoscopic Resection cohort (clinicaltrials.gov identifiers: NCT01368289 and 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 was obtained from each participant before enrollment.

Between July 2008 and July 2021, consecutive participants were enrolled from 3 high-volume Australian Colonic Endoscopic Resection sites (Westmead Hospital, Princess Alexandra Hospital, and Greenslopes Hospital) in Australia. All sites have an established tissue resection program that includes EMR and ESD. All endoscopic procedures were performed by 1 of 5 study investigators (accredited gastroenterologist with advanced training and an established tertiary referral practice in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their direct

supervision. EMR was performed with a standardized technique that was modified over time as technical innovations emerged.¹²⁻¹⁷

Histopathology evaluation

After endoscopic resection, specimens were collected and processed for histopathology review in accordance with the Australasian Gastrointestinal Pathology Society guidelines.¹⁸ Histopathology review was completed by expert GI pathologists at their respective sites. Cancer was defined by neoplastic invasion into the submucosa.¹⁹

Data extraction and analysis

Prospectively collected data were patient characteristics (age, sex, American Society of Anesthesiologists classification), LNPCP characteristics (location, size, Paris classification, surface granularity, Kudo pit pattern, submucosal invasive cancer [SMIC], resection technique), and histopathology evaluation.

Statistical analysis

SPSS version 27.0 (IBM Corp, Armonk, NY, USA) was used for data analysis. The continuous variables of age and lesion size are summarized as median (interquartile range) after assessment of non-normality using the Shapiro-Wilk test. Categorical variables are summarized as frequencies (%). Mann-Whitney tests were used to test for differences in continuous distributions between groups, whereas χ^2 tests (or exact permutation tests if required) were used to test for association between categorical variables. All variables associated with lesion location (rectal vs nonrectal) at the $P < .1$ level were considered as candidate variables for inclusion in multivariable models. Multiple logistic regression with backward stepwise variable selection was used to identify those candidate variables independently associated with lesion location. Odds ratios with 95% confidence intervals (CIs) were used to quantify the strength of association. All analyses were exploratory, and 2-tailed tests with a 5% significance level were used throughout.

Patient and public involvement

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

RESULTS

Between July 2008 and July 2021, 3405 LNPCPs in 2984 patients were referred for endoscopic resection (Fig. 1). Resection was not attempted in 101 LNPCPs (3%) because of a suspicion of cancer, 7 (<1%) because of appendiceal orifice involvement, 11 (<1%) because of difficult access or position, and 4 (<1%) because of ileocecal valve involvement. Most LNPCPs ($n = 3258$ [96%]) were removed by EMR, of which 3118 (96%) had

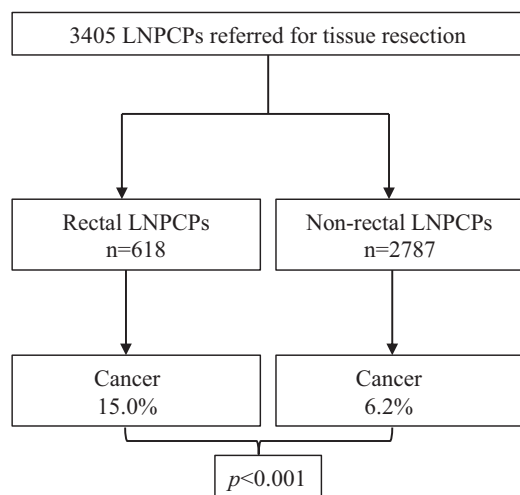


Figure 1. Flow diagram of consecutive patients referred with LNPCPs for tissue resection. LNPCP, Large nonpedunculated colorectal polyp ≥ 20 mm.

technical success, defined as complete excision of all visible adenomatous tissue.

Demographic and LNPCP characteristics

The median age of the 2984 patients was 69 years (interquartile range, 60-75), and 86% had an American Society of Anesthesiologists score of I or II. Overall, the median LNPCP size was 30 mm (interquartile range, 25-40 mm). Most lesions were granular (1879 [55%]) with tubulovillous histology as the most common (1750 [51%]).

Rectal LNPCPs were larger (median size, 40 mm vs 30 mm; $P < .001$) and more likely to be granular (79% vs 50%, $P < .001$) with a nodular component (53% vs 17%, $P < .001$) compared with colonic LNPCPs (Table 1). Rectal LNPCPs were also more likely to have tubulovillous histopathology (72% vs 47%, $P < .001$). As expected, rectal sessile serrated LNPCPs were infrequent, totaling 1% ($n = 6$) of all rectal LNPCPs. Cancer was more common in rectal LNPCPs compared with LNPCPs in the colon (15% vs 6%, $P < .001$). The adjusted odds ratios and 95% CIs for those variables independently associated with rectal versus nonrectal location in the best-fitting multiple logistic regression model are shown in Table 2. In summary, rectal LNPCPs are significantly larger, granular, nodular, or mixed nodular and more frequently have advanced endoscopic pit patterns. Most importantly, they more often contain cancer (adjusted odds ratio, 1.77; 95% CI, 1.25-2.53).

DISCUSSION

The rectum and colon are in a digestive continuum, and any contained pathology generally has been considered and managed uniformly. Accordingly, until very recent times all colorectal LNPCPs have been generally subjected

to the same endoscopic treatment algorithm, regardless of location. The tendency for rectal LNPCPs to have more advanced characteristics has strong implications for therapeutic decision-making.

Previously, many endoscopists from nonspecialist tissue resection centers have been comfortable with resection of rectal LNPCPs. Options for resection include EMR, ESD, transanal minimally invasive surgery, or transanal endoscopic surgery, although EMR is the most commonly used technique.²⁰⁻²⁴ Endoscopic resection has been demonstrated to have the lowest lifetime cost relative to other resection modalities for removal of rectal LNPCPs.²⁵ Nonspecialized endoscopists seem to be more willing to tackle a rectal LNPCP than a LNPCP at a site perceived as traditionally more challenging, such as the ileocecal valve. The perceived safety of extraperitoneal rectum and the reduced risk of serious sequelae from perforation may embolden the decision-making. This logic is flawed. The risk of cancer within a rectal LNPCP is greater, and the consequences of failed endoscopic cure include consideration of the most hazardous and complicated forms of colorectal surgery, including permanent ostomy formation.²⁶ The rectum should be regarded as a complex high-risk site, not because of its technical limitations but because of its increased risk of cancer and the implications for incomplete resection.

Our findings reflect significant differences of LNPCPs in the rectum compared with the remainder of the colon. Rectal LNPCPs are more likely to be larger and have villous or tubulovillous histology. Rectal LNPCPs are more likely to have a nodular component and contain high-grade dysplasia or cancer. These fundamental differences have strong implications for endoscopic management decisions.²⁰

This study found that rectal LNPCPs are more likely to have a nodular component compared with LNPCPs in the colon. By their nature, LNPCPs with a nodule are more likely to contain SMIC.^{14,27} Supporting this notion, a prospective, multicenter, observational study that assessed optical evaluation to predict cancer in LNPCPs found independent predictors for missed SMIC were size ≥ 40 mm, nodular morphology, and distal location.²⁸ In a systematic review and meta-analysis, LNPCPs with SMIC were more commonly located in the distal colon compared with the proximal colon (odds ratio, 2.5; 95% CI, 1.2-5.0).²⁹ Therefore, rectal LNPCPs with a nodular (Paris 0-Is) component or optical features concerning for SMIC require en-bloc resection.

It has previously been suggested that optical evaluation for SMIC in LNPCPs has limitations.³⁰ This study by Backes et al ($n = 343$) observed that during optical assessment of endoscopically unresectable LNPCPs (at least T1 stage colorectal cancer), specificity was good (94%) but sensitivity was lower (79%). More recently, the Australian Colonic Endoscopic Resection consortium in 1583 patients reported similar rates of specificity (95%) and sensitivity (67%).²⁸ However, they found significant

TABLE 1. Comparison of rectal and nonrectal LNPCPs

	Rectum (n = 618)	Colon (nonrectum) (n = 2787)	Total (n = 3405)	P value
Age, y	67 (59-74)	69 (60-76)	67.0 (12.3)	.001
Sex				
Male	330 (53.4)	1332 (47.8)	1662 (48.9)	<.011
Female	288 (46.6)	1455 (52.2)	1743 (51.2)	
American Society of Anesthesiologists score				
≤II	551 (89.2)	2376 (85.3)	2927 (86)	.923
>II	67 (10.8)	411 (14.7)	478 (14)	
Lesion size, mm	40 (30-60)	30 (25-40)	30 (25-40)	<.001
Paris classification				
Is	98 (15.9)	307 (11)	405 (11.9)	<.001
IIa	154 (24.9)	1729 (62)	1883 (55.3)	
IIa+Is	330 (53.4)	480 (17.2)	810 (23.8)	
Any "c" component	26 (4.2)	130 (4.7)	156 (4.6)	
Other	10 (1.6)	141 (5.1)	151 (4.4)	
Morphology				
Granular	488 (79.0)	1391 (49.9)	1879 (55.2)	<.001
Nongranular	72 (11.7)	759 (27.2)	831 (24.4)	
Mixed	51 (8.3)	149 (5.3)	200 (5.9)	
Other	7 (1.1)	488 (17.5)	495 (14.5)	
Kudo				
III	87 (14.3)	701 (25.2)	788 (23.3)	<.001
IV	443 (71.7)	1289 (46.2)	1732 (50.9)	
V	72 (11.7)	172 (6.2)	244 (7.2)	
Other	16 (2.6)	625 (22.4)	641 (18.9)	
Previously attempted	70 (11.3)	297 (10.7)	367 (10.8)	.56
Submucosal fibrosis	157 (25.4)	669 (24.0)	826 (24.2)	.31
Histopathology				
Tubular adenoma	63 (10.2)	741 (26.6)	804 (23.6)	<.001
Tubulovillous adenoma	445 (72.0)	1305 (46.8)	1750 (51.4)	
Villous	17 (2.8)	17 (.6)	34 (1.0)	
Sessile serrated lesion	6 (1.0)	636 (22.8)	642 (18.9)	
Other	87 (14.1)	88 (3.2)	175 (5.1)	
High-grade dysplasia	176 (28.4)	492 (17.7)	668 (19.6)	<.001
Invasive cancer	93 (15.0)	172 (6.2)	265 (7.8)	<.001

Values are median (interquartile range) or n (%).

LNPCP, Large nonpedunculated colorectal polyp ≥20 mm.

differences when optical evaluation performance was stratified by morphology. There was a greater sensitivity (91% vs 53%, $P < .027$) and specificity (96% vs 94%, $P < .027$) when comparing flat with nodular LNPCPs. Optical evaluation performance is therefore dependent on LNPCP morphology. The inherent challenges of accurate optical assessment of bulky LNPCPs have previously been published.¹⁴ Nodular morphology and larger size were associated

with SMIC.¹⁴ We have found that LNPCPs with these features are more common in the rectum. This knowledge is important when planning resection in terms of allowing more time for assessment and is relevant for endoscopy list planning.³¹

Advanced histology is more common in rectal LNPCPs. Villous histology and high-grade dysplasia are independent risk factors for LNPCP recurrence.³²⁻³⁴ Regardless of whether rectal LNPCPs are resected en bloc or piecemeal,

TABLE 2. Multivariate analysis assessing variables independently associated with location, rectum vs colon (excluding rectum)

Variable	Adjusted odds ratio	95% Confidence interval		P value
		Lower	Upper	
Size (per 10 mm)	1.22	1.15	1.29	<.001
Paris 0-1s	1.88	1.40	2.52	<.001
Paris 0-IIa+Is	3.07	2.42	3.90	<.001
Granular	2.70	2.02	3.63	<.001
Mixed granular	2.01	1.30	3.11	.002
Kudo IV	1.67	1.28	2.18	<.001
Kudo V	3.31	2.16	5.08	<.001
Tubulovillous adenoma	1.35	1.07	1.71	.011
Villous adenoma	3.56	1.64	7.73	.001
Cancer	1.77	1.25	2.53	.001

best practice endoscopic resection techniques such as margin ablation by snare-tip soft coagulation should be used to reduce recurrence risk.^{17,35,36}

This study found that cancer was more common in rectal LNPCPs. The risk of local recurrence of early rectal cancer is higher than for early colon cancer when treated with endoscopic resection alone.³⁷ EMR is the accepted first-line technique for LNPCPs,^{20,21} but this technique may not achieve cure for LNPCPs containing SMIC. ESD offers inherent advantages over EMR including reliable en-bloc resection, which allows for improved histologic resection completeness and potential cure of LNPCPs containing SMIC.³⁸ Previous studies have demonstrated that selective resection algorithms for LNPCPs should be applied given the significant costs and resource use associated with ESD relative to EMR as well as the higher required skill level.^{39,40} Specific rectal LNPCP resection algorithms are needed given the increased risk of SMIC containing LNPCPs.

The ramifications for a suboptimally managed rectal LNPCP could be considered greater in the rectum compared with the colon. Generally, surgery in the distal colon and rectum is associated with greater risk relative of morbidity compared with a right hemicolectomy.^{26,41,42} Patients with rectal lesions removed by a low or ultra-low anterior resection have an increased risk of incontinence (12%)⁴³ and sexual dysfunction (20%-46%)⁴⁴ and a 10% to 20% risk of permanent stoma.^{45,46} Low anterior resection has 30-day morbidity and mortality rates of 25% and 6%, respectively.⁴⁷ Our data suggest different resection algorithms should be used for rectal LNPCPs given their higher risk of SMIC, which may lead to reduced rates of incomplete resection and thus a reduced need for surgery. Improved knowledge of predicting cancer and SMIC risk allows a greater likelihood of successful resection on the first attempt,

leading to improved outcomes for patients and significant cost savings.^{39,48-50}

Interestingly, within the rectum, the anorectal junction is a unique environment in which the risk of SMIC is low. A recent prospective observational study found that the cancer rate at the anorectal junction was low (3% [n = 100]).²⁴ Of note, there was no recurrence at surveillance colonoscopy 1 for LNPCPs treated with snare-tip soft coagulation postresection.^{17,24,35} EMR can therefore be considered as a first-line technique for most anorectal junction LNPCPs.

A limitation of this study is that patients were not randomized and were from an expert group, which may limit the generalizability of the results. However, to our knowledge, this is the only published dataset comparing LNPCPs in the rectum with the rest of colon.

In conclusion, among a large, multicenter, observational cohort, rectal LNPCPs were more likely to be larger, granular, and nodular with a villous component and more frequently contained high-grade dysplasia and cancer. These data add critically important insights to inform endoscopic treatment selection and enhance clinical outcomes for rectal LNPCPs. Through scientific research, resection guidelines for LNPCPs of the colon have largely been established, and EMR is justifiably the predominant strategy.^{51,52} The rectum is a different organ and should be regarded as a specialized site because of its increased risk of SMIC and the potential for significant sequelae if the endoscopic treatment is incomplete. Our data indicate that given this complexity, rectal LNPCPs should be managed at specialized tissue resection sites. To achieve the best patient outcomes, the ability to undertake ESD would appear to be a necessary requirement for those endoscopists performing endoscopic resection in the rectum. ESD should be the favored technique for rectal LNPCPs considered at any risk for harboring SMIC. Further research is needed to develop rectum-specific resection algorithms.

REFERENCES

- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017;67:7-30.
- Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87-108.
- Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;66:683-91.
- Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008;134:1570-95.
- Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472-7.
- Rotondano G, Bianco MA, Buffoli F, et al. The Cooperative Italian FLIN Study Group: prevalence and clinico-pathological features of colorectal laterally spreading tumors. *Endoscopy* 2011;43:856-61.
- Tate DJ, Desomer L, Awadie H, et al. EMR of laterally spreading lesions around or involving the appendiceal orifice: technique, risk factors for failure, and outcomes of a tertiary referral cohort (with video). *Gastrointest Endosc* 2018;87:1279-88.
- Nanda KS, Tutticci N, Burgess NG, et al. Endoscopic mucosal resection of laterally spreading lesions involving the ileocecal valve: technique, risk factors for failure, and outcomes. *Endoscopy* 2015;47:710-8.
- Ponugoti PL, Broadley HM, Garcia J, et al. Endoscopic management of large ileocecal valve lesions over an 18-year interval. *Endosc Int Open* 2019;7:E1646-51.
- Cohen JF, Korevaar DA, Altman DG, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* 2016;6:e012799.
- von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147: 573-7.
- Klein A, Bourke MJ. Advanced polypectomy and resection techniques. *Gastrointest Endosc Clin North Am* 2015;25:303-33.
- Jideh B, Bourke MJ. How to perform wide-field endoscopic mucosal resection and follow-up examinations. *Gastrointest Endosc Clin North Am* 2019;29:629-46.
- Burgess NG, Hourigan LF, Zanati SA, et al. Risk stratification for covert invasive cancer among patients referred for colonic endoscopic mucosal resection: a large multicenter cohort. *Gastroenterology* 2017;153:732-42.
- Fahrtash-Bahin F, Holt BA, Jayasekeran V, et al. Snare tip soft coagulation achieves effective and safe endoscopic hemostasis during wide-field endoscopic resection of large colonic lesions (with videos). *Gastrointest Endosc* 2013;78:158-63.
- Tate DJ, Desomer L, Klein A, et al. Adenoma recurrence after piecemeal colonic EMR is predictable: the Sydney EMR recurrence tool. *Gastrointest Endosc* 2017;85:647-56.
- Sidhu M, Shahidi N, Gupta S, et al. Outcomes of thermal ablation of the mucosal defect margin after endoscopic mucosal resection: a prospective, international, multicenter trial of 1000 large nonpedunculated colorectal polyps. *Gastroenterology* 2021;161:163-70.
- Kumarasinghe M, Bourke MJ, Brown I, et al. GIPS-AGPS recommendations for pathologic assessment and reporting of EMR/ESD. Available at: <http://www.agps.org.au/guidelines.php2019>. Accessed April 20, 2021.
- Rex DK, Hassan C, Bourke MJ. The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management. *Gastrointest Endosc* 2017;86:253-63.
- Kaltenbach T, Anderson JC, Burke CA, et al. Endoscopic removal of colorectal lesions 2014: recommendations by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2020;158:1095-129.
- Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy* 2017;49:270-97.
- Holt BA, Bassan MS, Sexton A, et al. Advanced mucosal neoplasia of the anorectal junction: endoscopic resection technique and outcomes (with videos). *Gastrointest Endosc* 2014;79:119-26.
- Morino M, Risio M, Bach S, et al. Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference. *Surg Endosc* 2015;29:755-73.
- Shahidi N, Sidhu M, Vosko S, et al. Endoscopic mucosal resection is effective for laterally spreading lesions at the anorectal junction. *Gut* 2020;69:673-80.
- Yu JX, Russell WA, Ching JH, et al. Cost effectiveness of endoscopic resection vs transanal resection of complex benign rectal polyps. *Clin Gastroenterol Hepatol* 2019;17:2740-8.
- Vennix S, Pelzers L, Bouvy N, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev* 2014:Cd005200.
- Yamada M, Saito Y, Sakamoto T, et al. Endoscopic predictors of deep submucosal invasion in colorectal laterally spreading tumors. *Endoscopy* 2016;48:456-64.
- Vosko S, Shahidi N, Sidhu M, et al. Optical evaluation for predicting cancer in large non-pedunculated colorectal polyps is accurate for flat lesions. *Clin Gastroenterol Hepatol* 2021;19:2425-34.e4.
- Bogie RMM, Veldman MHJ, Snijders L, et al. Endoscopic subtypes of colorectal laterally spreading tumors (LSTs) and the risk of submucosal invasion: a meta-analysis. *Endoscopy* 2018;50:263-82.
- Backes Y, Schwartz MP, Ter Borg F, et al. Multicentre prospective evaluation of real-time optical diagnosis of T1 colorectal cancer in large non-pedunculated colorectal polyps using narrow band imaging (the OPTICAL study). *Gut* 2019;68:271-9.
- Sidhu M, Tate DJ, Desomer L, et al. The size, morphology, site, and access score predicts critical outcomes of endoscopic mucosal resection in the colon. *Endoscopy* 2018;50:684-92.
- Chang J-J, Chien C-H, Chen S-W, et al. Long term outcomes of colon polyps with high grade dysplasia following endoscopic resection. *BMC Gastroenterology* 2020;20:376.
- Moss A, Bourke MJ, Williams SJ, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. *Gastroenterology* 2011;140:1909-18.
- Moss A, Williams SJ, Hourigan LF, et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut* 2015;64:57-65.
- Klein A, Tate DJ, Jayasekeran V, et al. Thermal ablation of mucosal defect margins reduces adenoma recurrence after colonic endoscopic mucosal resection. *Gastroenterology* 2019;156:604-13.
- Whitfield AM, Burgess NG, Bahin FF, et al. Histopathological effects of electrosurgical interventions in an in vivo porcine model of colonic endoscopic mucosal resection. *Gut* 2022;71:864-70.
- Ikematsu H, Yoda Y, Matsuda T, et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. *Gastroenterology* 2013;144:551-9; quiz e14.
- Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2015;47:829-54.
- Bahin FF, Heitman SJ, Rasouli KN, et al. Wide-field endoscopic mucosal resection versus endoscopic submucosal dissection for laterally spreading colorectal lesions: a cost-effectiveness analysis. *Gut* 2018;67:1965.
- Fuccio L, Repici A, Hassan C, et al. Why attempt en bloc resection of non-pedunculated colorectal adenomas? A systematic review of the prevalence of superficial submucosal invasive cancer after endoscopic submucosal dissection. *Gut* 2018;67:1464-74.

41. Bokey EL, Chapuis PH, Fung C, et al. Postoperative morbidity and mortality following resection of the colon and rectum for cancer. *Dis Colon Rectum* 1995;38:480-6; discussion 6-7.
42. Peery AF, Shaheen NJ, Cools KS, et al. Morbidity and mortality after surgery for nonmalignant colorectal polyps. *Gastrointest Endosc* 2018;87:243-50.
43. Duran E, Tanriseven M, Ersoz N, et al. Urinary and sexual dysfunction rates and risk factors following rectal cancer surgery. *Int J Colorectal Dis* 2015;30:1547-55.
44. Celentano V, Cohen R, Warusavitarne J, et al. Sexual dysfunction following rectal cancer surgery. *Int J Colorectal Dis* 2017;32:1523-30.
45. Climent M, Martin ST. Complications of laparoscopic rectal cancer surgery. *Min Invas Surg* 2018;2:45.
46. Lindgren R, Hallböök O, Rutegård J, et al. What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial. *Dis Colon Rectum* 2011;54:41-7.
47. Cuccurullo D, Pirozzi F, Sciuto A, et al. Relaparoscopy for management of postoperative complications following colorectal surgery: ten years experience in a single center. *Surg Endosc* 2015;29:1795-803.
48. Jayanna M, Burgess NG, Singh R, et al. Cost analysis of endoscopic mucosal resection vs surgery for large laterally spreading colorectal lesions. *Clin Gastroenterol Hepatol* 2016;14:271-8.
49. Russo P, Barbeiro S, Awadie H, et al. Management of colorectal laterally spreading tumors: a systematic review and meta-analysis. *Endosc Int Open* 2019;7:E239-59.
50. Bourke MJ, Neuhaus H. Colorectal endoscopic submucosal dissection: when and by whom? *Endoscopy* 2014;46:677-9.
51. Hassan C, Repici A, Sharma P, et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. *Gut* 2016;65:806-20.
52. Heitman SJ, Bourke MJ. Endoscopic submucosal dissection and EMR for large colorectal polyps: "the perfect is the enemy of good." *Gastrointest Endosc* 2017;86:87-9.

Registration of Clinical Trials

Gastrointestinal Endoscopy follows the **International Committee of Medical Journal Editors (ICMJE)**'s Uniform Requirements for Manuscripts Submitted to Biomedical Journals. All clinical trials eventually submitted in GIE must have been registered through one of the registries approved by the ICMJE, and proof of that registration must be submitted to GIE along with the article. For further details and explanation of which trials need to be registered as well as a list of ICMJE-acceptable registries, please go to <http://www.icmje.org>.

Complimentary and personal copy for Cronin O, Gupta S, Gauci J, Whitfield A, O'Sullivan T, Abuarisha M, Wang H, Lee E, Williams S, Burgess N et al.

Brought to you by Thieme

www.thieme.com

**Endoscopic resection of large
anastomotic polyps is safe
and effective**

Endoscopy

2024

125-130
10.1055/a-2174-2967

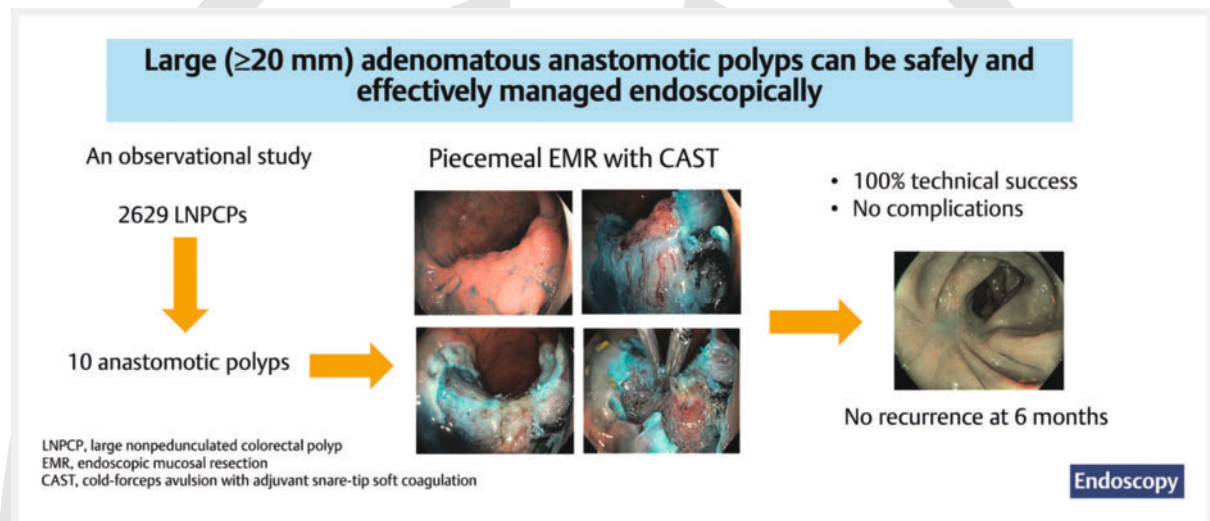
This electronic reprint is provided for non-commercial and personal use only: this reprint may be forwarded to individual colleagues or may be used on the author's homepage. This reprint is not provided for distribution in repositories, including social and scientific networks and platforms.

Copyright & Ownership
© 2024. Thieme. All rights reserved.
The journal *Endoscopy* is owned by Thieme.
Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany
ISSN 0013-726X


 **Thieme**

Endoscopic resection of large anastomotic polyps is safe and effective

GRAPHICAL ABSTRACT



Authors

Oliver Cronin^{1,2}, Sunil Gupta^{1,2} , Julia Gauci^{1,2}, Anthony Whitfield^{1,2}, Timothy O'Sullivan^{1,2}, Muhammad Abuarisha^{1,2}, Hunter Wang^{1,2}, Eric Yong Tat Lee^{1,2}, Stephen J Williams^{1,2}, Nicholas Graeme Burgess^{1,2} , Michael J. Bourke^{1,2}

Institutions

- 1 Gastroenterology and Hepatology, Westmead Hospital, Westmead, Australia
- 2 Medicine, The University of Sydney Westmead Clinical School, Sydney, Australia

submitted 28.4.2023

accepted after revision 12.9.2023

accepted manuscript online 12.9.2023

published online 10.11.2023

Bibliography

Endoscopy 2024; 56: 125–130

DOI 10.1055/a-2174-2967

ISSN 0013-726X

© 2023. Thieme. All rights reserved.

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author

Michael J. Bourke, MBBS FRACP, Department of Gastroenterology and Hepatology, Westmead Hospital, University of Sydney, Westmead Clinical School, Suite 106a, Hawkesbury Road 151–155, 2145 Sydney, Australia
michael@citywestgastro.com.au

ABSTRACT

Background Large (≥ 20 mm) adenomatous anastomotic polyps (LAAPs) are uncommon. Data pertaining to their prevalence, characteristics, and the efficacy of endoscopic resection (ER) are absent. A safe and effective strategy for ER would reduce morbidity and healthcare costs.

Methods Large nonpedunculated colorectal polyps of ≥ 20 mm (LNPCPs) referred for ER were prospectively studied. Multiple data points were recorded including anastomotic location, polyp morphology, resection modality, complications, and technical success.

Results Over 7 years until November 2022, 2629 lesions were referred. Of these, 10 (0.4%) were LAAPs (median size 35 mm [interquartile range (IQR) 30–40 mm]). All LAAPs were removed by piecemeal endoscopic mucosal resection (EMR), most ($n=9$; 90%) in combination with cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST). On comparison of the LAAP group with the conventional LNPCP group, CAST was more commonly used (90% vs. 9%; $P<0.001$) and deep mural injury (DMI) type II was more frequent (40% vs. 11%, $P=0.003$); however, significant DMI (III–V) did not occur. At 6 month (IQR 5.25–6 months) surveillance, there was no recurrence in any of the 10 cases. There were no serious adverse events.

Conclusions LAAPs present unique challenges owing to their location overlying an anastomosis. Despite these chal-

lenges they can be safely and effectively managed endoscopically without recurrence at endoscopic follow-up.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the burden of disease is projected to increase by 60% by 2030 [1,2,3]. The majority of CRCs develop from premalignant polyps. Most non-metastatic CRCs are treated by surgical excision. Postoperatively, regular surveillance colonoscopies are recommended to ensure that recurrence or synchronous lesions are detected and treated early [4].

Although uncommon, it is not surprising that there is a potential for large (≥ 20 mm) adenomatous anastomotic polyps (LAAPs) to develop at the site of a colonic anastomosis. These may be due to de novo polyp formation, recurrence related to inadequate margins at the initial resection, or a discrete polyp that was present but not identified at the time of surgery. LAAP removal is more likely to be challenging owing to the altered luminal anatomy and the underlying postsurgical fibrosis. It is probable that many such patients are managed by further surgery. Data are therefore limited and evidence for the efficacy of endoscopic resection (ER) is absent. An effective and safe strategy for the ER of LAAPs is required. The burden of CRC is expected to increase and further data on management of LAAPs would be valuable. We therefore evaluated our experience with LAAPs.

Methods

This manuscript has been prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [5,6]. All authors had access to the study data and reviewed and approved the final manuscript.

Between November 2015 and July 2022, eligible participants were enrolled at a single high volume endoscopic tissue resection center in Australia. Eligibility criteria included the presence of a LAAP in the context of previous colorectal surgery. All endoscopic procedures were performed by one of four study investigators (accredited gastroenterologists with advanced training and an established tertiary referral practice in colorectal ER) or a senior interventional endoscopy fellow under the direct supervision of one of the investigators.

Resection was performed with a standardized technique [7,8,9,10,11,12]. The lesion was assessed optically using high definition white light, narrow-band imaging (NBI), and near focus. Submucosal injection (indigo carmine and Gelofusine) was used before endoscopic mucosal resection (EMR) with a hot snare. The size of the snare was decided by the endoscopist at the time of the resection. Any poorly lifting areas were removed with cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST). Intra-procedural bleeding was defined as bleeding that required the use of coagulation forceps for hemostasis.

Recurrence post-anastomotic polypectomy was defined as neoplastic tissue seen optically or histologically at surveillance colonoscopy, performed 6 months after resection. All polypectomy scars were biopsied.

Histopathology evaluation

After ER, specimens were collected and processed for histopathology review, in accordance with the Australasian Gastrointestinal Pathology Society guidelines [13]. Histopathology review was completed by expert gastrointestinal pathologists. Cancer was defined by neoplastic invasion into the submucosa [14].

Data extraction and analysis

Prospectively collected data included: (i) patient characteristics (age, sex, American Society of Anesthesiologists [ASA] classification); (ii) LNPCP characteristics (location, size, Paris classification, surface granularity, Kudo pit pattern, submucosal invasive cancer [SMIC]) and resection technique; (iv) histopathologic evaluation.

Statistical analysis

SPSS version 27.0 (IBM Corp., Armonk, New York, USA) was used for data analysis. The continuous variables age and lesion size were summarized as median (interquartile range [IQR]) following assessment of non-normality using Shapiro–Wilk's test. Categorical variables were summarized as frequencies (%). Mann–Whitney tests were used to test for differences in continuous distributions between the groups. Chi-squared tests (or exact permutation tests if required) were used to test for association between the categorical variables.

Patient and public involvement

Neither patients nor the general public were involved in the design or execution of this study.

Results

Over 84 months until November 2022, 2629 LNPCPs in 2350 patients were referred for ER. Of these, 10 lesions (0.4%) were classified as LAAPs.

Demographic and lesion characteristics

The median patient age was 75 years (IQR 70–80 years). Median lesion size was 35 mm (IQR 30–40 mm). The majority of lesions were granular ($n=6$; 60%), Paris 0-IIa ($n=5$; 50%), and had tubulovillous histology ($n=6$; 60%) (► **Table 1**).

Most anastomoses were colo–colonic ($n=6$; 60%) and most LAAPs ($n=9$; 90%) were removed by piecemeal EMR in combination with CAST (► **Table 2**; ► **Fig. 1**, ► **Fig. 2**, ► **Fig. 3**). On comparison of the LAAP group with the conventional LNPCP group,

CAST was more commonly used (90% vs. 9%; $P < 0.001$) and deep mural injury (DMI) type II was more frequent (40% vs. 11%; $P = 0.003$); however, significant DMI (III–V) did not occur. Clip closure was performed in 70% of LAAP cases. Technical success was 100% and at 6-month surveillance (IQR 5.25–6 months), there was no recurrence in any of the 10 cases. There were no serious adverse events, and no perforation or bleeding in the LAAP group. There was also no recurrence identified at second surveillance colonoscopy, which was completed in nine patients (90%) at 19 months (IQR 15–22.5 months) after the initial resection. One patient (10%) did not have a second surveillance colonoscopy owing to their frailty.

Discussion

LAAPs present unique challenges for ER for several reasons. Many anastomoses have inflammatory change, which can create difficulty for lesion and margin recognition. Because of the adherence of the mucosal layer to the scarred and potentially chronically ischemic anastomosis, the risk of DMI or incomplete snare resection is enhanced, which increases the need for adjuvant therapy and for clip closure of DMI type II [15]. Another challenge is the presence of surgical clips, which can impede assessment and resection. Finally, the scarred ridge line (► Fig. 1d) of the anastomosis with depressed contours on

► **Table 1** Characteristics of the 10 included patients and their large anastomotic polyps.

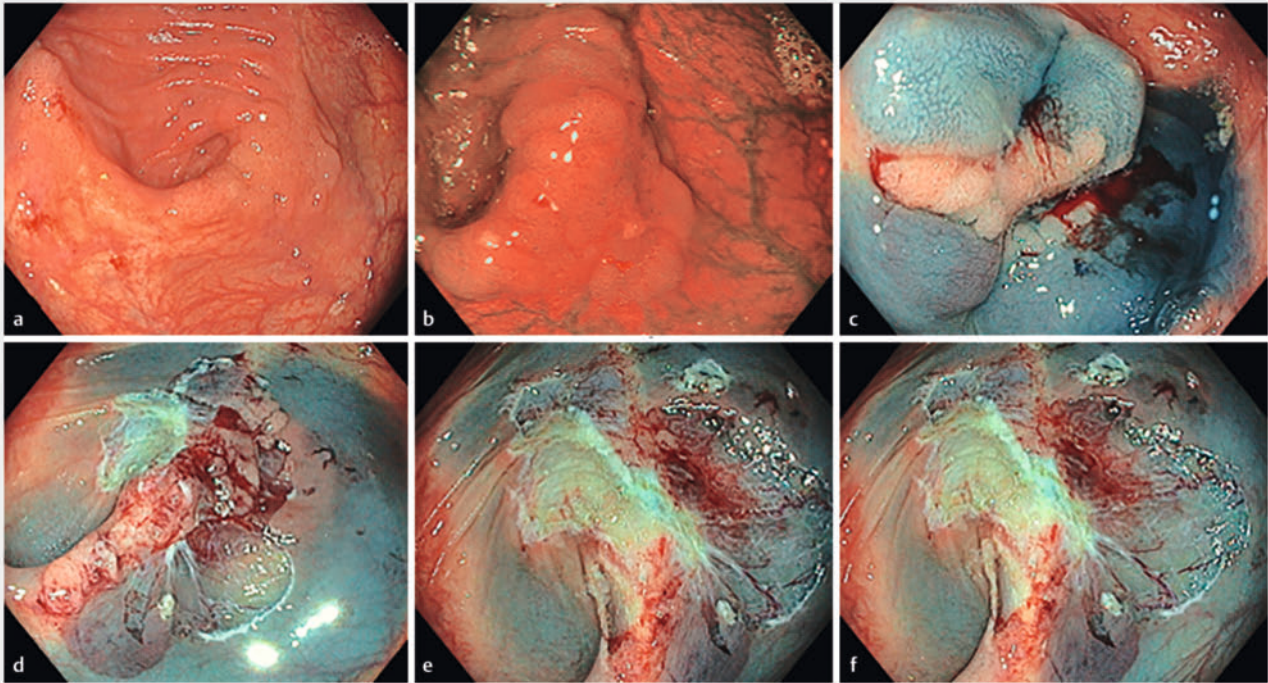
Patient	Age, years/ sex	Time interval, years*	Surgical histology	Anastomotic polyp size, mm	Paris type	Morphology	Histology
1	70/Male	32	Adenocarcinoma	30	0-IIa	Granular	Tubular
2	52/Female	15	Tubulovillous adenoma	35	0-IIb	Non-granular	Tubular
3	86/Male	12	Adenocarcinoma	30	0-IIb	Non-granular	Tubulovillous
4	71/Male	34	Familial adenomatous polyposis	35	0-IIb	Granular	Tubulovillous
5	78/Female	10	Adenocarcinoma	20	0-IIa	Granular	Tubulovillous
6	84/Male	5	Adenocarcinoma	40	0-IIa	Non-granular	Tubulovillous
7	65/Male	1	Adenocarcinoma	12	0-IIc	Granular	Tubulovillous
8	76/Male	29	Adenocarcinoma	40	0-IIa	Granular	Tubular
9	73/Male	1	Tubulovillous adenoma	80	0-IIa + Is	Granular	Tubular
10	81/Male	3	Adenocarcinoma	25	0-IIa	Non-granular	Tubulovillous

Time in years from initial surgical resection to diagnosis of anastomotic polyp.

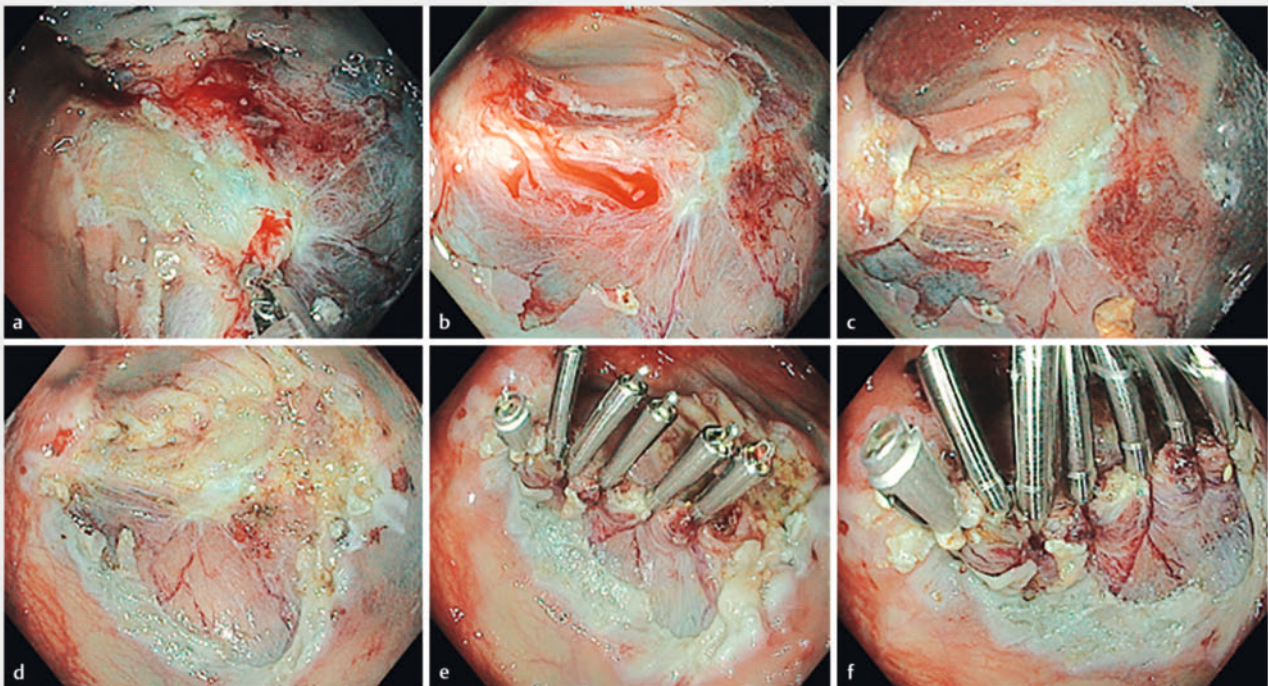
► **Table 2** Procedure and follow-up details for the 10 large anastomotic polyps that were resected endoscopically.

Patient	pEMR	CAST	Intraprocedural bleeding	DMI	Clipped	Surveillance colonoscopy, months post-resection	Recurrence at surveillance
1	Yes	Yes	No	No	Yes	6	No
2	Yes	Yes	No	No	Yes	6	No
3	Yes	Yes	No	II	Yes	6	No
4	Yes	Yes	No	No	Yes	4	No
5	Yes	No	No	No	No	6	No
6	Yes	Yes	Yes	II	Yes	6	No
7	Yes	Yes	Yes	No	No	6	No
8	Yes	Yes	No	II	Yes	7	No
9	Yes	Yes	No	II	Yes	5	No
10	Yes	Yes	No	No	No	6	No

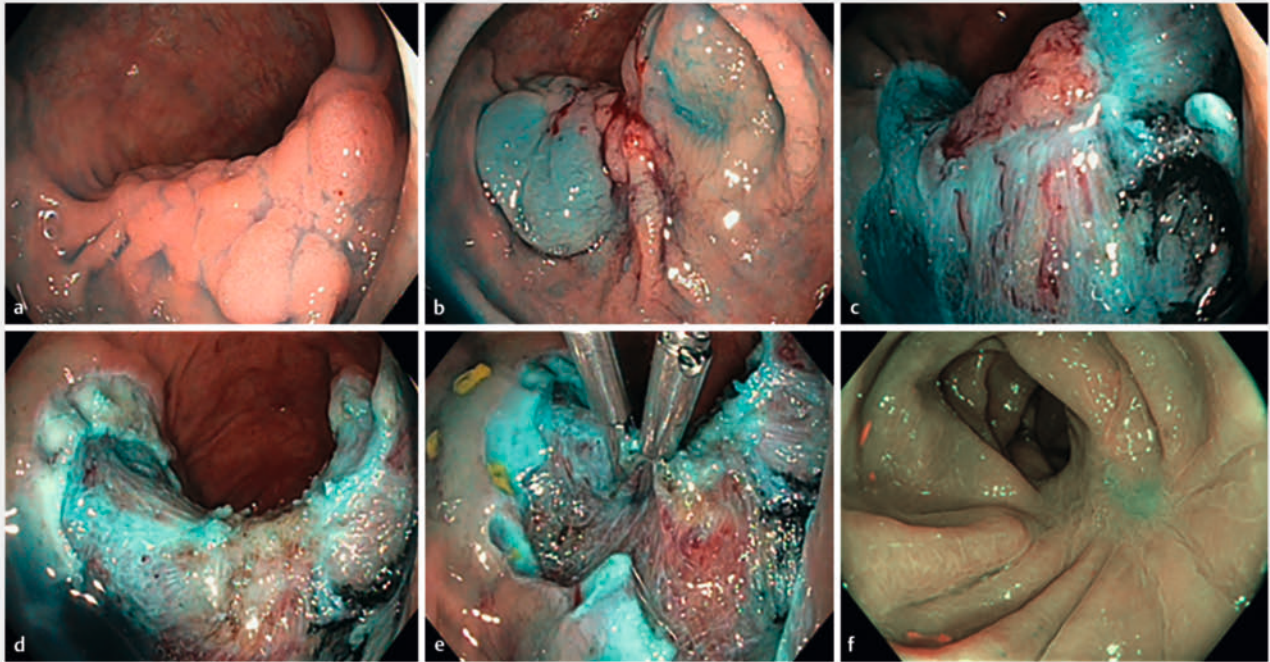
pEMR, piecemeal endoscopic mucosal resection; CAST, cold-forceps avulsion with snare-tip soft coagulation; DMI, deep mural injury.



► **Fig. 1** Endoscopic views of the resection of a 30-mm Paris 0-IIa large adenomatous anastomotic polyp showing: **a** a lesion at the anastomosis under white light with near focus; **b** narrow-band imaging; **c** central nonlifting zone after submucosal injection with indigo carmine and Gelo-fusine; **d–f** sequential snare resection of areas with adequate submucosal lifting with interrogation of the defect for deep mural injury with topical chromoendoscopy after each snare resection.



► **Fig. 2** Endoscopic views of the resection of a 30-mm Paris 0-IIa large adenomatous anastomotic polyp showing: **a–d** cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) applied to the central nonlifting segment that was resistant to snare capture; **e, f** through-the-scope clips applied to close a deep mural injury type II.



► **Fig. 3** Endoscopic views of the resection of a 40-mm Paris 0-IIa large adenomatous anastomotic polyp showing: **a** the lesion at the anastomosis; **b** central nonlifting after submucosal injection with indigo carmine and Gelofusine; **c** sequential snare resection of areas with adequate submucosal lifting; **d** cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) applied to the central nonlifting segment that was resistant to snare capture, with thermal ablation to the defect margin by snare-tip soft coagulation; **e** through-the-scope clips applied to close a deep mural injury type II; **f** a bland scar seen on narrow-band imaging at 6-month surveillance.

either side can compromise the efficacy of conventional submucosal injection and resection techniques.

There are no published data on the efficacy or safety of ER for LAAPs. We have proposed techniques that can definitively treat LAAPs effectively and safely. Technical success was achieved in all cases without adverse events. At first surveillance colonoscopy at 6 months, there were no recurrences.

Most LAAPs (7/10; 70%) in this series occurred ≥ 5 years after initial surgical resection. These lesions were likely de novo lesions, given the duration from surgery [16]. Three LAAPs occurred within 5 years of surgery. Most likely these were due to a separate polyp not seen at the time of surgery that became involved in the anastomosis.

All LAAPs in this series were resected piecemeal after thorough optical assessment with white light and NBI, which should be used to guide the resection technique [17]. En bloc resection either by EMR or preferably endoscopic submucosal dissection (ESD) is important if there are morphological features consistent with SMIC. In this case series, all polyps were optically assessed as being benign. For scarred nonlifting lesions, some endoscopists may advocate using ESD or endoscopic full-thickness resection (EFTR). Such methods are resource intensive and potentially more hazardous [18]. Our data demonstrate that piecemeal EMR can effectively and safely remove LAAPs without the need for more complex resection techniques.

CAST (► **Fig. 2a**) is a well validated, safe, and effective technique for the treatment of scarred nonlifting lesions [19]. Meti-

culous, precise, and methodical use of the biopsy forceps is essential to ensure no adenomatous tissue remains. Controlled, purposeful closure of the biopsy forceps by an experienced assistant is equally important to prevent imprecision or slippage of the biopsy forceps. Adjuvant snare-tip soft coagulation of the avulsion bed and surrounding areas ensures thermal destruction of any remaining neoplastic cells [19,20].

Effective treatment of adenomatous tissue at an anastomosis is important for a number of reasons. Because of the fibrosis typically encountered at an anastomosis, resection is more challenging and time-consuming. Resection in this setting may also theoretically carry enhanced risks of bleeding and perforation owing to neovascularization and fibrosis. For these reasons it is essential that techniques are evoked to achieve complete resection at the first resection attempt.

There are limitations to this study. First, this is a small case series. It is however the only published case series. The data were derived prospectively from a high volume tissue resection center. Larger case series or trials would be difficult owing to the infrequency of anastomotic polyps. This analysis provides meaningful outcome data for this clinically important problem.

In conclusion, this case series is the only published dataset that addresses the uncommon but clinically important question of how to effectively treat a LAAP. We have demonstrated that ER of LAAPs is effective and safe, without a high risk of bleeding or perforation. We have shown that the nonlifting areas at an anastomosis can be effectively treated with CAST.

Significant DMI did not occur and none of the cases showed recurrence at 6-month endoscopic surveillance. Larger datasets are required to address any nuances that may be associated with the anastomotic location or histology of LAAPs.

Conflict of Interest

M. Bourke has received research support from Olympus Medical, Cook Medical, and Boston Scientific. O. Cronin, S. Gupta, J. Gauci, A. Whitfield, T. O'Sullivan, M. Abuarisha, H. Wang, E. Lee, S. Williams, and N.G. Burgess declare that they have no conflict of interest.

Funding

Cancer Institute NSW

References

- [1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; 67: 7–30 doi:10.3322/caac.21387
- [2] Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87–108 doi:10.3322/caac.21262
- [3] Arnold M, Sierra MF, Laversanne M et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017; 66: 683–691 doi:10.1136/gutjnl-2015-310912
- [4] Cancer Council Australia Clinical Guidelines. Clinical practice guidelines for surveillance colonoscopy. wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer/Colonoscopy_surveillance
- [5] Cohen JF, Korevaar DA, Altman DG et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* 2016; 6: e012799 doi:10.1136/bmjopen-2016-012799
- [6] von Elm E, Altman DG, Egger M et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577 doi:10.1016/j.ijvsu.2014.07.013
- [7] Klein A, Bourke MJ. Advanced polypectomy and resection techniques. *Gastrointest Endosc Clin N Am* 2015; 25: 303–333 doi:10.1016/j.giec.2014.11.005
- [8] Jideh B, Bourke MJ. How to perform wide-field endoscopic mucosal resection and follow-up examinations. *Gastrointest Endosc Clin N Am* 2019; 29: 629–646 doi:10.1016/j.giec.2019.05.002
- [9] Burgess NG, Hourigan LF, Zanati SA et al. Risk stratification for covert invasive cancer among patients referred for colonic endoscopic mucosal resection: a large multicenter cohort. *Gastroenterology* 2017; 153: 732–742.e1
- [10] Fahrtash-Bahin F, Holt BA, Jayasekera V et al. Snare tip soft coagulation achieves effective and safe endoscopic hemostasis during wide-field endoscopic resection of large colonic lesions (with videos). *Gastrointest Endosc* 2013; 78: 158–163.e1
- [11] Tate DJ, Desomer L, Klein A et al. Adenoma recurrence after piecemeal colonic EMR is predictable: the Sydney EMR recurrence tool. *Gastrointest Endosc* 2017; 85: 647–656.e6
- [12] Sidhu M, Shahidi N, Gupta S et al. Outcomes of thermal ablation of the mucosal defect margin after endoscopic mucosal resection: a prospective, international, multicenter trial of 1000 large nonpedunculated colorectal polyps. *Gastroenterology* 2021; 161: 163–170.e3
- [13] Kumarasinghe M, Bourke MP, Brown I et al. Pathological assessment of endoscopic resections of the gastrointestinal tract: a comprehensive clinicopathologic review. *Mod Pathol* 2020; 33: 986–1006 doi:10.1038/s41379-019-0443-1
- [14] Rex DK, Hassan C, Bourke MJ. The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management. *Gastrointest Endosc* 2017; 86: 253–263 doi:10.1016/j.gie.2017.03.1546
- [15] Burgess NG, Bassan MS, McLeod D et al. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. *Gut* 2017; 66: 1779–1789 doi:10.1136/gutjnl-2015-309848
- [16] Vleugels JLA, Hazewinkel Y, Fockens P et al. Natural history of diminutive and small colorectal polyps: a systematic literature review. *Gastrointest Endosc* 2017; 85: 1169–1176.e1
- [17] Vosko S, Shahidi N, Sidhu M et al. Optical evaluation for predicting cancer in large nonpedunculated colorectal polyps is accurate for flat lesions. *Clin Gastroenterol Hepatol* 2021; 19: 2425–2434.e4
- [18] Bahin FF, Heitman SJ, Rasouli KN et al. Wide-field endoscopic mucosal resection versus endoscopic submucosal dissection for laterally spreading colorectal lesions: a cost-effectiveness analysis. *Gut* 2018; 67: 1965–1973 doi:10.1136/gutjnl-2017-313823
- [19] Tate DJ, Bahin FF, Desomer L et al. Cold-forceps avulsion with adjunctive snare-tip soft coagulation (CAST) is an effective and safe strategy for the management of non-lifting large laterally spreading colonic lesions. *Endoscopy* 2018; 50: 52–62
- [20] Shahidi N, Vosko S, Gupta S et al. Previously attempted large nonpedunculated colorectal polyps are effectively managed by endoscopic mucosal resection. *Am J Gastroenterol* 2021; 116: 958–966 doi:10.14309/ajg.0000000000001096



Selection of endoscopic resection technique for large colorectal lesion treatment

Oliver Cronin^{a,b,c}, Francesco Vito Mandarino^{a,c} and Michael J. Bourke^{a,c}

Purpose of review

Large nonpedunculated colorectal polyps ≥ 20 mm (LNPCPs) comprise 1% of all colorectal lesions. LNPCPs are more likely to contain advanced histology such as high-grade dysplasia and submucosal invasive cancer (SMIC). Endoscopic resection is the first-line approach for management of these lesions. Endoscopic resection options include endoscopic mucosal resection (EMR), cold-snare EMR (EMR), endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (EFTR). This review aimed to critically evaluate current endoscopic resection techniques.

Recent findings

Evidence-based selective resection algorithms should inform the most appropriate endoscopic resection technique. Most LNPCPs are removed by conventional EMR but there has been a trend toward C-EMR for endoscopic resection of LNPCPs. More high-quality trials are required to better define the limitations of C-EMR. Advances in our understanding of ESD technique, has clarified its role within the colorectum. More recently, the development of a full thickness resection device (FTRD) has allowed the curative endoscopic resection of select lesions.

Summary

Endoscopic resection should be regarded as the principle approach for all LNPCPs. Underpinned by high-quality research, endoscopic resection has become more nuanced, leading to improved patient outcomes.

Keywords

colonoscopy, colorectal cancer, endoscopic full thickness resection, endoscopic mucosal resection, endoscopic submucosal dissection, polyp, polypectomy

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality [1]. Most CRCs develop from the stepwise acquisition of molecular abnormalities along the adenoma–carcinoma and serrated pathways [2–4]. This pathogenic trajectory presents a strategic window for the potential prevention of CRC by the endoscopic resection of premalignant polyps. Compelling evidence underscores the efficacy of screening colonoscopy and polypectomy in diminishing the 10-year risk of CRC-related mortality [risk ratio 0.82, 95% confidence interval (CI) 0.70–0.93] [5]. The national polyp study ($n = 2602$) in long-term follow-up revealed a 53% reduction in risk [relative risk (RR) 0.47, 95% CI 0.26–0.80] among participants who underwent polypectomy [6]. Underpinned by high-quality research, improvements in our understanding of the fundamentals of endoscopic resection, as well as concurrent technical innovations have allowed for the curative endoscopic resection of advanced benign lesions and

also lesions containing submucosal invasive cancer (SMIC).

Most colorectal lesions are less than 10 mm in size, lack advanced histology and are amenable to en bloc or piecemeal removal with a cold snare [7–9]. Large nonpedunculated colorectal lesions ≥ 20 mm (LNPCPs) comprise $\sim 1\%$ of all polyps. They have a variable propensity to harbour overt and covert SMIC [10]. Currently, there are a range

^aDepartment of Gastroenterology and Hepatology, Westmead Hospital, ^bDepartment of Gastroenterology, Northern Health and ^cWestmead Clinical School, University of Sydney, Sydney, New South Wales, Australia

Correspondence to Michael J. Bourke, MBBS, FRACP, Clinical Professor of Medicine, Department of Gastroenterology and Hepatology, Westmead Hospital, University of Sydney, Westmead Clinical School, Suite 106a, 151-155 Hawkesbury Road, Sydney, NSW 2145, Australia. E-mail: michael@citywestgastro.com.au

Curr Opin Gastroenterol 2024, 40:000–000

DOI:10.1097/MOG.0000000000001041

Endoscopy

KEY POINTS

- Curative management of large nonpedunculated colorectal polyps requires comprehensive planning.
- Endoscopic mucosal resection (EMR), cold-EMR, endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (EFTR) each have strengths and weaknesses.
- Selective endoscopic resection algorithms should guide selection of resection technique and account for lesion and patient specific factors.

of effective techniques available for their endoscopic management.

Selection of the most appropriate technique is contingent upon multiple factors, including lesion size, morphology, location and the perceived risk of SMIC [10,11,12[†]]. In addition, patient-specific factors must be considered including comorbidities, anticoagulant and antiplatelet medications. This nuanced approach ensures that the chosen management strategy is tailored to the unique characteristics of both the lesion and the patient.

Endoscopic resection is the recommended first-line modality for the management of LNPCPs [13,14]. Compared with surgery, endoscopic resection is equally effective and has a superior morbidity and healthcare cost profile [15,16]. Technical success requires a collaborative, methodical approach. It starts with planning, comprehensive communication with endoscopy staff, patients and their families. It relies on a thorough optical assessment. Management should ideally be undertaken at a centre with access to all endoscopic resection techniques including: endoscopic mucosal resection (EMR), cold-snare EMR (C-EMR), endoscopic submucosal dissection (ESD) and endoscopic full thickness resection (EFTR) (Figs. 1–3). This review aimed to critically analyse current endoscopic resection techniques and to evaluate where each fit within a selective endoscopic resection algorithm.

PRE-RESECTION

Optimizing patient outcomes necessitates meticulous planning, particularly in the preprocedural phase. This includes a comprehensive evaluation of the patient's medical history, functional status, co-morbidities and current medications.

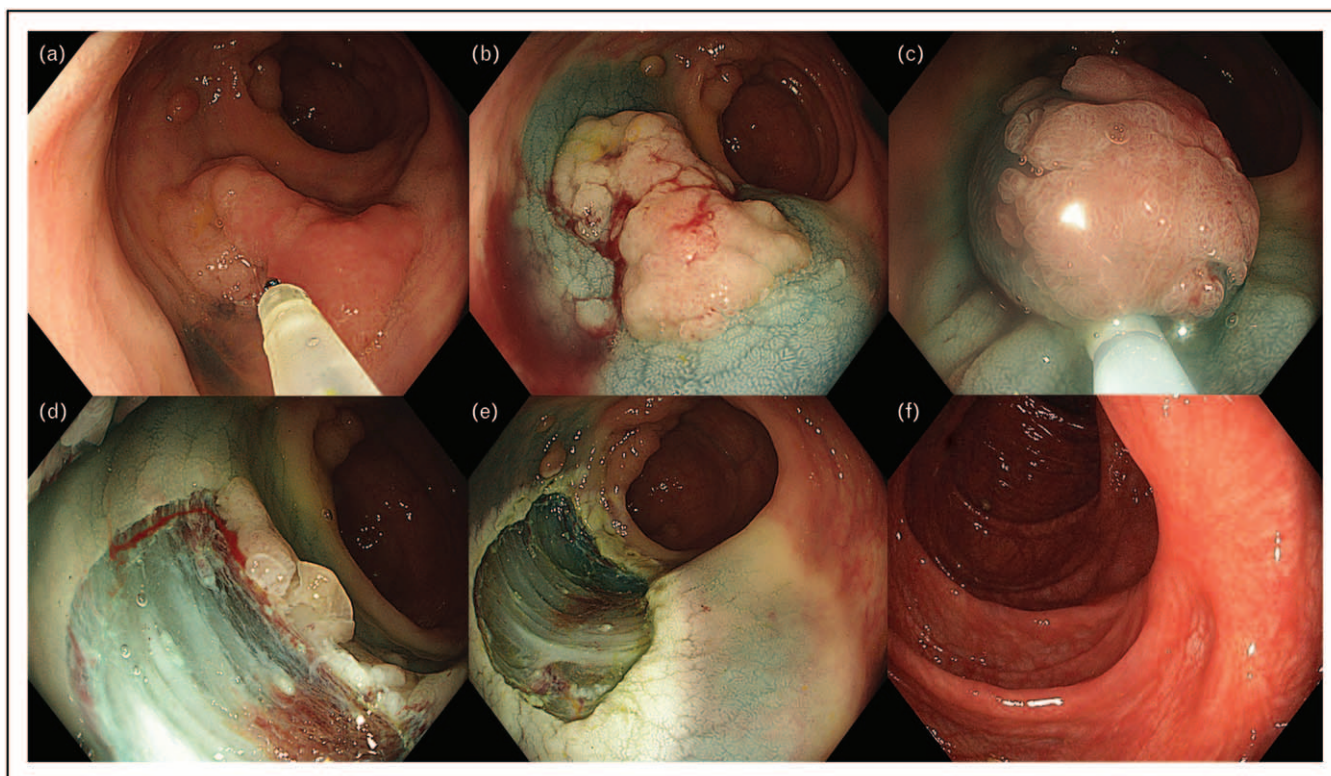


FIGURE 1. A 40 mm Granular Paris 0-IIa LNPCP in the mid-ascending colon resected by conventional endoscopic mucosal resection. A 40 mm granular Paris 0-IIa LNPCP assessed with high-definition white light (a). Sequential submucosal injection and piecemeal resection (b–d) followed by thermal ablation of the margin (e). Surveillance colonoscopy demonstrating a bland scar at the site of resection (f).

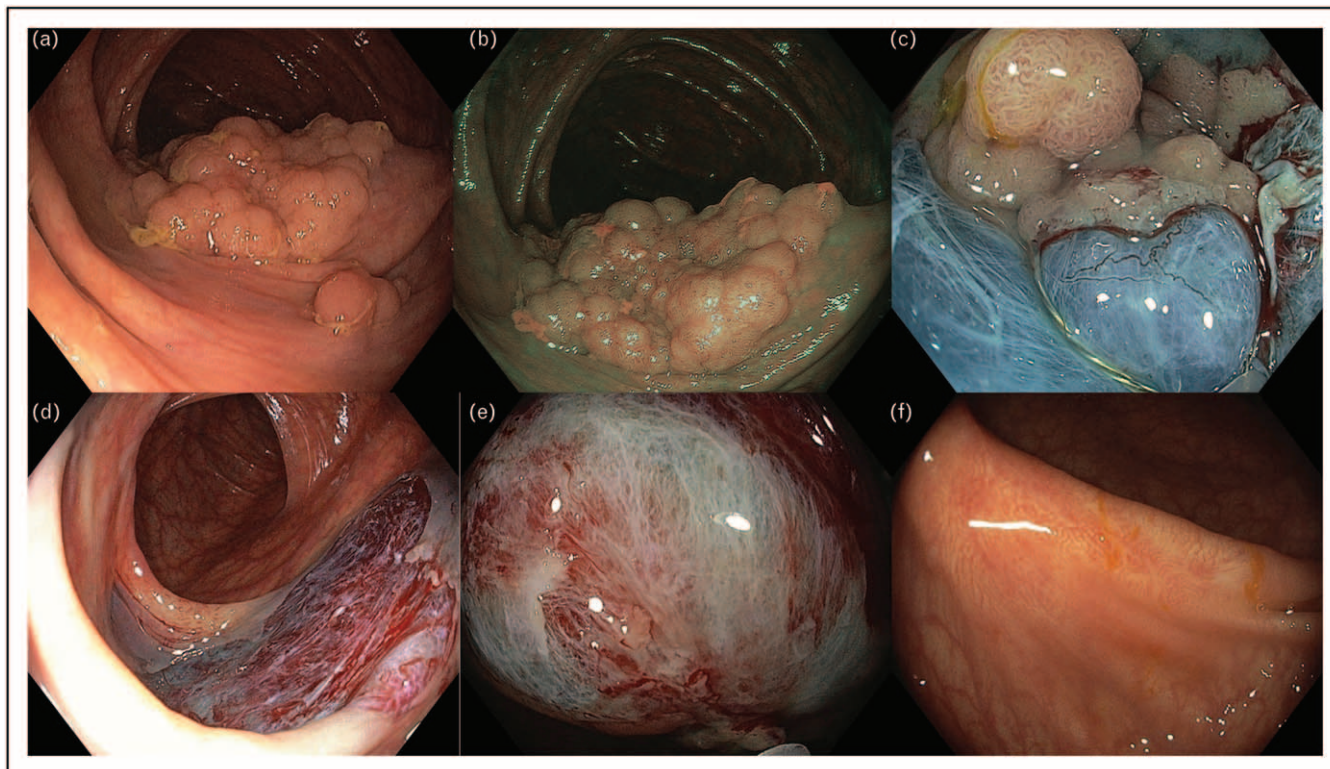


FIGURE 2. A 35 mm Granular Paris 0-IIa LNCP in the distal transverse colon resected by cold endoscopic mucosal resection. A 35 mm granular Paris 0-IIa LNCP assessed with (a) high-definition white light and (b) narrow band imaging (NBI). Piecemeal cold snare resection with sequential snare overlap (c), resected with a wide margin (d–e). Surveillance colonoscopy demonstrating a bland scar at the site of resection (f).

The preprocedural planning phase extends to the endoscopy room where a collaborative discussion with nursing and anaesthetic staff provides great value. This collaborative approach ensures that all team members are well informed about critical procedural steps, necessary equipment and the anticipated duration of the procedure. Furthermore, it is advantageous to address any site-specific challenges that may arise during the procedure, such as expected fibrosis encountered in previously attempted lesions [17].

Other important discussion points include any specific medications such as surgical antibiotic prophylaxis or local anaesthetic for lesions at the anorectal junction (ARJ). An equipment check should ensure the availability of all appropriate resection devices such as snares and ESD knives [18,19]. It is imperative that endoscopic resection is conducted exclusively with carbon dioxide insufflation [20]. Furthermore, essential ancillary devices, such as through-the-scope clips for closure and haemostatic forceps to address intra-procedural bleeding, should be prepositioned in the procedure room.

Patient positioning is important and can improve efficiencies. The ideal orientation is with the patient positioned so that the fluid pool is

opposite the lesion. Thus, leveraging gravity to optimize lesion elevation and ensure a clear working field for tissue resection or the management of any potential complications. Consequently, adopting a supine or right lateral position may be deemed necessary. Precise positioning of the colonoscope to align the lesion at a 6 o'clock position is imperative for optimal visualization and intervention. Depending on the lesion's location, the adoption of a retroflexed position may further enhance access and aide comprehensive optical assessment. Time spent early on patient positioning, promotes procedural efficacies, mitigates potential challenges and optimizes outcomes.

Pre-resection diagnosis is important to optimize decision-making and patient outcomes. Thorough optical assessment stands as a cornerstone in diagnostic precision. The risk of overt (optical features of SMIC present) or covert (optical features of SMIC absent) cancer is contingent upon various parameters, including the size, location, morphology, granularity and microvascular and surface pit patterns of the LNCP [10,12[¶]]. Classification systems, such as the Kudo pit pattern (KPP) and the Japan Narrow-Band Imaging Expert Team (JNET) classification,

Endoscopy

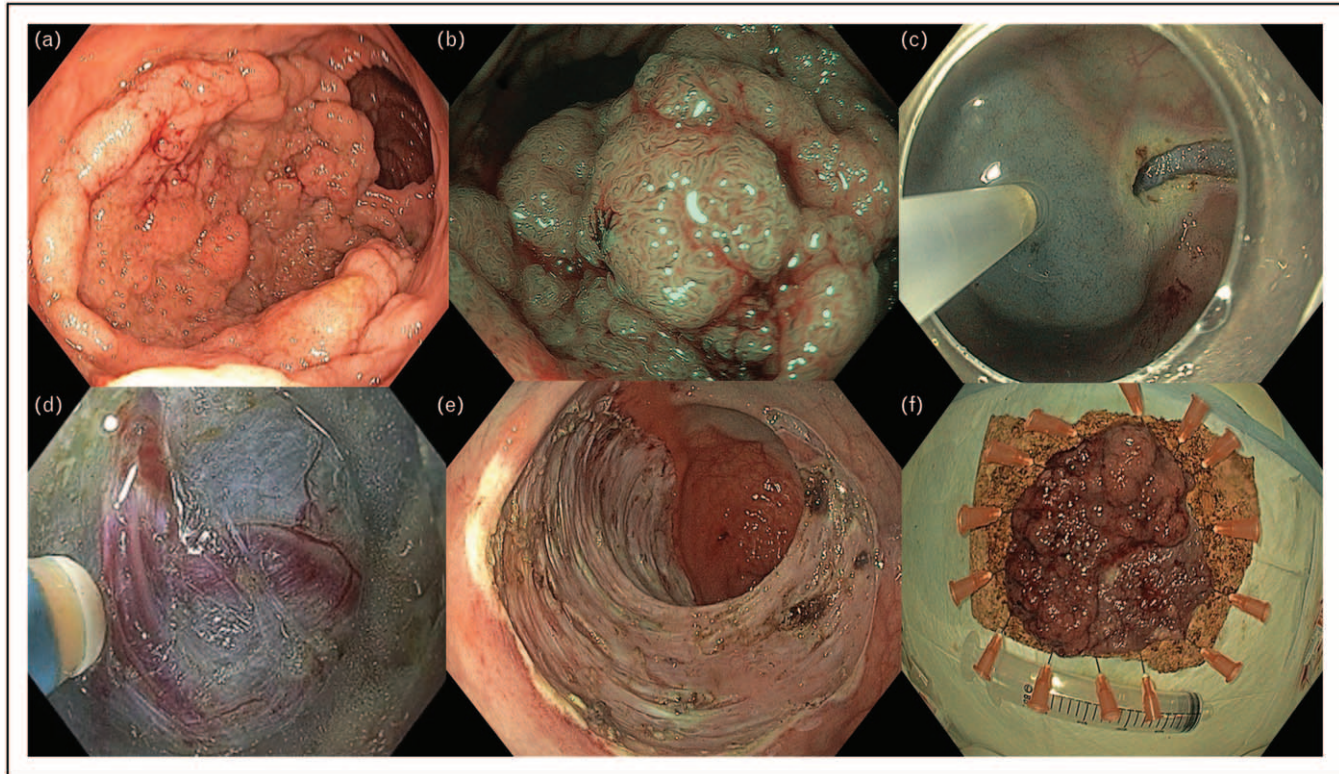


FIGURE 3. A 50 mm Granular Paris 0-IIa+Is LNPCP in the rectum resected by endoscopic submucosal dissection. A 50 mm Granular Paris 0-IIa+Is LNPCP assessed with (a) high-definition white light and (b) narrow band imaging (NBI). En bloc submucosal dissection and resection (c–e). Post-resection en bloc ex-vivo specimen (f).

provide helpful frameworks for this multifaceted assessment [21,22]. Proficiency in understanding these systems is helpful; however, quite simply benign lesions have surface homogeneity, loss of this homogeneity raises concern for SMIC. A pragmatic approach to enhance familiarity and utilization could involve prominently displaying large posters of these classification systems in endoscopy rooms and reporting areas.

Flat benign lesions typically exhibit surface homogeneity characterized by a regular pit and microvascular pattern. In contrast, the presence of high-grade dysplasia or cancer manifests as a distinct demarcated area of disruption within this otherwise regular pattern. Rigorous examination of such areas is paramount to ensuring accurate optical diagnosis and guiding the formulation of an appropriate resection strategy. Bulky lesions may harbour SMIC within and risk is best stratified by surface morphology and location.

Traditionally, the ‘optical biopsy’ was thought to be inaccurate. Recent advancements have highlighted the exceptional accuracy of optical assessment, particularly for flat (Paris 0-IIa) LNPCPs [23]. In a large, prospective, single-centre cohort study ($n = 1583$), the sensitivity and specificity for

predicting cancer in Paris 0-IIa LNPCPs were more than 90%. This study reported the chance of a missed cancer in a flat (Paris 0-IIa) lesion was 6 in 1000 cases.

Conversely, optical diagnosis for SMIC for nodular lesions is less accurate with a sensitivity of 53% and specificity of 94%, resulting in a 6% missed SMIC rate [23]. Excluding lesions with overt SMIC, a large multicentre, prospective study ($n = 2277$) revealed that covert SMIC was associated with Paris 0-Is and Paris 0-IIa+Is morphology, nongranularity, size, and distal location [10]. Corroborating this finding, a large prospective cohort study ($n = 3405$) reported that rectal LNPCPs have a higher likelihood of harbouring SMIC compared with their nonrectal colonic counterparts (15 vs. 6%, $P < 0.001$) [12[¶]]. These advancements in understanding the optical diagnostic accuracy have refined our understanding of SMIC risk and influence the most appropriate endoscopic resection technique.

A pre-resection biopsy has been traditionally used for pre-resection diagnosis; however, this is often inaccurate. In a large, retrospective study ($n = 586$), compared with the post-resection specimen, pre-resection biopsy was inaccurate in 40% of lesions [24[¶]].

RESECTION

A selective endoscopic resection algorithm should guide therapeutic decisions for LNPCP management, integrating all known lesion parameters to predict histopathology and therefore maximize the chance of a curative resection.

Endoscopic mucosal resection

EMR remains the foundation for the effective removal of LNPCPs demonstrating superior safety, efficacy and cost-effectiveness compared with surgery [25–27]. Advancements over the past decade, informed by high-quality studies have enhanced EMR safety and efficacy. Key refinements include CO₂ insufflation, chromo-injectate utilization in the submucosal space, systematic inject and sequential snare resection, incorporation of a 2–3 mm margin of normal mucosa during endoscopic resection, water jet expansion of the defect to identify residual adenoma and the early recognition of significant deep mural injury (DMI) [20,28,29]. Following adenoma resection, thermal ablation of the margin is performed to achieve a 3–5 mm rim of ablated mucosa [30]. With the addition of thermal ablation, recurrence rates have reduced from ~20% to below 2% [30,31].

In a recent large RCT ($n = 414$), the efficacy of snare tip soft coagulation (STSC) was compared with argon plasma coagulation (APC) for thermal ablation of the margin [32[■]]. Although not significantly different, recurrence rate at first surveillance colonoscopy was 4.6 vs 9.3% for the STSC and APC groups, respectively [32[■]]. The authors concluded that STSC is the favoured technique given it is more efficient to apply, less expensive and more carbon friendly than APC.

Cold-endoscopic mucosal resection

At present, because of limited data, conventional EMR is preferred over C-EMR for LNPCP resection. The safety profile of C-EMR is appealing for piecemeal resection of Paris 0-IIa LNPCPs, however, the upper size limit for effective removal without excessive recurrence is unknown. A large, prospective, multicentre cohort study ($n = 286$ lesions) comparing conventional EMR to C-EMR for 6–15 mm polyps favoured the use of C-EMR over EMR [33[■]]. At present, US consensus guidelines recommend either EMR or C-EMR for resection of lesions 10–19 mm [13]. Recently, the first large, prospective randomized controlled trial (RCT) compared C-EMR to conventional EMR for 15–50 mm Paris 0-IIa lesions was published. At 6-month surveillance colonoscopy, recurrence was significantly greater in the C-EMR

group [(15/87, 17%) vs. (1/93, 1%); $P < 0.001$]. Significant DMI [(0, 0%) vs. (24/93, 26%); $P < 0.001$] and delayed perforation [(0,0%) vs. (1/93, 1%); $P = 0.33$] only occurred in the EMR group. Clinically significant postprocedural and intraprocedural bleeding were greater in the EMR arm [(1/87, 1.1%) vs. (7/93, 7.5%); $P = 0.038$] and [(0/87, 0%) vs. (10/93, 10.8%); $P = 0.002$] respectively [34[■]].

These findings suggest there is an upper limit to lesion size for C-EMR after which recurrence becomes overwhelming burdensome. This cut-off might differ between patients. For example, an elderly patient taking anticoagulation may not be bothered by recurrence, and any recurrence would be unlikely to shorten that patient's length or quality of life. Conversely, a delayed perforation or bleed post EMR could prove more challenging for that patient, swinging the endoscopic resection pendulum in favour of C-EMR.

In contrast to adenomas, C-EMR is always recommended as the primary modality for endoscopic resection of serrated lesions, irrespective of size. A large, prospective study ($n = 562$) demonstrated comparable technical success and recurrence rates between C-EMR and EMR, whereas bleeding (0 vs. 5%) and significant DMI (0 vs. 3%) were more common in the EMR group [35].

Endoscopic submucosal dissection

The rectum represents a highly intricate and high-risk anatomical site, characterized by unique challenges distinct from those encountered in the colon. The heightened risk of covert SMIC [12[■],36] rather than technical limitations underscores its complexity. Additionally, the stakes are greater. Failed endoscopic cure necessitates the need for some of the most complex forms of colorectal surgery, associated with the risk of ostomy formation [37], increased risk of incontinence (12%) [38] and sexual dysfunction (20–46%) [39] along with a 10–20% risk of a permanent stoma [40,41]. Low anterior resection, a common surgical approach, is associated with a 30-day morbidity and mortality of 25 and 6%, respectively [42], emphasizing the serious implications of surgery in the left colon. In this context, endoscopic resection emerges as an organ-sparing, minimally invasive alternative, mitigating the need for complex surgery in many cases [43].

In a large multicentre observational study ($n = 618$), rectal LNPCPs were more likely to contain cancer (15 vs. 6%, $P < 0.001$), 50% of which is covert, compared with the remainder of the colon [12[■]]. To achieve R0 (curative) resection, en bloc resection is required.

Originally developed for treatment of early gastric cancer, ESD has evolved into an established

Endoscopy

technique in the colorectum. Using an electro-surgical knife for fine dissection, ESD allows precise en bloc resection of large lesions with more precision and control compared with EMR. A rectum-specific selective resection algorithm (SRA) has demonstrated superior outcomes compared with a Universal EMR algorithm (UEA). In a large study ($n=480$), LNPCPs underwent ESD if they had features suggestive of overt SMIC (1000 μm , KPP V) or covert SMIC (Paris 0-1 s, or a dominant nodule). All LNPCPs with SMIC amenable to R0 resection that underwent ESD achieved cure [11]. Implementing a rectum-specific SRA avoids the piecemeal resection of cancer.

In a recent large RCT ($n=360$), Jacques and colleagues compared EMR and ESD for LNPCPs at least 25 mm. Lesions within 15 cm of the ARJ were excluded [44^{***}]. The rate of SMIC was 6% in keeping with previous studies [12^{*}]. Although ESD had lower recurrence rate (0.6 vs 5.1%), adverse events were greater (36 vs. 25%). The procedure time for ESD and EMR was 47 vs. 15 min, respectively. Accounting for the opportunity and resource cost of ESD compared with EMR, as well as the low rate of covert SMIC outside of the rectum, this study underscored the importance of a selective endoscopic resection approach. EMR is well tolerated, efficient and less expensive than ESD. ESD is an indispensable tool, which should be reserved for lesions at high risk of superficial early overt SMIC or covert SMIC such as bulky rectal lesions [45].

Endoscopic full-thickness resection

High-risk lesions require en bloc resection for cure. Until recently, the only endoscopic resection options were en bloc EMR and ESD, but both have limitations. EMR is less precise and may struggle in achieving R0 resection of lateral and vertical margins, especially in fibrotic lesions with advanced histology [46]. Although ESD offers superior margin control, it is technically challenging, resource intensive and has limited accessibility, particularly in Western countries [47–50]. Additionally, ESD may face challenges in achieving a curative vertical resection margin. To address these issues, an integrated endoscopic full-thickness resection device (FTRD, Ovesco Endoscopy, Tübingen, Germany) was developed for select gastrointestinal lesions. The FTRD, featuring a single-clip closure and resection device enables EFTR without exposing the peritoneum to luminal contents during the procedure [51–53]. In contrast to ESD, EFTR does not have a lengthy learning curve and does not necessarily require knowledge of third-space endoscopy or resection planes [54]. Two large national registries have reported high curative results for select lesions with

T1 cancer or high-grade dysplasia [55,56]. However, a limitation of the FTRD is the lesion size, determined by the volume of tissue that can be pulled into the distal over-the scope cap and the risk of delayed perforation which is 1% [57^{*}]. A study ($n=69$) has demonstrated efficacy of a hybrid EMR/EFTR technique for resection of larger lesions but more data is required on long-term durability [58]. Due to the relative novelty of EFTR, long-term efficacy data is lacking.

POST-RESECTION CONSIDERATIONS

Regardless of the endoscopic resection modality, it is vital that clear, written and verbal instructions are provided to the patient and their next of kin. Instructions should include when and how to contact medical staff should there be any issues. This ensures prompt recognition and effective management of any complications.

Post-resection surveillance is required for all resected lesions, the timing of which differs depending on the resected histology. Patients should ideally be scheduled for follow-up on the day of their index resection to ensure there are no errors in communication and they are not lost to follow-up.

The management of covert SMIC identified postpiecemeal endoscopic resection has historically presented challenges. In a recent, large observational study ($n=3372$), 143 (4%) cases exhibited covert SMIC postpiecemeal resection [59^{***}]. Surgical resection was performed in 109 cases of which 62 (63%) contained no residual cancer. Among cases with residual intramucosal cancer ($n=24$), an R1 histological deep margin identified all instances. Poor differentiation and/or lymphovascular invasion conferred a high risk of lymph node metastasis (12/33) whereas cases lacking these features presented a very low risk ($<1\% < 0/35$). Most patients with covert SMIC resected piecemeal displayed no residual malignancy. Residual malignancy risk could be predicted by poor differentiation, lymphovascular invasion and an R1 deep margin.

In a large multicentre study ($n=2255$) of non-curative colorectal ESDs, none (0%) of the sm1 lesions had residual CRC after surgical resection and none of the $>sm1$ lesions had residual CRC if lymphovascular invasion (LVI) and poor differentiation were absent. LVI or poor differentiation warrant consideration of surgery because of the high risk of lymph node metastasis [60^{***}].

CONCLUSION

This review compares various endoscopic resection techniques and underscores the intricate balance of

choosing the most appropriate technique for any given lesion and patient. EMR, C-EMR, ESD and EFTR all offer distinct value but each also have their weaknesses. Ultimately, endoscopic resection is becoming more nuanced. Endoscopists should not only account for lesion sub-types, each with differing challenges and risks, but they also need to account for patient-specific factors, embracing the paradigm of precision medicine. Current SRAs, based on high-quality evidence, provide fundamental guidance to achieve the best outcomes for our patients. These are likely to be further refined in the immediate future.

Acknowledgements

None.

Financial support and sponsorship

The Cancer Institute of New South Wales provided funding for a research nurse and data manager to assist with the administration of our research. There was no influence regarding study design or conduct, data collection, management, analysis, interpretation, preparation, review or approval of the manuscript.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Patel SG, Karlitz JJ, Yen T, *et al.* The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol Hepatol* 2022; 7:262–274.
2. Levin B, Lieberman DA, McFarland B, *et al.*, American Cancer Society Colorectal Cancer Advisory Group, US Multi-Society Task Force, American College of Radiology Colon Cancer Committee. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008; 134:1570–1595.
3. Kedrin D, Gala MK. Genetics of the serrated pathway to colorectal cancer. *Clin Transl Gastroenterol* 2015; 6:e84.
4. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 2004; 287:G7–G17.
5. Bretthauer M, Løberg M, Wieszczyn P, *et al.*, NordICC Study Group. Effect of colonoscopy screening on risks of colorectal cancer and related death. *N Engl J Med* 2022; 387:1547–1556.
6. Zauber AG, Winawer SJ, O'Brien MJ, *et al.* Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; 366:687–696.
7. Rex DK. Have we defined best colonoscopic polypectomy practice in the United States? *Clin Gastroenterol Hepatol* 2007; 5:674–677.
8. Gupta N, Bansal A, Rao D, *et al.* Prevalence of advanced histological features in diminutive and small colon polyps. *Gastrointest Endosc* 2012; 75:1022–1030.
9. Repici A, Hassan C, Vitetta E, *et al.* Safety of cold polypectomy for <10 mm polyps at colonoscopy: a prospective multicenter study. *Endoscopy* 2012; 44:27–31.
10. Burgess NG, Hourigan LF, Zanati SA, *et al.* Risk stratification for covert invasive cancer among patients referred for colonic endoscopic mucosal resection: a large multicenter cohort. *Gastroenterology* 2017; 153:732.e1–742.e2.

11. Shahidi N, Vosko S, Gupta S, *et al.* A rectum-specific selective resection algorithm optimizes oncologic outcomes for large nonpedunculated rectal polyps. *Clin Gastroenterol Hepatol* 2023; 21:72.e2–80.e2.
12. Cronin O, Sidhu M, Shahidi N, *et al.* Comparison of the morphology and histopathology of large nonpedunculated colorectal polyps in the rectum and colon: implications for endoscopic treatment. *Gastrointest Endosc* 2022; 96:118–124.

This study demonstrated that the risk of covert cancer in the rectum is 2.5 times that seen in rest of the colon.

13. Kaltenbach T, Anderson JC, Burke CA, *et al.* Endoscopic removal of colorectal lesions: recommendations by the US Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2020; 115:435–464.
14. Ferlitsch M, Moss A, Hassan C, *et al.* Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2017; 49:270–297.
15. Jayanna M, Burgess NG, Singh R, *et al.* Cost analysis of endoscopic mucosal resection vs surgery for large laterally spreading colorectal lesions. *Clin Gastroenterol Hepatol* 2016; 14:271.e2–278.e2.
16. Ahlenstiel G, Hourigan LF, Brown G, *et al.*, Australian Colonic Endoscopic Mucosal Resection (ACE) Study Group. Actual endoscopic versus predicted surgical mortality for treatment of advanced mucosal neoplasia of the colon. *Gastrointest Endosc* 2014; 80:668–676.
17. Shahidi N, Vosko S, Gupta S, *et al.* Previously attempted large nonpedunculated colorectal polyps are effectively managed by endoscopic mucosal resection. *Am J Gastroenterol* 2021; 116:958–966.
18. Holt BA, Bassan MS, Sexton A, *et al.* Advanced mucosal neoplasia of the anorectal junction: endoscopic resection technique and outcomes (with videos). *Gastrointest Endosc* 2014; 79:119–126.
19. Shahidi N, Sidhu M, Vosko S, *et al.* Endoscopic mucosal resection is effective for laterally spreading lesions at the anorectal junction. *Gut* 2020; 69:673–680.
20. Bassan MS, Holt B, Moss A, *et al.* Carbon dioxide insufflation reduces number of postprocedure admissions after endoscopic resection of large colonic lesions: a prospective cohort study. *Gastrointest Endosc* 2013; 77:90–95.
21. Kudo S, Tamura S, Nakajima T, *et al.* Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc* 1996; 44:8–14.
22. Sano Y, Tanaka S, Kudo SE, *et al.* Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. *Dig Endosc* 2016; 28:526–533.
23. Vosko S, Shahidi N, Sidhu M, *et al.* Optical evaluation for predicting cancer in large nonpedunculated colorectal polyps is accurate for flat lesions. *Clin Gastroenterol Hepatol* 2021; 19:2425.e4–2434.e4.
24. Ma MX, Tate DJ, Sidhu M, *et al.* Effect of pre-resection biopsy on detection of advanced dysplasia in large nonpedunculated colorectal polyps undergoing endoscopic mucosal resection. *Endoscopy* 2023; 55:267–273.

This study reported that a pre-resection biopsy is often inaccurate and is, therefore, less important compared with a thorough optical assessment.

25. Cronin O, Bourke MJ. Endoscopic management of large non-pedunculated colorectal polyps. *Cancers (Basel)* 2023; 15:3805.
26. Shahidi N, Bourke MJ. How to manage the large nonpedunculated colorectal polyp. *Gastroenterology* 2021; 160:2239.e1–2243.e1.
27. Jideh B, Bourke MJ. How to perform wide-field endoscopic mucosal resection and follow-up examinations. *Gastrointest Endosc Clin N Am* 2019; 29:629–646.
28. Bourke MJ, Bhandari P. How I remove polyps larger than 20 mm. *Gastrointest Endosc* 2019; 90:877–880.
29. Moss A, Bourke MJ, Metz AJ. A randomized, double-blind trial of succinylated gelatin submucosal injection for endoscopic resection of large sessile polyps of the colon. *Am J Gastroenterol* 2010; 105:2375–2382.
30. Klein A, Tate DJ, Jayasekaran V, *et al.* Thermal ablation of mucosal defect margins reduces adenoma recurrence after colonic endoscopic mucosal resection. *Gastroenterology* 2019; 156:604.e3–613.e3.
31. Sidhu M, Shahidi N, Gupta S, *et al.* Outcomes of thermal ablation of the mucosal defect margin after endoscopic mucosal resection: a prospective, international, multicenter trial of 1000 large nonpedunculated colorectal polyps. *Gastroenterology* 2021; 161:163.e3–170.e3.
32. Rex DK, Haber GB, Khashab M, *et al.* Snare tip soft coagulation vs argon plasma coagulation vs no margin treatment after large nonpedunculated colorectal polyp resection: a randomized trial. *Clin Gastroenterol Hepatol* 2024; 22:552.e4–561.e4.

This study underscored the importance of thermal ablation of the margin with snare-tip soft coagulation.

33. Rex DK, Anderson JC, Pohl H, *et al.* Cold versus hot snare resection with or without submucosal injection of 6- to 15-mm colorectal polyps: a randomized controlled trial. *Gastrointest Endosc* 2022; 96:330–338.

This study demonstrated that cold snare resection is effective for the resection of lesions 6–15 mm.

34. O'Sullivan T, Cronin O, van Hattem W, *et al.* Cold vs hot snare endoscopic mucosal resection for large (≥ 15 mm) flat nonpedunculated colorectal polyps: a randomized controlled trial. *Gut* 2024 [under review].

This study is the first large RCT to directly compare efficacy and long-term outcomes of cold-EMR to conventional EMR for the resection of LNPPCs.

35. van Hattem WA, Shahidi N, Vosko S, *et al.* Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: a retrospective comparison across two successive periods. *Gut* 2021; 70:1691–1697.

Endoscopy

36. Bar-Yishay I, Shahidi N, Gupta S, *et al*. Outcomes of deep mural injury after endoscopic resection: an international cohort of 3717 large non-pedunculated colorectal polyps. *Clin Gastroenterol Hepatol* 2022; 20:e139–e147.
37. Vennix S, Pelzers L, Bouvy N, *et al*. Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev* 2014; CD005200.
38. Duran E, Tanriseven M, Ersoz N, *et al*. Urinary and sexual dysfunction rates and risk factors following rectal cancer surgery. *Int J Colorectal Dis* 2015; 30:1547–1555.
39. Celentano V, Cohen R, Warusavitarne J, *et al*. Sexual dysfunction following rectal cancer surgery. *Int J Colorectal Dis* 2017; 32:1523–1530.
40. Climent M, Martin ST. Complications of laparoscopic rectal cancer surgery. *Mini-invasive Surg* 2018; 2:45.
41. Lindgren R, Hallböök O, Rutegård J, *et al*. What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial. *Dis Colon Rectum* 2011; 54:41–47.
42. Cuccurullo D, Pirozzi F, Sciuto A, *et al*. Relaparoscopy for management of postoperative complications following colorectal surgery: ten years experience in a single center. *Surg Endosc* 2015; 29:1795–1803.
43. Mulita F, Liolis E, Akinosoglou K, *et al*. Postoperative sepsis after colorectal surgery: a prospective single-center observational study and review of the literature. *Prz Gastroenterol* 2022; 17:47–51.
44. Jacques J, Schaefer M, Wallenhorst T, *et al*. Endoscopic en bloc versus piecemeal resection of large nonpedunculated colonic adenomas: a randomized comparative trial. *Ann Intern Med* 2024; 177:29–38.
- This key study clarifies the role of ESD and EMR in the colorectum. As reflected in this study, a selective resection algorithm leads to improved outcomes.
45. Burgess NG, Bourke MJ. Endoscopic submucosal dissection versus endoscopic mucosal resection of large colon polyps: use both for the best outcomes. *Ann Intern Med* 2024; 177:89–90.
46. Kuroha M, Shiga H, Kanazawa Y, *et al*. Factors associated with fibrosis during colorectal endoscopic submucosal dissection: does pretreatment biopsy potentially elicit submucosal fibrosis and affect endoscopic submucosal dissection outcomes? *Digestion* 2021; 102:590–598.
47. Bahin FF, Heitman SJ, Rasouli KN, *et al*. Wide-field endoscopic mucosal resection versus endoscopic submucosal dissection for laterally spreading colorectal lesions: a cost-effectiveness analysis. *Gut* 2018; 67:1965–1973.
48. Arezzo A, Passera R, Marchese N, *et al*. Systematic review and meta-analysis of endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions. *United European Gastroenterol J* 2016; 4:18–29.
49. Saito Y, Uraoka T, Matsuda T, *et al*. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2007; 66:966–973.
50. ASGE Technology Committee. Maple JT, Abu Dayyeh BK, *et al*. Endoscopic submucosal dissection. *Gastrointest Endosc* 2015; 81:1311–1325.
51. Schmidt A, Beyna T, Schumacher B, *et al*. Colonoscopic full-thickness resection using an over-the-scope device: a prospective multicentre study in various indications. *Gut* 2018; 67:1280–1289.
52. Xu M, Wang XY, Zhou PH, *et al*. Endoscopic full-thickness resection of colonic submucosal tumors originating from the muscularis propria: an evolving therapeutic strategy. *Endoscopy* 2013; 45:770–773.
53. Sedarat A. Clips for closure of full-thickness defects. *Techn Gastrointest Endosc* 2015; 17:129–135.
54. Zhang X, Ly EK, Nithyanand S, *et al*. Learning curve for endoscopic submucosal dissection with an untutored, prevalence-based approach in the United States. *Clin Gastroenterol Hepatol* 2020; 18:580.e1–588.e1.
55. Zwager LW, Bastiaansen BAJ, van der Spek BW, *et al*, Dutch eFTR Group. Endoscopic full-thickness resection of T1 colorectal cancers: a retrospective analysis from a multicenter Dutch eFTR registry. *Endoscopy* 2022; 54:475–485.
56. Meier B, Stritzke B, Kuellmer A, *et al*. Efficacy and safety of endoscopic full-thickness resection in the colorectum: results from the German Colonic FTRD Registry. *Am J Gastroenterol* 2020; 115:1998–2006.
57. Zwager LW, Mueller J, Stritzke B, *et al*. Adverse events of endoscopic full-thickness resection: results from the German and Dutch nationwide colorectal FTRD registry. *Gastrointest Endosc* 2023; 97:780.e4–789.e4.
- This is the largest registry reporting adverse events following full-thickness resection.
58. Mahadev S, Vareedayah AA, Yuen S, *et al*. Outcomes of a hybrid technique using EMR and endoscopic full-thickness resection for polyps not amenable to standard techniques (with video). *Gastrointest Endosc* 2021; 94:358.e1–367.e1.
59. Gibson DJ, Sidhu M, Zanati S, *et al*. Oncological outcomes after piecemeal endoscopic mucosal resection of large nonpedunculated colorectal polyps with covert submucosal invasive cancer. *Gut* 2022; 71:2481–2488.
- This study reported that the risk of residual malignancy after the piecemeal resection of a LNPCP greater than 20 mm with covert SMIC is low. Residual malignancy can be ascertained with three key variables: poor differentiation, lymphovascular invasion, and R1 deep margin.
60. Santos-Antunes J, Pioche M, Ramos-Zabala F, *et al*. Risk of residual neoplasia after a local-risk resection of colorectal lesions by endoscopic submucosal dissection: a multinational study. *J Clin Med* 2023; 12:5356.
- This key study reported that for lesions removed by ESD with a noncurative margin, the risk of residual cancer is low unless there are high-risk features (lymphovascular invasion, poor differentiation).