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Improving the safety and efficacy of colorectal neoplasia endoscopic resection

Faculty of Medicine and Health

The University of Sydney

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Statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

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A list of authorship statements is included in Appendix 2.

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.

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ABSTRACT

INTRODUCTION

Endoscopic mucosal resection (EMR) is standard of care for the management of benign large non-pedunculated colorectal polyps (LNPCPs); however, electrocautery related complications and colonoscopy surveillance remain a burden for patients and health services. Alarmingly, despite the superior safety and cost-effectiveness of EMR, colorectal surgery continues to be inappropriately utilised in many centres for the resection of benign polyps. This thesis investigated key research gaps within endoscopic resection modalities, surveillance outcomes, optical diagnosis and EMR training pathways.

METHODS

Large prospective single and multicentre trials were conducted to address the aims of this thesis. Studies underwent ethics approval with written, informed consent obtained from all patients.

RESULTS

Cold snare EMR of LNPCPs, whilst safer than conventional hot snare EMR, is at the expense of significantly higher recurrence rates.

In the presence of a clear resection scar at first surveillance colonoscopy, recurrence is exceedingly rare at long-term follow up for contemporary hot snare EMR with margin thermal ablation.

Early post-resection surveillance remains critical, with synchronous LNPCPs highly prevalent in EMR cohorts and a more frequent finding when index lesions are non-granular.

Risk assessment for submucosal invasive cancer is predictable using LNPCP characteristics and can be simplified in a decision tree algorithm to optimise optical diagnosis and resection modality selection.

Challenging lesions for EMR-naïve endoscopists can be accurately predicted and incorporated into a numerical score to guide case selection for EMR training.

CONCLUSIONS

Overall, this thesis has widespread implications on endoscopic practice with a likely influence on international consensus guidelines. Optimisation of technique, training

pathways and surveillance intervals will potentially reduce procedural burden and improve outcomes for patients and health services.

Table of Contents

Statement of originality……..….. 2

Author attributions statement…….……. 3

Acknowledgements…….……. 4

Abstract……. …….…. 5

Table of Contents……..7

List of Publications……8

Abbreviations……9

List of Figures…….. 11

List of Tables ……. 13

Chapter 1: Introduction……... 15

Chapter 2: Contemporary clinical practice for the endoscopic resection of colorectal neoplasia: a literature review ……..... *27*

Part 1: Improvements in colorectal endoscopic resection technique and surveillance pathways…..…… 50

Chapter 3……..... 51

Chapter 4…….. 74

Chapter 5…… 99

Part 2: Optimisation of lesion selection for endoscopic resection training and tertiary referral ……..119

Chapter 6……... 120

Chapter 7…… 142

Chapter 8: Integrated Discussion……..……...165

Chapter 9: Conclusions…….. 175

Appendices (I-III) ……. 177

List of Publications in Thesis

Chapter 2:

O'Sullivan T, Bourke MJ. **Endoscopic Resection of Neoplasia in the Lower GI Tract: A Clinical Algorithm.** Visc Med. 2024 Aug;40(4):217-227. doi: 10.1159/000539219. Epub 2024 Jun 26. PMID: 39157731; PMCID: PMC11326768.

Chapter 3:

O'Sullivan T, Cronin O, van Hattem WA, Mandarino FV, Gauci JL, Kerrison C, Whitfield A, Gupta S, Lee E, Williams SJ, Burgess N, Bourke MJ. **Cold versus hot snare endoscopic mucosal resection for large (≥15 mm) flat non-pedunculated colorectal polyps: a randomised controlled trial.** Gut. 2024 Oct 7;73(11):1823-1830. doi: 10.1136/gutjnl-2024-332807. PMID: 38964854.

Chapter 4:

O'Sullivan T, Mandarino FV, Gauci JL, Whitfield AM, Kerrison C, Elhindi J, Neto do Nascimento C, Gupta S, Cronin O, Sakiris A, Prieto Aparicio JF, Arndtz S, Brown G, Raftopoulos S, Tate D, Lee EY, Williams SJ, Burgess N, Bourke MJ. **Impact of margin thermal ablation after endoscopic mucosal resection of large (≥20 mm) non-pedunculated colonic polyps on long-term recurrence.** Gut. 2024 Sep 30:gutjnl-2024-332907. doi: 10.1136/gutjnl-2024-332907. Epub ahead of print. PMID: 39349006.

Chapter 5:

O'Sullivan T, Tate D, Sidhu M, Gupta S, Elhindi J, Byth K, Cronin O, Whitfield A, Craciun A, Singh R, Brown G, Raftopoulos S, Hourigan L, Moss A, Klein A, Heitman S, Williams S, Lee E, Burgess NG, Bourke MJ. **The Surface Morphology of Large Nonpedunculated Colonic Polyps Predicts Synchronous Large Lesions.** Clin Gastroenterol Hepatol. 2023 Aug;21(9):2270-2277.e1. doi: 10.1016/j.cgh.2023.01.034. Epub 2023 Feb 12. PMID: 36787836.

Chapter 6:

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Chapter 7:

O'Sullivan T, Sidhu M, Gupta S, Byth K, Elhindi J, Tate D, Cronin O, Whitfield A, Wang H, Lee E, Williams S, Burgess NG, Bourke MJ. **A novel tool for case selection in endoscopic mucosal resection training. Endoscopy.** 2023 Dec;55(12):1095-1102. doi: 10.1055/a-2121-1148. Epub 2023 Jun 30. PMID: 37391184.

Table of Abbreviations

ACE, Australian Colonic Endoscopic Resection
AE, Adverse event
AO, Appendiceal orifice
APC, Argon plasma coagulation
ARJ, Anorectal junction
ASA, American Society of Anaesthesiologists
AUROC, Area under the receiver operating characteristic
CAST, Cold avulsion with snare tip soft coagulation
C-EMR, Cold EMR
CHAID, Chi squared automatic interaction detection
CI, Confidence interval
COVID, Coronavirus disease
CRC, Colorectal cancer
CRR, Complete resection rate
CSP, Cold snare polypectomy
CSPEB, Clinically significant post-EMR bleeding
CSS, Case selection score
DMI, Deep mural injury
EFTRD, endoscopic full thickness resection device
EMR, Endoscopic mucosal resection
EMR-CSS, Endoscopic mucosal resection-case selection score
ESD, Endoscopic submucosal dissection
ESGE, European Society of Gastrointestinal Endoscopy
G, Granular
H-EMR, Hot EMR
HGD, High grade dysplasia
ICV, Ileocaecal valve
IPB, Intraprocedural bleeding
IPP, Intraprocedural perforation
IQR, Interquartile range
IRR, Incomplete resection rate
ITT, Intention to treat
LNPCP, Large non-pedunculated colonic polyp
LSL, Laterally spreading lesion
MTA, Margin thermal ablation
NBI, Narrow band imaging
NICE, Narrow band imaging International Colorectal Endoscopic
NG, Non-granular
OR, Odds ratio
PCCRC, Post-colonoscopy colorectal cancer
PP, Per protocol
RCT, Randomised controlled trial
RR, Relative risk
RRA, Recurrent residual adenoma
SC1, First colonoscopy surveillance
SC2, Second colonoscopy surveillance
SCC, Squamous cell carcinoma
SD, Standard deviation
SERT, Sydney endoscopic recurrence tool

SMIC, Submucosal invasive cancer
SMSA, Size morphology, site and access
SSL, Sessile serrated lesion
STSC, Snare tip soft coagulation
TSA, Traditional serrated adenoma
TVA, Tubulovillous adenoma

List of Figures

Chapter 2
Figure 1 – Evidence-based endoscopic resection algorithm for the colorectum

Chapter 3
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; LNPCP, large non-pedunculated colorectal polyp; PP, per-protocol; SC1, first surveillance colonoscopy.

Chapter 4
Figure 1 - Endoscopic mucosal resection with adjuvant margin thermal ablation. Row 1 LNPCP prior to EMR; row 2 EMR defect with complete MTA. EMR, endoscopic mucosal resection; LNPCP, large non-pedunculated colonic polyp; MTA, margin thermal ablation.
Figure 2 - Bland EMR scars at SC1 are unlikely to develop recurrence at subsequent surveillance. EMR, endoscopic mucosal resection; SC1, first surveillance colonoscopy.
Figure 3 - Patient flow from LNPCP resection to SC2 (MTA arm). EMR, endoscopic mucosal resection; LNPCP, large non-pedunculated colonic polyp; MTA, margin thermal ablation; SC1, first surveillance colonoscopy; SC2, second SC; SERT, Sydney Endoscopic Recurrence Tool; SMIC, submucosal invasive cancer.
Figure 4 - Patient flow from LNPCP resection to SC2 (Control arm). EMR, endoscopic mucosal resection; MTA, margin thermal ablation; SC1, first surveillance colonoscopy; SC2, second SC; SMIC, submucosal invasive cancer.

Chapter 5
Figure 1 – Recruitment of LNPCPs with exclusions SSL, sessile serrated lesion; TSA, traditional serrated lesion; LNPCPs, Large non-pedunculated polyps.
Figure 2 – NG-LNPCPs have subtle appearances and are difficult to detect and endoscopically resect

Chapter 6
Figure 1 - Decision tree analysis targeting submucosal invasive cancer (SMIC) in the study cohort and illustrating the terminal nodes ('large non-pedunculated colonic polyp subtypes'). Left colon, rectosigmoid; right colon, proximal colon.
Figure 2 - Decision-making algorithm highlighting large nonpedunculated colonic polyp subtypes where the potential SMIC risk is >10%.
Figure 3 - Examples of risk assessment of large nonpedunculated colonic polyps using the simple algorithm for potential SMIC showing: a–c step 1 = nodular lesion; step 2 = location, rectosigmoid → potential SMIC risk 19% (en bloc resection performed); d–f step 1 = flat → potential SMIC risk 4% irrespective of location (resected by piecemeal endoscopic mucosal resection after surface optical evaluation).

Chapter 7
Figure 1 - Endoscopic images of example large adenomatous nonpedunculated colonic polyps (LNPCPs) of 20–25mm in size, showing: a–c a flat 22-mm LNPCP of the transverse colon with a score of 1, indicating that it is suitable to be attempted early during endoscopic mucosal resection (EMR) training; d–f a nodular 25-mm LNPCP at the anorectal junction with a score of 3, indicating that it carries a higher risk of intraprocedural complications or technical failure and therefore is not suitable to be attempted early during EMR training.

SUPPLEMENTARY FIGURES

- Figure 1 - Participant flow throughout study period.
- Figure 2 - Receiver operating characteristic curves within training and validation cohorts. AUC, area under the curve
- Figure 3 - Decision tree analysis model confirming the same set of variables identified in the best fitting regression model

List of Tables

Chapter 3
Table 1 - Baseline characteristics of study cohort *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.
Table 2 - Primary and secondary outcome measures with Intention to treat analysis. EMR, endoscopic mucosal resection
Table 3 - Lesion characteristics of cold snare endoscopic mucosal resection recurrences DMI, deep mural injury; IPB, intraprocedural bleeding

Chapter 4
Table 1 - Surveillance outcomes for MTA cases enrolled in RCT (a) and standard of care (b) MTA, margin thermal ablation; RCT, randomised controlled trial; SC1, first surveillance colonoscopy; SC2, second SC.
Table 2 - Baseline LNPCP characteristics of SC2 cohort and controls. *Six missing histopathology cases. †<1000 μm submucosal invasion, clear margins, no lymphovascular invasion, low tumour budding, well differentiated. AO, appendiceal oriface; HGD, high-grade dysplasia; ICV, ileocaecal valve; LNPCP, large non-pedunculated colonic polyp; SC2, second surveillance colonoscopy; SMIC, submucosal invasive cancer; TSA, traditional serrated adenoma; TVA, tubulovillous adenoma.
Table 3 - Recurrence rate at SC2 for EMR with MTA following a clear SC1. EMR, endoscopic mucosal resection; MTA, margin thermal ablation; SC2, second surveillance colonoscopy.
Table 4 - Baseline LNPCP characteristics of missing cases compared with SC2 cohort following MTA. *14 missing histopathology. AO, appendiceal oriface; ICV, ileocaecal valve; LNPCP, large non-pedunculated colonic polyp; MTA, margin thermal ablation; SC2, second surveillance colonoscopy.

Chapter 5
Table 1 – Baseline characteristics of single LNPCP vs synchronous disease cohort IQR, interquartile range; LNPCP, large nonpedunculated colonic polyp. [a]Paris classification/morphology (8 missing), Histopathology (174 missing).
Table 2 – Multiple logistic regression model for prediction of synchronous disease NOTE. With interaction term (granularity by location): left colon NG (OR, 4.78; 95% CI, 2.95–7.73), right colon NG (OR, 1.99; 95% CI, 1.39–2.86). G, granular; NG, non-granular.
Table 3 - Relationship between dominant LNPCP characteristics and characteristics of synchronous LNPCPs NOTE. Flat vs raised, 2 missing; G vs NG, 4 missing, 12 mixed. G, granular; NG, non-granular.

SUPPLEMENTARY TABLES
- Table 1 - Distribution of synchronous disease stratified by dominant lesion location, granularity and size
- Table 2 - Characteristics of synchronous LNPCPs IQR, interquartile range. [a]3 LNPCPs with incomplete data, 2 missing Paris, 13 histopathology data points missing. [b]22 granularity mixed or unspecified – not subject to final analysis.

Chapter 6

Table 1 - Baseline characteristics of the 2451 large nonpedunculated colonic polyps included in the study * Missing data for Paris type, n = 1.
Table 2 - Distribution of each large non-pedunculated colonic polyp characteristic by submucosal invasive cancer (SMIC) status, together with odds ratios (ORs) and 95%CIs derived from multivariable regression analysis. * Per 10-mmincrease in size.
†Missing data for Paris type, n = 1 in the no SMIC group.
Table 3 - Large nonpedunculated colonic polyp (LNPCP) and submucosal invasive cancer (SMIC) frequency ("gain") by terminal node subtype, together with percentage SMIC within each subtype, index ratio, and "potential SMIC" category. * Ratio of percentage with SMIC within subtype compared with percentage with SMIC for the total LNPCP cohort.

SUPPLEMENTARY TABLES

- Table 1 - LNPCPs containing SMIC stratified by covert and overt status*4 missing Kudo data – all underwent EMR $\pm$ despite benign surface appearances, high suspicion for SMIC due to poor submucosal lifting
- Table 2 - Frequency of SMIC status by morphology, colon location, granularity and size together with prevalence (%) and 95%CI of SMIC for each terminal node ('LNPCP subtype')

Chapter 7

Table 1 - Baseline patient and lesion characteristics and outcomes of the training and validation cohorts. IQR, interquartile range; EMR, endoscopic mucosal resection; STSC, snare-tip soft coagulation
Table 2 - Best fitting multiple logistic regression model in the new training cohort
Table 3 - The endoscopic mucosal resection case selection score (EMR-CSS)
Table 4 - Performance of the endoscopic mucosal resection case selection score (EMR-CSS) in the training and validation cohorts
Table 5 - Optimum cutoff scores for the endoscopic mucosal resection case selection score (EMR-CSS) within: a the training cohort; b the validation cohorts.

SUPPLEMENTARY TABLES

- Table 1 - Univariable analysis in training cohort. EMR, endoscopic mucosal resection

Chapter 1

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common malignancy within Australia.[1] In 2021, it ranked as the second highest cause of cancer-related death and is historically the third highest driver of cancer-related health expenditure.[2-3] Early detection and removal of precursor neoplastic polyps at colonoscopy is the foundation of CRC prevention, reducing both its incidence and mortality.[4-6] While the overwhelming majority of polyps are benign, large non-pedunculated colonic polyps (LNPCPs) represent distinctive lesions with a 5-7% risk of submucosal invasive cancer (SMIC).[7] Historically these lesions were managed with surgical resection. Following significant technical innovations in the last 10 years however, endoscopic resection is positioned as the preferred treatment modality for benign LNPCPs across multiple international consensus guidelines.[8-9] EMR is curative for benign lesions in 98% of cases with surgical resection rarely required.[10] Compared to surgery, EMR is a cost-effective alternative that demonstrates a superior safety profile.[11-12] Despite this, technical improvements are necessary to reduce adverse events whilst ensuring endoscopic cure. Such innovations will ensure patients receive the least invasive procedure whilst minimising hospitalization and procedural burden on the broader health service.

In this thesis, the following key areas related to colorectal endoscopic resection and surveillance were identified for prospective research:

1) The safety and efficacy of cold snare polypectomy in its application to large non-pedunculated colorectal polyps.
2) The implications of high-quality colonoscopy and contemporary EMR practice on post endoscopic resection surveillance intervals

In contrast to international guideline recommendations, a large proportion of benign LNPCPs continue to be resected with colorectal surgery. Within the United States alone, of 1,230,458 surgeries, 25% of resections were for non-malignant colorectal polyps.[13] An additional retrospective study of the English Bowel Cancer Screening Programme reported the use of surgery as a primary therapy for complex polyps ranged between 7-36%.[14] With the majority of colonoscopy conducted outside tertiary centres, this highlights potential inaccuracies in LNPCP optical evaluation and cancer diagnosis. Moreover, >12% of

LNPCPs referred to tertiary centres comprise previously attempted lesions which are ultimately amenable to endoscopic resection when appropriate techniques are employed.[15] EMR training and proceduralist competency therefore remains heterogenous amongst endoscopists with a clear discord in outcomes to that reported in tertiary centres.

The following additional areas related to optical evaluation and colorectal endoscopic resection training were identified for further research:

1) Simplification of LNPCP optical assessment for predicting the risk of invasive cancer and enhancing decision-making when selecting resection modality.

2) Decision making tools to assist lesion selection for endoscopic resection training

Based on the above, this thesis has the following aims:
1) Conduct a randomized trial comparing the efficacy and safety of cold snare EMR against conventional hot snare EMR for the resection of adenomatous LNPCPs.

2) Prospectively evaluate long-term surveillance outcomes in a cohort of LNPCPs that have undergone contemporary EMR with margin thermal ablation.

3) Investigate the prevalence of lesion specific risk factors for synchronous colonic neoplasia post-EMR.

4) Identify combinations of LNPCP characteristics ('LNPCP subtypes') associated with an increased prevalence of SMIC and display them in a simplified decision-making algorithm.

5) Develop a case selection score that identifies LNPCPs at risk of outcomes which would prove technically challenging for an "EMR-naïve" endoscopist developing competency.

To address the aims of the thesis, prospective multi-centre trials (national and international centres) were conducted with ethics approval gained from the Western Sydney Local Health District-Human Research and Ethics Committee (WSLHD-HREC) (Appendix 3).

The thesis has been divided into 3 sections: 1) Contemporary clinical practice for the endoscopic resection of colorectal neoplasia: a literature review. 2) Improvements in colorectal endoscopic resection technique and surveillance pathways 2) Optimisation of lesion selection for endoscopic resection training and tertiary referral. The corresponding studies are presented as individual chapters within this thesis.

Part 1: Improvements in colorectal endoscopic resection technique and surveillance pathways

Despite demonstrating superior safety and equivalent efficacy to surgical resection, electrocautery-related adverse events of delayed bleeding and perforation remain a limitation of conventional hot snare endoscopic mucosal resection (H-EMR) technique. Such events may result in hospitalization, repeat endoscopic intervention or emergent surgical resection. [11,16-25]

For smaller polyps however, compared to hot snare polypectomy, cold snare resection demonstrates superior safety and comparable efficacy.[26-28] Such findings extend to larger (≥20mm) serrated lesions with cold snare resection proven to be a safe and effective modality.[29-31] High-quality trials examining cold snare resection for adenomatous LNPCPs are lacking with available data limited to observational studies. Negligible rates of perforation and delayed bleeding have been demonstrated however this finding appears to be at the expense of endoscopic recurrence.[32-34] Whether cold snare resection can provide a safe and effective resection modality for adenomatous LNPCPs requires further evaluation in randomized studies.

AIM 1: Conduct a randomized trial comparing the efficacy and safety of cold snare EMR against conventional H-EMR for the resection of adenomatous LNPCPs.

Colonoscopy surveillance following endoscopic resection is burdensome for both patients and the broader health service. In accordance with consensus guidelines, surveillance colonoscopy at six and 18-months post-resection is conducted to identify and treat recurrent and residual adenoma at the resection scar. [8-9]

This conservative approach has been necessary due to recurrence identified at first colonoscopy surveillance (SC1) historically exceeding rates of 13%.[35] Furthermore, despite the presence of a bland scar at SC1, second colonoscopy surveillance (SC2), identified recurrence in 4% of cases.[10] Since the introduction of margin thermal ablation (MTA) to the post-EMR defect with snare tip soft coagulation (STSC), recurrence is significantly reduced in both randomized and real-world studies.[36-39] Long term

recurrence outcomes and the utility of conservative surveillance intervals are unknown in the era of MTA. If proven to be a durable technique, surveillance intervals post-EMR with MTA can be extended to reduce procedural burden for patients and health-services.

AIM 2: prospectively evaluate long-term surveillance outcomes in a cohort of LNPCPs that have undergone EMR with MTA.

When recommending surveillance intervals post endoscopic resection, detection of synchronous neoplasia is an integral component that demands consideration. Additional large lesions are detected in over 18% of EMR cases, many of which are not discovered during the index or subsequent resection procedures. [40-44] Such findings reinforce the importance of early surveillance post-endoscopic resection, regardless of the frequency of recurrence post MTA.

Individual lesion characteristics of size, granularity and morphology are well defined predictors of underlying histology and SMIC.[7] Whether these features represent a broader colonic neoplastic process and predict the presence of synchronous neoplasia is unknown. Defining LNPCP phenotypes predictive of synchronous disease would identify a patient cohort potentially requiring enhanced post-resection surveillance.

AIM 3: investigate the relationship between LNPCP characteristics and the presence of synchronous colonic lesions.

Part 2: Optimisation of lesion selection for endoscopic resection training and tertiary referral

Despite significant advances in endoscopic resection techniques, numerous patients continue to undergo unnecessary operations for benign, endoscopically resectable lesions. Large studies report colorectal surgery for non-malignant colorectal polyps in more than 25% of all procedures. [45] Whilst surgery provides definitive oncological resection for deeply invasive cancer, for most LNPCPs this is unnecessary with benign pathology readily identifiable following systematic optical assessment. LNPCP surface pit and vascular patterns are well described features of LNPCPs that accurately identify the presence of submucosally invasive cancer.[46] Moreover, individual LNPCP characteristics including location, morphology, granularity, and size, accurately stratify the risk of SMIC.[7] The interaction of these

characteristics, is inherently complex and application in a real-world context is challenging for endoscopists of all levels of experience and proficiency. Inability to identify benign disease in LNPCPs is a potential driver of inappropriate surgical referral. A simplified method of identifying LNPCP subtypes with different risks of SMIC would serve as a tool to facilitate targeted surface optical evaluation and selection of the most appropriate resection modality.

AIM 4: identify combinations of LNPCP characteristics ('LNPCP subtypes') associated with an increased prevalence of SMIC and display them in a simplified decision-making algorithm that stratifies the risk of potential cancer.

Failed endoscopic resection of benign colorectal neoplasia represents an additional cohort of patients potentially receiving unnecessary surgical management. In a meta-analysis of 6779 polyps, 28% of surgically resected lesions were for non-curative endoscopic resection.[35] Within tertiary centres, >12% of referred lesions are previously attempted yet ultimately curable with expert endoscopic resection.[15] Such findings highlight the heterogeneity of competency within endoscopic resection practice. Currently, demonstrating competency in conventional hot snare EMR is poorly defined. Absolute case numbers are the mainstay within the literature with no consideration given to the variability in procedural complexity and heterogeneity of LNPCPs.[47-48] Appreciating the variability of lesion complexity is crucial to appropriate case selection when developing EMR competency. Other existing scoring systems which grade polypectomy complexity are not EMR specific and fail to consider specific technical aspects of EMR, and bias towards grading all lesions as complex due to the weighting of size. [49-52] An EMR specific selection tool which reflects technical and lesion-specific nuances is lacking.

AIM 5: develop a case selection score that identifies LNPCPs at risk of outcomes which would prove technically challenging for an "EMR-naïve" endoscopist developing competency.

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Chapter 2

Contemporary clinical practice for the endoscopic resection of colorectal neoplasia: a literature review

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Summary:

- Comprehensive literature review of colorectal neoplasia endoscopic resection

Endoscopic Resection of neoplasia in the lower GI tract: a clinical algorithm

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ABSTRACT

Background: Colorectal cancer is a highly prevalent malignancy and a significant driver of cancer mortality and health-related expenditure worldwide. Polyp removal reduces the incidence and mortality of colorectal cancer. In 2024, endoscopists have an array of resection modalities at their disposal. Each technique requires a unique skillset and has individual advantages and limitations. Consequently, resection in the colorectum requires an evidence-based algorithm-approach that considers these factors.

Summary: A literature review of endoscopic resection for colonic neoplasia was conducted. Best supporting scientific evidence was summarised for the endoscopic resection of diminutive polyps, large ≥20mm lesions and polyps containing invasive cancer. Factors including resection modality, complications and lesion selection were explored to inform an algorithm-approach to colorectal resection.

Key Messages: Endoscopic resection in the colorectum is not a one size fits all approach. Detailed understanding of polyp size, location, morphology and predicted histology are critical factors that inform appropriate endoscopic resection practice.

INTRODUCTION

Colorectal cancer (CRC) is a highly prevalent malignancy and a significant driver of cancer mortality and health-related expenditure worldwide.[1-4] Within Europe, CRC is the second most common cancer and the third largest cause of cancer-related deaths.[4] Early detection of precursor neoplastic polyps is the foundation of CRC prevention. Colonic adenomas, the most common precancerous polyp, progress in a stepwise fashion to invasive cancer after the sequential accumulation of mutations.[5-9] More recently described, serrated polyps also harbour malignant potential, however, in contrast to adenomas, have a distinct carcinogenesis pathway and pathological phenotype.[10-13] Detection and removal of polyps reduces the incidence and mortality of colorectal cancer at rates exceeding 75% and 50% respectively.[14-16] Despite these measures, post-colonoscopy colorectal cancer (PCCRC) remains a worldwide problem. A pooled analysis of 9167 participants identified 52% of PCCRC as probable missed lesions and 19% as related to incomplete resection of an earlier, non-invasive lesion.[17] Such findings highlight the importance of accurate polyp detection and high-quality polyp resection technique.

Polyps <10mm

Non-pedunculated polyps <10mm in size are effectively and safely removed with cold snare resection. Historically, hot snare polypectomy was an effective resection modality at the expense of electrocautery related complications of post-procedural bleeding and perforation. Multiple randomized studies have now placed cold snare polypectomy as the standard of care due to significantly reduced complications while maintaining equivalent complete resection rates.[18-20] While the substitution of cold biopsy forceps appeared a cheaper alternative to cold snare polypectomy, both randomized studies and metanalyses report significantly greater incomplete resection with forceps, particularly with growing polyp size.[21-22] High quality cold snare technique is the most critical aspect of achieving complete polyp resection with IRR at <1.5% in randomized studies when this approach is adopted.[23]

Polyps 10-20mm

As polyp size increases, correct resection modality becomes critical to assure both complete resection and accurate histopathological diagnosis. A prospective study which biopsied defect margins following polypectomy found 10.1% of polyps were incompletely resected with rates significantly higher for large (10-20 mm) compared to small (5-9 mm)

lesions (17.3% vs 6.8%; relative risk = 2.1).[24] Furthermore submucosal invasive cancer (SMIC) becomes more prevalent in larger lesions with large (≥20mm) non-pedunculated polyps (LNPCPs) containing SMIC in 5-7% of cases.[25-27] Endoscopic removal of polyps ≥10mm consequently requires a nuanced approach that considers these factors in both the selection and implementation of resection techniques. Increasingly cold snare resection is being used for polyps of 10-20mm in size. In contrast, the management of LNPCPs is well described, having been the subject of innumerable high-quality studies.

Large (≥20mm) non-pedunculated colorectal polyps

Historically, LNPCPs were managed with surgical resection. This ensured definitive removal of the culprit lesion and facilitated complete histopathological examination and diagnosis of underlying cancer. Despite these theoretical advantages, in practice, a significant proportion of LNPCPs demonstrate benign histology. A study of 1,230,458 surgeries reported 25% of resections were for non-malignant colorectal polyps.[28] A retrospective study of the English Bowel Cancer Screening Programme observed the use of surgery as a primary therapy for complex polyps ranged from 7-36%.[29] Surgical resection of non-malignant LNPCPs confers no oncological benefit but incurs significant morbidity and mortality.[30-31] A prospective study of 12,732 elective surgeries for non-malignant colorectal polyps reported a major postoperative adverse event in 14% of cases. Within 30 days of resection, 7.8% of patients were readmitted and 3.6% required additional major surgery. Furthermore, in-hospital mortality was 0.8% [95% confidence interval: 0.7%–0.9%].[32] A similar study described morbidity rates of 25.3% [95% confidence interval: 24.2%-26.4%], with postoperative adverse events conferring an increase in hospital stay (10.3 vs 5.0 days; $P < 0.0001$) and hospitalization costs ($77,015.24 vs $40,258.30; $P < 0.0001$).[33]

Endoscopic removal of LNPCPs has superseded the surgical resection of benign colorectal neoplasia and become standard clinical practice within international consensus guidelines.[34-35] Endoscopic mucosal resection (EMR) is the mainstay of endoscopic colorectal resection, utilising electrocautery-based snare resection with submucosal fluid injection to perform a well described inject and resect technique.[36-38] For benign LNPCPs, EMR is curative in 98% of cases with surgical resection rarely required.[39] When compared to surgery, EMR is a cost-effective alternative that demonstrates a superior safety profile. Endoscopic management of LNPCPs when compared to surgical resection reduces inpatient

hospitalization length of stay by 2.81 nights per patient (95% confidence interval, 2.69-2.94; P <0.001) at a potential total cost saving of US $10,284,909 with a mean cost difference per patient of US $7602 (95% confidence interval, $8458-$9220; P <0.001).[40] A large modelling study found the predicted surgical mortality rate for a cohort of 1050 EMR patients was 3.3% which was significantly greater than the actual endoscopic mortality rate of zero recorded (p<0.0001).[41] A retrospective study reflected these findings in a real world setting with a lower adverse event rate for endoscopic resection versus primary surgical resection (10% vs 18%; P = 0.09) and reduced costs compared to surgery (USD $2152 vs USD $15,264; P < 0.001).[42] Despite these advantages, EMR has limitations that bear consideration.

Post procedural complications

While advantageous in facilitating efficient tissue transection and immediate haemostasis, electrocautery has adverse events which are a limitation of EMR technique. Clinically significant post-EMR bleeding (CSPEB) occurs in 6% of EMR procedures.[43] On multivariable analysis, proximal colon location (odds ratio, 3.72; P <0.001), use of electrosurgical current not controlled by a microprocessor (odds ratio, 2.03; P = 0.038), and intraprocedural bleeding (odds ratio, 2.16; P = 0.016) are significant predictors of CSPEB.[44] Additional studies identify lesion size as a risk factor with CSPEB increased by 13% for every 1 mm increase in polyp diameter (odds ratio (OR) 1.13, 95% confidence interval (CI) 1.05-1.20, P<0.001).[45] Hospitalization and observation are necessary for all cases of CSPEB, with 55% of cases conservatively managed and 44% requiring repeat colonoscopy to facilitate haemostasis.[43] While theoretically plausible, coagulation of non-bleeding visible vessels in the EMR defect is ineffective at reducing CSPEB. A randomized trial assessing the intervention found CSPEB occurred in 9 patients receiving prophylactic coagulation (5.2%) and 14 controls (8.0%; P = 0.30).[46] Prophylactic clip closure of post-EMR defects has proven to be the most effective preventative measure for CSPEB. A meta-analysis of four randomized trials found proximal colon prophylactic clipping prevented CSPEB with an odds ratio of 0.31 (95% confidence interval [CI], 0.17-0.54).[47-49] Consequently prophylactic clipping of right colon EMR defects is now standard practice and reduced CSPEB to rates <5%.

Delayed perforation, while a rare occurrence, is a feared complication which incurs significant morbidity. In a single centre study of 165 colonoscopic perforations, patients underwent primary repair or resection with primary anastomosis in 29% and 33% of cases

respectively. When presentation was delayed greater than 24 hours, feculent contamination was more likely (44% vs 11%; P = 0.02) and surgical ostomy more frequent (64% vs 33%; P = 0.02). Overall operative morbidity was 36%, with a mortality rate of 7%.[50] Fortunately, identification of significant muscle injury using the Sydney deep mural injury (DMI) classification has made perforation largely preventable when high risk injuries (DMI II-V) undergo complete clip closure.[51-52] A prospective study of 3717 LNPCPs identified significant DMI in 2.7% of cases with successful defect closure in 97%. Consequently only 3% of these cases underwent surgery related to DMI.[53]

Recurrence

Historically, the main limitation of EMR was endoscopic recurrence detected at surveillance colonoscopy. A 2015 prospective study of 1000 successful EMRs observed recurrent or residual adenoma (RRA) in 16.0% (95% CI 13.6% to 18.7%) of cases at first endoscopic surveillance. While this was successfully treated endoscopically in 93.1% (95% CI 88.1% to 96.4%) of cases, this required additional procedures. Ultimately 98.1% (95% CI 96.6% to 99.0%) of cases were adenoma-free and avoided surgery at 16 months following EMR.[39] While other studies reported similar findings, some centres observed recurrence rates > 30%.[54-55] A meta-analysis of 50 studies reported endoscopic recurrence in 735/5334 patients (13.8%, 95% CI 12.9% to 14.7%).[56]

Both procedural and lesion specific factors predict incomplete resection and recurrence including submucosal fibrosis, LNPCP location, size and histology. Of 127 unsuccessful EMR procedures, 43 LNPCPs required a two-stage resection procedure for residual polyp, with submucosal fibrosis more frequently observed in such cases ($P <$ 0.001).[57] Furthermore, a study of 158 previously attempted non-lifting fibrotic lesions, while endoscopically treatable in the majority of cases, still encountered technical failure in 4.4% of cases.[58] Lesion locations of the ileocaecal valve (ICV), appendiceal orifice (AO) and anorectal junction (ARJ) present specific challenges and incur increased rates of recurrence. In a prospective series of ICV resections, early adenoma recurrence was detected in 7/40 patients (17.5 %).[59] ARJ LNPCPs demonstrate similar findings, with detectable adenoma at SC1 in 15.4% of cases, exceeding that of other colonic locations.[60] AO LNPCPs, when compared to other colonic LNPCPs, demonstrate complete clearance of visible adenoma less frequently (92.6% PA-LSLs vs 97.6% LSLs, P = 0.14).[61] LNPCPs with a size ≥ 30 mm (OR=2.688, CI 1.036-6.993; OR=4.982, CI 1.894-13.101) and/or high-

grade dysplasia (HGD) (OR 1.72; p=0.029) are significantly more likely to encounter recurrence.[62] Moreover, intraprocedural factors of significant bleeding requiring endoscopic haemostasis, are more likely to result in residual adenoma (OR 1.78; p=0.024).[63]

Extending resection margins appeared to be the logical solution to minimising recurrence. However, a prospective study comparing a 5mm margin to standard resection margins found no significant difference in recurrence (39/333 patients (11.7%) for standard EMR vs 30/296 patients (10.1%) with extended resection (P = 0.15)).[64] Ultimately, the incorporation of adjuvant endoscopic techniques has proven to be the single-most effective measure for the prevention of recurrence in EMR. As early as 2002, adjuvant thermal therapies were investigated, with argon plasma coagulation (APC) initially proving to be an effective modality for reducing recurrence. An observational study demonstrated recurrence rates as low as 2.2% with adjuvant APC.[65] A further randomized trial found 1/10 recurrences with adjuvant APC compared to 7/11 with nil adjuvant therapy (p = 0.02).[66] Most significant in this trial was the lack of benefit ablation provided for visible residual tissue. The advantages of this technique were apparent when thermal therapy was applied to defect margins (margin thermal ablation; MTA) despite the absence of endoscopically visible adenomatous tissue.

The EMR landscape dramatically transformed in 2019 when a large cohort received adjuvant thermal therapy to defect margins using coagulation current delivered through the tip of a conventional hot snare. When STSC (snare tip soft coagulation (ERBE; soft coag effect 4 80 Watts)) was applied to defect margins, recurrence at first surveillance colonoscopy was significantly reduced compared to conventional EMR (10/192, 5.2% vs 37/176, 21.0%; P < 0.001).[67] Additional real-world studies confirmed the success of the technique. A prospective study of over 1000 LNPCPs found the frequency of RRA at SC1 was 1.4% (10/707).[68] A further study of 824 LNPCPs detected recurrence at first surveillance colonoscopy in 14 (3.6%) LNPCPs in the STSC group, compared with 96 (31.6%) in the conventional EMR group (P < 0.001; RR = 0.14; 95% CI, 0.07-0.29).[69] Overall a meta-analysis of six adjuvant STSC studies reported pooled odds of recurrence of 0.27 (0.18-0.42; p<0.001) with a crude recurrence rate of 6%.[70]

A three-arm trial comparing STSC and APC with no MTA found both techniques to be safe with a significant reduction in recurrence with MTA compared to no treatment (p=0.001 STSC, p=0.01 APC). While the study was underpowered to demonstrate a significant difference in recurrence between STSC and APC, crude rates were nearly double for APC (9.3 vs 4.6%).[71] A meta-analysis of 10 studies found irrespective of modality, MTA significantly reduced recurrence with a risk difference of 0.17.[72] In light of its equivalent safety, reduced cost and carbon footprint and superior effectiveness to APC, STSC is the preferred modality for MTA in EMR.

Submucosal Invasive Cancer

Despite the safety and effectiveness of endoscopic resection for benign colonic neoplasia, recognition and treatment of SMIC-containing lesions remains challenging.

Optical evaluation of LNPCP mucosal surface vascular and pit pattern facilitates the identification of underlying SMIC.[73-76] Within flat LNPCPs, this process is highly accurate, with a specificity of 96.3%. Precision diminishes however once LNPCPs exhibit nodular features with a sensitivity of 52.7%.[77] The presence of SMIC in LNPCPs with otherwise benign appearing surface features represents a unique challenge for endoscopists. These cases of 'covert' cancer are well characterised and accurately predicted based on LNPCP morphology and location. Rectosigmoid LNPCPs, and those exhibiting nodular or non-granular morphological features demonstrate significantly greater risk of covert SMIC. Moreover, it is the combination of these factors that assumes primacy, with certain LNPCP subtypes harbouring the greatest covert SMIC risk. In particular, nodular, non-granular lesions of the rectosigmoid have a covert SMIC risk exceeding 20%.[27] While well characterised, clinical application of this knowledge is complex and a hindrance to real-time decision making. A recent study incorporated LNPCP SMIC risk stratification into a decision-tree structure to simplify this process.[78]

In addition to accurate identification, appropriate endoscopic resection is crucial to facilitate oncological cure and avoid unnecessary colorectal surgery. For all cases of SMIC within colorectal polyps, the risk of lymph node metastasis is dependent on positive resection margins, depth of submucosal invasion >1000um, lymphovascular invasion, tumour budding, and poor differentiation.[79-81] In a recent meta-analysis, deep submucosal invasion alone was not a significant predictor for lymph node metastasis and, therefore, when solely present,

should be reconsidered as an indicator for surgery.[82] In select cases where these adverse features are not present, the risk of lymph node metastasis is exceptionally low, and patients are endoscopically cured of their disease, avoiding unnecessary colorectal surgery. Paramount to achieving these outcomes is en bloc resection to permit accurate histological assessment and ensure specimen orientation and margin status are appropriately assessed. While appropriate for benign neoplasia, piecemeal resection of SMIC requires surgical resection to facilitate accurate histological diagnosis and assessment of lymph node metastases.

Endoscopic submucosal dissection (ESD) is an established resection technique that facilitates en bloc resection of LNPCPs irrespective of size. Consequently, its ability to provide complete histopathological staging and potential cure of low risk SMIC, has seen it gain traction within endoscopic practice. Historically, the ability of the technique to provide en bloc resection exceeds rates of 90%.[83-86] Meta-analyses have reported per-lesion estimates for endoscopically complete resection of 96 % (95 %CI 91 % – 98 %) and R0 resection rate of 88% (95 %CI 82 % – 92 %).[83] Consequently, widespread use of ESD for the management of LNPCPs has been conducted within many endoscopy centres.

A universal ESD approach to colorectal neoplasia however is not warranted and an inappropriate use of scarce resources in Western centres. In contrast to snare based EMR technique, ESD is a time-consuming, costly and technically demanding procedure. Paucity of training centres and ESD experts in addition to steep learning curves, presents significant training barriers in western centres. In contrast to Asian centres, limited cases of gastric neoplasia provide small numbers of easier-to-remove lesions and training opportunities.[87] Colonic EMR is exceptionally safe with same day discharge appropriate in the majority of cases. Within ESD cohorts however, surgery is required in 1.1% of ESD-related adverse events.[88] Procedure related perforations occur in 4.8% of cases with prolonged hospital admission necessary to facilitate patient observation.[89]

For benign neoplasia, ESD offers no benefit over conventional EMR but rather should be reserved for en bloc resection of SMIC. In a recent randomized trial comparing colorectal ESD and EMR for LNPCPs, recurrence was below 5.5% in both arms and consequently a poor justification for colonic ESD as a treatment for benign pathology. This same trial reported 22 cases of SMIC, only six of which were potentially curable low-risk SMIC. Overall, the number needed to treat to prevent one surgery for cancer was approximately 60.

In fact, almost the same number of patients ultimately required surgery in both treatment arms when considering the increased complication rate of ESD. Moreover, 70% of SMIC cases within the study had endoscopic evidence of superficial SMIC, meaning en bloc resection targeting these higher risk lesions could be utilised.[90] A prospective study of 1814 LNPCPs resected with ESD, had similar findings, reporting only 134 cases of potentially curable T1a cancers. Overall, a universal ESD approach resulted in 1535 benign lesions receiving unnecessary en bloc resection techniques.[91]

When considering these factors, selective use of ESD has received significant attention. Targeting lesions with a high risk of SMIC not only minimises referrals but utilises the ability of ESD to achieve en bloc curative resection of low risk SMIC. Such an approach has cost benefits to the broader health service with a 2018 study finding selective ESD to be the least expensive strategy when compared to universal ESD and EMR approaches.[92] In contrast to the proximal colon, the rectum represents a distinct location with an increased risk of SMIC.[93] Given the implications of surgery for this location, selective resection algorithms targeting the rectum have been argued as the ideal treatment algorithm. This was investigated in an Australian study that performed ESD on rectal LNPCPs demonstrating Kudo pit pattern Vi consistent with superficial SMIC (submucosal invasion <1000 um) or those with morphological features consistent with covert SMIC risk (Paris 0-Is or 0-IIa+Is nongranular, Paris 0- IIa+Is granular with a dominant nodule ≥10 mm). 7/8 (87.5%) cancers that were potential candidates for curative oncologic resection appropriately received ESD with a cure rate of 100%.[94]

Given the safety and effectiveness of EMR for the treatment of benign LNPCPs, ESD cannot be considered a resection modality that provides additional benefit in these circumstances. Selective use of ESD for high risk LNPCPs in the rectum utilises the ability of the procedure to obtain endoscopic cure of early cancer and facilitate optimal patient outcomes and appropriate resource allocation.

Full thickness colonic resection with endoscopic devices (endoscopic full thickness resection device; EFTRD) has recently been investigated for the treatment of colonic neoplasia. A meta-analysis of 26 studies reported a technical success rate with EFTRD of 90.0% (95% CI: 87.0–92.3) and a pooled estimate of histologically complete resection of 77.8% (95% CI: 74.7–80.6). Adverse events occurred in 8.0% (95% CI: 5.8–10.4) of cases

with emergency surgery necessary in 1.0% (95% CI: 0.4–1.8).[95] The German EFTRD registry reported outcomes of 1,178 EFTRD procedures, 18.4% of which were for early carcinomas. Technical success was 88.2% and R0 resection achieved in 80.0%. Adverse events occurred in 12.1% of cases with 2% requiring surgical treatment. Residual/recurrent lesions were present in 13.5% of lesions at follow up.[96]

The concept of EFTR is conceptually appealing, however the current reality is not ideal. Incomplete resection and adverse events remain problematic for EFTRD in comparison to the more precise and controlled modality of ESD. Within the literature there is a lack of comparative studies between EFTRD and ESD for the treatment of colorectal neoplasia. While a technically intuitive device with a short learning curve, full thickness injury necessitates accurate defect closure to avoid delayed post-procedural adverse events. EFTRD of advanced cancerous lesions in otherwise poor surgical candidates is a promising application of this emerging technique. At present however, appropriate patient selection necessitates a case-by-case discussion in a multidisciplinary setting.

Areas for further investigation

Despite the advances in endoscopic resection, many benign LNPCPs continue to be referred for surgical resection. Whether this represents a deficiency in proceduralist competency or an inability to optically diagnose colonic neoplasia remains unclear. Currently, competency in EMR is poorly defined and EMR specific tools to assist lesion selection for training are lacking. [97-98]

Despite EMR proving more cost-effective than surgery, tight surveillance intervals post-resection impose a procedural burden on both patients and health services. This conservative approach was necessary given the significant risk of recurrence. Since the introduction of MTA to standard practice, recurrence is significantly reduced and argues for widened surveillance intervals. At present, long term EMR surveillance outcomes are unknown in the era of MTA and as such, intervals remain unchanged. Moreover, the frequency of synchronous neoplasia cannot be understated when considering wider surveillance intervals. In patients with LNPCPs, additional large lesions are detected in over 18% of cases.[99-103]

Given its relative safety and comparable efficacy for small polyps, cold snare resection of lesions >10mm in size is an attractive solution to the electrocautery-related complications of

hot EMR. Within non-dysplastic large, serrated lesions, cold snare resection has proven to be a safe and highly efficacious resection modality.[104-106] Adverse events are exceedingly rare and recurrence rates comparable to conventional hot snare EMR. Consequently, cold EMR is the standard of care for non-dysplastic serrated polyps.

High-quality studies examining cold snare resection for adenomatous LNPCPs are lacking with evidence limited to observational data. Available data demonstrates it is a safe procedure with negligible rates of perforation and delayed bleeding. Superior safety is however at the expense of endoscopic recurrence, with rates exceeding 10%.[107-109] Whether cold snare resection can surpass conventional hot EMR for adenomatous LNPCPs warrants further evaluation in randomized studies.

CONCLUSION

An evidence based endoscopic resection algorithm for the colorectum

In 2024, endoscopists have an array of modalities at their disposal for the resection of colorectal neoplasia. Each technique requires a unique skillset and has individual advantages and limitations (Fig 1). Consequently, resection in the colorectum is not a one size fits all approach, but is dependent on polyp size, location, morphology and predicted histology. An evidence-based algorithm-approach that considers these factors is therefore a necessity.

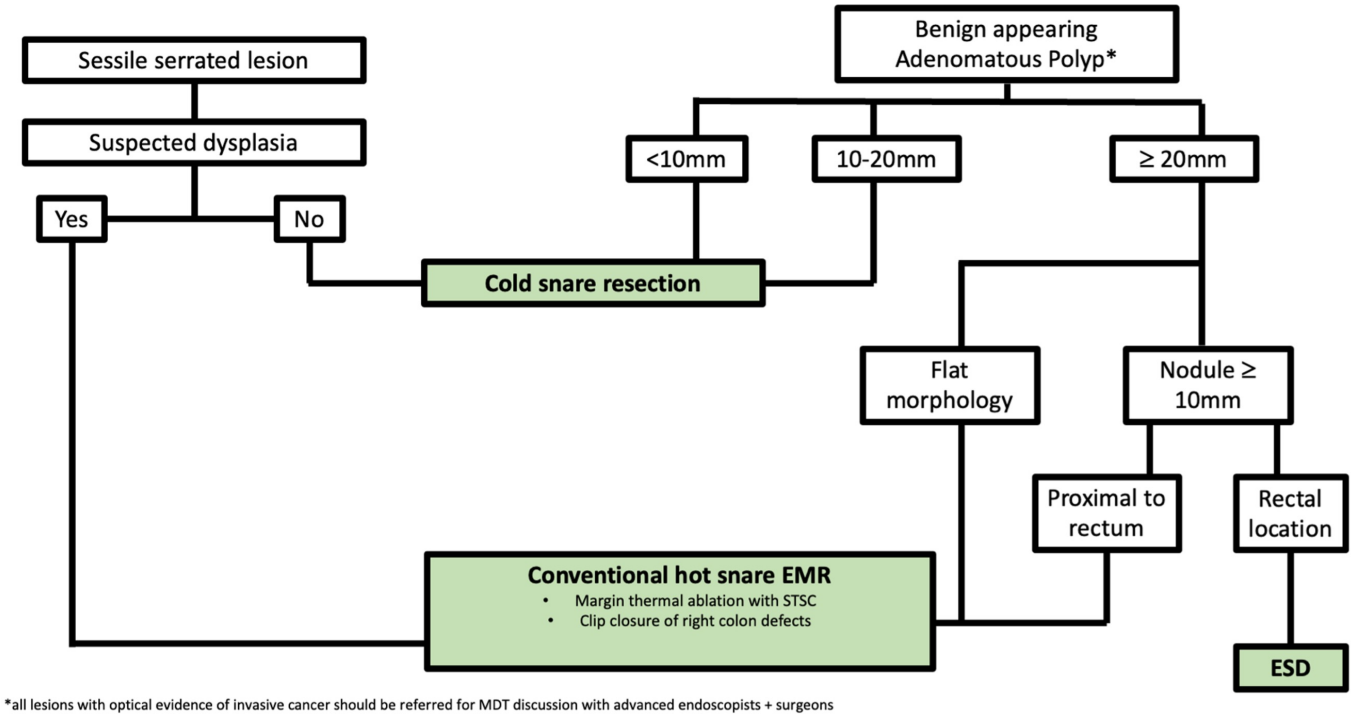
Non-dysplastic serrated lesions, irrespective of size, are safely and effectively resected with cold snare resection, with hot snare EMR reserved for cases of suspected dysplasia.

Benign non-pedunculated adenomas <10mm in size are universally resected with cold snare polypectomy, avoiding adverse events associated with electrocautery. Adenomas 10-20mm are subject to ongoing study, however, cold snare resection will likely be the favourable modality in such cases.

Prior to the resection of LNPCPs, endoscopists must consider an individual lesion's risk of SMIC. This starts with optical assessment of surface pit and vascular patterns. If Kudo Vn or NICE 3 features are evident, deeply invasive submucosal cancer is present and surgery is necessary to facilitate definitive resection. In the absence of adverse optical features, rectal LNPCPs with Kudo pit pattern Vi, or any dominant nodule ≥10 mm should receive en bloc resection in an ESD centre due to an increased risk of SMIC.

LNPCPs in the remainder of the colon, in the absence of optical features of invasive cancer, should be resected with conventional hot snare EMR with adjuvant margin STSC. Right colon lesions should undergo clip closure post resection to reduce CSPEB and all defects thoroughly inspected for evidence of DMI II-V.

Figure 1



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Part I

Improvements in colorectal endoscopic resection technique and surveillance pathways

Chapter 3

Publication:

O'Sullivan T, Cronin O, van Hattem WA, Mandarino FV, Gauci JL, Kerrison C, Whitfield A, Gupta S, Lee E, Williams SJ, Burgess N, Bourke MJ. **Cold versus hot snare endoscopic mucosal resection for large (≥15 mm) flat non-pedunculated colorectal polyps: a randomised controlled trial.** Gut. 2024 Oct 7;73(11):1823-1830. doi: 10.1136/gutjnl-2024-332807. PMID: 38964854.

Summary:

- Single centre randomized controlled trial comparing conventional hot snare EMR with piecemeal cold snare EMR for adenomatous polyps 15-50mm in size.
- 177 patients randomized (87 cold EMR arm and 90 hot EMR arm)
- Cold EMR significantly safer with reduced delayed bleeding 7/90 (7.8%) vs 1/87 (1.1%); RR 6.77, 95% CI 0.85-53.9; p = 0.034) and no cases of delayed perforation (1/90 (1.1%) vs 0; p=0.32).
- Cold EMR demonstrated significantly greater recurrence rates on intention to treat analysis (16/87, 18.4% vs 1/90, 1.1%; RR 16.6, 95%CI 2.24-122; p<0.001).

Contribution:

- One of the first published randomised studies assessing cold EMR of large adenomatous lesions
- These results provide the platform for further studies assessing predictors of recurrence and cost-effectiveness.

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

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Conflict of Interest

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

The remaining authors have no financial, professional, or personal conflicts of interest to disclose

Data transparency statement

All data relevant to the study are included in the article. Individual participant data will not be shared.

Contributorship statement

Tim O'Sullivan - acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis

Oliver Cronin - acquisition of data

Arnott van Hattem - Study concept and design, acquisition of data

Francesco Mandarino - acquisition of data, analysis and interpretation of data

Julia Gauci - acquisition of data

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Michael Bourke - acquisition of data, analysis and interpretation of data, drafting of the manuscript, study concept and design, study supervision/guarantor,

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

KEY MESSAGES

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.

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] 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 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 pre-procedure, 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 (Gelofusine; 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, Tubingen, 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.

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 >60 s, 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 $\chi 2$ 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 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 predominately 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%).

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 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 multicentre 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 post-procedure 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 multicentre studies. [12, 47] 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, 48–50] 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.

FIGURE LEGEND

Table 1: Baseline characteristics of study cohort *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.

Table 2: Primary and secondary outcome measures with Intention to treat analysis. EMR, endoscopic mucosal resection

Table 3: Lesion characteristics of cold snare endoscopic mucosal resection recurrences DMI, deep mural injury; IPB, intraprocedural bleeding

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; LNPCP, large non-pedunculated colorectal polyp; PP, per-protocol; SC1, first surveillance colonoscopy.

Table 1

	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%)
Nongranular	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%)

Table 2

	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

Table 3

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

Figure 1

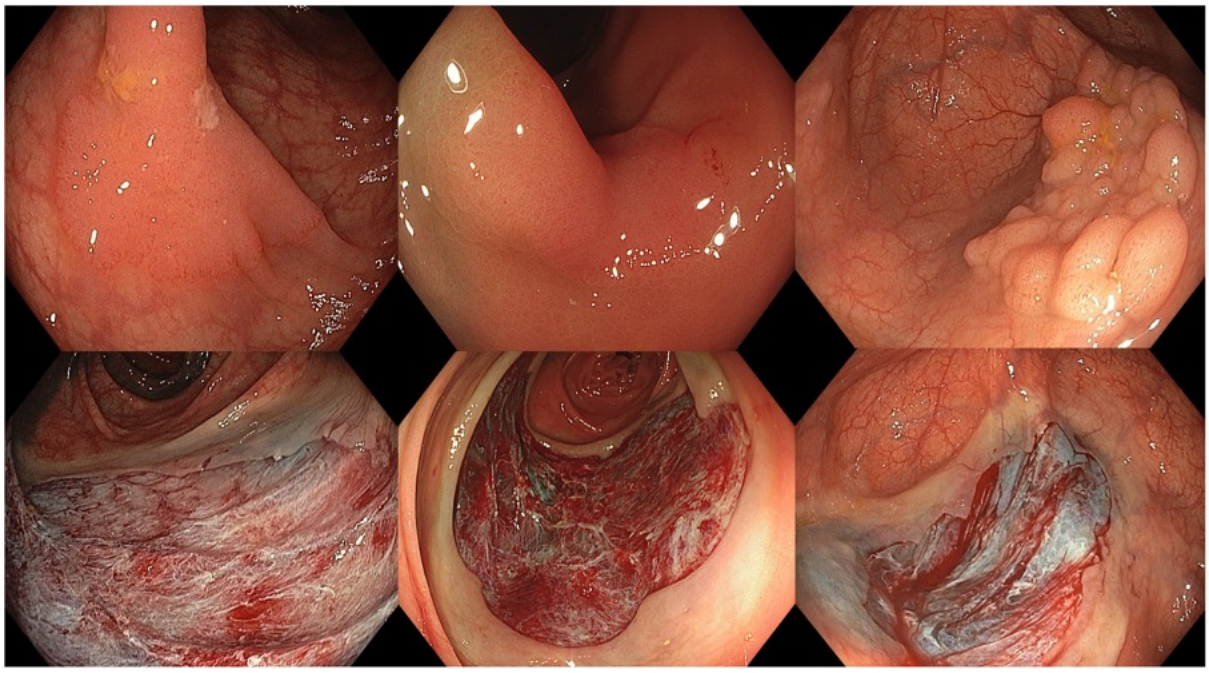
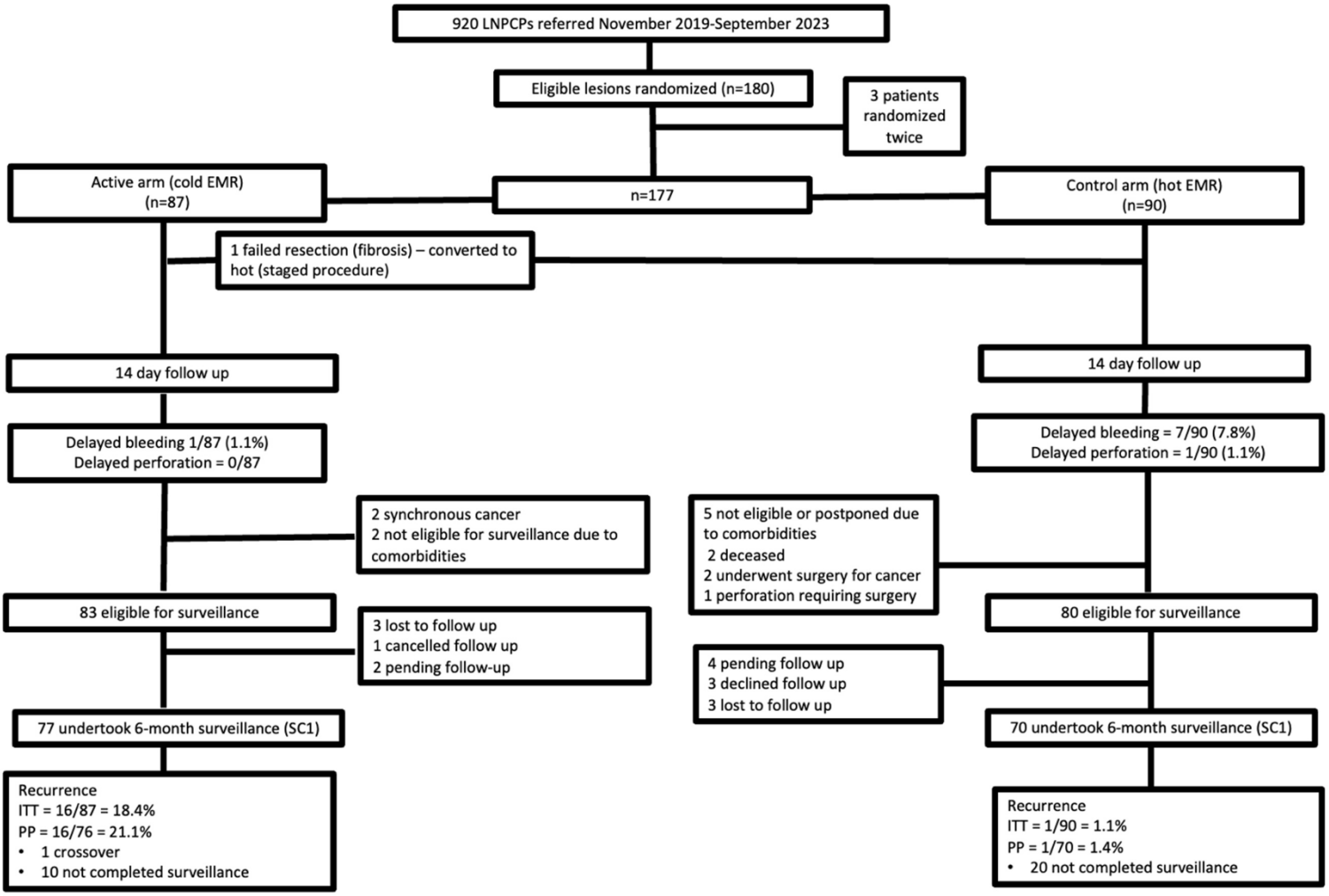


Figure 2



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Chapter 4

Publication:

O'Sullivan T, Mandarino FV, Gauci JL, Whitfield AM, Kerrison C, Elhindi J, Neto do Nascimento C, Gupta S, Cronin O, Sakiris A, Prieto Aparicio JF, Arndtz S, Brown G, Raftopoulos S, Tate D, Lee EY, Williams SJ, Burgess N, Bourke MJ. **Impact of margin thermal ablation after endoscopic mucosal resection of large (≥20 mm) non-pedunculated colonic polyps on long-term recurrence.** Gut. 2024 Sep 30:gutjnl-2024-332907. doi: 10.1136/gutjnl-2024-332907. Epub ahead of print. PMID: 39349006.

Summary:

- Prospective multicentre study of >1000 LNPCPs that have undergone contemporary EMR with margin thermal ablation (MTA).
- Of 472 patients with a bland scar at first colonoscopy surveillance, one recurrence was identified at second surveillance (SC2) in lesions that underwent EMR with MTA
- Recurrence was significantly less at SC2 compared to historical controls without MTA (1/472 (0.2%) vs 9/260 (3.5%); $p<0.001$).

Contribution:

- These findings argue for a paradigm shift in post-resection surveillance pathways for contemporary EMR with MTA.
- If recurrence or synchronous disease is not identified at first colonoscopy surveillance, repeat colonoscopy in 3-5 years may reduce procedural and financial burdens for patients and health services.

Impact of margin thermal ablation after endoscopic mucosal resection of large (≥20mm) non-pedunculated colonic polyps on long term recurrence

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Statistical analysis: TO, JE

Study supervision: MJB

Conflict of Interest

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

The remaining authors have no financial, professional, or personal conflicts of interest to disclose

Gregor Brown: Research Support: Olympus Medical

Data transparency statement

All data and analytic methods relevant to the study are included in the article. Individual participant data will not be shared or made available to other researchers

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ABSTRACT

Background and aims

The efficacy of colorectal endoscopic mucosal resection (EMR) is limited by recurrence and the necessity for conservative surveillance. Margin thermal ablation (MTA) after EMR has reduced the incidence of recurrence at the first surveillance colonoscopy at 6 months (SC1). Whether this effect is durable to second surveillance colonoscopy (SC2) is unknown. We evaluated long-term surveillance outcomes in a cohort of LNPCPs that have undergone MTA.

Methods

LNPCPs undergoing EMR and MTA from four academic endoscopy centres were prospectively recruited. EMR scars were evaluated at SC1 and in the absence of recurrence, SC2 colonoscopy was conducted in a further 12 months. A historical control arm was generated from LNPCPs that underwent EMR without MTA. The primary outcome was recurrence at SC2 in all LNPCPs with a recurrence-free scar at SC1.

Results

1152 LNPCPs underwent EMR with complete MTA over 90 months until October 2022. 854 LNPCPs underwent SC1 with 29/854 (3.4%) LNPCPs demonstrating recurrence. 472 LNPCPs free of recurrence at SC1 underwent SC2. 260 LNPCPs with complete SC2 follow-up formed the control arm from January 2012 to May 2016. Recurrence at SC2 was significantly less in the MTA arm versus controls (1/472 (0.2%) vs 9/260 (3.5%); $p<0.001$)).

Conclusion

LNPCPs that have undergone successful EMR with MTA and are free of recurrence at SC1 are unlikely to develop recurrence in subsequent surveillance out to 2 years. Provided the colon is cleared of synchronous neoplasia, the next surveillance can be potentially extended to 3–5 years. Such an approach would reduce costs and enhance patient compliance.

KEY MESSAGES

WHAT IS ALREADY KNOWN ON THIS TOPIC

Long-term surveillance outcomes for large non-pedunculated colonic polyps after endoscopic mucosal resection with adjuvant margin thermal ablation are unknown.

WHAT THIS STUDY ADDS

Large non-pedunculated colonic polyps that have undergone successful endoscopic resection with margin thermal ablation and are free of recurrence at the first surveillance colonoscopy are very unlikely to develop recurrence in subsequent surveillance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

Provided the colon is cleared of synchronous neoplasia, these findings argue for lengthening second endoscopic surveillance to 3–5 years postresection.

BACKGROUND

Endoscopic mucosal resection (EMR) is a safe and effective treatment for large (≥20 mm) non-pedunculated colonic polyps (LNPCPs).[1–5] Infrequent adverse events and high endoscopic cure rates position EMR as standard of care across expert guidelines.[6–9] Historically, its efficacy and cost-effectiveness were limited by endoscopic recurrence which necessitated conservative surveillance colonoscopy intervals at 6 (SC1) and 18 months **(**SC2) postresection.

Margin thermal ablation (MTA) to the post-EMR defect with snare tip soft coagulation (STSC), has dramatically reduced the incidence of recurrence at SC1. Recurrence is demonstrated in less than 5% of cases at SC1 in both clinical trials and real-world studies with a fourfold reduction compared with the conventional EMR technique.[10–12] Currently, the incidence of recurrence in the era of MTA is unknown beyond SC1. If this effect is durable, subsequent surveillance intervals in patients cleared of synchronous polyps could be potentially lengthened. This study prospectively evaluated long-term surveillance outcomes in a cohort of LNPCPs that have undergone MTA.

MATERIALS AND METHODS

Study design

Data at four academic endoscopy centres were prospectively collected for consecutive adenomatous LNPCPs that underwent EMR with complete adjuvant MTA. Data were entered into the Australian Colonic Endoscopic (ACE) Resection Database, a prospective observational study of all patients referred for endoscopic resection of LNPCPs. Analysed patients included those in the active (MTA) arm from the principal site of the formative randomised trial conducted from July 2013 to May 2016 as well as all patients from June 2016 to November 2022 once MTA became standard practice. To facilitate comparative analysis, a historical control arm of adenomatous LNPCPs that underwent EMR without MTA was created using identical surveillance eligibility criteria within the ACE database. Cases were selected from procedures performed after January 2012 until MTA became standard practice in May 2016. This included cases in the control arm from the principal site of the randomised trial. A 4-year period from 2012 was chosen as it represented a state of standardised EMR practice by which time carbon dioxide insufflation, succinylated gelatin submucosal injection and 190 series colonoscopes were increasingly used. The scientific protocol, data collection sheets and patient consent form were reviewed and approved by the

Human Research Ethics Committee and registration was obtained (NCT01368289; NCT02000141). All authors had access to the study data and reviewed and approved the final manuscript. Polyposis syndromes were excluded from analysis due to their altered surveillance intervals.

EMR procedure

All LNPCPs were identified at a previous colonoscopy by a nationally accredited consultant endoscopist (surgeon or gastroenterologist). EMR was performed by either a study investigator (accredited gastroenterologist with advanced training at a tertiary referral practice in colorectal endoscopic resection) or a senior interventional endoscopy fellow under their supervision. 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 180/190 series variable-stiffness colonoscopes (HQ180/190 PCF/CF; Olympus, Tokyo, Japan) were used for 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). 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. A standardised, previously described, inject and resect EMR technique was used.[13–16] 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 STSC (ERBE VIO 300D, SOFT COAG: 80W, Effect 4; ERBE, Tubingen, Germany) (figure 1). The resected tissue was retrieved by suctioning into a polyp trap or collection with a Roth Net. Resection specimens were evaluated by specialist gastrointestinal pathologists.

Clinical follow-up and endoscopic surveillance

At 14 days, all patients were contacted by a study coordinator and underwent a structured telephone interview to identify periprocedural adverse events.

All patients who underwent successful endoscopic resection without SMIC underwent SC1 6 months following index resection. Scars were optically evaluated under high-definition white-light and NBI with meticulous photo documentation and biopsies taken from bland

scars to confirm the absence of recurrence at endoscopist discretion (figure 2). Recurrence when identified was treated with either hot snare excision or cold biopsy forcep avulsion with adjuvant STSC (CAST).[17] Repeat colonoscopy with scar interrogation was then conducted 6 months later.

In the absence of recurrence or resection of additional LNPCPs, second surveillance (SC2) colonoscopy was conducted 12 months following SC1 for repeat interrogation of the EMR scar.

During the study period, a proportion of patients had SC1 deferred as part of an ongoing investigative study. Following the publication of the Sydney Endoscopic Recurrence Tool (SERT) in 2016, in the presence of a low score,[18] patients were deemed low risk of recurrence and SC1 deferred until 18 months postresection. These cases were excluded due to deviations from standard surveillance protocols.

In cases of missing surveillance, attempts were made to identify the underlying reason (refusal, failure to attend or inappropriate recommendations for future surveillance intervals).

Study data

Dates of both index and surveillance procedures were collected. Characteristics were obtained from the index LNPCP including Paris classification, surface granularity (granular vs non-granular), size, location and histopathological diagnosis. At SC1, endoscopically visible and histologically confirmed recurrence in the EMR scar was recorded and synchronous LNPCPs resected. At SC2, EMR scars were once again interrogated and endoscopically visible and histologically confirmed recurrence recorded.

Outcome measures

The primary aim of the study was to compare SC2 recurrence rates between LNPCPs that undergo EMR with or without MTA when a bland EMR scar is present at SC1. Secondary outcome measures included compliance with SC2, mean surveillance interval of SC2 and recurrence at SC1.

Statistical analysis

Jamovi V.2.3.19 statistics software analysed the data. All tests were conducted at a significance level of 0.05 with a two-sided alternative hypothesis. Continuous variables were summarised using median (IQR) or mean (SD). Categorical variables were summarised using

frequencies and percentages. 95% CIs were calculated when relevant. Univariate analysis was conducted to identify differences in prognostic variables between treatment and control arms. Analysis was performed with $\chi 2$ tests for categorical variables and Mann-Whitney U tests for continuous variables. Due to the rare event rate, multivariable analysis was not feasible.

Missing outcome data were evaluated with complete case analysis and accompanying worst-best and best-worst case analyses. Due to the missing data occurring in the dependent variable, multiple imputation was not used as this would inappropriately increase SE.[19]

RESULTS

A total of 1256 adenomatous LNPCPs underwent EMR with MTA between June 2016 and October 2022. 110 cases were included from the active (MTA) arm of the previous randomised trial (table 1). 87 synchronous lesions along with 13 cases of known polyposis syndromes were excluded. Four cases had to be abandoned with 1152 LNPCPs remaining (figure 3).

A historical control cohort was generated from 650 adenomatous LNPCPs that underwent EMR without MTA between January 2012 and May 2016. 113 cases were included from the control arm of the previous randomised trial (table 1). 59 synchronous LNPCPs were excluded with 591 LNPCPs remaining (figure 4).

SC1 outcomes

MTA arm

In the context of an additional research study, 41/1152 LNPCPs with a low SERT score had SC1 delayed to 18 months and were consequently excluded.[18] 20/1152 LNPCPs had two-stage procedures and were ineligible for conventional surveillance.[20]. 38/1152 LNPCPs did not undertake SC1 due to comorbidities and 16/1152 were not due SC1 at the time of data collection. 62/1152 patients had evidence of SMIC with adverse features and underwent surgery prior to SC1 if medically fit. 5/1152 underwent surgery for technical limitations or complications. Of the 958 SC1 eligible patients, 33/958 patients were identified as failing to attend or refusing further surveillance. 71/958 were lost to follow-up.

854 LNPCPs undertook SC1. 29/854 (3.4%) (95% CI 2.3% to 4.8%) demonstrated recurrence. These LNPCPs were larger (40 mm (IQR 30–60 mm)) and more frequently

located in challenging locations with 11/29 (37.9%) at the appendiceal orifice or ileocaecal valve. A further 2/29 (6.9%) were LNPCPs involving a surgical anastomosis. Following exclusion of these locations at higher risk of recurrence, 16 cases of recurrence remained (16/782) with a crude rate of 2% (95% CI 1.2% to 3.3%).

Control arm

7/591 LNPCPs had two-stage procedures and were ineligible for conventional surveillance. 9/591 LNPCPs did not undertake SC1 due to comorbidities and five patients died prior to surveillance procedures. 49 patients had evidence of SMIC with adverse features and underwent surgery if medically fit. Five patients required surgery for failed resection or complications. Of the 516 SC1 eligible patients, 10 were identified as failing to attend or refusing further surveillance. 33/516 were lost to follow-up.

473 LNPCPs undertook SC1. 93/473 (19.7%) (95% CI 16.2% to 23.5%) demonstrated recurrence. The index LNPCP in these cases was larger 40 mm (IQR 35–55 mm)) and more frequently located in the ascending colon (20.4%) with a predominant granular (65.6%), nodular (Paris 0–Is/IIa+Is) morphology (54.8%).

SC2 outcomes

MTA arm

Of the 825 LNPCPs with a bland scar at SC1, 48/825 were ineligible for SC2 due to comorbidities. 107/825 were not due SC2 at the time of data collection and six patients were deceased. Four patients underwent surgery for an SC1 diagnosis of metachronous cancer.

Of SC2 eligible cases, 34 were identified as failing to attend follow-up or refusal of endoscopic surveillance. 36 missing cases had an inappropriate surveillance recommendation exceeding 18 months after index resection. 118 additional cases were lost to follow-up with no information available to explain the drop-out.

472 SC2 procedures were conducted at a mean interval of 23.2 months (95% CI 22.1 to 24.3) from index resection. Characteristics of the index LNPCP are demonstrated in table 2. 185/472 (39.2%) LNPCPs were resected from the caecum/ ascending colon with a predominately flat (Paris 0–IIa/IIc) 254/472 (53.8%), granular 342/472 (72.5%) morphology.

One isolated case (0.2%, 95% CI 0% to 1.2%) of recurrence occurred at SC2. The index LNPCP was a 20 mm Paris 0–IIa+Is granular tubulovillous adenoma (TVA) located on the ileocaecal valve (ICV).

Control arm

Of the 380 LNPCPs with a bland scar at SC1, 31/380 were ineligible for SC2 due to comorbidities. Four patients were deceased, and one patient underwent surgery for an SC1 diagnosis of metachronous cancer.

84/344 SC2 eligible cases had missing SC2 outcomes. Eight patients refused or did not attend surveillance procedures and seven received the wrong SC2 recommendation. 260 SC2 procedures were conducted at a mean interval of 24.4 months (95% CI 22.5 to 26.2) from index resection. Baseline lesion characteristics were well matched to the MTA arm (table 2). High-grade dysplasia (HGD) and granular morphology were significantly greater in the MTA cohort (25.1% vs 15.4%; p=0.003 and 72.5% vs 56.2%; p<0.001).

Nine cases of recurrence (3.5%, 95% CI 1.6% to 6.5%) were identified at SC2 with a median size of 40 mm (IQR 35–60mm) and more frequently located in the caecum (22.2%) with a predominant granular (66.7%), flat (Paris 0–IIa/IIc) morphology (66.7%).

Primary outcome

Compared with the historical control arm without MTA, there was a significant difference in recurrence at SC2 for LNPCPs that underwent MTA (1/472 (0.2%) vs 9/260 (3.5%); p<0.001, relative risk reduction 94% (table 3).

Analysis of missing data

Baseline LNPCP characteristics of missing SC2 cases (n=188) in the MTA arm were compared with the complete SC2 cohort (n=472). There was no significant difference in morphology and granularity. Moreover, recognised predictors of recurrence (HGD, size ≥40 mm and location) [18] were not significantly over-represented in missing cases (table 4).

Best-worst and worst-best-case analyses were conducted on missing SC2 data. For the worst-best analysis, missing SC2 cases in the margin ablation arm (n=188) were allocated the recurrence rate of the control arm (3.5%) yielding 6 additional recurrences (7/660; 1.1%). Missing SC2 cases in the control arm (n=84) were allocated no additional recurrence cases (9/344, 2.6%). For the best-worse analysis, missing SC2 cases in the margin ablation arm

(n=188) were allocated no additional recurrences (1/660, 0.2%). Missing SC2 cases in the control arm (n=84) were allocated a worst-case recurrence rate of 4% as demonstrated in our previous study.[8] Three additional recurrences were added (12/344, 3.5%).

Despite using conservative estimations for the analysis, the best-worse analysis maintained significantly reduced recurrence rates in the MTA arm (0.2% vs 3.5%; p<0.001). Worst-best analysis also maintained an increased rate of recurrence in the control arm and almost reached statistical significance (1.1% vs 2.6%; p=0.062).

DISCUSSION

Post-EMR surveillance for LNPCPs is conservative, with multiple colonoscopies required in the 3 years following index resection. This procedural burden has been necessary due to historically high recurrence rates and the concomitant risk of synchronous neoplasia. Since the introduction of MTA, recurrence has dramatically declined, however, it remains unknown whether these outcomes are durable. This study has demonstrated that when resection sites are clear at SC1, recurrence is very unlikely to develop at subsequent surveillance out to 2 years.

Recurrence has been a historical limitation of EMR, with cases identified up to 18 months after index resection. In a multicentre prospective series of 1000 LNPCPs, residual or recurrent adenoma (RRA) was detected at SC1 in 16% of cases.[8] A meta-analysis of 50 studies reported similar findings, with endoscopic recurrence in 735/5334 cases (13.8%, 95% CI 12.9% to 14.7%).[1] Surveillance 6 months postresection has consequently been necessary to facilitate early detection and management of recurrence. In a single-centre prospective study, RRA at SC1 was <5 mm in size in 48% of cases and unifocal in 78.7%. Early detection makes endoscopic therapy highly effective with hot snare resection or CAST, affecting long-term adenoma remission in>90% cases.[21] Ultimately benign LNPCPs are endoscopically cured in 98.1% of cases.[8]

Attempts to lengthen surveillance intervals remain theoretical, with no firm recommendations permeating into clinical practice guidelines. Selective surveillance pathways have been postulated, targeting specific lesions at lower risk of recurrence. Features such as lesion size ≥40 mm (OR 2.47; p<0.001), intraprocedural bleeding (OR 1.78; p=0.024) and HGD (OR 1.72; p=0.029) have been identified as predictors of recurrence at SC1 and subsequently incorporated into clinical prediction scores. Utilisation of such scores into selective surveillance pathways, however, has not become standard clinical practice.[18] Furthermore,

while most cases of recurrence are detected at SC1, 4% is identified at SC2 following a clear scar at first surveillance. This concept of 'delayed recurrence' has been a compelling argument for scheduled conservative surveillance after EMR, irrespective of findings at SC1.[8]

Since the incorporation of adjuvant thermal ablation to post-EMR defect margins, recurrence rates have dramatically declined and the EMR landscape transformed. First described in a randomised trial in 2018, STSC to defect margins saw a fourfold reduction in recurrence at SC1 with a rate of 5.1%.[10] A more recent multicentre randomised trial saw a similar reduction with an adjusted RR of 0.37 (95% CI 0.17 to 0.83; p=0.015).[22] Both studies demonstrated the technique to be safe, which is scientifically supported in porcine models.[23] Comparable recurrence rates have been demonstrated in two large real-world studies of over 500 patients with crude rates <4% and no significant adverse events.[11-12] At present, however, no studies have evaluated longer-term outcomes and in particular whether 'delayed recurrence' remains a significant issue in the era of MTA.

This study has demonstrated that in the presence of a recurrence-free EMR scar at SC1, recurrence at SC2 is exceedingly rare in the era of MTA. Of the 472 patients who underwent SC2, only 1 case of recurrence was identified. This was a 20 mm Paris 0–IIa+Is granular TVA located on the ileocaecal valve. The ICV is a technically challenging location and has previously demonstrated higher rates of recurrence and consequently is excluded from many studies examining recurrence.[24] Moreover, the villous architecture of ileal mucosa makes optical examination of scars at the ICV challenging. Subtle diminutive unifocal recurrence at SC1 could consequently be overlooked and not evident until SC2.

Compared with the historical control group of EMR without MTA, recurrence is significantly less frequent at SC2 when MTA is performed (1/472 (0.2%) vs 9/260 (3.5%); p<0.001). Both arms were matched for predictors of recurrence including LNPCP size and location (table 2), whereas HGD and granular morphology were significantly greater in the MTA cohort (25.1% vs 15.4%; p=0.003 and 72.5% vs 56.2%; p<0.001).[18, 24, 25] Granularity, however, is not a described predictor of recurrence and is unlikely to confound recurrence outcomes. Conversely, while HGD is a documented predictor of recurrence, its over-representation in the MTA cohort did not translate into significantly greater recurrence rates. Based on these findings, no lesion-specific predictors of recurrence are demonstrated to be confounders within this study.

While the strength of this study was its multicentre design and large case numbers, several limitations bear consideration. Despite applying the same surveillance eligibility criteria, we recognise the control arm is smaller than the MTA SC2 cohort. Significantly greater SC1 recurrence rates partly explain this difference due to the reduced number of bland EMR scars eligible for analysis at SC2. Furthermore, referrals have steadily grown across all research sites and increased case volume over time. Specifically, one research site joined the ACE database later and consequently contributed fewer cases. While the control group could have been selected from a wider time interval, this would encroach on a period where EMR technique was evolving and negatively impact the standardisation of EMR procedures within the cohort.

The second limitation is patient non-adherence and missing SC2 outcome data. Ultimately, this demonstrates the real-world nature of this study and a limitation of current surveillance protocols and the procedural burden it imposes on patients. Furthermore, we identified 36 cases where external referrers inappropriately recommended SC2 at 3–5 years post-SC1. Overall, the median time to SC2 for the entire cohort was 19 months (IQR 17–25) with 25% of cases exceeding 25 months. It is clear despite current recommendations; surveillance protocols are still poorly understood by general endoscopists. Simplification of this process will ultimately assist in reducing heterogeneity in clinical practice.

Loss to SC2 follow-up is a random event with missing cases extremely unlikely to harbour a greater risk of recurrence. Recurrent residual adenoma is an endoscopic finding with no clinical symptoms alerting patients or clinicians to its presence. It is, therefore, implausible to consider recurrence itself as the reason for failing to attend follow-up. Furthermore, table 4 demonstrates that lesion characteristics of missing SC2 cases do not differ from the cohort with completed follow-up. Critically, variables predictive of recurrence including size, location and HGD, are not over-represented in missing cases.

The results of this study argue for a paradigm shift in the surveillance of post-EMR patients in the era of MTA. EMR with MTA, unlike conventional EMR, provides durable endoscopic remission in long-term follow-up. Delayed recurrence is rare and SC2 at 18 months does not appear to be necessary. In the event that recurrence or significant synchronous disease is not identified at SC1, repeat colonoscopy in 3–5 years will potentially reduce procedural and financial burdens placed on both patients and the broader health service. Such conclusions can only be considered when a high-quality colonoscopy examination is conducted to detect

synchronous neoplasia at SC1. Multiple studies have demonstrated that this is a significant issue for LNPCPs, particularly for non-granular morphology.[26] Synchronous large lesions are detected in 18.1% of cases with the cumulative development of advanced adenomas or polyps ≥20 mm significantly higher at 36 months post index colonoscopy.[27-28] Such findings highlight the importance of SC1 as a meticulous examination of the entire colon and not just the EMR scar.

These results are specific to the subset of adenomatous LNPCPs that undergo EMR with complete MTA. Refined surveillance intervals remain necessary for patients with demonstrable recurrence at SC1, this area is also in a state of flux. Our findings are only applicable to adenomatous LNPCPs. Serrated polyps are a separate entity that are well managed by wide field cold snare EMR with negligible procedural risk and low recurrence rates.[29]

We also recognise that these results originate from expert centres that perform high-quality EMR. Consequently, our SC1 recurrence rates may not be reproducible in other centres. Irrespective of SC1 recurrence, however, this study has demonstrated that provided a high-quality examination of the EMR scar at SC1 confirms the absence of recurrence then recurrence at SC2 is extremely rare. While bland scars were not biopsied in all cases, 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 (ESGE) guideline recommends against routine scar biopsy.[30–33]

In conclusion, LNPCPs that have undergone successful EMR with MTA and are free of recurrence at SC1 are very unlikely to develop recurrence in subsequent surveillance out to 2 years. Provided the colon is cleared of synchronous neoplasia, these findings argue for lengthening SC2 to 3–5 years postresection. Such an approach will reduce costs and enhance patient compliance.

FIGURE LEGEND

Table 1: Surveillance outcomes for MTA cases enrolled in RCT (a) and standard of care (b) MTA, margin thermal ablation; RCT, randomised controlled trial; SC1, first surveillance colonoscopy; SC2, second SC.

Table 2: Baseline LNPCP characteristics of SC2 cohort and controls. *Six missing histopathology cases. †<1000 μm submucosal invasion, clear margins, no lymphovascular invasion, low tumour budding, well differentiated. AO, appendiceal oriface; HGD, high-grade dysplasia; ICV, ileocaecal valve; LNPCP, large non-pedunculated

colonic polyp; SC2, second surveillance colonoscopy; SMIC, submucosal invasive cancer; TSA, traditional serrated adenoma; TVA, tubulovillous adenoma.

Table 3: Recurrence rate at SC2 for EMR with MTA following a clear SC1. EMR, endoscopic mucosal resection; MTA, margin thermal ablation; SC2, second

surveillance colonoscopy.

Table 4: Baseline LNPCP characteristics of missing cases compared with SC2 cohort following MTA. *14 missing histopathology. AO, appendiceal oriface; ICV, ileocaecal valve; LNPCP, large non-pedunculated colonic polyp; MTA, margin thermal ablation; SC2, second surveillance colonoscopy.

Figure 1: Endoscopic mucosal resection with adjuvant margin thermal ablation. Row 1 LNPCP prior to EMR; row 2 EMR defect with complete MTA. EMR, endoscopic mucosal resection; LNPCP, large non-pedunculated colonic polyp; MTA, margin thermal ablation.

Figure 2: Bland EMR scars at SC1 are unlikely to develop recurrence at subsequent surveillance. EMR, endoscopic mucosal resection; SC1, first surveillance colonoscopy.

Figure 3: Patient flow from LNPCP resection to SC2 (MTA arm). EMR, endoscopic mucosal resection; LNPCP, large non-pedunculated colonic polyp; MTA, margin thermal ablation; SC1, first surveillance colonoscopy; SC2, second SC; SERT, Sydney Endoscopic Recurrence Tool; SMIC, submucosal invasive cancer.

Figure 4: Patient flow from LNPCP resection to SC2 (Control arm). EMR, endoscopic mucosal resection; MTA, margin thermal ablation; SC1, first surveillance colonoscopy; SC2, second SC; SMIC, submucosal invasive cancer.

Table 1

(a) Randomized trial cases	Control arm (n=113)	Active arm (n=110)
Underwent SC1	94	102
Recurrence at SC1	22/94	2/102
Underwent SC2	52	83
Recurrence at SC2	1/52	0/83

(b) Standard care cases	Control arm (n=537)	Active arm (n=1146)
Underwent SC1	379	754
Recurrence at SC1	71/379	27/754
Underwent SC2	208	389
Recurrence at SC2	8/208	1/389

Table 2

LNPCP Characteristic	SC2 cohort N = 472	Control arm N = 260	P value
Size (median, IQR)	35mm (30-45)	35mm (30-50)	0.99
Location			
Rectum	89 (18.9%)	45 (17.3%)	0.75
Sigmoid	40 (8.5%)	28 (10.8%)	
Descending	30 (6.4%)	9 (3.5%)	
Transverse	93 (19.7%)	53 (20.4%)	
Ascending	112 (23.7%)	63 (24.2%)	
Caecum	73 (15.5%)	44 (16.9%)	
ICV	32 (6.8%)	16 (6.2%)	
AO	3 (0.6%)	2 (0.8%)	
Paris Classification			0.11
Nodular (0-Is)	218 (46.2%)	104 (40%)	
Flat (0-IIa/IIb or 0-IIc)	254 (53.8%)	156 (60%)	
Morphology			<0.001
Granular	342 (72.5%)	146 (56.2%)	
Non-granular	109 (23.1%)	97 (37.3%)	
Mixed	17 (3.6%)	12 (4.6%)	
Unspecified	4 (0.8%)	5 (1.9%)	
Histopathology*			0.67
Tubular adenoma	136 (29.2%)	87 (33.5%)	
TVA	322 (69.1%)	168 (64.6%)	
Villous	3 (0.6%)	2 (0.8%)	
TVA + TSA	5 (1.1%)	3 (1.2%)	

HGD	117 (25.1%)	40 (15.4%)	0.003
Low-risk SMIC±	4 (0.8%)	2 (0.8%)	0.91

* six missing histopathology cases

± <1000μm submucosal invasion, clear margins, no lymphovascular invasion, low tumour budding, well differentiated

Table 3

	MTA cohort	Control arm	P value	Relative risk reduction
SC2 Recurrences	1/472 (0.2%)	9/260 (3.5%)	<0.001	94%

Table 4

LNPCP Characteristic	SC2 cohort N = 472	Missing cases N = 188	P value
Size (≥40mm)	215 (45.6%)	86 (45.7%)	0.96
Location			
Rectum	89 (18.9%)	45 (23.9%)	0.29
Sigmoid	40 (8.5%)	14 (7.4%)	
Descending	30 (6.4%)	8 (4.3%)	
Transverse	93 (19.7%)	33 (17.6%)	
Ascending	112 (23.7%)	35 (18.6%)	
Caecum	73 (15.5%)	35 (18.6%)	
ICV	32 (6.8%)	14 (7.4%)	
AO	3 (0.6%)	4 (2.1%)	
Paris Classification			0.45
0-Is component	218 (46.2%)	93 (49.5%)	
0-IIa or IIb	254 (53.8%)	95 (50.5%)	
Morphology			0.09
Granular	342 (72.5%)	152 (80.9%)	
Non-granular	109 (23.1%)	30 (16%)	
Mixed	17 (3.6%)	5 (2.7%)	
Unspecified	4 (0.8%)	0 (0)	
High grade dysplasia*	117 (25.1%)	44 (24.7%)	0.93

*14 missing histopathology

Figure 1

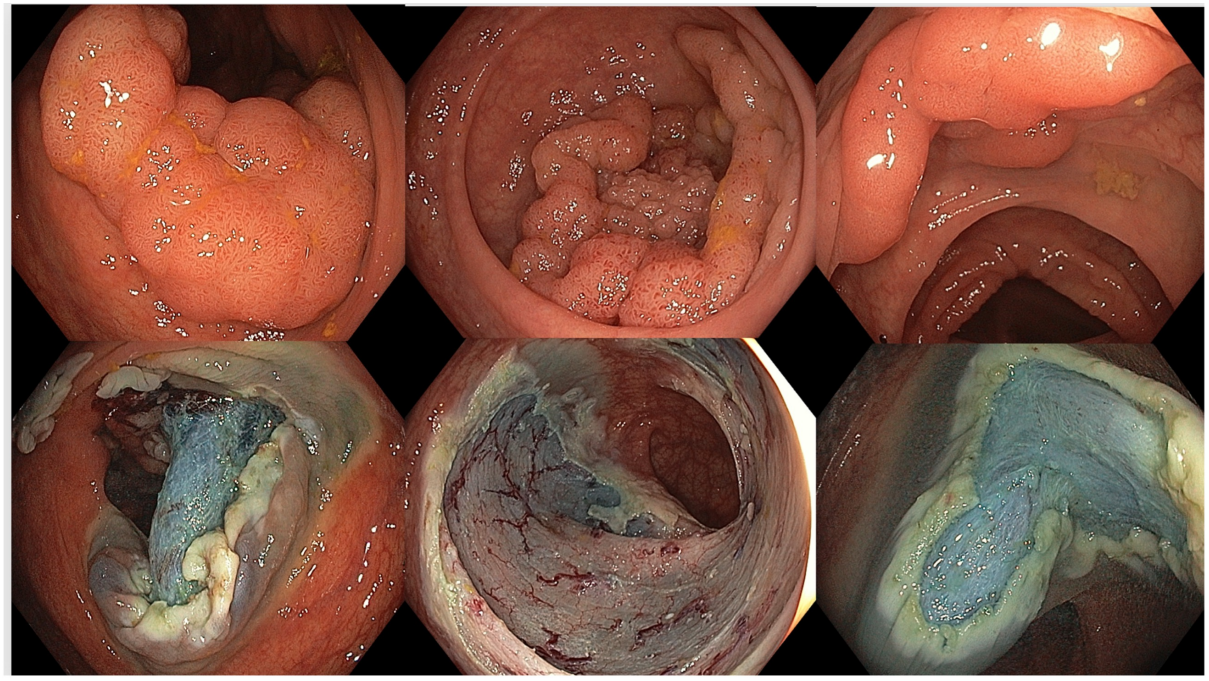


Figure 2

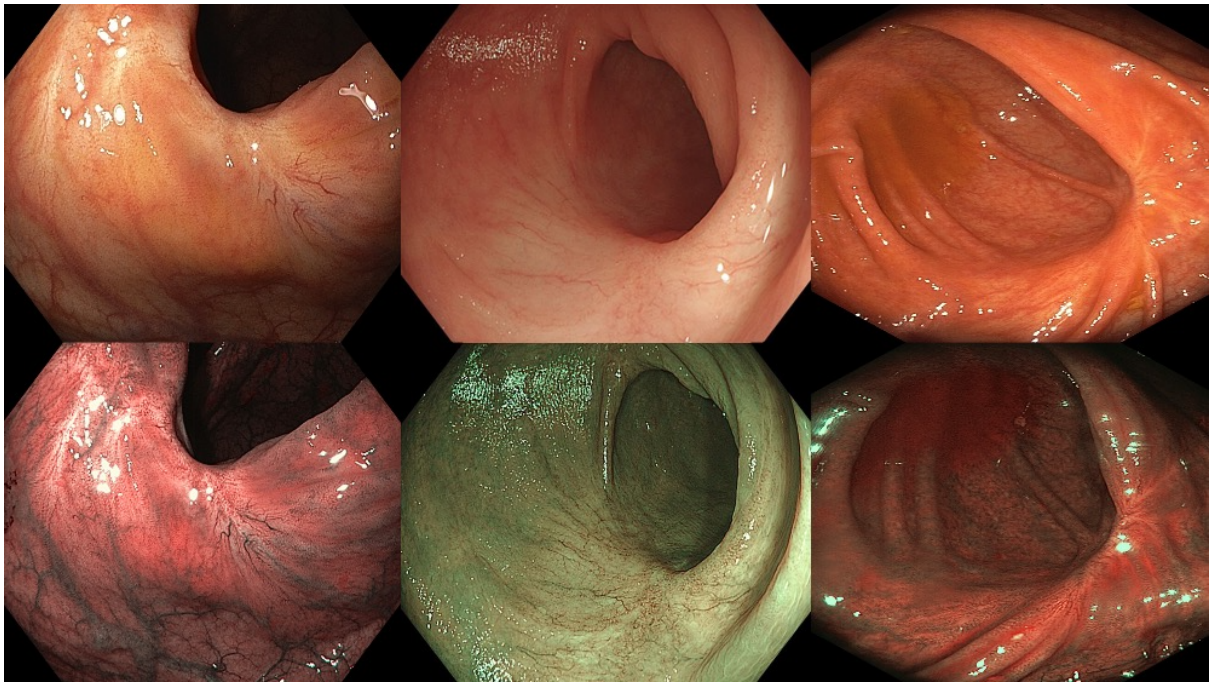


Figure 3

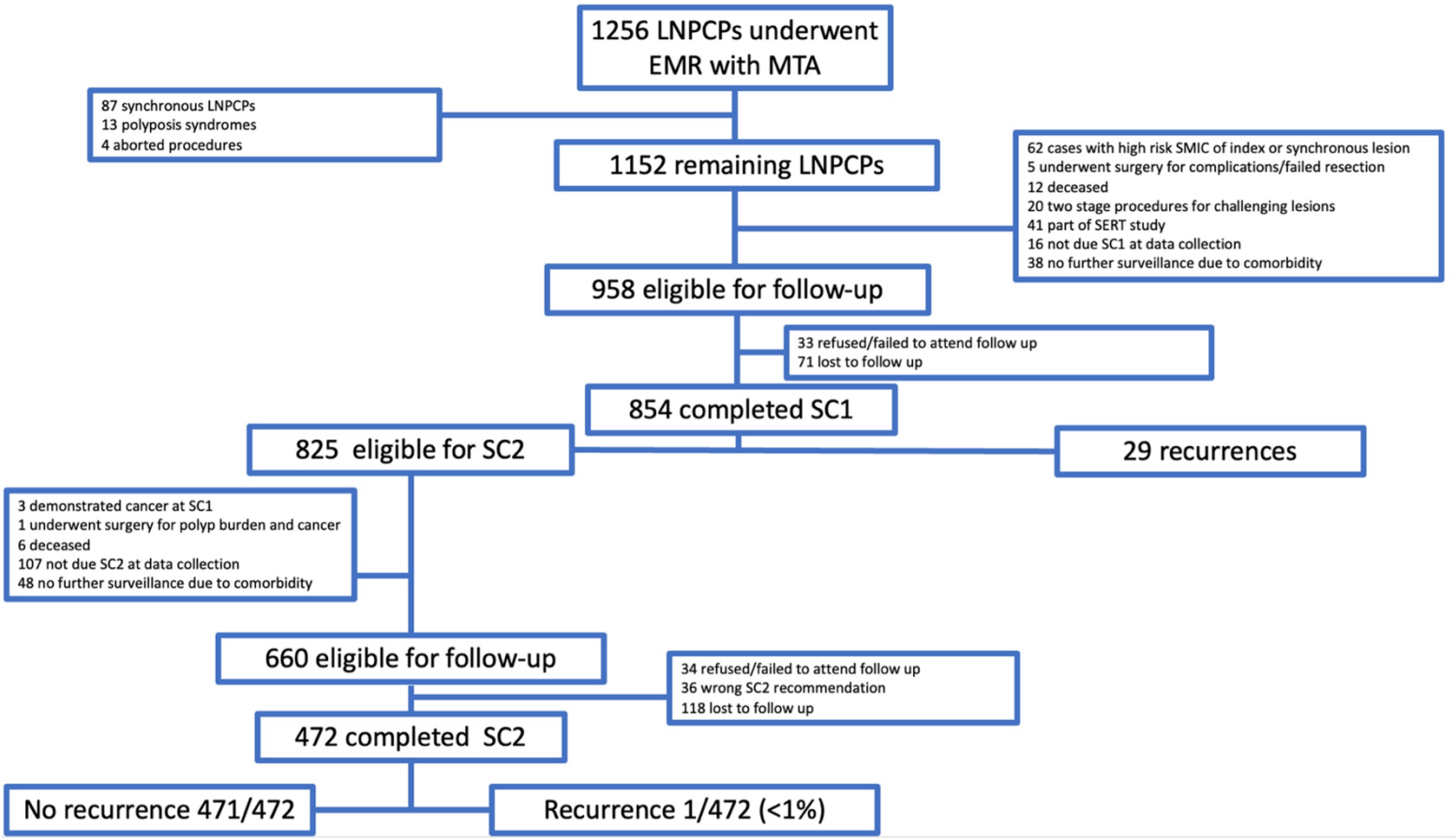
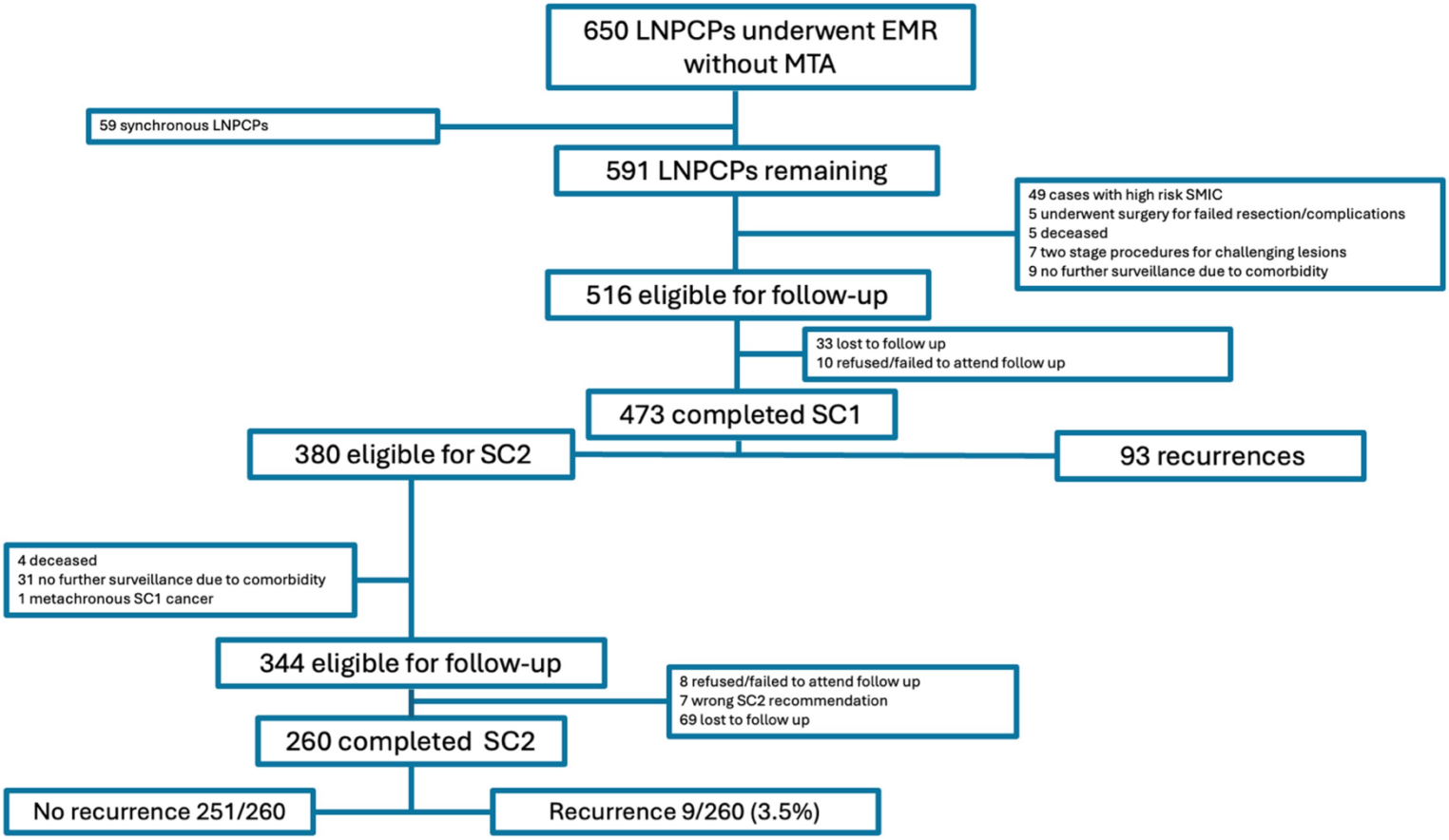

1256 LNPCPs underwent EMR with MTA
87 synchronous LNPCPs
13 polyposis syndromes
4 aborted procedures
1152 remaining LNPCPs
62 cases with high risk SMIC of index or synchronous lesion
5 underwent surgery for complications/failed resection
12 deceased
20 two stage procedures for challenging lesions
41 part of SERT study
16 not due SC1 at data collection
38 no further surveillance due to comorbidity
958 eligible for follow-up
33 refused/failed to attend follow up
71 lost to follow up
854 completed SC1
825 eligible for SC2
29 recurrences
3 demonstrated cancer at SC1
1 underwent surgery for polyp burden and cancer
6 deceased
107 not due SC2 at data collection
48 no further surveillance due to comorbidity
660 eligible for follow-up
34 refused/failed to attend follow up
36 wrong SC2 recommendation
118 lost to follow up
472 completed SC2
No recurrence 471/472
Recurrence 1/472 (<1%)

Figure 4



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Chapter 5

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Summary:

- Multicentre prospective study of >3000 endoscopically resected LNPCPs.
- 6.9% demonstrated synchronous pathology.
- Non-granular morphology was a significant predictor of synchronous neoplasia. This was further influenced by lesion location with left colon nongranular-LNPCPs demonstrating greater risk (OR 4.78 95% CI 2.95-7.73) than right colon nongranular LNPCPs (OR 1.99 95% CI 1.39-2.86).

Contribution:

- This study highlights that early surveillance post endoscopic resection is paramount in order to detect synchronous neoplasia.
- Surveillance intervals may require tailoring to individual lesion phenotypes

The surface morphology of large non pedunculated colonic polyps predicts synchronous large lesions

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Conflict of Interest

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Data transparency statement

All data relevant to the study are included in the article. Individual participant data will not be shared.

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Abbreviations

ACE, Australian Colonic Endoscopic Resection

CI, confidence interval

CRC, colorectal cancer

EMR, endoscopic mucosal resection

ESD, endoscopic submucosal dissection

G, Granular

IQR, interquartile range

LNPCP, large non-pedunculated colorectal polyp ≥ 20mm

NBI, narrow band imaging

NG, non-granular

OR, odds ratio

PCCRC, post-colonoscopy colorectal cancer

SCC, squamous cell carcinoma

SMIC, submucosal invasive cancer

STSC, snare tip soft coagulation

ABSTRACT

Background and Aims:

Large (≥20 mm) nonpedunculated colorectal polyps (LNPCPs) may have synchronous LNPCPs in up to 18% of cases. The nature of this relationship has not been investigated. We aimed to examine the relationship between individual LNPCP characteristics and synchronous colonic LNPCPs.

Methods:

Consecutive patients referred for resection of LNPCPs over 130 months until March 2022 were enrolled. Serrated lesions and mixed granularity LNPCPs were excluded from analysis. Patients with multiple LNPCPs resected were identified, and the largest was labelled as dominant. The primary outcome was the identification of individual lesion characteristics associated with the presence of synchronous LNPCPs.

Results:

There were 3149 of 3381 patients (93.1%) who had a single LNPCP. In 232 (6.9%) a synchronous lesion was detected. Solitary lesions had a median size of 35 mm with a predominant Paris 0-IIa morphology (42.9%) and right colon location (59.5%). In patients with ≥2 LNPCPs, the dominant lesion had a median size of 40mm, Paris 0-IIa (47.6%) morphology, and right colon location (65.9%). In this group, 35.8% of dominant LNPCPs were non-granular compared with 18.7% in the solitary LNPCP cohort. Non-granular (NG)-LNPCPs were more likely to demonstrate synchronous disease, with left colon NG-LNPCPs demonstrating greater risk (odds ratio, 4.78; 95% confidence interval, 2.95–7.73) than right colon NG-LNPCPs (odds ratio, 1.99; 95% confidence interval, 1.39–2.86).

Conclusions: We found that 6.9% of LNPCPs have synchronous disease, with NG-LNPCPs demonstrating a greater than 4-fold increased risk. With post-colonoscopy interval cancers exceeding 5%, endoscopists must be cognizant of an individual's LNPCP phenotype when examining the colon at both index procedure and surveillance. ClinicalTrials.gov, NCT01368289; NCT02000141; NCT02198729.

Key words: neoplasia; colonoscopy; polypectomy; adenoma

BACKGROUND AND AIMS:

Large (≥20 mm) nonpedunculated colonic polyps (LNPCPs) are safely and effectively removed with endoscopic mucosal resection (EMR).[1-2] These lesions have an increased risk of high-grade dysplasia and submucosal invasive cancer (SMIC).[3–6] Synchronous disease is well-documented, with up to 18% of LNPCPs harbouring additional lesions ≥20 mm throughout the colon. Moreover, synchronous LNPCPs are often not detected during the index or resection procedures.[7–11] Whether individual LNPCP subtypes are associated with a greater frequency of synchronous disease is unknown.

Although endoscopic resection of LNPCPs significantly reduces the incidence and mortality of colorectal cancer,[12-13] an increased burden of synchronous lesions is a risk factor for interval malignancy.[14–16] It has been found that 7.4% of all detected colorectal cancers are post-colonoscopy colorectal cancer (PCCRC).[17] This warrants consideration in an era where snare tip soft coagulation (STSC) of EMR margins delivers negligible recurrence rates and argues for lengthier surveillance intervals.[18-19]

This study aimed to investigate the relationship between LNPCP characteristics and the presence of synchronous colonic lesions. Identification of a LNPCP phenotype predictive of synchronous disease would identify a patient cohort warranting meticulous examination of the colon at the outset and enhanced surveillance to prevent PCCRC.

METHODS

Study Design and Patient Selection

We analysed the Australian Colonic Endoscopic Resection (ACE) cohort. The ACE cohort (NCT01368289; NCT02000141) is a multicenter, observational study of consecutively referred patients for the resection of LNPCPs. Over 130 months until March 2022, consecutive participants were enrolled at 1 of 7 sites with established tissue resection programs. Exclusion criteria included LNPCPs of either serrated histopathology or mixed granularity. Institutional ethics approval was obtained, and informed consent was collected. All authors had access to the study data and reviewed and approved the final manuscript.

Procedure

Colonoscopy was performed using Olympus 180/190 high-definition variable-stiffness colonoscopes (Olympus, Tokyo, Japan). All endoscopic procedures were performed by either

a study investigator (accredited gastroenterologist with advanced training in colorectal endoscopic resection) or a senior interventional endoscopy fellow under direct supervision. EMR was performed in a standardized fashion across all centres, with subsequent innovations adopted as supporting data emerged.[20–22] A subgroup of LNPCPs underwent endoscopic submucosal dissection (ESD) as part of a selective ESD protocol (NCT02198729).[23] Optical evaluation was performed under high-definition white-light and narrow band imaging to exclude surface features of SMIC.[5]

Specimens were collected and processed for histopathology review in accordance with Australasian Gastrointestinal Pathology Society guidelines.[24] Histopathology review was completed by expert gastrointestinal pathologists at their respective sites.

Collected Data, Definitions, and Outcomes

Prospectively collected data included LNPCP characteristics of location, size, Paris classification, and surface granularity in addition to histopathologic diagnosis.

Location was divided into right and left colon. The right colon was defined as proximal to and including the mid-transverse colon.[25] LNPCP morphology was described according to the Paris classification and was further grouped as flat vs nodular. Flat LNPCPs were Paris 0-IIa, IIb, or IIc, whereas nodular LNPCPs contained a sessile component (Paris 0-Is or 0-IIa+Is). Lesion size was documented as both a continuous and binary variable (≤35 mm or >35 mm). Granularity was classified as granular (G) or non-granular (NG) in appearance.

All patients who underwent resection of multiple LNPCPs were identified. Lesions were classified as synchronous if detected at index resection procedure or first or second surveillance colonoscopy at 6 or 18 months, respectively, after EMR. The largest LNPCP was labelled as the dominant lesion, and other LNPCPs were classified as synchronous disease. To minimize selection bias, patients with solitary LNPCPs who underwent surgical resection or non-attempted resection were excluded to minimize unaccounted synchronous disease within resection specimens or unexamined colonic segments.

The primary outcome was the relationship between lesion morphology and the prevalence of synchronous LNPCPs. As a secondary endpoint, within the synchronous disease population, LNPCP characteristics shared between the dominant lesion and additional LNPCPs were identified.

Statistical Analysis

SPSS version 26.0 (IBM, Armonk, NY) was used for data analysis. All tests were conducted at a significance level of 0.05 with a two-sided alternative hypothesis.

For the primary outcome, continuous variables were summarized as median (interquartile range) or mean with standard deviation and categorical variables as frequency and percentage. Univariate analysis was performed with X2 tests for categorical variables and Mann-Whitney test for continuous variables. To test association between LNPCP characteristics and the occurrence of synchronous disease, multiple logistic regression was used with odds ratios (ORs) and associated confidence intervals (CIs). Because of the large sample population and only 4 exposure variables, 3-level interaction terms were investigated via backward stepwise regression with a significance level of $P < 0.05$.

In patients with ≥2 synchronous LNPCPs, a second was selected at random for comparison with the largest (dominant) LNPCP. LNPCP characteristics were summarized in contingency tables, and level of agreement between LNPCPs was calculated and tested with kappa scores. A kappa score of 0.21–0.4 was deemed fair agreement and 0.41–0.6 moderate agreement.

RESULTS

Synchronous vs Solitary LNPCPs

A total of 3381 patients were eligible for final analysis after exclusions (Figure 1). There were 3149 patients (93.1%) who had an isolated LNPCP, with 232 (6.9%) demonstrating synchronous LNPCPs. Of the patients with multiple LNPCPs, the majority (86%) had 1 additional LNPCP, 9.9% with 2 synchronous LNPCPs, 3.4% with 3, and 0.4% with 4. Of the 506 synchronous LNPCPs, 247 (91.1%) were ≤35 mm in size, granular (60.6%), Paris 0-IIa morphology (60.2%), and right colon location (69.7%) (Supplementary Table 2). Tubulovillous adenoma was the predominant histology (48.1%), with 4.7% containing cancer and 12.8% high-grade dysplasia. Solitary LNPCPs had a median size of 35 mm, with predominant Paris classification of 0-IIa (42.9%) and 0-IIa + Is (30.9%). There were 1874 LNPCPs (59.5%) in the right colon (Table 1). In patients with multiple LNPCPs, the dominant LNPCP showed similar characteristics to solitary LNPCPs, with median size of 40 mm, Paris 0-IIa (110 [47.6%]) or 0-IIa + Is (57 [24.7%]) morphology, and 153 (65.9%) in the right colon.

Of all granular LNPCPs, 149 of 2708 (5.5%) had synchronous disease compared with 83 of 673 NG-LNPCPs (12.3%) (Supplementary Table 1). Of patients within the synchronous

disease cohort, 35.8% of the dominant LNPCPs were NG compared with 18.7% in the solitary LNPCP cohort (Table 1). Univariate analysis identified morphology (P = 0.017) and granularity (P <0.001) as LNPCP characteristics that significantly differed between the synchronous and solitary LNPCP cohorts.

Multivariable logistic regression was conducted to assess the odds of synchronous disease for the variables of size, location, granularity, and morphology. Because of a significant interaction between granularity and LNPCP location (P = 0.004), the odds of synchronous disease based on granularity were stratified by colonic location (Table 2). Left colon NG-LNPCPs were 4.78 times more likely to demonstrate synchronous disease (OR, 4.78; 95% CI, 2.95–7.73), whereas right colon NG-LNPCPs were twice as likely (OR, 1.99; 95% CI, 1.39–2.86). For LNPCPs >35 mm, synchronous disease was present in 17.9% of left colon NG-LNPCPs and 15.7% of right colon NG-LNPCPs. LNPCP size was also a significant predictor of synchronous disease, with LNPCP >35 mm at 1.65 greater odds of additional LNPCPs (95% CI, 1.25–2.18; P<0.001). LNPCP morphology (flat vs nodular) was not a significant predictor of synchronous disease.

Synchronous LNPCP Shared Characteristics

For patients with synchronous disease, LNPCP characteristics were compared with those of the dominant LNPCP (Table 3). There were 71.4% (kappa 0.35) of synchronous LNPCPs that originated from the same colonic segment (right vs left colon), and 72.4% (kappa 0.41) of LNPCPs were of the same granularity. LNPCPs were not necessarily of a similar size, with 57.5% (kappa 0.18) demonstrating a comparable diameter. There were 67.1% (kappa 0.3) of LNPCPs that shared the same morphology.

DISCUSSION

In addition to their increased risk of advanced histology, up to 18% of LNPCPs harbor additional LNPCPs throughout the colon. With 7.4% of colorectal cancers occurring after colonoscopy, detection of these lesions is as vital as the index LNPCP resection. Whether individual LNPCP subtypes can predict the presence of synchronous disease is unknown.

This study has shown that LNPCP granularity, size, and location influence the likelihood of synchronous disease. The risk of synchronous disease was nearly 5-fold higher for left colon NG-LNPCPs and 2-fold higher for right colon NG-LNPCPs. Lesion size was an independent predictor of synchronous disease, with lesions >35mm being 1.65 times more likely to have

synchronous LNPCPs. When compared with the dominant LNPCP, synchronous LNPCPs were of the same granularity in 72.4% cases, with a moderate agreeance on kappa score (0.41). The 71.4% of LNPCPs were also within the same colonic segment, with a trend toward moderate agreeance with a kappa score of 0.35.

It is established that NG-LNPCPs are challenging to locate because of their flatter profile and frequently subtle appearance (Figure 2). These LNPCPs also demonstrate a higher prevalence of SMIC. A large prospective study of 2277 LNPCPs found NG-LNPCPs were frequently associated with SMIC (OR, 2.80; 95% CI, 1.89–4.16).[4] When compared with G-LNPCP morphology, NG-LNPCPs have a significantly higher frequency of submucosal invasion (14% vs 7%; $P < 0.01$).[26]

The occurrence of synchronous disease for LNPCPs is well-established within the literature. A retrospective study of 802 LNPCPs demonstrated 67.2% of large polyps had concurrent disease, with a clear predilection for the proximal colon.[7] A similar study of 728 patients found 80.2% of patients had at least 1 synchronous adenoma; 18.1% were ≥20 mm.[10] When compared with polyps <20 mm in size, cumulative development of advanced adenomas and cancer in polyps ≥20 mm in size is significantly higher (22.9% vs 9.5%; $P<0.001$) at 36 months after index colonoscopy.[9] Even within 12 months of initial colonoscopy, a study of 290 patients identified additional LNPCPs ≥10 mm in size in 30% of patients.[11] Our study demonstrates lower rates of synchronous disease at 6.9%. This is likely a consequence of the study site being a tertiary referral center with either smaller or less challenging LNPCPs resected by referring endoscopists or detected at surveillance performed outside of our center. In addition, our database did not capture lesions <20 mm in size that were resected during the EMR procedure.

Despite the widespread practice of colonoscopic polyp surveillance for colorectal cancer prevention, interval malignancy remains a significant healthcare burden.[27–30] Although a proportion of these cases are a clear consequence of previous incomplete polyp resection,[15] undetected synchronous disease represents a substantial number of cases. A cohort study identified 52% of interval cancers as probable missed synchronous disease.[14] In a retrospective study of 45 interval cancers, incomplete polyp resection was deemed a contributor in 27%, with the remaining cases likely synchronous disease.[31] Similarly, the Polyp Prevention Trial found 53.8% of interval cancers were a consequence of both synchronous LNPCPs and incomplete polyp resection.[32] Although previous large LNPCPs

or high-grade dysplasia have been identified as predictive of synchronous disease,[7] no previous studies have evaluated whether a particular LNPCP subtype is more predictive.

Our findings illustrate that compared with G-LNPCPs, NG-LNPCPs predispose to synchronous dysplasia throughout the colon. This synchronicity phenomenon has previously been described within oncology literature as a localized “field effect”.[33] Rather than localization of clonal expansion to the one malignant lesion, neoplasia extends in a wider field, driving synchronous pathology. This is well-documented in malignancies of the aerodigestive tract, with up to 15% of patients with head and neck cancers found to have synchronous primary oesophageal squamous cell carcinoma (SCC).[34] Multiple Lugol-voiding lesions have been identified as an independent risk factor (OR, 21.4; P <0.001) for synchronous SCC, suggesting regional changes, rather than discrete lesions, as a driving factor for synchronous disease.[35] Our study resonates with these findings, with synchronous pathology showing a trend toward contiguous colonic segments and a clear difference in the overall risk between the right and left colon. Such findings suggest an environmental or epigenetic factor at play, with the exact nature or mechanism of this process unknown.

This relationship has applications to endoscopic practice; none are more apparent than surveillance intervals. Current guidelines recommend 6-month surveillance colonoscopy after EMR[19] to assess for residual adenoma at the resection site. Historically this was paramount, because not only was recurrence significant, but when detected early, it was easily removed and endoscopically cured. Thermal ablation of the margin of the post-EMR defect using STSC has dramatically changed the landscape, with real-world data reporting recurrence rates of <1.5%.[18] Although not yet widely reported, such low recurrence rates present an argument for less rigorous surveillance intervals. The findings of this study indicate that paradigm shifts in surveillance cannot be implemented without consideration of each patient’s “LNPCP-specific phenotype”. Moreover, they mandate that once a LNPCP is identified, it is imperative that a high-quality screening colonoscopy be performed to rule out synchronous disease, particularly in NG-LNPCPs.

The strengths of this study include its prospective recruitment, large number of LNPCPs, and detailed LNPCP characterization at baseline. Because the study was undertaken in a high-volume referral center that specialized in complex endoscopic resection, a limitation is the lack of data available regarding resection of synchronous disease by another endoscopist

before referral. Although performed to minimize bias, we recognize the exclusion of patients who underwent surgical resection for suspected invasive disease or procedure-related adverse events omits a population who may have harboured synchronous disease. Examination of surgical specimens for additional polyps would have been ideal; however, it was not feasible in this study.

In conclusion, this study demonstrates that synchronous LNPCPs are not uncommon, occurring in 6.9% of such patients. The granularity of individual LNPCPs goes beyond predicting outcomes for single polyps, with NG-LNPCPs demonstrating up to 4-fold greater risk of synchronous disease. To reduce post-colonoscopy interval cancer, endoscopists must be cognizant of this "at risk" cohort when performing EMR and implementing surveillance colonoscopy.

FIGURE LEGEND

Table 1 – Baseline characteristics of single LNPCP vs synchronous disease cohort IQR, interquartile range; LNPCP, large nonpedunculated colonic polyp. [a]Paris classification/morphology (8 missing), Histopathology (174 missing).

Table 2 – Multiple logistic regression model for prediction of synchronous disease NOTE. With interaction term (granularity by location): left colon NG (OR, 4.78; 95% CI, 2.95–7.73), right colon NG (OR, 1.99; 95% CI, 1.39–2.86). G, granular; NG, non-granular.

Table 3 - Relationship between dominant LNPCP characteristics and characteristics of synchronous LNPCPs NOTE. Flat vs raised, 2 missing; G vs NG, 4 missing, 12 mixed. G, granular; NG, non-granular.

Figure 1 – Recruitment of LNPCPs with exclusions SSL, sessile serrated lesion; TSA, traditional serrated lesion; LNPCPs, Large non-pedunculated polyps.

Figure 2 – NG-LNPCPs have subtle appearances and are difficult to detect and endoscopically resect

Supplementary table 1 - Distribution of synchronous disease stratified by dominant lesion location, granularity and size

Supplementary table 2 - Characteristics of synchronous LNPCPs IQR, interquartile range. [a]3 LNPCPs with incomplete data, 2 missing Paris, 13 histopathology data points missing. [b]22 granularity mixed or unspecified – not subject to final analysis.

Table 1

	Single LNPCP n = 3149	**Dominant LNPCP in Synchronous disease n = 232**	**P value**
Size*			
Median (IQR)	35mm (25-50mm)	40mm (30-50mm)	0.170
≤35mm	1697 (53.9%)	111 (47.8%)	
>35mm	1452 (46.1%	121 (52.2%)	0.075
LNPCP morphology			
Flat	1566 (49.8%)	134 (58%)	0.017 (flat vs nodular)
Paris 0-IIa*	1349 (42.9%)	110 (47.6%)	
Paris 0-IIb	73 (2.3%)	10 (4.3%)	
Paris 0-IIc	115 (3.7%)	13 (5.6%)	
Paris 0-III	1	0	
Paris 0-IIb	28 (0.9%)	1 (0.4%)	
Nodular	1576 (50.2%)	97 (42%)	
Paris 0-Is	606 (19.3%)	40 (17.3%)	
Paris 0-IIa+Is	970 (30.9%)	57 (24.7%)	
Location			0.053
Left	1275 (40.5%)	79 (34.1%)	
Right	1874 (59.5%)	153 (65.9%)	
Histology*			<0.001
Tubular Adenoma	976 (32.6%)	79 (36.1%)	
Tubulovillous adenoma	1835 (64.2%)	131 (59.8%)	
Villous adenoma	90 (3.2%)	1 (0.5%)	
Cancer	18 (0.6%)	3 (1.4%)	
Other	72 (2.5%)	2 (0.9%)	
Granularity			<0.001
Granular	2559 (81.3%)	149 (64.2%)	
Non-granular	590 (18.7%)	83 (35.8%)	

* Paris classification/morphology (8 missing), Histopathology (174 missing); LNPCP, large non-pedunculated colonic polyp; IQR, interquartile range

Table 2

Variable	Coefficient	P value	Odds ratio	95% confidence interval
Size (>35mm)	0.50	<0.001	1.65	1.24-2.18
Location (Left colon vs right colon)	0.59	0.045	1.81	1.26-2.60
Granularity (NG-G)	1.56	<0.001	4.78	2.95-7.73
Granularity by location	-0.88	0.004	0.42	0.23-0.75
Constant	-3.50	<0.001	0.03	0.02-0.04

G, granular; NG, non-granular

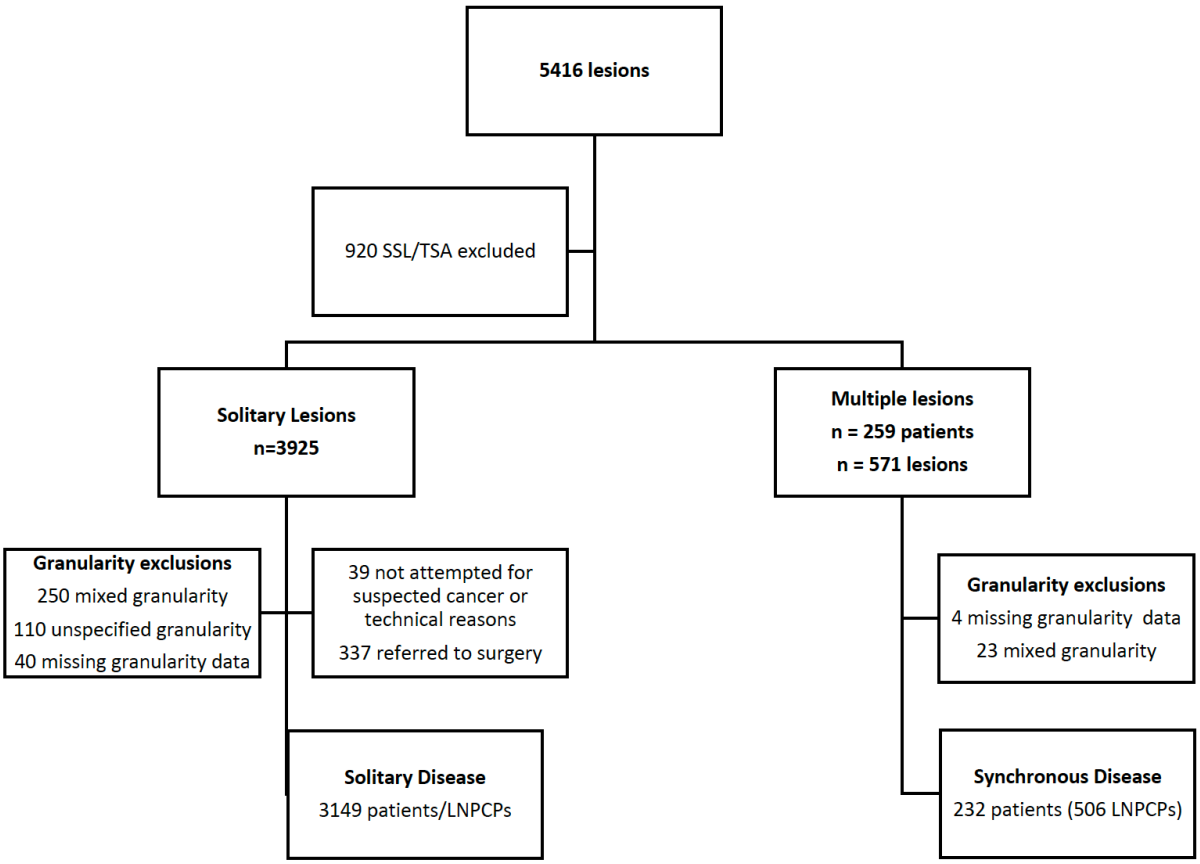
With interaction term (granularity by location) - left colon NG (OR 4.78 95% CI 2.95-7.73), right colon NG (OR 1.99 95% CI 1.39-2.86)

Table 3

		% synchronous lesions with shared characteristics	Kappa (Standard error)
Dominant LNPCP characteristics	**Location (right vs left)**	71.4%	0.35 (0.07)
	Flat vs raised	67.1%	0.30 (0.06)
	Size (≤35mm vs >35mm)	57.5%	0.18 (0.04)
	G vs NG	72.4%	0.41 (0.07)

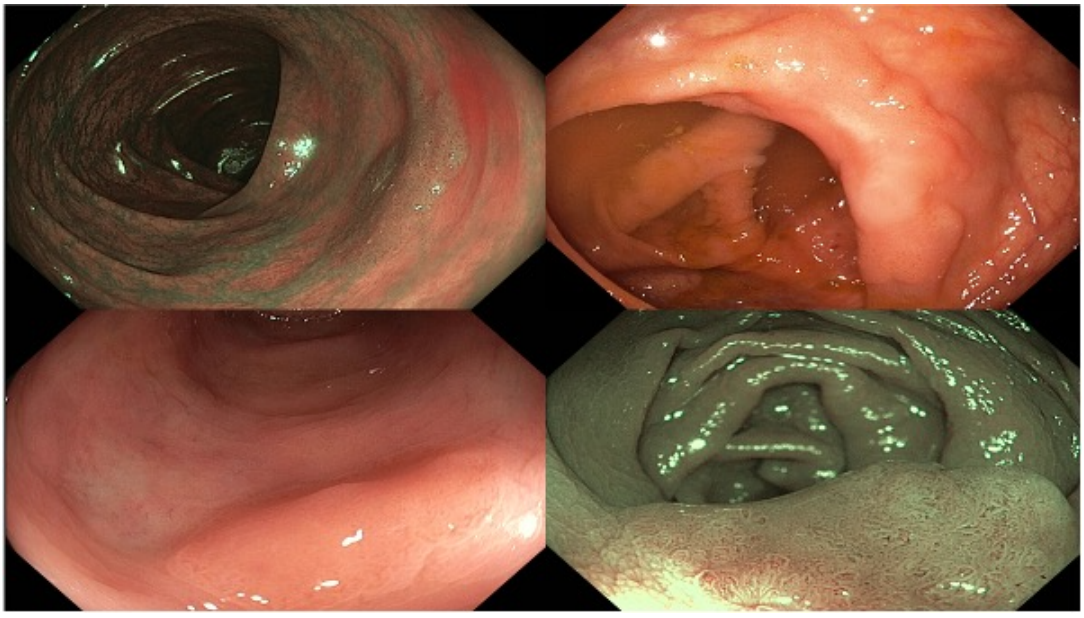
G, granular; NG, non-granular; *Flat vs raised two missing; G vs NG four missing, twelve mixed

Figure 1



SSL, sessile serrated lesion; TSA, traditional serrated lesion; LNPCPs, large non-pedunculated polyps

Figure 2



Supplementary table 1

Size	Lesion	Total number of lesions	%Synchronous disease (95% CI)
≤35mm	Left granular	440	3.4% (1.7-5.1%)
	Right granular	877	4.9%(3.5-6.3%)
	Left Non-granular	168	13.1% (8-18.2%)
	Right Non-granular	323	9.6% (6.4-12.8%)
>35mm	Left Granular	679	4.4% (2.9-5.9%)
	Right Granular	712	8.6% (6.5-10.7%)
	Left Non-Granular	67	17.9% (8.7-27.1%)
	Right Non-granular	115	15.7% (9.1-22.4%)

Supplementary Table 2

	Baseline Characteristics n=274*
Size	25mm (IQR 20-30mm)
Median (IQR)	
≤35mm	247 (91.1%)
>35mm	24 (8.9%)
LNPCP morphology	
Flat	182 (67.7%)
Paris 0-IIa	162 (60.2%)
Paris 0-IIb	8 (3%)
Paris 0-IIc	9 (3.3%)
component	
Paris 0-IIa+IIb	3 (1.1%)
Nodular	87 (32.3%)
Paris 0-Is	49 (18.2%)
Paris 0-IIa+Is	38 (14.2%)
Location	
Left	82 (30.3%)
Right	189 (69.7%)
Histology	
Tubular Adenoma	120 (46.5%)
Tubulovillous	124 (48.1%)
adenoma	
Villous adenoma	1 (0.4%)
Cancer	12 (4.7%)
High grade dysplasia	35 (12.8%)
Other	1 (0.4%)
Granularity^	
Granular	151 (60.6%)
Non-granular	98 (39.4%)

*3 LNPCPs with incomplete data, 2 missing Paris, 13 histopathology data points missing ^22 granularity mixed or unspecified – not subject to final analysis; IQR, interquartile range

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Part II

Optimisation of lesion selection for endoscopic resection training and tertiary referral

Chapter 6

Publication:

O'Sullivan T, Craciun A, Byth K, Gupta S, Gauci JL, Cronin O, Whitfield A, Abuarisha M, Williams SJ, Lee EYT, Burgess NG, Bourke MJ. **A simplified algorithm to evaluate the risk of submucosal invasive cancer in large (≥20 mm) nonpedunculated colonic polyps.** Endoscopy. 2024 Aug;56(8):596-604. doi: 10.1055/a-2282-4794. Epub 2024 Mar 6. PMID: 38447957.

Summary:

- A prospective single centre study of over 2000 LNPCPs referred for endoscopic resection identified SMIC in 273 (11.1%) lesions.
- Lesion characteristics of size, morphology and location were predictors of SMIC
- A decision tree analysis was conducted utilising significant predictors of SMIC to provide an algorithm framework illustrating SMIC risk in simplified terms.
- Highest risk LNPCPs were depressed morphology, nodular rectosigmoid and nodular nongranular lesions

Contribution:

- Provides readily available lesion-specific risks of potential SMIC
- When used as an adjunct to surface optical evaluation, this algorithm gives endoscopists the confidence to accurately assess SMIC risk and guide selection of resection modality.

A simplified algorithm to evaluate the risk of submucosal invasive cancer in large (≥20mm) non-pedunculated colonic polyps.

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Conflict of Interest

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

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Data transparency statement

All data relevant to the study are included in the article. Individual participant data will not be shared.

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Abbreviations

ACE, Australian Colonic Endoscopic Resection

CI, confidence interval

CRC, colorectal cancer

EMR, endoscopic mucosal resection

ESD, endoscopic submucosal dissection

G, Granular

IQR, interquartile range

LNPCP, large non-pedunculated colorectal polyp ≥ 20mm

NBI, narrow band imaging

NG, non-granular

OR, odds ratio

PCCRC, post-colonoscopy colorectal cancer

SMIC, submucosal invasive cancer

STSC, snare tip soft coagulation

ABSTRACT

Background

Recognition of submucosal invasive cancer (SMIC) in large (≥20mm) nonpedunculated colonic polyps (LNPCPs) informs selection of the optimal resection strategy. LNPCP location, morphology, and size influence the risk of SMIC; however, currently no meaningful application of this information has simplified the process to make it accessible and broadly applicable. We developed a decision-making algorithm to simplify the identification of LNPCP subtypes with increased risk of potential SMIC.

Methods

Patients referred for LNPCP resection from September 2008 to November 2022 were enrolled. LNPCPs with SMIC were identified from endoscopic resection specimens, lesion biopsies, or surgical outcomes. Decision tree analysis of lesion characteristics identified in multivariable analysis was used to create a hierarchical classification of SMIC prevalence.

Results

2451 LNPCPs were analysed: 1289 (52.6%) were flat, 1043 (42.6%) nodular, and 118 (4.8%) depressed. SMIC was confirmed in 273 of the LNPCPs (11.1%). It was associated with depressed and nodular vs. flat morphology (odds ratios [ORs] 35.7 [95%CI 22.6–56.5] and 3.5 [95%CI 2.6–4.9], respectively; P<0.001); rectosigmoid vs. proximal location (OR 3.2 [95%CI 2.5–4.1]; P<0.001); nongranular vs. granular appearance (OR 2.4 [95%CI 1.9–3.1]; P<0.001); and size (OR 1.12 per 10-mm increase [95%CI 1.05–1.19]; P<0.001). Decision tree analysis targeting SMIC identified eight terminal nodes: SMIC prevalence was 62% in depressed LNPCPs, 19% in nodular rectosigmoid LNPCPs, and 20% in nodular proximal colon nongranular LNPCPs.

Conclusions

This decision-making algorithm simplifies identification of LNPCPs with an increased risk of potential SMIC. When combined with surface optical evaluation, it facilitates accurate lesion characterization and resection choices.

BACKGROUND

Large (≥20mm) nonpedunculated colonic polyps (LNPCPs) are effectively and safely resected by endoscopic mucosal resection (EMR), with 98% of lesions cured and surgery avoided [1-3]. Despite this, recognition of submucosal invasive cancer (SMIC) remains a challenge, particularly in bulky lesions [4-5]. Ideally lesions with SMIC are resected en bloc to facilitate accurate histologic assessment and satisfy criteria should low risk superficial SMIC be present. Recently it has emerged that individual LNPCP variables including location, morphology, granularity, and size influence the risk of SMIC [4]. When the complex interaction between the effects of these variables is examined, certain LNPCP subtypes demonstrate significantly greater risk of SMIC. The application of this knowledge is inherently complex, hindering its accessibility in a real-world context. This problem remains a major challenge for endoscopists of all levels of experience and proficiency. A simplified method of identifying LNPCP subtypes with different risks of SMIC would serve as a tool to facilitate targeted surface optical evaluation and selective use of en bloc resection.

METHODS

Study design and patient selection

From September 2008 until November 2022, consecutive participants were enrolled from a single tertiary referral center. All LNPCPs were detected by an accredited endoscopist (gastroenterologists and surgeons) and referred to our center for consideration of endoscopic resection. Lesions were not proven cancers prior to referral and it was the belief of the referring endoscopist that the LNPCP was most likely benign. Exclusion criteria included serrated histopathology and resections that were not attempted for technical reasons. LNPCPs not attempted owing to poor submucosal lifting and significant submucosal fibrosis remained in the cohort when invasive cancer was strongly suspected.

Institutional ethics approval was obtained for study registration and informed consent was collected. All authors had access to the study data and reviewed and approved the final manuscript.

Procedure

Colonoscopy was performed using Olympus 180/190 high definition, variable stiffness colonoscopes (Olympus, Tokyo, Japan). All endoscopic procedures were performed by either a study investigator (accredited gastroenterologist with advanced training and experience in

colorectal endoscopic resection and LNPCP characterization) or a senior interventional endoscopy fellow under direct supervision.

EMR was performed in a standardized fashion, with subsequent innovations adopted as supporting data emerged [6-9]. A subgroup of LNPCPs underwent endoscopic submucosal dissection (ESD) as part of a selective ESD protocol (NCT02198729) [10]. Optical evaluation was performed under high-definition white-light, narrow-band imaging (NBI), and near focus, once these became available, to identify surface features of SMIC. A study conducted in our center found dye-based chromoendoscopy did not provide incremental benefit in the optical diagnosis of SMIC [11]. As such, this was not incorporated into standard practice in our unit.

LNPCPs were consistently described using the Kudo classification throughout the duration of the study. Procedural documentation and LNPCP morphology descriptions were reported in a standardized fashion to maintain consistency between proceduralists and minimize incomplete data.

Specimens were collected and processed for histopathology review, in accordance with Australasian Gastrointestinal Pathology Society guidelines [12]. Histopathology review was completed by expert gastrointestinal pathologists and, where SMIC was identified, consensus opinion was obtained. Furthermore, cases of identified cancer were discussed at a multidisciplinary meeting with both pathologists and gastroenterologists in attendance.

Collected data, definitions, and outcomes

Prospectively collected data included LNPCP location, size, Paris classification, surface granularity, and histopathologic diagnosis.

SMIC was defined as neoplasia invading beyond the muscularis mucosae into the submucosa. SMIC was deemed overt if Kudo Vi or Vn features were evident on surface optical evaluation. Endoscopic resection of SMIC was performed either on LNPCPs that were optically suspicious for potentially curable superficial SMIC (Kudo Vi) or in cases of piecemeal EMR in which SMIC was “covert” and not recognized prior to resection owing to the absence of Kudo Vi or Vn features. LNPCPs not resected owing to optical evidence of deeply invasive cancer had malignancy confirmed through cold forceps biopsies. If biopsies could not confidently provide a diagnosis of cancer, lesions were only deemed to have SMIC following evaluation of the surgical outcomes. Unless the patient was deemed medically unfit

or the lesion was curatively resected with en bloc techniques, all cases of SMIC underwent surgical resection.

LNPCP location was divided into the proximal colon and rectosigmoid. The rectosigmoid was defined as the rectum and sigmoid colon; the proximal colon as proximal to and including the descending colon. LNPCP morphology was described according to the Paris classification and was further grouped as “flat” vs. “nodular” or “depressed.” Flat LNPCPs were Paris 0-IIa or IIb, nodular LNPCPs contained a sessile component (Paris 0-Is or 0-IIa + Is with a nodule exceeding 2.5mm in size), and depressed lesions contained Paris 0-IIc foci. LNPCP size was measured using endoscopic devices of known size, such as snares, as a frame of reference. Size was considered as both a continuous and binary variable (<40 or ≥40 mm). Granularity was classified as granular or nongranular in appearance. Mixed granularity LNPCPs with both granular and nongranular features were classified as nongranular. High SMIC prevalence was defined as a probability exceeding 10%, as described in previous studies [4].

The primary aim of the study was to identify combinations of LNPCP characteristics (“LNPCP subtypes”) that were associated with an increased prevalence of SMIC in the study cohort and display these in a simplified decision-making algorithm that stratifies the risk of potential cancer in LNPCPs otherwise thought to be benign by the referring endoscopist.

Statistical analysis

IBM SPSS Statistics version 29.0 (IBM, Armonk, New York, USA) was used to analyse the data. All analyses were exploratory and per LNPCP. Two-tailed tests with a significance level of 5% were used throughout. Continuous variables are summarized as the median (interquartile range [IQR]) or mean (SD). Categorical variables are summarized as frequency and percentage. LNPCP size is summarized using median (IQR). The dichotomized size variable (≥40 vs. <40mm) maximized the sum of sensitivity and specificity when classifying SMIC status (present vs. absent).

Chi-squared tests were used to test for univariable association between each categorical variable and the presence of SMIC; the Mann–Whitney test was used for size. Odds ratios (ORs) with 95%CIs, estimated using logistic regression analysis, were used to quantify the strength of the univariable associations. We identified the best fitting multivariable logistic regression model using backward stepwise variable selection from the main effects (size,

granularity, morphology, and colon side) and their pairwise interactions with P value for removal <0.1.

Classification trees were then used to explore whether a simple decision tree based on only four predictor variables and constrained to have a minimum number of 200 cases in any parent node and 100 in any child node could better communicate a clinical decision pathway. The analysis was used to classify the LNPCPs into groups based on the predictor variables morphology, granularity, location, and size according to the dependent variable SMIC status (present vs. absent). The chi squared automatic interaction detection (CHAID) method was used to grow the tree to a maximum depth of five levels, ensuring the minimum number of LNPCPs at parent and child nodes were 200 and 100, respectively. This guaranteed the 95%CI for percentage SMIC within any terminal node was no wider than ±10% about the observed value. P values associated with the splits were Bonferroni adjusted.

All lesions and the overall SMIC rate appear at the first level of the tree. The variable with the greatest impact on the dependent variable (SMIC rate) is then identified and breaks down the population into child nodes. This process of selection of the most influential variable is repeated at each child node at each level using the remaining variables. Five-fold cross-validation was used to confirm the structure of the classification tree and the stability of the proportions. The "gain" (number with SMIC in the node) summary table was produced for the terminal nodes and used to further simplify the potential risk of SMIC for LNPCPs into four categories. The Nagelkerke R^2 value, which quantifies the goodness of fit of logistic regression models, was used to compare the fit for this simple four category "potential SMIC" variable to that of the best fitting logistic regression model and to that using the subtype categories identified by the terminal nodes of the decision tree.

RESULTS

A total of 3039 LNPCPs were assessed in the study period; 512 serrated lesions were excluded, along with 19 LNPCPs that were not resected because of technical difficulties including poor endoscopic access. There were 23 patients who had missing histology or lesion data, and granularity was unclassified for 22 LNPCPs; 12 LNPCPs had insufficient tissue or nonadenomatous histology (lipoma, colitis, lymphoma).

Overall, 2451 LNPCPs from 2260 enrolled patients were included, with a median size of 35mm (IQR 25–50mm), predominant proximal colon location (n = 1669; 68.1%), flat morphology (n = 1289; 52.6%), and granular appearance (n = 1603; 65.4%) (Table 1). SMIC

was identified in 273/2451 LNPCPs (11.1%). Covert SMIC was present in 42.8% of all cancers (Table 1s, Supplementary material) and 4.7% of all LNPCPs. Overt SMIC was present in 6.3% of all LNPCPs.

LNPCP characteristics associated with SMIC

SMIC was associated with: depressed (73/118; 61.9%) and nodular (144/1043; 13.8%) vs. flat (56/1289; 4.3%) morphology (OR 35.7 [95%CI 22.6–56.5] and OR 3.5 [95%CI 2.6–4.9], respectively; P<0.001); rectosigmoid (154/782; 19.7%) vs. proximal (119/1669; 7.1%) colonic location (OR 3.2 [95%CI 2.5–4.1]; P<0.001); nongranular (146/848; 17.2%) vs. granular (127/1603; 7.9%) appearance (OR 2.4 [95%CI 1.9–3.1]; P<0.001); and size ≥40mm (160/1135; 14.1%) vs. <40mm (113/1316; 8.6%) cohort (OR 1.7 [95%CI 1.4–2.3]; P<0.001) (Table 2).

Decision tree analysis targeting SMIC (Fig. 1) identified eight terminal nodes ("LNPCP subtypes"): SMIC prevalence was 62% in 118 depressed LNPCPs; 22% in 363 nodular rectosigmoid LNPCPs ≥40mm; 12% in 160 nodular rectosigmoid LNPCPs <40mm; and 20% in 125 nodular proximal colon nongranular LNPCPs. The lowest prevalence (1%) occurred in 596 flat proximal colon granular LNPCPs. The decision tree that used LNPCP size as a continuous variable was identical to that which used dichotomized size and had a depth of 3. Table 2s (Supplementary material) shows the percentage SMIC prevalence, with 95%CI, within each LNPCP subtype for the study cohort.

Table 3 shows the "gain" (number with SMIC in node) summary table for the terminal nodes (subtypes) and four broad categories of "potential SMIC" risk, based on SMIC prevalence for each LNPCP subtype: high (>50%); elevated (>10%–50%); unlikely (2.5%–10%); and very unlikely (<2.5%). The Nagelkerke R^2 value, quantifying goodness of fit of the logistic regression model, for SMIC status using this four-level "potential SMIC" categorical independent variable was 0.257. This is very similar to that using the eight-level subtype variable (Nagelkerke $R^2 = 0.265$) and that for the best fitting logistic regression model, which incorporated four main effects and colonic location by granularity interaction ($R^2= 0.274$).

The decision tree results were further simplified into a SMIC decision-making algorithm that highlights high risk LNPCPs with a risk of potential SMIC >10% (Fig. 2). Table 3 provides a more detailed breakdown of the LNPCP subtype risk categories.

DISCUSSION

Detection of covert and overt SMIC in LNPCPs remains a considerable challenge. This is a problem that impacts endoscopists of all levels of experience and proficiency. We have recently shown that SMIC can be reliably detected in flat lesions through the expression of invasive features on the surface of the lesion [13]; however, the accuracy of this is greatly diminished in bulky lesions. While EMR is proven to be safe and effective for the treatment of LNPCPs, those containing SMIC are not considered cured by piecemeal resection, according to accepted criteria [1-3, 14-16]. Various factors feed into SMIC estimation and can be used to improve optical diagnosis and optimize the resection modality. Current methods are challenging to apply in a real-world setting. A simple approach that can be easily applied by all endoscopists is needed.

SMIC has previously been reported in 7.6%–8.5% of endoscopically resected LNPCPs and, when identified and appropriately resected, may be cured [4-5]. En bloc resection of SMIC is curative when favourable histologic features are present, including superficial invasion (<1000μm), no lymphovascular invasion, and absence of poor differentiation. Under these circumstances, surgical resection is generally not necessary [17]. Even when SMIC is inadvertently resected piecemeal, it seems the same curative criteria that are used for en bloc resection apply, although data are limited. If SMIC is well differentiated with no lymphovascular invasion, the risk of lymph node metastasis is negligible. Furthermore, if the deep margin is clear, despite piecemeal resection, it seems the risk of local recurrence is insignificant [18].

Optical evaluation of the surface vascular and pit patterns of LNPCPs can accurately detect SMIC in flat lesions. The probability of optical evaluation not detecting SMIC in a flat LNPCP was 0.6% in a large prospective study; in contrast, because of their bulky morphology limiting inspection, optical evaluation missed 5.9% of cases of SMIC within nodular LNPCPs ($P<0.001$) [13]. A prospective series of 2277 LNPCPs found the sensitivity of Kudo pit pattern for identifying SMIC was only 40.4%, with 138/171 histologically confirmed cancers demonstrating benign surface features [4]. These cases of “covert” SMIC present a significant challenge in the detection and management of SMIC in LNPCPs and highlight the importance of risk characterization independent of the surface features.

The individual LNPCP characteristics of size, morphology, location, and granularity inform the baseline risk of SMIC, irrespective of the surface pit and vascular patterns. Compared with flat lesions, nodular or depressed morphology demonstrates a greater probability of

SMIC [19-20]. Overall, nongranular LNPCPs are more likely to contain SMIC compared with their granular counterparts [4]. Whereas LNPCPs located in the proximal colon have a low risk of SMIC, lesions in the distal colon, particularly the rectosigmoid, are at far greater risk [4, 21]. While these individual risk factors are widely reported, their collective influence on SMIC risk is now also well recognized [4, 22-23]. The interaction of these characteristics is however complex and difficult to apply in a real-world setting. Moreover, a simple algorithm estimating risk in a given LNPCP subtype has been lacking.

Given the complex interaction of LNPCP characteristics when predicting SMIC risk, we used a decision tree approach to identify subtypes with different risks of SMIC based on morphology, granularity, colonic location, and polyp size. Paris morphology has been shown to have poor interobserver agreement among experts [24] and was therefore not included as an independent predictor in the decision tree analysis.

Our novel algorithm offers readily available lesion-specific risks of potential SMIC according to the LNPCP subtype (Fig. 2 and Fig. 3). This can assist endoscopists in stratifying the risk of cancer in an LNPCP that is otherwise thought to be benign. Endoscopists first need to characterize the LNPCP as depressed, flat, or nodular. Depressed LNPCPs require no further characterization and have a 62% prevalence of SMIC. For such lesions, in the absence of surface features of deep submucosal invasion, endoscopists should proceed with an en bloc resection modality. LNPCPs that are not depressed are then divided into flat or nodular. Irrespective of granularity or location, flat LNPCPs confer a low prevalence of SMIC (4.3%: granular, 1.8%; nongranular, 7.7%). Endoscopists must be mindful of this risk profile prior to commencing optical assessment, which has been demonstrated to be highly accurate in flat lesions [13]. For lesions that are nodular, location assumes primacy as a discriminatory variable. In the proximal colon, nodular nongranular LNPCPs have a high probability (20%) of SMIC, whereas nodular granular LNPCPs have a low prevalence of SMIC (5%). In contrast, all rectosigmoid nodular LNPCPs are high risk, irrespective of their granularity or size (19%). Once high-risk lesion subtypes have been identified, fastidious optical evaluation of their surface features should be conducted to exclude the presence of deep submucosal invasion. If these features are absent, an en bloc resection modality is required.

This decision-making algorithm is a tool that can be used by endoscopists of all levels of experience and training to stratify the risk of potential cancer in an LNPCP that is otherwise thought to be benign. Risk calculations, which necessitated prerequisite knowledge of twelve

LNPCP subtypes, can now be conducted on individual lesions using binary questions addressing LNPCP size, morphology, location, and granularity. The flowchart presentation is intuitive, with potential SMIC risk often calculated using between one and three LNPCP characteristics (Fig. 2). A detailed understanding of SMIC risk of an LNPCP is necessary before conducting optical evaluation of the lesion's surface. This particularly applies to flat LNPCPs. Conversely, the inaccuracy of optical evaluation within nodular LNPCPs requires accurate risk stratification to inform the resection strategy.

With the use of our algorithm, high risk nodular lesions can be easily identified and subsequently targeted in validated en bloc selective resection protocols. One such protocol performed ESD on high-risk lesions of the rectum, which included Paris 0-Is or 0-IIa + Is nongranular LNPCPs or 0-IIa + Is granular LNPCPs with a dominant nodule ≥10mm. Selective resection accurately captured cases of SMIC, with curative oncologic resection achieved in all cases satisfying the criteria for low risk SMIC [10]. Despite the utility of this algorithm, not all lesions with SMIC are detected, emphasizing the importance of high-quality optical evaluation during lesion assessment.

This algorithm is specific to adenomatous LNPCPs, with serrated lesions excluded from the final analysis. In contrast to adenomatous polyps, serrated lesions demonstrate a unique carcinogenesis pathway and have distinct endoscopic appearances and resection approaches [25]. Unlike adenomas, serrated lesions with cytologic dysplasia are well described precancerous lesions that are endoscopically detectable [26]. Furthermore, it must be emphasized that all LNPCPs referred for endoscopic resection in our study were thought to be benign by the referring endoscopists. Cases of overt cancer were only subsequently diagnosed by our service. Consequently, covert and overt cancers were retained within the study to accurately construct a tool that stratifies the risk of potential cancer in LNPCPs otherwise thought to be benign by the referring endoscopists.

The strength of this study is the large cohort of LNPCPs that were prospectively collected and characterized at a single expert referral center with substantial expertise in LNPCP characterization, assessment, and resection. A theoretical limitation is the real-world variability in classifying lesion morphology and size; however, our algorithm has simplified this process and does not rely on variables such as Paris classification, which may have poor agreement between proceduralists [24, 27]. We do acknowledge however that this study lacks data on the level of agreement between our proceduralists regarding lesion description. This

is a derivation study without external validation. To ascertain the generalizability of the results, external validation in an independent dataset is required to obtain data on algorithm accuracy. We also recognize that our rate of SMIC (11%) exceeds that of previous studies; however, this is likely a consequence of including overtly cancerous lesions that were referred to us for assessment and endoscopic treatment, which we then sent directly to surgery.

Being a tertiary referral center there is unavoidable referrer bias as we recognize that some endoscopically resectable cancers detected by referrers may not have been considered for resection and referred directly to surgery. While subject to debate among experts, a recent study highlighted incomplete retrieval of piecemeal resection specimens as a theoretical source of missed foci of SMIC [28]. We recognize a large proportion of our EMR cases were piecemeal resections and as such lack the histologic accuracy obtained from an en bloc specimen.

In conclusion, this study has defined an algorithm to stratify the likelihood of potential SMIC in an LNPCP otherwise thought to be benign. The algorithm encourages systematic LNPCP assessment prior to endoscopic resection and provides all endoscopists with greater confidence in decision-making around treatment selection.

FIGURE LEGEND

Table 1 - Baseline characteristics of the 2451 large nonpedunculated colonic polyps included in the study * Missing data for Paris type, n = 1.

Table 2 - Distribution of each large non-pedunculated colonic polyp characteristic by submucosal invasive cancer (SMIC) status, together with odds ratios (ORs) and 95%CIs derived from multivariable regression analysis. * Per 10-mmincrease in size.

†Missing data for Paris type, n = 1 in the no SMIC group.

Table 3 - Large nonpedunculated colonic polyp (LNPCP) and submucosal invasive cancer (SMIC) frequency (“gain”) by terminal node subtype, together with percentage SMIC within each subtype, index ratio, and “potential SMIC” category. * Ratio of percentage with SMIC within subtype compared with percentage with SMIC for the total LNPCP cohort.

SUPPLEMENTARY TABLES

- **Supplementary Table 1** LNPCPs containing SMIC stratified by covert and overt status*4 missing Kudo data – all underwent EMR ± despite benign surface appearances, high suspicion for SMIC due to poor submucosal lifting
- **Supplementary Table 2** Frequency of SMIC status by morphology, colon location, granularity and size together with prevalence (%) and 95%CI of SMIC for each terminal node (‘LNPCP subtype')

Figure 1 - Decision tree analysis targeting submucosal invasive cancer (SMIC) in the study cohort and illustrating the terminal nodes (‘large non-pedunculated colonic polyp subtypes’). Left colon, rectosigmoid; right colon, proximal colon.

Figure 2 - Decision-making algorithm highlighting large nonpedunculated colonic polyp subtypes where the potential SMIC risk is >10%.

Figure 3 - Examples of risk assessment of large nonpedunculated colonic polyps using the simple algorithm for potential SMIC showing: a–c step 1 = nodular lesion; step 2 = location, rectosigmoid → potential SMIC risk 19% (en bloc resection performed); d–f step 1 = flat → potential SMIC risk 4% irrespective of location (resected by piecemeal endoscopic mucosal resection after surface optical evaluation).

Figure 1

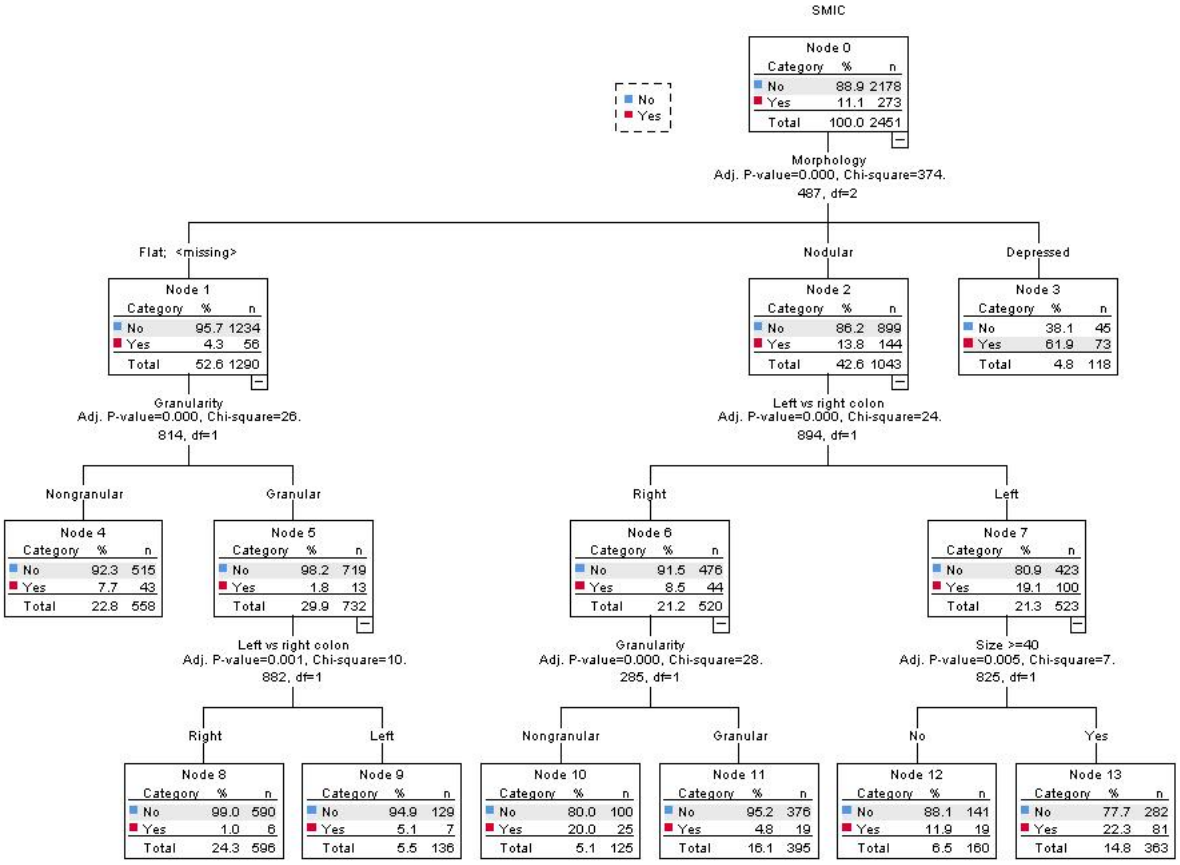

Figure 2

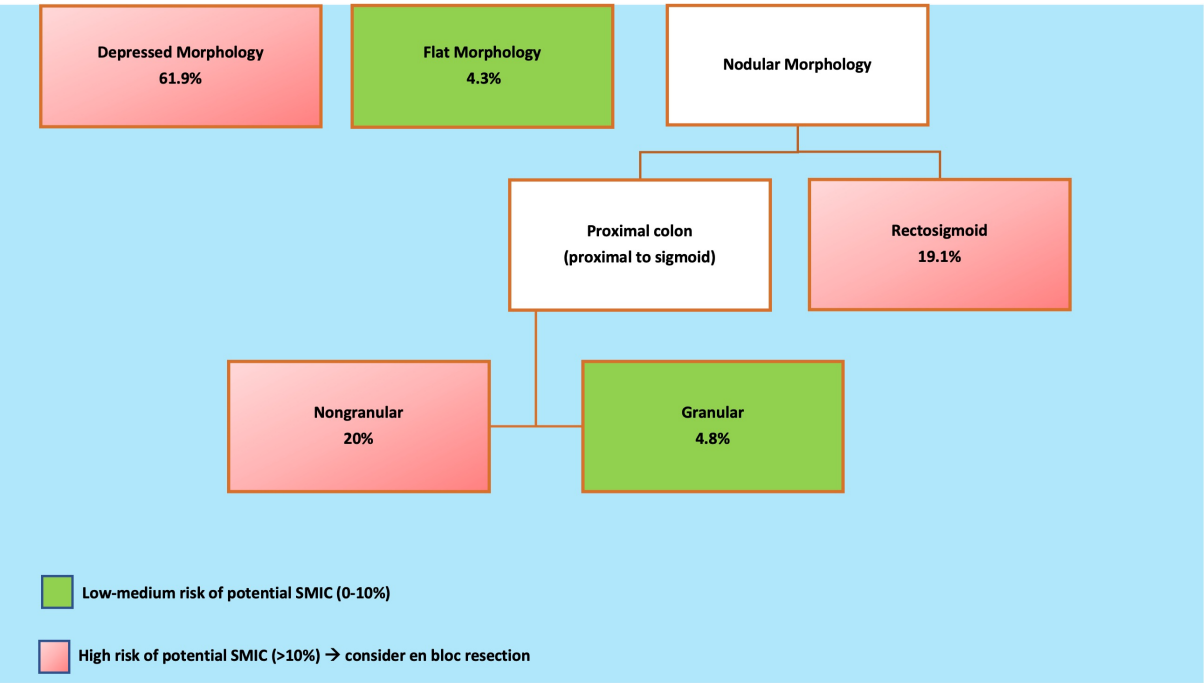

Figure 3

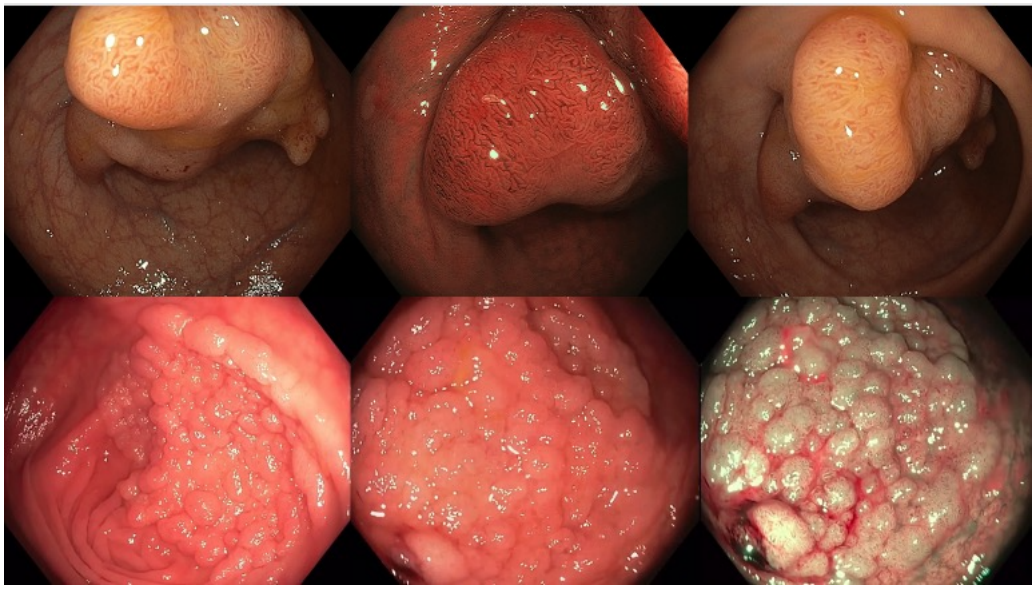

Table 1

		N=2451	%
Histopathology	Tubular adenoma	699	28.5%
	Tubulovillous adenoma	1461	59.6%
	Villous adenoma	18	0.7%
	SMIC	273	11.1%
Size (median IQR)		35mm (25-50)	
Location	Rectosigmoid	782	31.9%%
	Proximal colon	1669	68.1%%
Morphology *	Flat	1289	52.6%
	Nodular	1043	42.6%
	Depressed	118	4.8%
Granularity			
	Granular	1603	65.4%
	Non-granular	848	34.6%

*Missing – 1 Paris. G, Granular; NG nongranular; SMIC, submucosal invasive cancer

Table 2

Variable	Values taken	no SMIC (n=2178)		SMIC (n=273)		p-value	Odds Ratio	95%CI for OR	
								lower	upper
Size (mm) - *median (LQ-UQ)*		*35*	*(25-45)*	*40*	*(30-50)*	<0.001	1.12 per 10mm increase	1.05	1.19
Size	**<40mm**	1203	55.2%	113	41.4%	<0.001	1	-	-
	>=40mm	975	44.8%	160	58.6%		1.75	1.35	2.26
Size	**<35mm**	966	44.40%	99	36.30%	0.011	1	-	-
	>=35mm	1212	55.60%	174	63.70%		1.40	1.08	1.82
Morphology*	**Flat**	1223	56.6%	56	20.5%	<0.001	1	-	-
	Nodular	899	41.3%	144	52.7%		3.53	2.56	4.86
	Depressed	45	2.1%	73	26.7%		35.72	22.59	56.46
Granularity	**Granular**	1476	67.8%	127	46.5%	<0.001	1	-	-
	Nongranular	702	32.2%	146	53.5%		2.42	1.87	3.12
Colon location	**Proximal**	1550	71.2%	119	43.6%	<0.001	1	-	-
	Rectosigmoid	628	28.8%	154	56.4%		3.19	2.47	4.13

Table 3

Terminal node	LNPCP Subtype	LNPCP frequency		Gain (number with SMIC)		Percent SMIC within subtype	Index ratio*	Potential SMIC category
		N	%	n	%			
3	depressed	118	4.8%	73	26.7%	61.9%	5.6	High risk (>50%)
13	nodular, rectosigmoid, >=40mm	363	14.8%	81	29.7%	22.3%	2.0	Elevated risk (>10%)
10	nodular, proximal colon, NG	125	5.1%	25	9.2%	20.0%	1.8	
12	nodular, rectosigmoid, <40mm	160	6.5%	19	7.0%	11.9%	1.1	
4	flat, NG	558	22.8%	43	15.8%	7.7%	0.7	Unlikely (2.5%-10%)
9	flat, rectosigmoid, G	136	5.5%	7	2.6%	5.1%	0.5	

11	nodular, proximal colon, G	395	16.1%	19	7.0%	4.8%	0.4	
8	flat, proximal colon, G	596	24.3%	6	2.2%	1.0%	0.1	Very unlikely (<2.5%)
Total LNPCP cohort		**2451**	**100%**	**273**	**100%**	**11.1%**	**1**	-

*Ratio of percent with SMIC within subtype compared to that for the total LNPCP cohort

Supplementary Table 1

	Covert (n=115; 42.8%)	Overt (n=154; 57.2%)	Total* = 269
Age	66.6 (±0.5)	70 (±0.5)	
Gender			
Male	60 (38%)	98 (62%)	158 (58.7%)
Female	55 (49.5%%)	56 (50.5%)	111 (41.3%)
Resection modality			
EMR	100 (66.7%)	50 (33.3%)	150 (55.8%)
ESD	7 (17.9%)	32 (82.1%)	39 (14.5%)
No attempted resection	8 (8.8%)[±]	72 (91.2%)	80 (29.7%)

LNPCPs containing SMIC stratified by covert and overt status

*4 missing Kudo data – all underwent EMR

[±] despite benign surface appearances, high suspicion for SMIC due to poor submucosal lifting

Supplementary Table 2

Morphology	Location	Granularity	Size	SMIC		Total	Percent SMIC	Terminal Node	SMIC Prevalence for node 'subtype'	
				No	Yes				Percentage	(95%CI)
Flat	Proximal	Granular	<40	400	3	403	0.7%	8	1.0%	(0.5%, 2.2%)
Flat	Proximal	Granular	>=40	190	3	193	1.6%			
Flat	Rectosigmoid	Granular	<40	57	4	61	6.6%	9	5.1%	(2.5, 10.2)
Flat	Rectosigmoid	Granular	>=40	71	3	74	4.1%			
Flat	Proximal	Nongranular	<40	326	16	342	4.7%	4	7.7%	(5.8%, 10.2%)
Flat	Proximal	Nongranular	>=40	127	15	142	10.6%			
Flat	Rectosigmoid	Nongranular	<40	47	11	58	19.0%			
Flat	Rectosigmoid	Nongranular	>=40	15	1	16	6.3%			

Nodular	Proximal	Granular	<40	159	5	164	3.0%	11	4.8%	(3.1%, 7.4%)
Nodular	Proximal	Granular	>=40	217	14	231	6.1%			
Nodular	Proximal	Nongranular	<40	44	10	54	18.5%	10	20.0%	(13.9%, 27.9%)
Nodular	Proximal	Nongranular	>=40	56	15	71	21.1%			
Nodular	Rectosigmoid	Granular	<40	115	12	127	9.4%	12	11.9%	(7.7%, 17.8%)
Nodular	Rectosigmoid	Nongranular	<40	26	7	33	21.2%			
Nodular	Rectosigmoid	Granular	>=40	251	66	317	20.8%	13	22.3%	(18.3%, 26.9%)
Nodular	Rectosigmoid	Nongranular	>=40	31	15	46	32.6%			
Depressed	Proximal	Granular	<40	5	4	9	44.4%	3	61.9%	(52.9%, 70.1%)
Depressed	Proximal	Granular	>=40	4	4	8	50.0%			
Depressed	Proximal	Nongranular	<40	15	22	37	59.5%			
Depressed	Proximal	Nongranular	>=40	7	8	15	53.3%			
Depressed	Rectosigmoid	Granular	<40	3	2	5	40.0%			
Depressed	Rectosigmoid	Granular	>=40	3	7	10	70.0%			
Depressed	Rectosigmoid	Nongranular	<40	6	17	23	73.9%			
Depressed	Rectosigmoid	Nongranular	>=40	2	9	11	81.8%			

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Chapter 7

Publication:

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Summary:

- Prospective cohort of 1993 large adenomatous lesions that underwent conventional hot snare EMR.
- 26.4% of procedures were identified as 'challenging' due to the presence of intraprocedural bleeding, intraprocedural perforation or failed resection.
- Lesion size, location of ileocaecal valve, appendiceal orifice and anorectal junction, and nodular morphology were predictors of 'challenging' lesions.
- Predictive variables incorporated into a 6-point numerical *case selection score (EMR-CSS)*
- A cutoff of 2 predicted challenging resection with a sensitivity of 81.64% (95% CI 76.34-86.19%).

Contribution:

- This selection tool accurately identifies LNPCPs at risk of outcomes which would prove technically challenging for an "EMR-naïve" endoscopist
- This novel tool provides endoscopists with preprocedural awareness of anticipated difficulties to guide case selection and allocation of procedural time, resources, and staffing.

A novel tool for case selection in Endoscopic Mucosal Resection training

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Conflict of Interest

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Data transparency statement

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

Abbreviations

ACE, Australian Colonic Endoscopic Resection

ARJ, anorectal junction

CAST, cold avulsion snare tip soft coagulation

CI, confidence interval

CSPEB, clinically significant post-EMR bleeding

DMI, deep mural injury

EMR, endoscopic mucosal resection

ICV, ileocaecal valve

IQR, interquartile range

IPP, intraprocedural perforation

IPB, intraprocedural Bleeding

LNPCP, large non-pedunculated colorectal polyp ≥ 20mm

POSSUM, physiological and operative severity score

ROC, receiver operating characteristic

SMIC, submucosal invasive cancer

SMSA, size morphology site access

STSC, snare tip soft coagulation

ABSTRACT

Background

As endoscopic mucosal resection (EMR) of large (≥ 20mm) adenomatous nonpedunculated colonic polyps (LNPCPs) becomes widely practiced outside expert centres, appropriate training is necessary to avoid failed resection and inappropriate surgical referral. No EMR-specific tool guides case selection for endoscopists learning EMR. This study aimed to develop an EMR case selection score (EMR-CSS) to identify potentially challenging lesions for "EMR-naïve" endoscopists developing competency.

Methods

Consecutive EMRs were recruited from a single centre over 130 months. Lesion characteristics, intraprocedural data, and adverse events were recorded. Challenging lesions with intraprocedural bleeding (IPB), intraprocedural perforation (IPP), or unsuccessful resection were identified, and predictive variables identified. Significant variables were used to form a numerical score and receiver operating characteristic curves were used to generate cutoff values.

Results

Of 1993 LNPCPs, 286 (14.4%) were in challenging locations (anorectal junction, ileocecal valve, or appendiceal orifice), 368 (18.5%) procedures were complicated by IPB and 77 (3.9%) by IPP; 110 (5.5%) procedures were unsuccessful. The composite end point of IPB, IPP, or unsuccessful EMR was present in 526 cases (26.4%). Lesion size, challenging location, and sessile morphology were predictive of the composite outcome. A six-point score was generated with a cutoff value of 2 demonstrating 81% sensitivity across the training and validation cohorts.

Conclusions

The EMR-CSS is a novel case selection tool for conventional EMR training, which identifies a subset of adenomatous LNPCPs that can be successfully and safely attempted in early EMR training.

INTRODUCTION

Endoscopic mucosal resection (EMR) is the established standard of care for large (≥ 20mm) nonpedunculated colonic polyps (LNPCPs). Up until recently, its safety and cost-effectiveness were compromised by the occurrence of several well characterized adverse events (AEs) including perforation, bleeding, and recurrence [1–4]. The occurrence of these events is mitigated when important recent innovations are embraced, such as inspection of the post-EMR defect for evidence of significant deep mural injury (DMI), prophylactic clipping of right colon lesions, and thermal ablation of the post EMR defect margin [5–10]. When performed by experts, endoscopic cure and the avoidance of surgery is achievable in almost all patients [11]. Despite these outcomes, in the real-world setting, procedure related AEs, failed resection, and surgical referral remain problematic [12–14]. Such incongruence highlights the importance of accurately defining procedural competency, as EMR uptake increases outside tertiary centres.

The demonstration of competency in conventional hot snare EMR is however poorly defined, with absolute case numbers receiving the greatest attention within the literature [15-16]. No consideration is given to heterogeneity among LNPCPs and the consequent variability in procedural complexity. Building EMR competency requires an appreciation of the variability of lesion complexity and appropriate case selection to allow incremental advances in ability. The size, morphology, site, access (SMSA) score, which grades polypectomy complexity, has demonstrated utility in predicting failed resection and AEs with EMR [17–20]; however, its shortcoming for case selection is its inability to consider the specific technical aspects of EMR, and a general bias towards grading all lesions as either SMSA III or IV.

Using data from an expert centre, this study aimed to develop a case selection score (CSS) that identifies LNPCPs at risk of outcomes that would prove technically challenging for an "EMR-naïve" endoscopist who is still developing competency.

METHODS

Data were prospectively collected from a single tertiary centre on consecutive LNPCPs for which conventional EMR was attempted between September 2008 and February 2022. Institutional ethics approval was obtained, and informed consent was collected from all patients. The selection score was developed and validated retrospectively within this dataset. For patients with multiple LNPCPs, only the largest lesion was included. As this study was

specific to the conventional EMR technique, serrated lesions and LNPCPs selected for cold snare resection and endoscopic submucosal dissection (ESD) were excluded [21-22].

During the study period, multiple randomized trials were undertaken, and participants were included in this study cohort: thermal ablation of post-EMR defect margins, prophylactic right colon clipping for delayed bleeding prophylaxis, and cold EMR vs. hot snare EMR [5,8]. The primary end point in these trials was directed towards post-procedural outcomes, with the intervention having no bearing on the outcomes evaluated in this study. Lesions ≥15mm in size were recruited in some of these trials and subsequently remain in the final analysis.

EMR procedure

EMR procedures were performed by one of four senior endoscopists with extensive EMR experience or an advanced endoscopy fellow under direct supervision – four or five fellows rotated through the unit on a cycle of 1–2 years throughout the study period. All fellows were fully qualified gastroenterologists with accreditation in colonoscopy and conventional polypectomy.

Intravenous sedation was given to patients using a combination of fentanyl, midazolam, and propofol. Insufflation of the colon was initially performed with air, moving to carbon dioxide in 2010. Colonoscopy was performed using Olympus 180/190 series high-definition variable-stiffness colonoscopes (180/190 PCF/CF; Olympus, Tokyo, Japan). A previously described inject and-resect EMR technique was used [23]. A microprocessor controlled electrosurgical generator (Endocut effect 3, VIO300D; ERBE Elektromedizin, Tübingen, Germany) with fractionated current was used for electrocautery. The submucosal injectate comprised normal saline until 2010, when it was replaced with succinylated gelatin (Gelofusine; B. Braun Australia Pty Ltd., Bella Vista, Australia). The fluid was dyed with indigo carmine blue (80 mg/500mL solution) and epinephrine was added to achieve a final concentration of 1:100 000. Snare-tip soft coagulation (STSC; Soft coagulation, 80 W, effect 4; ERBE) was performed at the lesion margins after 2017, once it had been found to reduce endoscopic recurrence at the first surveillance colonoscopy [5, 7].

Data collection

Baseline demographics were collected. Individual LNPCP characteristics, including location, size, morphology, and Paris classification [24], were documented. Paris 0-IIa, IIb, and IIc lesions were categorized as flat morphology, and IIa+Is or Is as raised.

Lesion location was divided into right or left colon (proximal and distal to the splenic flexure) or challenging location (anorectal junction [ARJ], ileocecal valve [ICV], or appendiceal orifice). Procedure-specific factors recorded included lesion access, submucosal lifting, and successful EMR. Access was defined as difficult if either reaching the lesion or maintaining a stable scope position during resection were deemed challenging. Lesions were labelled poorly lifting based on well described signs [23]. An EMR was deemed unsuccessful if, at procedure termination, endoscopically visible polyp tissue remained at the resection site.

Adverse events

Intraprocedural bleeding (IPB) was defined as oozing or pulsatile bleeding requiring endoscopic control with thermal therapy or clips [25]. Intraprocedural perforation (IPP) was defined, as per the Sydney DMI classification, as a visible target sign or full-thickness hole, corresponding to DMI types III/IV/V [9]. Clinically significant post endoscopic bleeding (CSPEB) was bleeding after completion of the EMR and discharge from the endoscopy unit that resulted in emergency department presentation, hospitalization, or re-intervention within 14 days [25]. Delayed perforation was a perforation occurring after the completion of the EMR procedure.

Primary end point

The primary aim of the study was to develop a tool that identifies LNPCP subtypes for which EMR should not be attempted by endoscopists early in their EMR training. A composite end point of IPB, IPP, or unsuccessful EMR was used to develop a predictive model. Haemostasis of IPB requires thermal therapy or clip closure. Similarly, IPP necessitates fastidious clip closure to ensure complete mucosal apposition. Compared with basic snare manipulation and submucosal injection, these advanced techniques are technically challenging for a trainee. Unsuccessful EMR occurs in a cohort of lesions which, by their intrinsic nature, cannot be successfully resected and as such are poor training cases.

Statistical analysis

Study participants were randomly assigned in a 1:1 ratio to the training or validation cohorts. The score for predicting a “poor” composite outcome was developed in the training cohort.

The primary outcome measure was the diagnostic utility of this tool in differentiating between “good” and “poor” outcomes in the independent validation cohort. The area under the receiver operating characteristic curve (AUROC) was used to assess the diagnostic utility of the tool. The sensitivity and specificity associated with different cutoff points were calculated for the training and validation cohorts. These and other metrics used to quantify diagnostic test performance were calculated with 95%CIs in the validation cohort.

IBM SPSS Statistics version 27 was used to analyse the data. Categorical variables were summarized using frequencies and percentages, with median (interquartile range [IQR]) for continuous variables. In the training cohort, chi-squared tests were used to test for association between the composite outcome and categorical variables, and Mann–Whitney U tests for continuous variables. Those variables that demonstrated a univariable association ($P < 0.2$) with the composite outcome in the training cohort were included in a multiple logistic regression model with backward stepwise variable selection to identify independent predictors of the composite outcome. Decision-tree analysis was used in the training cohort to confirm that the same variables of interest were identified as those in the best fitting logistic regression model.

The score was derived from the regression coefficients of the best fitting logistic regression model in the training cohort. The score was calculated for each subject in the training and validation cohorts. The AUROC and sensitivity and specificity of different cutoff values were determined for each cohort. The Medcalc diagnostic test evaluation calculator was used to estimate the evaluation metrics and 95%CIs in the validation cohort using the recommended cutoff point of the score.

RESULTS

A total of 2913 lesions in 2576 patients were recruited over the study period. Following exclusions, 1993 lesions were eligible for analysis (Fig. 1 Supplementary material). The median (IQR) lesion size was 35 (30–50) mm, and there was a predominance of granular (67.7%) and right colon (63.2%) lesions (Table 1). Lesions were found to be in challenging locations (ARJ, ICV, or appendiceal orifice) in 286 cases (14.4%), with 709 lesions (35.6%) being difficult to access, and 271 (13.6%) having been previously attempted. IPB was encountered in 368 patients (18.5%) and IPP in 77 (3.9%). EMR was unsuccessful in 110 lesions (5.5 %). The composite end point of IPB, IPP, or unsuccessful EMR was present for 526 lesions (26.4%) (Table 1).

Univariable analysis for the training cohort identified lesion size (P < 0.001), nodular morphology (P < 0.001), and challenging location (P = 0.005) as being significant factors affecting outcome (Table 1 Supplementary material). The best fitting logistic regression model identified lesion size (P < 0.001), challenging location (P =0.005), and raised morphology (P = 0.001) as being the significant predictors (Table 2). Coefficients from the model were transformed into a six-point numerical score (Table 3).

A cutoff of 2 best predicted the composite outcome (Table 4) in 209 /256 cases within the training cohort, with a sensitivity of 81.6% (95%CI 76.3%–86.2%) (Table 5) and an AUROC of 0.682 (Fig. 2 Supplementary material). The score performed similarly within the validation cohort, with a cutoff of 2 predicting the composite outcome in 219/269 cases, giving a sensitivity of 81.4% (95% CI 76.2%–85.9%) (Table 5) and an AUROC of 0.687 (Fig. 2 Supplementary material). The decision-tree analysis model confirmed the same set of variables as those identified as being independent predictors in the best fitting multiple logistic regression model (Fig. 3 Supplementary material).

DISCUSSION

EMR is established as the standard of care for the resection of LNPCPs, with high quality evidence demonstrating its safety and effectiveness. Its subsequent endorsement within international guidelines encourages its widespread practice [26, 27]. Real-world outcomes do not however reflect those of expert centres, with failed resection and surgical referral remaining problematic [12–14]. Consequently, EMR training and competency development is gaining increasing traction. Currently, endoscopists developing EMR competence have no EMR-specific tool to guide case selection prior to LNPCP resection.

Formal training and competency assessment for EMR remains poorly developed. Published competency measures focus on absolute numbers of procedures, determined by either hard outcomes, including recurrence, or subjective assessment tools [15-16]. No consideration is currently given to the individual lesion difficulty when formulating these measures. Whilst snare resection is one aspect of EMR, managing complications requires further advanced skills, and lesions at risk of technical failure are poor training models. Real-world data suggest that lesion difficulty warrants consideration in training pathways, with the rates of failed resection and surgical referral exceeding that of expert centres [12–14, 28]. A meta-analysis found 503/6442 patients underwent surgery owing to noncurative endoscopic resection [28]. Our prospective study identified 12.2% of LNPCPs as being previously

attempted, yet these were amenable to endoscopic resection when appropriate endoscopic techniques were employed [14]. A 14-year retrospective analysis of the Healthcare Cost and Utilization Project in the USA reported the incidence of colorectal surgical resection for benign disease nearly doubled from 5.9 to 9.4 per 100 000 adults [12].

The SMSA score is a readily available tool to predict the complexity of standard polypectomy [17]. A retrospective study of 1668 lesions found a positive correlation between increasing scores and incomplete endoscopic resection, surgical referral, and AEs [18]. Subsequently the SMSA score has been validated within EMR cohorts to predict procedural outcomes. A prospective study of 242 lesions found polyp clearance was influenced by lesion complexity [19]. A retrospective study of 2675 lesions identified the SMSA score to be predictive of failed EMR, with intraprocedural and post EMR bleeding occurring less frequently for low scoring SMSA lesions [20]. Despite these findings, the SMSA score could be improved as a case selection tool for EMR procedures.

The SMSA score fails to consider the specific nuances of the EMR technique or morphological features intrinsic to LNPCPs. Nongranular and previously attempted non-lifting lesions are well known to be challenging but are not included in the SMSA score [14, 29]. Additionally, locations associated with increased technical difficulty, such as the appendiceal orifice, ARJ, and ICV, do not feature within the SMSA categories [30–32]. Presently, complexity grading is heavily influenced by lesion size, with all LNPCPs automatically classified as level III/IV owing to their size being ≥ 20mm. Within previous validation studies, SMSA II lesions have comprised only < 7% of all EMR cases [20]. Until now, an “SMSA-like” score to guide case selection and consider these deficiencies has been lacking.

Our study has created a case selection tool, the EMR-CSS, from a large EMR cohort to guide adenomatous LNPCP selection for endoscopists training in conventional colonic EMR. In contrast to the SMSA score, EMR variables such as submucosal lifting, previous attempts, lesion morphology, and challenging locations (ICV, ARJ, or appendiceal orifice) have been incorporated into the model development, with the size categories also adjusted to reflect an LNPCP cohort. The composite end point of IPB, IPP, or technical failure was chosen to reflect what would be challenging cases for EMR trainees. Lesions at risk of technical failure are poor candidates for training cases and both IPP and IPB require advanced endoscopic techniques, such as accurate clip closure and targeted thermal therapy.

Endoscopic adenoma recurrence has previously been used as an indicator of EMR competency. Historically this was necessary, given the clinical significance of residual recurrent adenoma post-EMR; however, recent clinical trials and real-world studies have consistently demonstrated recurrence rates < 5% with the incorporation of STSC to the EMR defect margin [5,7]. Negligible recurrence rates within our cohort made it a poor marker of polyp complexity; however, we recognize that this is conditional on STSC being performed correctly. Whether the effectiveness of STSC differs for trainees is yet to be explored and warrants further investigation.

This score applies to LNPCPs resected with a conventional hot snare technique, with ESD cases actively excluded. ESD was performed on lesions with optical features of overt superficial submucosal invasive cancer (SMIC), with rectal LNPCPs also selectively resected as part of an algorithm targeting covert SMIC [22]. Serrated lesions and LNPCPs resected with a cold EMR technique were also excluded from the analysis. Cold snare excision of serrated lesions is a safe practice, with negligible recurrence, and is now the standard of care within our and other expert centres [21, 33-34]. Not only does electrocautery increase the risk of DMI and delayed bleeding, but it requires additional competencies in comparison with cold snare techniques. We anticipate that wide-field cold snare resection for suitable LNPCPs will have a somewhat different learning curve to conventional EMR and, as such, it requires its own case selection methods.

Overall, our multivariate analysis identified LNPCP size, morphology, and challenging location as being significant predictors of technical failure, IPB, or IPP. When tested on the validation cohort, the subsequent score accurately identified high risk lesions in 219/269 cases. Specifically, all LNPCPs < 20mm in size were deemed low risk, in addition to flat lesions of 20–35mm. Once a nodular (Paris 0-Is) component develops or if the location is challenging, the risk of AEs increases (Fig. 1).

This contrasts with the SMSA score, which identifies flat morphology as being of higher complexity. Furthermore, right colon lesions do not confer the same risk that is suggested in the SMSA score; instead, it is the challenging EMR locations of ICV, ARJ, or the appendiceal orifice that are predictive. Whereas the SMSA score has previously identified the right colon as being associated with higher risk, the EMR-CSS suggests that this may not be the case and that it is in fact a reflection of the right colon containing both the appendiceal orifice and the ICV.

Interestingly, previously attempted non-lifting lesions and poor endoscopic access were not predictive of the composite outcome in our model. Within this cohort, this reflects the utility of adjuvant techniques, such as cold avulsion snare-tip soft coagulation (CAST), which is a simple, effective, and safe method of resecting these lesions. ESD is proposed as a means of treating non-lifting lesions; however, CAST is very effective, efficient, and less resource-intensive, with further comparative studies being required [14, 35]. In an expert centre, poor access is frequently negated with the appropriate use of patient position changes, retroflexion, and water immersion.

This novel case selection tool has applications for both health services and endoscopists developing EMR proficiency. At an individual level, preprocedural awareness of the anticipated difficulty guides case selection and appropriate allocation of procedural time, resources, and staffing. Not only can the tool be used by fellows training in EMR, but it can also be used in inexperienced EMR services or by endoscopists practicing independently but still on the learning curve. In some circumstances, this may identify LNPCPs that are more appropriately referred to expert centres or treated under the supervision of an EMR mentor. More broadly, incorporation of this tool into future competency thresholds will provide an accurate representation of procedural proficiency and allow training pathways to become more streamlined and targeted to individual lesions.

This study has some limitations. The score was generated and validated from a retrospective analysis of our prospectively recruited cohort study. Furthermore, we recognize it was undertaken within a tertiary centre where procedures are performed by expert endoscopists, with outcomes reflecting those found in the literature. However, we feel this was necessary when generating a score to identify LNPCP subtypes at risk of AEs. Doing so from a trainee population with heterogeneous competency would reflect trainee behaviour, rather than lesion behaviour. We recognize that prospective application of this tool within training cohorts and in nontertiary centres is necessary to assess its accuracy in a real-world training environment.

In conclusion, the EMR-CSS is a novel, readily applicable case selection tool for endoscopists training in conventional EMR, which identifies a subset of adenomatous LNPCPs that can be successfully and safely attempted early in EMR training. This scoring system will help EMR trainees recognize their limitations, guide case selection, and improve the accuracy of future competency markers.

FIGURE LEGEND

SUPPLEMENTARY FIGUREs

- **Figure 1:** Participant flow throughout study period.
- **Figure 2 -** Receiver operating characteristic curves within training and validation cohorts. AUC, area under the curve
- **Figure 3 -** Decision tree analysis model confirming the same set of variables identified in the best fitting regression model
- **Table 1** - Univariable analysis in training cohort. EMR, endoscopic mucosal resection

MANUSCRIPT FIGURES

- **Figure 1:** Endoscopic images of example large adenomatous nonpedunculated colonic polyps (LNPCPs) of 20–25mm in size, showing: a–c a flat 22-mm LNPCP of the transverse colon with a score of 1, indicating that it is suitable to be attempted early during endoscopic mucosal resection (EMR) training; d–f a nodular 25-mm LNPCP at the anorectal junction with a score of 3, indicating that it carries a higher risk of intraprocedural complications or technical failure and therefore is not suitable to be attempted early during EMR training.
- **Table 1** - Baseline patient and lesion characteristics and outcomes of the training and validation cohorts. IQR, interquartile range; EMR, endoscopic mucosal resection; STSC, snare-tip soft coagulation
- **Table 2** - Best fitting multiple logistic regression model in the new training cohort
- **Table 3** - The endoscopic mucosal resection case selection score (EMR-CSS)
- **Table 4** - Performance of the endoscopic mucosal resection case selection score (EMR-CSS) in the training and validation cohorts
- **Table 5** - Optimum cutoff scores for the endoscopic mucosal resection case selection score (EMR-CSS) within: a the training cohort; b the validation cohorts.

Table 1

Baseline characteristics of training and validation cohorts						
	Training cohort		Validation cohort		Total cohort	
	n = 996	%	n = 997	%	n = 1993	%
Age median (IQR)	69 (62-76)		69 (61-75)		69 (61-76)	
Sex						
Male	531	53.3%	553	55.5%	1084	54.4%
Female	465	46.7%	444	44.5%	909	45.6%
Size (mm)						
Median (IQR)	35mm (25-50)		40mm (30-50)		35mm (30-50)	
≤ 20	137	13.8%	121	12.1%	258	12.9%
21 - 35	409	41.1%	374	37.5%	783	39.3%
36 - 55	318	31.9%	346	34.7%	664	33.3%
56+	132	13.3%	156	15.6%	288	14.5%
Colon location						
Left	361	36.2%	373	37.4%	734	36.8%
Right	635	63.8%	624	62.6%	1259	63.2%
Challenging location	135	13.6%	151	15.1%	286	14.4%
Granularity						
Non-granular	322	32.8%	311	31.7%	633	32.3%
Granular	659	67.2%	669	68.3%	1328	67.7%
Nodular component	451	45.3%	417	41.9%	868	43.6%
Paris						
0-Is	134	13.5%	115	11.6%	249	12.5%
0-IIa	471	47.3%	511	51.4%	982	49.3%
0-IIb	28	2.8%	29	2.9%	57	2.9%
0-IIc	29	2.9%	31	3.1%	60	3.0%
0-IIa + Is	317	31.9%	302	30.4%	619	31.1%

0-IIa + IIb	16	1.6%	7	0.7%	23	1.2%
Previous attempt	135	13.6%	136	13.6%	271	13.6%
Non-lifting	90	9.6%	68	7.2%	158	8.4%
Difficult access	344	34.5%	365	36.6%	709	35.6%
EMR unsuccessful	53	5.3%	57	5.7%	110	5.5%
STSC	431	43.4%	427	42.8%	858	43.1%
IP Bleed	176	17.7%	192	19.3%	368	18.5%
IP Perforation	43	4.3%	34	3.4%	77	3.9%
Delayed bleed	78	7.8%	74	7.4%	152	7.6%
Delayed perforation	3	0.3%	4	0.4%	7	0.4%
Composite outcome (IP bleeding, technical failure, IP perforation)	256	25.7%	270	27.1%	526	26.4%

STSC, snare tip soft coagulation; IP, intraprocedural; EMR, endoscopic mucosal resection; IQR, interquartile range

Supplementary table 1

Univariable analysis in training cohort

	Good outcome		Poor outcome		p-value
	n	%	n	%	
Sex					
Male	386	52.2%	145	56.6%	0.216
Female	354	47.8%	111	43.4%	
Size					
≤ 20	121	16.4%	16	6.3%	**<0.001**
21 - 35	333	45.0%	76	29.7%	
36 - 55	219	29.6%	99	38.7%	
>55	67	9.1%	65	25.4%	
Colon location					
Left	263	35.5%	98	38.3%	0.432
Right	477	64.5%	158	61.7%	
Challenging location	87	11.8%	48	18.8%	**0.005**
Granular morphology					

Non-granular	243	33.3%	79	31.3%	0.563
Granular	486	66.7%	173	68.7%	
Nodular component	297	40.2%	154	60.2%	**<0.001**
Paris					
0-Is	100	13.5%	34	13.3%	**<0.001**
0-IIa	381	51.6%	90	35.2%	
0-IIb	23	3.1%	5	2.0%	
0-IIc	25	3.4%	4	1.6%	
0-IIa + Is	197	26.7%	120	46.9%	
0-IIa + IIb	13	1.8%	3	1.2%	
Previous Attempt	99	13.4%	36	14.1%	0.783
Non-lifting	62	8.8%	28	11.7%	0.197
Difficult access	246	33.2%	98	38.3%	0.144
EMR unsuccessful	0	0.0%	53	20.7%	

EMR, endoscopic mucosal resection

Table 2

Best fitting multiple logistic regression model in Training cohort						
Variables	**B**	**S.E.**	**Odds ratio**	**95% C.I.for OR**		**p-value**
				Lower	**Upper**	
Size (4 groups)						<0.001
(21-35) vs ≤20mm	0.502	0.298	1.651	0.921	2.961	0.092
(36-55) vs ≤20mm	1.111	0.298	3.037	1.695	5.444	<0.001
>55mm vs ≤20mm	1.783	0.327	5.947	3.131	11.296	<0.001
Sessile component	0.528	0.157	1.695	1.246	2.305	0.001
Challenging location	0.577	0.207	1.781	1.187	2.673	0.005
Constant	-2.281	0.276	0.102			<0.001

Table 3

EMR-CSS – EMR training case selection score

- **Size:**
  - Small (<20mm) 0 points
  - Medium (21-35mm) 1 point
  - Large (36-55mm) 2 points
  - Very large (>55 mm) 3 points
- **Nodular component:** 1 point
- **Challenging location (ARJ, ICV, AO)**: 1 point

≥2 = challenging lesion for early EMR trainees

Table 4

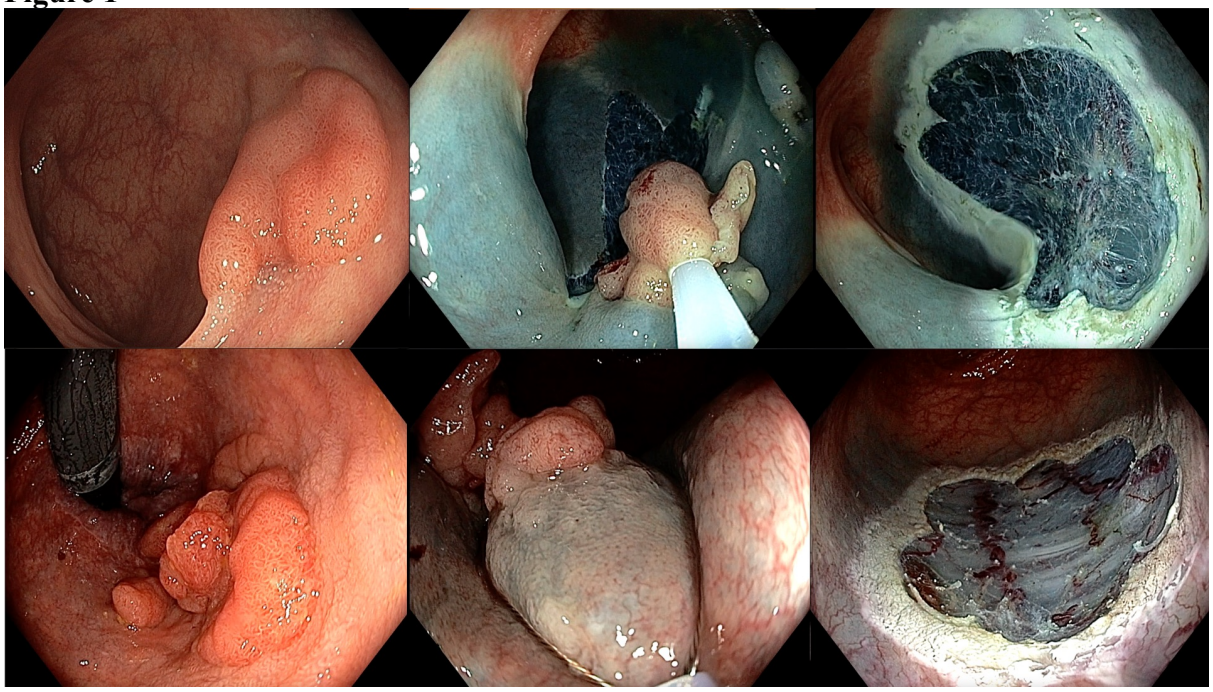
Performance of Score in Training and Validation cohorts				
Score	Training cohort		Validation cohort	
	Specificity	Sensitivity	Specificity	Sensitivity
≥1	0.10	0.96	0.11	0.97
≥2	0.42	0.82	0.42	0.81
≥3	0.73	0.56	0.71	0.59
≥4	0.92	0.24	0.90	0.30
5	0.99	0.05	0.99	0.05

Table 5

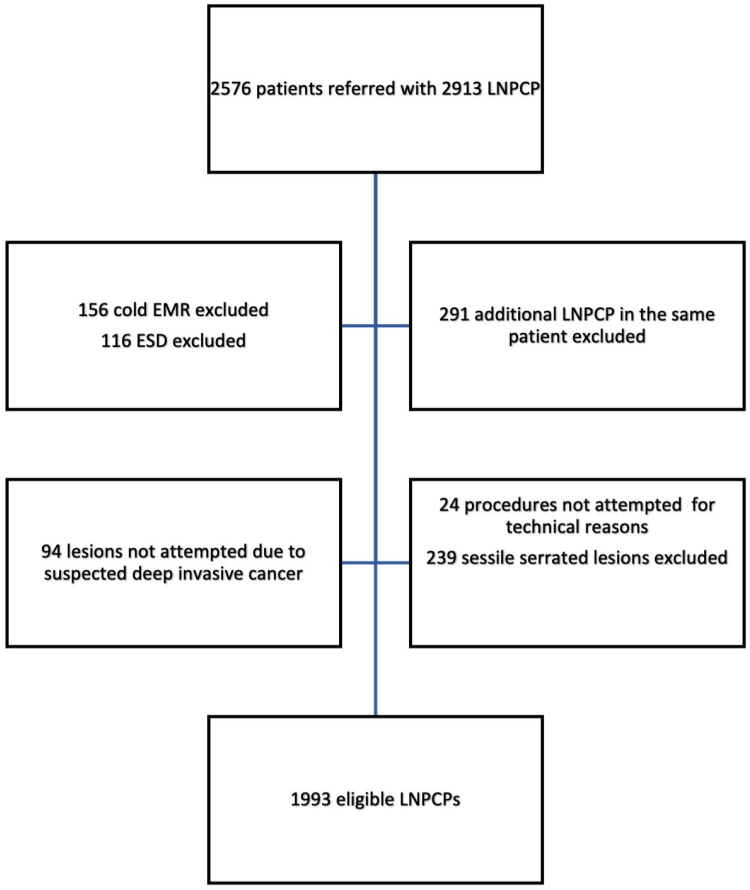
Training cohort			
EMR-CSS	Good outcome	Poor outcome	Total
<2 (predicted 'good')	310	47	357
≥2 (predicted 'poor')	429	209	638
Total	739	256	995

Validation cohort			
EMR-CSS	Good outcome	Poor outcome	Total
<2 (predicted 'good')	305	50	355
≥2 (predicted 'poor')	421	219	640
Total	726	269	995

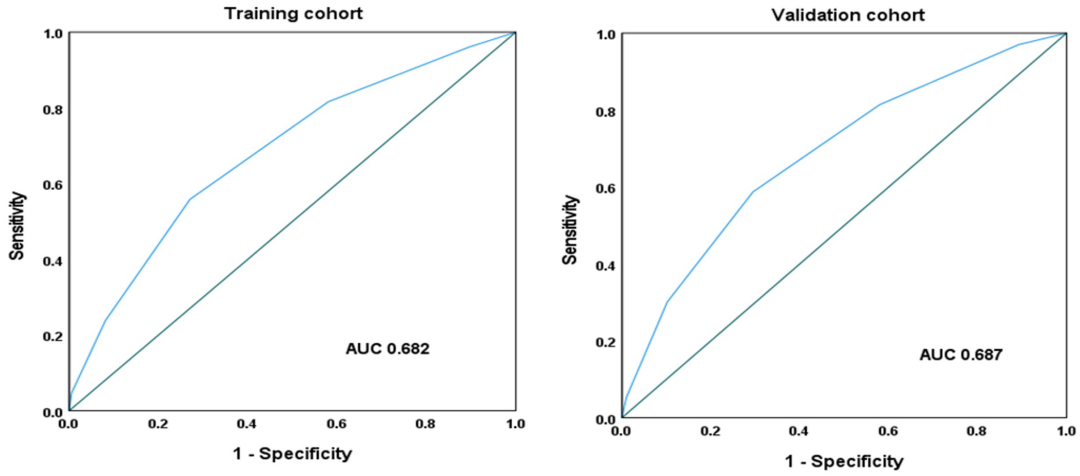
Figure 1



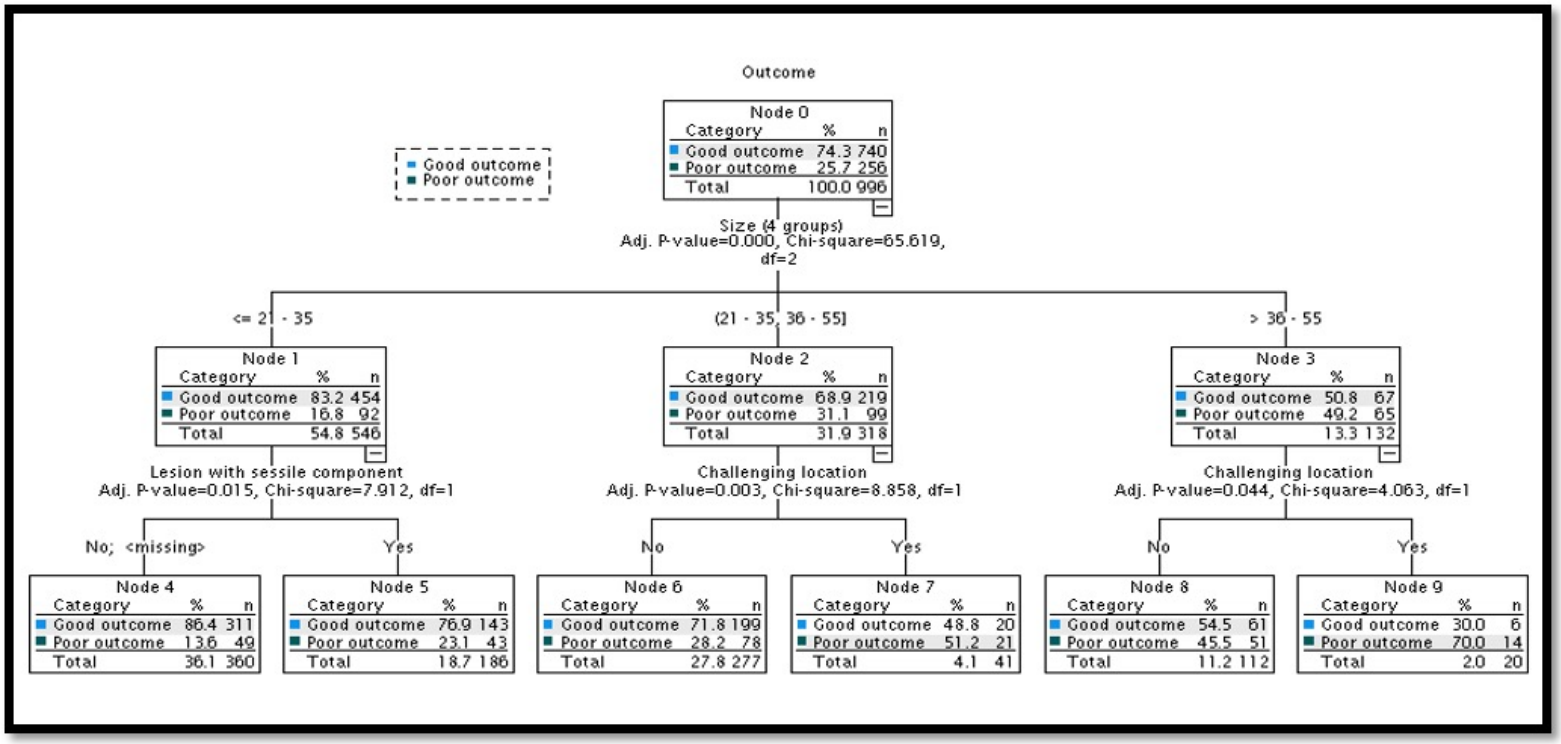
Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3



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Chapter 8
Integrated Discussion

Endoscopic mucosal resection (EMR) is standard of care for the management of benign LNPCPs within international consensus guidelines.[1-2] Major technical advances over the past 10 years have established EMR as a safe and effective resection modality for colorectal neoplasia. With superior safety and equivalent efficacy, EMR is a less invasive, more cost-effective treatment for benign colorectal neoplasia when compared to surgery.[3-6]

For smaller (<10mm) polyps, cold snare polypectomy has infrequent complications whilst maintaining excellent efficacy and complete resection rates.[7-9] Conventional hot snare EMR however, is yet to achieve all these results with electrocautery related complications and post endoscopic resection surveillance a persistent burden on both patients and the broader health service.[6] Moreover, larger benign lesions continue to be resected with colorectal surgery, subjecting patients to unnecessary risk and morbidity.[10-11]

Of the five investigative studies included in this thesis, three addressed key areas within colorectal endoscopic resection technique and surveillance intervals. The final two studies address current research gaps in optical diagnosis and training in colorectal endoscopic resection.

Part 1:
Improvements in colorectal endoscopic resection technique and surveillance pathways

Cold snare resection of LNPCPs

Conventional hot snare EMR demonstrates superior safety and cost-effectiveness compared to surgery.[3-4] Cold snare polypectomy avoids the thermal injury of electrocautery and for smaller polyps and large serrated lesions, remains a highly effective and safe resection modality.[7-9, 12-14] High-quality randomised trials examining cold snare resection for adenomatous LNPCPs however are lacking.

Chapter 3 presents the findings of a single centre randomized controlled trial comparing conventional hot snare EMR with piecemeal cold snare EMR for adenomatous polyps 15-

50mm in size. 177 patients were randomized with 87 in the cold EMR arm and 90 in the hot EMR arm. Overall, technical success was equivalent between treatment arms (98.9% C-EMR vs 100% H-EMR; p=0.31). Cold EMR was significantly safer with reduced rates of delayed bleeding 7/90 (7.8%) vs 1/87 (1.1%); RR 6.77, 95% CI 0.85-53.9; p = 0.034) and no cases of delayed perforation (1/90 (1.1%) vs 0; p=0.32). Despite its relative safety however, cold EMR demonstrated significantly greater recurrence rates on intention to treat analysis (16/87, 18.4% vs 1/90, 1.1%; RR 16.6, 95%CI 2.24-122; p<0.001).

These findings emphasise that irrespective of its safety profile, universal implementation of cold EMR for flat adenomas cannot be justified considering the significant recurrence rates. Incompletely resected polyps are a driver of post-colonoscopy colorectal cancer[15] and whilst easily treated at surveillance procedures, assume compliance with follow-up and necessitate an increased number of endoscopic treatments. Future economic analyses with accurate C-EMR data will provide a better understanding of the financial impact of these findings. Further studies are required to optimise resection technique and define predictors of recurrence to inform lesion selection. When delayed complications are unacceptable for individual patients, cold snare resection may be a sensible approach following appropriate patient counselling and lesion selection.

Long term surveillance outcomes of conventional EMR with MTA

Considering the historic frequency of endoscopic recurrence post colorectal EMR, surveillance procedures remain conservative at six (SC1) and 18-months (SC2) post-resection.[1-2] In many instances, four colonoscopies within an 18–24-month period are necessary and a considerable burden for patients and the broader health service. This practice is based on historical data reporting recurrence rates at SC1 and SC2 of 13% and 4% respectively.[5-6] Since the introduction of margin thermal ablation (MTA) to the post-EMR defect with snare tip soft coagulation (STSC), recurrence now occurs in <5% cases in both clinical trials and real-world settings.[16-18] Long term recurrence outcomes and the utility of conservative surveillance intervals are unknown for contemporary EMR practice which includes MTA.

Chapter 4 summarises the long-term surveillance findings of a large prospective multicentre study of >1000 LNPCPs that have undergone contemporary EMR with MTA. These results were compared to a historical control arm of EMR procedures without MTA. Of the 472 patients who completed SC2 follow-up, one recurrence was identified in the MTA EMR arm

compared to nine cases in the control arm (1/472 (0.2%) vs 9/260 (3.5%); p<0.001). Moreover, compliance by both referrers and patients with long term follow up was poor across both treatment arms with >200 missing SC2 cases, highlighting the burden of intensive surveillance pathways. 36 missing surveillance cases were a result of external referrers inappropriately recommending SC2 at 3-5 years post SC1. Furthermore, median time to SC2 for the entire cohort was 19 months (IQR 17-25) with 25% of cases exceeding 25 months.

These findings argue for a paradigm shift in the post-resection surveillance for contemporary EMR procedures with MTA. Unlike historic conventional EMR, EMR with MTA provides durable endoscopic remission at long term follow up. In the event that recurrence or significant synchronous disease is not identified at SC1, repeat colonoscopy in 3-5 years will potentially reduce procedural and financial burdens placed on both patients and the broader health service.

Prevalence and predictors of synchronous LNPCPs post endoscopic resection

Irrespective of recurrence outcomes in the era of MTA, the prevalence of synchronous colorectal neoplasia in EMR cohorts is a compelling argument for early post-resection surveillance. Multiple studies have demonstrated that this is a significant issue for LNPCPs, with synchronous large lesions detected in up to 18% of cases.[19-23] Whether individual LNPCP subtypes are associated with a greater frequency of synchronous disease is unknown. Establishing a lesion phenotype at heightened risk of synchronous pathology argues for tailored, lesion-specific surveillance pathways.

Chapter 5 presents a large multicentre prospective study of endoscopically resected LNPCPs. Of over 3000 LNPCPs, 6.9% demonstrated synchronous pathology at either the EMR procedure or post-resection surveillance. These lesions were often missed at the initial diagnostic colonoscopy, reinforcing the inattentional blindness experienced when encountering large polyps.

Following multivariate analysis incorporating multiple lesion characteristics, non-granular morphology was a significant predictor of synchronous neoplasia. This was further influenced by lesion location with left colon nongranular-LNPCPs demonstrating greater risk (OR 4.78 95% CI 2.95-7.73) than right colon nongranular LNPCPs (OR 1.99 95% CI 1.39-2.86). 71.4% (kappa 0.35) of synchronous LNPCPs originated from the same colonic segment (right vs left colon) and 72.4% (kappa 0.41) were of the same granularity.

This study reinforces that paradigm shifts in surveillance cannot be implemented without considering the risk of interval neoplasia and synchronous pathology. Despite the infrequency of recurrence at long term follow up, early surveillance post resection is paramount to detect synchronous colorectal neoplasia. Surveillance pathways may require tailoring to individual lesion phenotypes that consider the influence of morphology and location on the risk of synchronous disease.

Part 2: Optimisation of lesion selection for endoscopic resection training and tertiary referral

Decision making algorithm for predicting the risk of submucosal invasive cancer (SMIC)

LNPCPs demonstrate a heightened risk of SMIC of 5-7%. Recognition of SMIC however remains a challenge, with optical diagnosis a necessary adjunct to histopathological assessment.[24-25] Accurate identification of potential SMIC is vital when considering appropriate resection modality, with surgery not required in all cases. Whereas deeply invasive disease requires definitive surgical resection, low risk superficial-SMIC when endoscopically removed en bloc can facilitate oncological cure. Recently it has emerged that individual LNPCP variables of location, morphology, granularity, and size, influence the risk of SMIC.[24] Application of this knowledge is inherently complex and consequently limited in its accessibility in a real-world context. Moreover, this is an issue that transcends endoscopists of all levels of experience and proficiency.

Chapter 6 presents the findings of a prospective single centre study of over 2000 LNPCPs referred for endoscopic resection. SMIC was confirmed in 273 (11.1%) of lesions. Lesion characteristics of size, morphology and location were assessed in multivariate analysis and identified as predictors of SMIC as reported in previous studies.[24] These same predictors were then included in a decision tree analysis to provide an algorithm framework that illustrates SMIC risk in simplified terms. The highest risk LNPCPs were depressed morphology, nodular rectosigmoid and nodular nongranular lesions with a prevalence of SMIC in 61.9%, 19.1% and 20% of lesions respectively.

The resulting algorithm provides readily available lesion-specific risks of potential SMIC that assists endoscopists in understanding the risk of cancer in an LNPCP which is otherwise thought to be benign. When used as an adjunct to surface optical evaluation, the algorithm provides endoscopists of all levels of experience with the confidence to more accurately

assess SMIC risk and minimise the referral of benign lesions for unnecessary surgical resection.

Development of a case selection score to assist EMR training

In real-world settings, adverse events, failed resection and surgical referral remain problematic in the management of benign LNPCPs.[10-11] Within a large study of 1134 lesions, 12.2% of LNPCPs were referred for failed resection at non-expert centres.[26] With the majority of these cases successfully resected within a tertiary centre, the heterogeneity of procedural competency and formal EMR training comes into question. Currently, formal training and competency assessment for EMR remains poorly developed, with no consideration given to individual lesion difficulty.[27-28] Whilst well-validated scores assist endoscopists for grading difficulty within polypectomy, an EMR-specific tool that considers procedural and lesion nuances is lacking.[29-32]

Chapter 7 describes a prospective study of 1993 adenomatous lesions that underwent conventional hot snare EMR. 26.4% of procedures were identified as 'challenging' due to the presence of either intraprocedural bleeding, intraprocedural perforation or failed resection. Following multivariate analysis, lesion size, location of ileocaecal valve, appendiceal orifice and anorectal junction and nodular morphology were predictive of 'challenging' resection. Predictive variables were allocated a numerical value and a total score cutoff of 2, predicted challenging resection with a sensitivity of 81.64% (95% CI 76.34-86.19%). The score performed similarly within a validation cohort with the same cutoff predicting the composite outcome with a sensitivity of 81.41% (95%CI 76.24-85.88%).

Overall, this selection tool accurately identifies LNPCPs at risk of outcomes which would prove technically challenging for an "EMR-naïve" endoscopist developing competency. The tool provides endoscopists with preprocedural awareness of anticipated difficulties to help guide case selection and appropriate allocation of procedural time, resources, and staffing. This is applicable to both fellows training in EMR, but also inexperienced EMR endoscopists practicing independently but still on the learning curve.

Future directions

Despite the innovative findings of this thesis, there remain further unanswered questions within the field of colorectal endoscopic resection. These include:

1) The role of artificial intelligence in the identification of SMIC. Whilst surface appearance and lesion morphology reliably predict the risk of SMIC, this process lends itself to highly accurate machine-based learning platforms. Prospective evaluation of this technology in large colonic polyps is scarce.

2) Lesion selection for ESD. As access to colorectal ESD increases within endoscopy units, appropriate lesion selection requires further refinement. A selective vs universal colorectal resection approach remains debated within the literature.[33-35] Additional large scale interventional studies are required to refine the optimal approach which considers both procedural and oncological outcomes.

3) Predictors and preventers of endoscopic recurrence in cold snare EMR. Despite this thesis identifying endoscopic recurrence as a significant limitation of cold snare EMR of LNPCPs, further studies are required to understand endoscopic predictors to inform lesion selection. Furthermore, it remains unclear if margin thermal ablation to cold snare resection defects will reduce recurrence as significantly as that seen in conventional hot EMR cohorts.

These topics are beyond the scope of this thesis and are best addressed in further high-quality prospective studies.

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Chapter 9

Conclusions

Endoscopic resection is established standard of care for the management of benign colorectal neoplasia. Despite EMR proving to be a safer, more cost-effective modality, unnecessary surgical resection continues to occur for benign disease. Furthermore, colonoscopy surveillance and post-procedural adverse events remain a limitation of endoscopic resection and place a potential procedural burden on both patients and health services. Considering these limitations, this thesis has addressed key questions surrounding endoscopic resection modalities, surveillance protocols as well as optical diagnosis and training pathways.

The first thesis aim demonstrated in a randomised trial setting, cold snare EMR of LNPCPs, whilst a safe alternative to conventional hot snare EMR, is limited by significantly higher rates of recurrence. Widespread implementation of cold EMR is therefore unlikely to occur for the treatment of large adenomatous polyps but remain an option for select lesions or patients in which adverse events may be poorly tolerated.

The second aim of the thesis evaluated long-term surveillance outcomes of contemporary hot snare EMR with margin thermal ablation. Recurrence was found to be exceedingly rare at long term surveillance in patients with a clear resection scar at first follow-up colonoscopy. These findings argue for a lengthening of surveillance intervals post-EMR to reduce procedural burden for both patients and the broader health service.

Relaxation of post-EMR surveillance intervals, however, must consider the burden of synchronous colonic neoplasia within this cohort. The third aim of this thesis addressed the prevalence and predictors of synchronous LNPCPs in patients undergoing EMR. It was identified that synchronous disease is not only highly prevalent, but more frequent in non-granular lesions throughout the colon. These findings highlight the importance of early surveillance post-endoscopic resection with fastidious colonic examination and the need for a potentially nuanced approach for specific lesion subtypes.

The fourth thesis aim addressed optical diagnosis of invasive cancer to optimise selection of the appropriate resection modality or surgical referral. A simple decision-making algorithm was constructed utilising lesion morphology and location to accurately predict the risk of invasive cancer. Implementation of the algorithm in widespread endoscopic practice allows greater confidence in the identification of advanced pathology and guide both surgical referral or targeted en bloc endoscopic resection.

The final thesis aim discussed endoscopic resection training pathways and the lack of EMR-specific case selection tools for competency development. A lesion-specific case selection score was constructed to accurately predict technically challenging lesions for an “EMR-naïve” endoscopist through a composite endpoint of intraprocedural perforation, intraprocedural bleeding and failed resection. Pre-procedural prediction of high-risk cases facilitates identification of anticipated difficulties and guide case selection for both fellows training in EMR and inexperienced EMR endoscopists.

In conclusion the novel studies presented in this thesis have widespread implications on endoscopic practice with a likely influence on international consensus guidelines. The presented innovations in technique selection, optical diagnosis, endoscopic surveillance and training pathways will potentially reduce procedural burden and improve outcomes for both patients and health services.

Appendix I:
AWARDS AND PRESENTATIONS RELATED TO THESIS

Oral Presentations

Australian Gastroenterology Week (AGW); Brisbane, 2023
O'Sullivan T, Craciun A, Byth K, Gupta S, Gauci JL, Cronin O, Whitfield A, Abuarisha M, Williams SJ, Lee EYT, Burgess NG, Bourke MJ. **A simplified algorithm to evaluate the risk of submucosal invasive cancer in large (≥20 mm) nonpedunculated colonic polyps**. Endoscopy. 2024 Aug;56(8):596-604. doi: 10.1055/a-2282-4794. Epub 2024 Mar 6. PMID: 38447957.

Digestive Diseases Week (DDW); Washington DC, 2024
O'Sullivan T, Cronin O, van Hattem WA, Mandarino FV, Gauci JL, Kerrison C, Whitfield A, Gupta S, Lee E, Williams SJ, Burgess N, Bourke MJ. **Cold versus hot snare endoscopic mucosal resection for large (≥15 mm) flat non-pedunculated colorectal polyps: a randomised controlled trial.** Gut. 2024 Oct 7;73(11):1823-1830. doi: 10.1136/gutjnl-2024-332807. PMID: 38964854.

O'Sullivan T, Mandarino FV, Gauci JL, Whitfield AM, Kerrison C, Elhindi J, Neto do Nascimento C, Gupta S, Cronin O, Sakiris A, Prieto Aparicio JF, Arndtz S, Brown G, Raftopoulos S, Tate D, Lee EY, Williams SJ, Burgess N, Bourke MJ. **Impact of margin thermal ablation after endoscopic mucosal resection of large (≥20 mm) non-pedunculated colonic polyps on long-term recurrence.** Gut. 2024 Sep 30:gutjnl-2024-332907. doi: 10.1136/gutjnl-2024-332907. Epub ahead of print. PMID: 39349006.

Australian Gastroenterology Week (AGW); Adelaide, 2024
O'Sullivan T, Cronin O, van Hattem WA, Mandarino FV, Gauci JL, Kerrison C, Whitfield A, Gupta S, Lee E, Williams SJ, Burgess N, Bourke MJ. **Cold versus hot snare endoscopic mucosal resection for large (≥15 mm) flat non-pedunculated colorectal polyps: a randomised controlled trial.** Gut. 2024 Oct 7;73(11):1823-1830. doi: 10.1136/gutjnl-2024-332807. PMID: 38964854.

O'Sullivan T, Mandarino FV, Gauci JL, Whitfield AM, Kerrison C, Elhindi J, Neto do Nascimento C, Gupta S, Cronin O, Sakiris A, Prieto Aparicio JF, Arndtz S, Brown G, Raftopoulos S, Tate D, Lee EY, Williams SJ, Burgess N, Bourke MJ. **Impact of margin thermal ablation after endoscopic mucosal resection of large (≥20 mm) non-pedunculated colonic polyps on long-term recurrence.** Gut. 2024 Sep 30:gutjnl-2024-332907. doi: 10.1136/gutjnl-2024-332907. Epub ahead of print. PMID: 39349006.

Poster Presentations

United Gastroenterology Week (UEGW); Vienna, 2024
O'Sullivan T, Cronin O, van Hattem WA, Mandarino FV, Gauci JL, Kerrison C, Whitfield A, Gupta S, Lee E, Williams SJ, Burgess N, Bourke MJ. **Cold versus hot snare endoscopic mucosal resection for large (≥15 mm) flat non-pedunculated colorectal polyps: a randomised controlled trial.** Gut. 2024 Oct 7;73(11):1823-1830. doi: 10.1136/gutjnl-2024-332807. PMID: 38964854.

O'Sullivan T, Mandarino FV, Gauci JL, Whitfield AM, Kerrison C, Elhindi J, Neto do Nascimento C, Gupta S, Cronin O, Sakiris A, Prieto Aparicio JF, Arndtz S, Brown G,

Raftopoulos S, Tate D, Lee EY, Williams SJ, Burgess N, Bourke MJ. **Impact of margin thermal ablation after endoscopic mucosal resection of large (≥20 mm) non-pedunculated colonic polyps on long-term recurrence.** Gut. 2024 Sep 30:gutjnl-2024-332907. doi: 10.1136/gutjnl-2024-332907. Epub ahead of print. PMID: 39349006.

Appendix II:
AUTHOR CONTRIBUTIONS AND DECLARATIONS

Author contributions

Chapter 2

O'Sullivan T, Bourke MJ. **Endoscopic Resection of Neoplasia in the Lower GI Tract: A Clinical Algorithm.** Visc Med. 2024 Aug;40(4):217-227. doi: 10.1159/000539219. Epub 2024 Jun 26. PMID: 39157731; PMCID: PMC11326768.

Timothy O'Sullivan	Study concept and design, literature review, manuscript drafting and critical revision of the manuscript for important intellectual content
Michael J Bourke	Study concept and design, critical revision of the manuscript for important intellectual content and study supervision

Chapter 3

O'Sullivan T, Cronin O, van Hattem WA, Mandarino FV, Gauci JL, Kerrison C, Whitfield A, Gupta S, Lee E, Williams SJ, Burgess N, Bourke MJ. **Cold versus hot snare endoscopic mucosal resection for large (≥15 mm) flat non-pedunculated colorectal polyps: a randomised controlled trial.** Gut. 2024 Oct 7;73(11):1823-1830. doi: 10.1136/gutjnl-2024-332807. PMID: 38964854.

Timothy O'Sullivan	Acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis
Oliver Cronin	Acquisition of data.
Ari van Hattem	Study concept and design, acquisition of data
Francesco Vito Mandarino	Acquisition of data, analysis and interpretation of data
Julia Gauci	Acquisition of data
Clarence Kerrision	Acquisition of data
Anthony Whitfield	Acquisition of data
Sunil Gupta	Acquisition of data
Eric Lee	Acquisition of data
Stephen Williams	Acquisition of data
Nicholas Burgess	Acquisition of data

Michael J Bourke	Acquisition of data, analysis and interpretation of data, drafting of the manuscript, study concept and design and study, supervision/ guarantor

Chapter 4

O'Sullivan T, Mandarino FV, Gauci JL, Whitfield AM, Kerrison C, Elhindi J, Neto do Nascimento C, Gupta S, Cronin O, Sakiris A, Prieto Aparicio JF, Arndtz S, Brown G, Raftopoulos S, Tate D, Lee EY, Williams SJ, Burgess N, Bourke MJ. **Impact of margin thermal ablation after endoscopic mucosal resection of large (≥20 mm) non-pedunculated colonic polyps on long-term recurrence.** Gut. 2024 Sep 30:gutjnl-2024-332907. doi: 10.1136/gutjnl-2024-332907. Epub ahead of print. PMID: 39349006.

Timothy O'Sullivan	Study concept and design Acquisition of data Analysis and interpretation of data, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Statistical analysis
Francesco Vito Mandarino	Acquisition of data, Critical revision of the manuscript for important intellectual content
Julia Gauci	Acquisition of data, Critical revision of the manuscript for important intellectual content
Anthony Whitfield	Acquisition of data, Critical revision of the manuscript for important intellectual content
Clarence Kerrison	Acquisition of data, Critical revision of the manuscript for important intellectual content
James Elhindi	Statistical analysis
Catarina Neto do Nascimento	Acquisition of data, Critical revision of the manuscript for important intellectual content
Sunil Gupta	Acquisition of data, Critical revision of the manuscript for important intellectual content
Oliver Cronin	Acquisition of data, Critical revision of the manuscript for important intellectual content
Anthony Sakiris	Acquisition of data, Critical revision of the manuscript for important intellectual content
Juan Francisco Prieto Aparicio	Acquisition of data, Critical revision of the manuscript for important intellectual content

Sophie Arndtz	Acquisition of data, Critical revision of the manuscript for important intellectual content
Gregor Brown	Acquisition of data, Critical revision of the manuscript for important intellectual content
Spiro Raftopoulos	Acquisition of data, Critical revision of the manuscript for important intellectual content
David Tate	Acquisition of data, Critical revision of the manuscript for important intellectual content
Eric Lee	Acquisition of data, Critical revision of the manuscript for important intellectual content
Stephen Williams	Acquisition of data, Critical revision of the manuscript for important intellectual content
Nicholas Burgess	Acquisition of data, Critical revision of the manuscript for important intellectual content
Michael J Bourke	Study concept and design, Acquisition of data, Critical revision of the manuscript for important intellectual content, Study supervision, guarantor author

Chapter 5

O'Sullivan T, Tate D, Sidhu M, Gupta S, Elhindi J, Byth K, Cronin O, Whitfield A, Craciun A, Singh R, Brown G, Raftopoulos S, Hourigan L, Moss A, Klein A, Heitman S, Williams S, Lee E, Burgess NG, Bourke MJ. **The Surface Morphology of Large Nonpedunculated Colonic Polyps Predicts Synchronous Large Lesions.** Clin Gastroenterol Hepatol. 2023 Aug;21(9):2270-2277.e1. doi: 10.1016/j.cgh.2023.01.034. Epub 2023 Feb 12. PMID: 36787836.

Timothy O'Sullivan	Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Investigation: Equal; Methodology: Lead; Project administration: Lead; Software: Lead; Visualization: Lead; Writing – original draft: Lead; Writing – review & editing: Equal

David Tate	Conceptualization: Lead; Data curation: Lead; Investigation: Equal; Methodology: Lead; Project administration: Equal; Software: Lead; Validation: Equal; Visualization: Equal; Writing – original draft: Lead; Writing – review & editing: Equal
Mayenaaz Sidhu	Data curation: Supporting; Investigation: Supporting; Writing – review & editing: Supporting
Sunil Gupta	Data curation: Supporting; Investigation: Supporting; Writing – review & editing: Supporting
James Elhindi	Formal analysis: Equal; Writing – review & editing: Supporting
Karen Byth	Formal analysis: Equal; Writing – review & editing: Supporting
Oliver Cronin	Investigation: Supporting; Writing – review & editing: Supporting
Anthony Whitfield	Investigation: Supporting; Writing – review & editing: Supporting
Ana Craciun	Writing – review & editing: Supporting
Rajvinder Singh	Investigation: Supporting; Writing – review & editing: Supporting
Gregor Brown	Investigation: Supporting; Writing – review & editing: Supporting
Spiro Raftopoulos	Investigation: Supporting; Writing – review & editing: Supporting
Luke Hourigan	Investigation: Supporting; Writing – review & editing: Supporting
Alan Moss	Investigation: Supporting; Writing – review & editing: Supporting
Amir Klein	Investigation: Supporting; Writing – review & editing: Supporting
Steven Heitman	Investigation: Supporting; Writing – review & editing: Supporting
Stephen Williams	Investigation: Supporting; Writing – review & editing: Supporting

Eric Lee	Investigation: Supporting; Writing – review & editing: Supporting
Nicholas Burgess	Data curation: Equal; Funding acquisition: Equal; Investigation: Equal; Software: Equal; Writing – review & editing: Supporting
Michael J. Bourke	Conceptualization: Equal; Data curation: Equal; Funding acquisition: Equal; Investigation: Equal; Methodology: Equal; Project administration: Equal; Resources: Equal; Supervision: Lead; Validation: Lead; Visualization: Equal; Writing – review & editing: Equal

Chapter 6

O'Sullivan T, Craciun A, Byth K, Gupta S, Gauci JL, Cronin O, Whitfield A, Abuarisha M, Williams SJ, Lee EYT, Burgess NG, Bourke MJ. **A simplified algorithm to evaluate the risk of submucosal invasive cancer in large (≥20 mm) nonpedunculated colonic polyps.** Endoscopy. 2024 Aug;56(8):596-604. doi: 10.1055/a-2282-4794. Epub 2024 Mar 6. PMID: 38447957.

Timothy O'Sullivan	Study concept and design, Acquisition of data, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Statistical analysis
Ana Craciun	Acquisition of data, Critical revision of the manuscript for important intellectual content
Karen Byth	Critical revision of the manuscript for important intellectual content, Statistical analysis
Sunil Gupta	Acquisition of data, Analysis and interpretation of data, Critical revision of the manuscript for important intellectual content
Julia Gauci	Acquisition of data, Critical revision of the manuscript for important intellectual content
Oliver Cronin	Acquisition of data, Critical revision of the manuscript for important intellectual content

Anthony Whitfield	Acquisition of data, Critical revision of the manuscript for important intellectual content
Muhammad Abu Arisha	Acquisition of data, Critical revision of the manuscript for important intellectual content
Stephen Williams	Acquisition of data, Critical revision of the manuscript for important intellectual content
Eric Lee	Acquisition of data, Critical revision of the manuscript for important intellectual content
Nicholas Burgess	Acquisition of data, Critical revision of the manuscript for important intellectual content
Michael J. Bourke	Study concept and design, Acquisition of data, Critical revision of the manuscript for important intellectual content, Study supervision

Chapter 7

O'Sullivan T, Sidhu M, Gupta S, Byth K, Elhindi J, Tate D, Cronin O, Whitfield A, Wang H, Lee E, Williams S, Burgess NG, Bourke MJ. **A novel tool for case selection in endoscopic mucosal resection training. Endoscopy.** 2023 Dec;55(12):1095-1102. doi: 10.1055/a-2121-1148. Epub 2023 Jun 30. PMID: 37391184.

Timothy O'Sullivan	Study concept and design, Acquisition of data, Analysis and interpretation of data, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Statistical analysis
Mayenaaz Sidhu	Study concept and design, Acquisition of data, Analysis and interpretation of data, Critical revision of the manuscript for important intellectual content
Sunil Gupta	Acquisition of data, Analysis and interpretation of data, Critical revision of the manuscript for important intellectual content, Statistical analysis

Karen Byth	Statistical analysis, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content
James Elhindi	Statistical analysis
David Tate	Acquisition of data, Critical revision of the manuscript for important intellectual content
Oliver Cronin	Acquisition of data, Critical revision of the manuscript for important intellectual content
Anthony Whitfield	Acquisition of data, Critical revision of the manuscript for important intellectual content
Hunter Wang	Acquisition of data, Critical revision of the manuscript for important intellectual content
Eric Lee	Acquisition of data, Critical revision of the manuscript for important intellectual content
Stephen Williams	Acquisition of data, Critical revision of the manuscript for important intellectual content
Nicholas Burgess	Study concept and design, Acquisition of data, Critical revision of the manuscript for important intellectual content
Michael J Bourke	Study concept and design, Acquisition of data, Analysis and interpretation of data, Critical revision of the manuscript for important intellectual content, Study supervision

Appendix III:
HREC APPROVALS/PROTOCOLS

Date of Decision Notification: 08 Jul 2019

Dear Professor Michael Bourke,

4831 - 2019/ETH02170: The Australian Colonic Large Sessile Lesion Endoscopic Resection Study

We acknowledge your request for amendment dated 17 June 2019 and attached documentation in relation to the above study.

The Western Sydney Local Health District Human Research Ethics Committee is constituted in accordance with the National Statement on Human Conduct in Research, 2007 (NHMRC).

I am pleased to advise approval has been granted for the Request for Amendment / Modification for this multicentre research project being conducted at:

- Westmead Hospital – Coordinating Chief Investigator Prof Michael Bourke
- Blacktown Hospital (NSW) – Dr Farzan F Bahin
- Westmead Private Hospital (NSW) – Prof Michael Bourke
- Princess Alexandra Hospital (QLD) – Chief Investigator Dr Luke Hourigan
- Queen Elizabeth II Hospital (QLD) – Chief Investigator Dr Nicholas J Tutticci
- Lyell McEwin Hospital (SA) – Chief Investigator Prof Rajvinder Singh
- The Alfred Hospital (VIC) – Chief Investigator Prof Gregor Brown
- Western Health Footscray Hospital (VIC) – Chief Investigator A/Prof Alan Moss
- Western Health Sunshine Hospital (VIC) – Chief Investigator A/Prof Alan Moss
- Monash Health Clayton (VIC) – Chief Investigator Dr Michael Swan
- Dandenong Hospital (VIC) – Chief Investigator Dr Michael Swan
- University Hospital Geelong (VIC) – Chief Investigator Dr Sina Alexander
- St John of God Hospital, Geelong (VIC) - Chief Investigator Dr Sina Alexander
- St Vincent's Hospital , Melbourne (VIC) – Co-coordinating Investigator Dr Andrew Taylor
- Sir Charles Gairdner Hospital - Principal Investigator Dr Spiro Raftopoulos

The following documentation has been reviewed and approved.

- Study Protocol - version 5, dated 05 June 2019
- Data Sheet - Day 14 Post Procedure - no version, dated 28 June 2013
- Data Sheet - First follow up - no version, dated 28 June 2013
- Data Sheet - Second follow up - no version, dated 28 June 2013
- Data Sheet - Day of EMR - version 4.0, dated 10 August 2016

Your request to add Epworth Healthcare as a site and Gregor Brown as Principal Investigator to the study was reviewed and approved.

This amendment has also been reviewed and authorised by the Research Governance Officer for Western Sydney Local Health District. For non-Western Sydney Local Health District sites please ensure that the Research Governance Officer for each site named on this study receives the updated approved documentation about this amendment.

We appreciate your keeping us informed and look forward to receiving your next annual report.

Regards,

WSLHD Research Office
Research & Education Network
Westmead Hospital, Cnr Hawkesbury & Darcy Rds, Westmead NSW 2145
Tel 02 8890 9007

STUDY PROTOCOL

Project Title: The Australian Colonic LSL Endoscopic Resection Study. (ACE)

Co-ordinating Principal Investigator: Prof. Michael Bourke[a,b],

Investigators:
Dr Nicholas Burgess[a]
Dr Stephen Williams[a]
Dr David Tate[vz]
Dr Luke Hourigan[c,d]
Assoc. Prof. Rajvinder Singh[e]
Assoc. Prof. Gregor Brown[f,x]
Dr Simon Zanati[f,g]
Assoc. Prof. Alan Moss[g]
Dr Spiro Raftopoulos[h,i]
Dr Michael Swan[j,k,l]
Dr Sina Alexander[m,n]
Dr Nicholas Tutticci[o]
Dr David Hewett[o]
Dr Farzan Bahin[p]
Dr Steven Heitman[q]
Dr Ralph Lee[r]
Dr Amir Klein[t]
Dr Halim Awadie[a]
Dr Lobke Desomer[u]
Dr Andrew Taylor[w]
Dr Bronte Holt[w]
Dr Milan Bassan[y]
Dr Timothy O'Sullivan[Z, AA]
Dr Joshua Butt[BB]
Dr Anthony Whitfield[CC]
De Mayenaaz Sidhu[DD]

Sites: Departments of Gastroenterology and Hepatology, Endoscopy Units:
[a]Westmead Hospital, Sydney, NSW.
[b]Westmead Private Hospital, Sydney, NSW
[c]Princess Alexandra Hospital, Brisbane, QLD
[d]Greenslopes Private Hospital, Brisbane, QLD
[e]Lyall McEwin Hospital, Adelaide, SA
[f]The Alfred Hospital, Melbourne, VIC
[g]Western Hospital, Melbourne, VIC
[h]Sir Charles Gairdner Hospital, Perth, WA
[i]Hollywood Private Hospital, Perth, WA
[j]Monash Health Clayton, Melbourne, VIC
[k]Dandenong Hospital, Melbourne, VIC
[l]Jessie MacPherson Hospital, Melbourne, VIC
[m]University Hospital Geelong, Barwon Health, Geelong, VIC
[n]St John of God Hospital Geelong, Geelong, VIC
[o]Queen Elizabeth II Jubilee Hospital, Coopers Plains, QLD

[p]Blacktown District Hospital, Blacktown, Sydney, NSW
[q]Forzani & MacPhail Colon Cancer Screening Centre, Calgary, Canada
[r]The Ottawa Hospital – Civic Campus, Ottawa, Ontario, Canada
[s]AZ Delta Roeselare, Wilgenstraat 2, Belgium
[t]Rambam Health Care Campus, Haifa, Israel
[u]AZ Delta Roeselare, Belgium
[v]Cheltenham General Hospital, Gloucestershire, UK
[w]St Vincents Hospital, Melbourne, VIC
[x]Epworth Healthcare, Melbourne, VIC
[y]Liverpool Hospital, Sydney, NSW
[z]Royal Brisbane & Women's Hospital
[AA]Surgical, Treatment and Rehabilitation Service, Brisbane
[BB]Northern Health, Melbourne
[CC]Blacktown Mt Druitt Hospital, Sydney
[DD]Concord Hospital, Sydney

Protocol Version: 9

Background:

Colonoscopic polypectomy is well established as an effective way of reducing colorectal cancer mortality[1]. The majority of polyps detected and removed at colonoscopy are adenomas <10mm in size without advanced histology. These lesions have a low risk of progression to malignancy and are relatively easily removed by standard snare polypectomy with low complication rates[2]. Polyps that are sessile or flat and greater than 20mm in size are found in approximately 1% of all colonoscopies[3] and are more difficult to manage. These lesions, known as large sessile lesions (LSL), have a high rate of advanced histology[4]. Traditionally they have been managed by referral for open or laparoscopic surgery, which is definitive, but invasive, costly and associated with a significant mortality risk in patients with advanced age or comorbidities[5]. Endoscopic Mucosal Resection (EMR) has emerged in recent years as an alternative to surgery that is now becoming the standard of care. It is an outpatient procedure which is effective, safe and less costly than surgery when delivered at a tertiary referral centre[6].

The Australian Colonic Endoscopic Mucosal Resection study (ACE), comprises two multicentre prospective observational studies which examined EMR of colonic LSL (Ethics approval No.s HREC JH/TG 2008/9/6.1(2858) and HREC/13/WMEAD/233 (3778)). The project now has an extensive dataset from leading colonic endoscopic resection centres in Australia on more than 2000 lesions resected over 4 years since September 2008.

These studies have been successful in addressing several aspects of the resection of LSL, resulting in several high profile papers in internationally recognised journals. The collection of this data has produced robust information on the efficacy of the procedure[4], recurrence rates[7], bleeding complications[8,9] and mortality and costs when compared to surgery[10,11]. Single centre analysis of the ACE dataset at Westmead has also allowed insights into how to refine the procedure to improve outcomes. The target sign is now a recognised indication for the placement of clips to prevent perforation[12], CO2 insufflation for EMR has been shown to be superior to air insufflation[13] and succinylated gelatin (Gelofusine®) has been shown to be superior to normal saline as a submucosal lifting agent[14]. Assessment and management strategies for bleeding and deep mural injury or perforation have been derived from analysis of the data[9,15]. Snare tip soft coagulation of the resection margin post-EMR has been shown to reduce recurrence in a randomised controlled trial[16]. Several ACE study papers have been incorporated into review papers and international guidelines for the safe and effective performance of EMR[17,18].

There remain a number of unanswered questions regarding the endoscopic resection of large sessile lesions and a new study incorporating a greater number of endoscopy units around Australia will allow these to be addressed as well as answer questions on the clinical effectiveness of the technique. Enhancing the prediction of submucosal invasive cancer, advanced lesion classification, validation of the assessment of deep injury, treatment of lesion margins post resection to reduce recurrence, prevention and prophylaxis of bleeding, and subtype analyses of the different histological groups of colonic lesions will be examined.

Literature Review:

The ACE study was initially designed to assess the efficacy of and complications related to EMR of large sessile lesions. These lesions are uncommon, but are an important subgroup of bowel lesions as they contain a high proportion of incipient and inevitable bowel cancers. Few centres internationally have published studies on the resection of LSL and there are only 3 prospective studies which have accrued more than 200 patients[19–21]. The focus of these studies was generally on technical efficacy, and data on complications or lesion subtypes was limited. Through its unique dataset and collection of rare but clinically important lesions, the data generated through the ACE studies has provided an insight into the technical aspects of resection, and valuable data to examine other aspects of colon LSL.

Since its inception in 2008, the ACE studies have gathered data on over 2000 patients through a now well established tertiary referral service for the resection of LSL at 8 Australian major centres. The high throughput of cases and established research infrastructure means it has generated multiple internationally relevant studies and has adequate power to look at specific patient, lesion, technique and outcome subgroups. Due to these positive results, the data has now created several questions that could be addressed by maintaining the

same structure, but incorporating other study centres and broadening the data collection. Technological advances in endoscopy have meant that real time prediction of lesion histology is becoming more accurate[22], and the ACE study is well placed to expand lesion assessment data to provide robust evidence on the appearance of large colonic lesions and prediction of submucosal invasive cancer. The endoscopic appearance of sessile serrated polyps (SSPs) is also poorly described[23] and data will be collected on the prospective assessment of these lesions in the ACE study. Expanding the centres and endoscopists involved in the study means that the outcomes more closely reflect "real-world" outcomes and have increased applicability in terms of affecting clinical practice internationally. New aspects of resection will also be assessed in this prospective cohort. Validation of the Sydney Deep Mural Injury Classification grading system for will be added to the study and assessed to examine the effect of pro-active management of deep injury. Treatment of the margins of defects with snare tip soft coagulation to reduce recurrence will be assessed for clinical effectiveness. Kudo[24] and Sano[25,26] grades will be prospectively assessed for their prediction of sub mucosal invasive cancer. Clip closure of defects and endoscopic ultrasound of EMR defects to assess bleeding risk may also be examined. Incremental improvement in refining the technique of EMR by scrutinizing outcomes means that the acceptability and availability of the procedure is improved internationally, and it is seen as a safe, efficacious and cost effective technique.

The ACE study has been valuable as a way of providing a base population for interventional studies. Several studies will tie in to the expanded ACE data. These studies will be independently submitted for HREC approval and review.

Aims:

To enhance understanding of the risk factors for LSL, improve lesion assessment and prediction of submucosal invasive cancer, improve endoscopic resection efficacy, reduce complications of EMR and improve the understanding of the progression of large lesions to cancer.

Methodology:

Project Design:

Prospective, observational multi-centre study which aims to enrol all cases of LSL ≥20mm presenting to the above-mentioned centres and international facilities that have reached a data sharing agreement with WSLHD.

Inclusion Criteria:

- Patients referred for endoscopic resection of a large sessile colonic polyp or laterally spreading tumour ≥20mm in size.
- Age > 18 years
- Able to give informed consent to involvement in the clinical study

Exclusion Criteria:

- Unable to provide informed consent for involvement

Method of Screening:

Patients referred to a study centre for colonic EMR of a known sessile colonic polyp or laterally spreading lesion (LSL) ≥20mm in size

Sequence of Procedures: (for flowsheet see Appendix 1.)

1. Patient is referred to one of the above-mentioned centres and international facilities that have reached a data sharing agreement with WSLHD units for removal of a large sessile colonic polyp or LST ≥20mm in size.
2. All patients referred to this service are routinely mailed an information pack about the EMR procedure. If the referral information indicates that the patient is potentially eligible for the trial, written information about the study is included in this pack for the patient to read in advance of their arrival for the procedure.
3. The patient reads the supplied information and consent form.
4. Once checked into the endoscopy suite on the day of the procedure, the patient is met by one of the investigators to discuss the risks and benefits of the procedure and the study. An interpreter is used to assist with the discussion if required.
5. If the patient agrees to participate, the informed consent form is signed and witnessed with the help of an interpreter if required.
6. If the patient decides not to participate, the colonoscopy and EMR proceed as per usual.
7. Patient enters the endoscopy room and the procedure commences.
8. During the EMR procedure, data is recorded by the gastroenterology registrar or clinical research nurse regarding the technical aspects of the procedure. Still images of the colon are taken routinely during the procedure as part of the normal medical record in a standardized manner of the lesion, the resection procedure and the completed defect. De-identified video images may be collected of the procedure.
9. The patient is moved to recovery for observation. They are observed for 2 hours in first stage recovery and at this stage are nil by mouth. They are then observed in second stage recovery while consuming clear fluids for 4 hours. They are examined by the proceduralist prior to

discharge and provided with written post procedure information including a phone number to call in the event of any problems.

10. Overnight they remain on a clear fluid diet and resume a normal diet the following day.
11. Any adverse event is recorded prospectively on the data sheet as per the unit's standard practice. Adverse events include immediate or delayed bleeding, deep mural injury or perforation, persistent pain indicative of a serositis (inflammation of the outer layer of the bowel wall) or an unscheduled admission or readmission.
12. Patients are contacted by the research nurse by telephone 14 days following their procedure to assess ongoing symptoms and advise of any adverse events including admissions.
13. The formal histology results of the resected specimens are recorded on the follow-up data sheet. The slides are also reviewed as per usual endoscopy unit practice in the monthly gastroenterology unit histopathology meeting.
14. All patients return for a follow up procedure (scheduled colonoscopy) to check whether the lesion has been completely resected and to remove any recurrent or residual polyp. For the majority of patients this is at 5 months at the centre that performed the initial resection. A few patients will have lesions which are a low risk for recurrence and were resected "en-bloc", these patients may be booked for a 12 month follow up procedure, which may be performed by the referring institution.
15. Patients who have no, or low risk recurrence which is completely treated, are then followed up at 12 months, 3 years and 5 years at the referring institution. Endoscopy reports and histology are forwarded to the initial study centre for inclusion in the study. Patients with high risk or incompletely treated recurrence are managed by further endoscopic resection, or referral for surgery. This is based on the endoscopists assessment of the lesion and histology findings.
16. In the event that follow up information is not provided by the referring physician at the proscribed time points, a reminder letter will be sent to the referrer to ask them to review whether a follow up examination has been performed and to provide further information.
17. Patients who have significant adverse events may have their records for this event reviewed to create a more detailed picture of the complication.
18. The study outcomes will then be documented in manuscript form and submitted to a major internationally recognized peer reviewed journal for publication.
19. All participants will be mailed a letter outlining the results of the trial, and thanking them for their involvement.
20. All records of patients who participate in the trial will be marked so they are not destroyed by medical records for at least 15 years.

Data Security:

A REDCap (Research Electronic Data Capture) database will be used to enable secure and confidential collection, storage, and maintenance of the research data for this study. REDCap is a secure, web-based application designed exclusively to support data capture for research studies and is secured according to The University of Sydney's security protocols which conform to electronic data standards.

It is secured, and backed up daily, with privacy and confidentiality considerations are protected. Study staff at each site will need to login into the REDCap database with a unique username and password. Once in the database staff will only have access to data collected at their specific site. Only the principal investigator will have access to all study data.

All data entered into the REDCap database will be de-identified. A separate file (Excel spreadsheet) with identifying data will be maintained in order to allow patient follow up. This file will be password protected, with the password known only to the investigators.

Participant Withdrawal From the Study:

In accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Practice Guidelines, a participant is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or the institution. The Investigator may also withdraw the participant at any time in the interests of patient safety. Should a participant decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. Participants may be removed from the study if one or more of the following events occur:

- Withdrawal of consent
- Decision made by the investigators that removal from the study is in the patients best medical interest.
- Study stopped by ethics/regulatory authorities

The primary reason and additional reasons for withdrawal will be recorded in the participants medical record.

Statistics:

The ACE study aims to enrol patients for 10 years. This will result in 4000-5000 patients in the study. Comparison of quantitative variables will be performed by Students t-test and for qualitative variables by Pearson's χ^2 -test. A p value of < 0.05 will be considered significant. Statistical analyses will be performed with SPSS statistical software (IBM Corp. 2012. IBM SPSS Statistics, Version 22.0. Armonk, NY) with the help of an independent statistician.

Analyses and Outcome Measures:

The study will examine key outcome measures including procedural success, requirement for surgery, recurrence at scheduled surveillance colonoscopies, and clinical success (participants free from surgery or recurrence at surveillance colonoscopy). The study will also examine prediction of submucosal invasive cancer and prediction of LSL histology type. The study will report on key adverse events: bleeding (immediate and delayed), deep mural injury and perforation, pain, and surgery for adverse events and will examine demographic, clinical and technical predictors of these outcomes. Univariable analysis and multiple logistic regression of potential risk factors will primarily be used to examine outcomes. Enhancing the prediction of submucosal invasive cancer, advanced lesion classification, validation of the assessment of deep injury, treatment of lesion margins post resection to reduce recurrence, prevention and prophylaxis of bleeding, and subtype analyses of the different histological groups of colonic lesions are all areas where results from a large, prospective, multicentre cohort will influence international practice.

Ethical Issues:

All patients will be managed according to established best practice according to international research and consensus on EMR. Treatment does not differ according to whether or not the patient chooses to participate in the study.

The key ethical issues are:

1. Dependent Relationships
    - Most eligible participants will not be the regular patients of the investigators or the colonoscopists involved in the study. This is because the majority of the patients are referred from other medical specialists (Gastroenterologists or surgeons) to the tertiary referral service operated by the study centre Endoscopy Unit. Follow up after confirmed curative EMR is with the referring specialist. Vigilance in explaining the voluntary nature of participation will be exercised for all patients. It will be emphasized that a decision not to enroll in the study will have no ramifications whatsoever for the patients care and ongoing relationship with the treating medical team.
2. Conflict of Interest
    - None of the investigators have financial conflicts of interest.

Potential Significance of the Study:

The ACE study has already produced substantial internationally significant research output and the unique dataset is of considerable interest due to its potential to answer further questions about colon LSL and EMR. The areas of research will cover epidemiological factors associated with LSL, advanced lesion classification, refinement of the assessment of deep injury and subtype analyses of

the different histological groups comprising LSL. The research has the potential to influence advice on screening and surveillance of colorectal polyps and in particular large lesions, to improve the ability of endoscopists to identify and resect LSL safely and to improve the worldwide acceptance of endoscopic resection of LSL as an alternative to surgery, reducing costs for healthcare systems.

Budget:

The cost of investigator time is free.

Funding for the project at is through the Westmead Hospital Endoscopy Research Fund.

Budget:

Ethics Committee Application Fee	$50.00
Total:	$50.00

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Research Office File No: (6114)
Ethics Ref: 2019/ETH11826
Governance Ref:

18 September 2019

Prof Michael Bourke
Department of Endoscopy
Westmead Hospital

Dear Prof Bourke

Project title: Conventional endoscopic mucosal resection versus cold snare endoscopic mucosal resection of colonic lateral spreading lesions - A randomised controlled trial

Thank you for your correspondence addressing the matters raised in the HREC's letter dated 10 July 2019 following single ethical review of the above project at its meeting held on 9 July 2019.

This HREC has been accredited by the NSW Department of Health as a lead HREC to provide the single ethical and scientific review of proposals to conduct research within the NSW public health system. This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research and the CPMP/ICH Note for Guidance on Good Clinical Practice.
This proposal meets the requirements of the National Statement and I am pleased to advise that the HREC has now granted ethical approval of this research project to be conducted by you at:

- Westmead Hospital - Principal Investigator Prof Michael Bourke
- Auburn Hospital - Principal Investigator A/Prof Nicholas Burgess

The following documentation has been reviewed and approved by the HREC:

- 2019/ETH11826, version 4 dated 6 September 2019
- Protocol, version 3 dated 6 September 2019
- Participant Information Consent Form Main study version 3, dated 6 September 2019
- Day 14 datasheet version 1 dated 12 June 2019
- EMR datasheet version 1 dated 12 June 2019
- First F_U SC1 version 1 dated 12 June 2019
- Second F_U SC2 version 1 dated 12 June 2019

Please note the following conditions of approval:

- The Coordinating Chief Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- For clinical trials of implantable medical devices only – The Coordinating Chief Investigator will confirm to the HREC that a process has been established for tracking the participant, with consent, for the lifetime of the device and will immediately report any device incidents to the Therapeutic Goods Administration (TGA).
- The Coordinating Chief Investigator will immediately report any protocol deviation / violation, together with details of the procedure put in place to ensure the deviation / violation does not recur.
- The Coordinating Chief Investigator will provide to the HREC in the specific format via REGIS, proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project. .
- The Coordinating Chief Investigator must notify the HREC, giving reasons, if the project is discontinued at a site before the expected date of completion.
- The Coordinating Chief Investigator must provide an annual report to the HREC and a final report at completion of the study, in the specified format.
- HREC approval is valid for 5 years contingent upon submission of an annual report via REGIS.
- The HREC has the discretion to adopt other appropriate mechanisms for monitoring depending on the complexity, design and risk perceived including
    1. Discussion of relevant aspects of the project with investigators, at any time,
    2. Random inspection of research sites, data or consent documentation,
    3. Interview with research participants or other forms of feedback from them, and
    4. Request and review reports from independent agencies such as a Data Safety Monitoring Board.
- If your research project is an interventional trial, please ensure it is registered on one of the clinical trial registries, eg http://www.actr.org.au.
- It should be noted that compliance with the ethical guidelines is entirely the responsibility of the Coordinating Chief Investigator.

In all future correspondence concerning this study, please quote Research Office File number ***(6114).***
The HREC wishes you every success in your research.

Yours sincerely

Mrs Patricia Fa
Secretary
WSLHD Human Research Ethics Committee

cc: Research Governance Officer

PROJECT TITLE

Conventional versus Cold Snare Endoscopic Mucosal Resection of colonic Lateral Spreading Lesions - A randomised controlled trial

VERSION 5

11.10.2021

CONFIDENTIAL

STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

PROTOCOL SYNOPSIS

Title	**Conventional versus cold snare Endoscopic Mucosal Resection of colonic lateral spreading lesions - A randomised controlled trial**
Objectives	**To compare the efficacy and safety of conventional EMR versus cold snare EMR of colonic adenomas size 15-40mm**

GLOSSARY OF ABBREVIATIONS

CRC	COLORECTAL CANCER
LSL	LATERAL-SPREADING LESION
EMR	ENDOSCOPIC MUCOSAL RESECTION
CSP	COLD SNARE POLYPECTOMY
STSC	SNARE TIP SOFT COAG
IPB	INTRAPROCEDURAL BLEEDING
CSPB	CLINICALLY SIGNIFICANT POSTPOLYPECTOMY BLEEDING
DMI	DEEP MURAL INJURY
PPCS	POST POLYPECTOMY CAUTERISATION SYNDROME
CRR	COMPLETE RESECTION RATE
SC1	FIRST SURVEILLANCE COLONOSCOPY
ARR	ADENOMA RECURRENCE RATE

TABLE OF CONTENTS

1. INVESTIGATORS AND FACILITIES 4

1.1. Study locations……

1.2. Study management……

1.2.1. Principal Investigator……

1.2.2. Associate Investigator……

1.2.3. Statistician……

1.2.4. Endpoint Adjudication Committee……

1.2.5. Clinical trial coordinator……

1.3. Sponsor……

1.4. Funding and resources……

2. INTRODUCTION AND BACKGROUND 5

2.1. Background information……

2.2. Research question……

2.3. Rationale for current study……

2.4. Hypothesis……

2.5. Potential significance……

3. STUDY AIMS AND OBJECTIVES 8

3.1. Primary objectives……

3.2. Secondary objectives……

4. STUDY DESIGN 8

4.1. Type of study……

4.2. Number of subjects……

4.3. Expected duration of study……

4.4. Primary and secondary outcome measures……

5. STUDY TREATMENTS 9

5.1. Procedure……

5.2. Index treatment arms……

5.3. Surveillance colonoscopy……

5.4. Proceduralists……

5.5. Sequence of actions……

6. SUBJECT ENROLLMENT AND RANDOMISATION 12

6.1. Recruitment……

6.2. Eligibility criteria……

6.2.1. Inclusion criteria……

6.2.2. Exclusion criteria……

6.3. Randomisation and blinding……

6.4. Voluntary participation……
6.5. Study withdrawal……..
6.6. Trial closure……
6.7. Continuation of therapy……

7. STUDY VISITS AND PROCEDURE SCHEDULE 13

8. CLINICAL AND LABORATORY ASSESSMENTS 13

9. ADVERSE EVENT REPORTING 13
9.1. Definitions……..
9.2. Assessment and documentation of adverse events……
9.3. Patient Safety Monitoring……

10. STATISTICAL METHODS 15
10.1. Sample size estimation……
10.2. Statistical analysis plan……
10.3. Interim analysis……

11. DATA MANAGEMENT 15
11.1. Data collection……
11.2. Data storage……
11.3. Study record retention……

12. ADMINISTRATIVE ASPECTS 16
12.1. Confidentiality……
12.2. Independent HREC approval……
12.3. Modifications to the protocol……
12.4. Participant reimbursement……
12.5. Financial disclosure of interest……

13. USE OF DATA AND PUBLICATION POLICY 16

14. REFERENCES 17

1. INVESTIGATORS AND FACILITIES

1.1. Study Location

1.1.1. [a]Westmead Hospital, Sydney, New South Wales

1.1.2. [b]Auburn Hospital, Sydney, New South Wales

1.1.3. [c]Greenslopes Private Hospital, Brisbane, QLD

1.2. Study Management

1.2.1. Principal Investigator

- Prof. Michael Bourke[a]
- A/Prof. Nicholas Burgess[b]
- A/Prof. Luke Hourigan[c]

1.2.2. Associate Investigators

- Dr Stephen Williams
- Dr Eric Lee
- Dr Mayanaaz Sidhu
- Dr Arnout van Hattem
- Dr Iddo Bar-Yishay
- Dr Scott Schoeman
- Dr Neal Shahidi
- Dr Sergei Vosko

1.2.3. Statistician

- Dr Karen Byth

1.2.4. Endpoint Adjudication Committee

- Dr Martin Grehan
- Dr John Darke

1.2.5. Clinical Trial Coordinator

- Dr Arnout van Hattem

1.3. Sponsor

There is no commercial sponsorship of this project.

1.4. Funding and resources

No additional funding is needed for the research project as compared to standard clinical practice. The endoscopists and endoscopy fellows will do the research work at no additional cost to their salary.

2. INTRODUCTION AND BACKGROUND

2.1. Background Information

Colorectal cancer (CRC) is the third most common malignancy worldwide and the fourth leading cause of cancer related death [1], with rates being highest in Western countries [2]. Colonoscopy is considered the golden standard in colorectal cancer screening and endoscopic resection of precursor lesions (polyps) has been shown to reduce colorectal cancer death [3]. Polyps extending over 10mm, also referred to as lateral spreading lesions (LSL) if non-pedunculated [4], more often demonstrate advanced histological features and are considered to be at greater risk for malignant transition as compared to their smaller counterparts [5], [6]. Incomplete endoscopic resection of advanced adenomas may lead to adenoma recurrence and contribute to the development of so called 'interval cancers' [7], which occur during the 6 – 36 month period following complete colonoscopy [8], [9]. Interval cancers account for up to 6% of newly diagnosed CRC cases, highlighting the importance of complete resection.

Endoscopic mucosal resection (EMR) is a well-established inject and resect method for the removal of LSLs using chromo-gelofusin based submucosal lift and subsequent cauterisation assisted snare excision [10], [11]. Lesions up to 25mm in size may be removed enbloc, whereas larger lesions are generally removed in a piecemeal fashion. Contrary to enbloc resection, piecemeal EMR is historically associated with relatively high recurrence rates of 15-20% [12]. A recent four centre trial led by Westmead Hospital published in gastroenterology (impact factor 20.8) has shown that application of snare-tip soft coag (STSC) to the EMR defect margins considerably improves recurrence rates to around 7% in adenomatous LSL [13]. Common complications of EMR such as intra-procedural bleeding (IPB) or clinically significant post-procedural bleeding (CSPB), deep mural injury (DMI) and post-polypectomy coagulation syndrome (PPCS) are largely related to the use of cauterisation for tissue transection [14]. Although complication rates have improved and effects can often be managed endoscopically [15]–[17], further optimization of the EMR safety profile is needed in the background of an aging target population with multiple co-morbidities and widespread use of anticoagulants.

Cold snare polypectomy (CSP) has become the standard of care for removal of subcentimeter polyps [10]. CSP relies on the use of dedicated stiff thin wire snares [18] that are able to swiftly cut through mucosal tissue without the need for cauterisation, leaving intact the muscularis mucosa and the deeper submucosal layers, virtually excluding the risk of perforation. The absence of delayed cauterisation effect significantly reduces the risk of post-polypectomy bleeding, even in patients on anticoagulant therapy [19], [20]. Complete resection rates of polyps ranging from 6 to 10mm in size were found to be non-inferior in CSP as compared to cauterisation based resection [21]. Moreover, resecting a sufficient margin of normal mucosa surrounding the polyp (i.e. >1mm) yields an excellent 98% complete resection rate in polyps <10mm in size without increasing the risk of delayed bleeding [22]. Meta-analysis demonstrated a significantly shorter procedure time when applying the cold snare resection technique in small polyps [23]. Snare size limitations of dedicated cold snares however do not allow for en-bloc resection of polyps >10mm.

Recently, cold snare piecemeal EMR was shown to be safe and effective for the removal of large sessile serrated polyps (SSP) [24], [25]. Combined evidence from a limited number of small single centre mostly retrospective studies investigating cold snare piecemeal polypectomy in adenomas over 10mm demonstrated recurrence rates of around 11% whilst maintaining an excellent safety profile with minimal complication rates [26]. However, recurrence rates rise to 22% in the subgroup of polyps over 20mm. Thus far cold snare piecemeal polypectomy of lateral-spreading adenomas has not yet been compared to conventional EMR in prospective randomized fashion.

The significance of protrusions within a cold snare EMR defect has not been previously assessed. A previous study (n=257) which assessed protrusions during resection of small polyps ≤10mm by CSP found no residual adenomatous tissue on histopathologic examination however this has not been assessed with larger laterally spreading adenomas resected by cold EMR.

2.2. Research Question

Is conventional EMR superior to cold snare EMR in the complete resection of 15-40mm lateral spreading adenomas?

2.3. Rationale for current Study

Conventional EMR is well established for the resection of lateral spreading adenomas and has been shown to have low recurrence rates if performed correctly. EMR may however be technically challenging and relatively time-consuming. Also, cauterisation related complications occur relatively frequent and may be significant.

Cold snare polypectomy on the other hand is swift and effective in the resection of small polyps and has an excellent safety profile avoiding cauterisation related adverse. However, efficacy and safety of cold snare resection in lateral spreading adenomas has not been studied in a prospective trial. Recurrence rates may be negatively impacted by a combination of limited cold snare size increasing the number of resected pieces per lesion, and a more superficial resection plane.

A direct and prospective comparison of the efficacy and safety of conventional EMR vs. cold snare EMR for the removal of lateral spreading adenomas has not yet been performed.

2.4. Hypothesis

Conventional EMR of 15-40mm lateral spreading adenomas is expected to be superior with regard to complete resection- and adenoma recurrence rates as compared to cold snare EMR.

2.5. Potential significance

Significance: The current prospective randomized trial will determine whether conventional EMR is superior to cold snare EMR with regards to efficacy (complete resection and adenoma recurrence rates), procedure time, and complication rate for 15-40mm lateral

spreading adenomas. Trial results are expected to impact clinical guidelines and training requirements of physicians performing tissue resection.

Novelty: This will be the first trial to address conventional EMR and cold snare EMR in lateral spreading adenomas in a direct comparison.

Clinical impact: Results are expected to confirm conventional EMR as the treatment of choice for complete resection of lateral spreading adenomas. Cold snare EMR may however prove to be attractive alternative in a high-risk target population given the anticipated superior safety profile.

Patient benefit: Lateral-spreading adenomas are a frequent finding at screening colonoscopy. Optimizing the applied resection technique will lead to better patient outcomes with regard to adverse events without impacting the current standards in recurrence rate, thereby limiting the number of repeat procedures required and minimizing the odds of developing advanced neoplasia or interval cancer and associated morbidity and mortality.

Socio-economic impact: Optimizing treatment efficacy and safety will reduce the number of follow-up endoscopies as well as emergency department presentations and unexpected re-admission rates ultimately leading to a lower patient disease burden and lower associated healthcare costs.

3. STUDY AIMS / OBJECTIVES

3.1. Primary Objective

- Compare the complete resection rate (CRR) of 15-40mm lateral spreading adenomas and subsequent adenoma recurrence rate (ARR) at first surveillance colonoscopy (SC1) 6 months for conventional EMR vs. cold snare EMR.

3.2. Secondary Objectives

- Compare conventional EMR vs. cold snare EMR with regard to
    - Complete resection time and total procedure time.
    - Intra-procedural and post-procedural adverse events rates.
    - To assess the histology of cold snare protrusions during cold snare EMR.

4. STUDY DESIGN

4.1. Type of Study

Randomised controlled trial.

4.2. Number of Subjects

600 patients

300 in the conventional EMR arm

300 in the cold snare EMR arm

4.3. Expected Duration of Study

48 months

4.4. Primary and Secondary Outcome Measures

4.4.1. Primary Outcome Measures

- Complete resection rate (CRR) as determined by endoscopic assessment (no visible residual adenoma) and histological assessment (biopsies of resection margin)
- Adenoma recurrence rate (ARR) at SC1 as determined by endoscopic assessment (no visible recurrent adenoma) and histological assessment (scar biopsies)

4.4.2. Secondary Outcome measures

- Time needed to perform polyp resection measured from first snare positioning until complete resection is achieved based on endoscopic assessment, and total procedure time from insertion of the scope until all specimens have been collected and the scope withdrawal is completed.
- Intra-procedural and post-procedural complications rates (IPB / CSPB / DMI / PPCS) as previously described [17], [27], [28]

5. STUDY TREATMENTS

5.1. Standard procedure

Bowel preparation will be standardised and consist of split dosing made up of 2 sachets of a sodium picosulfate, magnesium oxide, citrate preparation (Picoprep; Pharmatel Fresenius Kabi, Sydney, Australia) and 1 L of polyethylene glycol. The final sachet of picosulfate is consumed 4–5 hours before admission. Conscious sedation using a combination of Midazolam, Fentanyl and Propofol will be performed during colonoscopy. Monitored anaesthetic care will be provided based on clinical indication. Carbon dioxide is used for insufflation. Standard high definition Olympus 190 series variable stiffness colonoscopes (HQ190 PCF/CF; Olympus Medical Systems, Tokyo, Japan), CF-EZ1500DL colonoscopes and CF-XZ1200L colonoscopes with a microprocessor-controlled generator (VIO 300D Endocut Q Effect 3; ERBE Electromedizin, Tubingen, Germany) will be used. Other equipment will include a 4K monitor, CV-1500 processor and a OIP-1 (CADe).

5.2. Index procedure treatment arms

5.2.1. Conventional EMR arm

Polyp size will be measured against an open snare of known size. Before resection all lesions will undergo careful inspection using high definition white-light and narrow-band imaging (NBI) to exclude features consistent with submucosal invasion. A standardized and previously described inject and resect technique will be applied using succinylated gelatin (Gelofusine; Braun, Melsungen, Germany) dyed with 0.4% indigo carmine and combined with Adrenaline 1:100000 for submucosal lift [11]. Snare excision is performed using a 15-20mm thick-wire Captivator II snare (Boston Scientific, Natick, Massachusetts, USA) with a microprocessor-controlled generator (VIO 300D Endocut Q Effect 3; ERBE Electromedizin, Tubingen, Germany). A rim of 1-3 mm of normal mucosa surrounding the polyp will be excised to achieve complete resection followed by careful interrogation of the EMR defect and defect margins. Any residual adenoma is to be re-resected in order to obtain complete resection of the lesion. The resected tissue will be retrieved by suctioning into a polyp trap or collected with a roth-net followed by regular processing for histological examination. When complete resection has been achieved according to *endoscopic assessment* four biopsies from the defect margin will be taken to confirm complete resection by *histological assessment*. Defect margins will subsequently be treated using STSC (Soft Coag mode 80W Effect 4; ERBE Electromedizin, Tubingen, Germany) as previously described [13]. Treatment of intra-procedural bleeding (IPB) or deep mural injury (DMI) will be left to the discretion of the endoscopist performing the procedure. An endoscopic tattoo is then placed 3cm distal to the polypectomy site.

5.2.2. Cold snare EMR arm

Polyp size will be measured against an open snare of known size. Before resection all lesions will undergo careful inspection using high definition white-light and narrow-band imaging (NBI) to exclude features consistent with submucosal invasion. A standardized and previously described inject and resect technique will be applied using succinylated gelatin (Gelofusine; Braun, Melsungen, Germany) dyed with 0.4% indigo

carmine and combined with Adrenaline 1:100000 for submucosal lift followed [11]. Snare excision is performed using a stiff thin-wired snare (TeleMed 10mm Hexagonal, TeleMed Systems Inc; Hudson, Massachusetts, USA). A rim of 1-3 mm of normal mucosa surrounding the polyp will be excised to achieve complete resection followed by careful interrogation of the defect and its margins. Any residual adenoma is to be re-resected in order to obtain complete resection of the lesion. The resected tissue will be retrieved by suctioning into a polyp trap followed by regular processing for histological examination. When complete resection has been achieved according to *endoscopic assessment* four biopsies from the defect margin will be taken to confirm complete resection by *histological assessment*. Treatment of intra-procedural bleeding (IPB) or deep mural injury (DMI) will be left to the discretion of the endoscopist performing the procedure. An endoscopic tattoo is then placed 3cm distal to the polypectomy site.

5.3. Surveillance colonoscopy (SC)

5.3.1. At 6 months following index colonoscopy (SC1)

Identification and careful inspection of the post-EMR scar will be done using high definition white-light and NBI. Targeted biopsies will be taken if endoscopic features suspicious for adenoma recurrence are present, followed by standard cold avulsion snare tip soft coagulation (CAST) treatment as previously described [29]. If no suspicious areas are present, two random scar biopsies will be obtained to confirm the endoscopic findings.

5.3.2. At 18 months following index colonoscopy (SC2)

Identification and careful inspection of the post-EMR scar will be done using high definition white-light and NBI. Targeted biopsies will be taken if endoscopic features suspicious for adenoma recurrence are present, followed by standard cold avulsion snare tip soft coagulation (CAST) treatment as previously described [29]. If no suspicious areas are present, random scar biopsies will be obtained to confirm the endoscopic findings.

5.4. Proceduralists

Procedures will be carried out by experienced endoscopists, all of whom have independently performed over a 1000 colonoscopies and have undergone a minimum of 12 months of advanced endoscopy training in colonic EMR in a tertiary referral centre, or by an advanced endoscopy fellow under their direct supervision.

5.5. Sequence of actions

1. All eligible patients referred for a colonoscopy will undergo the exam only after appropriate bowel preparation and signed consent for the procedure and trial participation has been obtained.
2. When a polyp meeting the inclusion criteria is detected, this patient will enter the audit.
3. The polyp is to be removed using an inject and resect technique as previously described. Applied resection method is dependant on the treatment-arm to which the patient is allocated.

4. The resection defect is carefully inspected using topical submucosal chromoendoscopy where appropriate. Residual adenoma will be re-resected.
5. Duration of the polypectomy is recorded beginning with the first snare positioning until complete resection is achieved based on endoscopic assessment.
6. After complete resection is achieved (endoscopic assessment) all four quadrants of the margin will be biopsied. Specimens to be collected separately for histological assessment.
7. If a cold EMR has been performed, the defect will be carefully examined for cold snare protrusions, and if present, these will be biopsied and sent separately for histological assessment.
8. Application of haemostatic clips to the polypectomy defect is left the discretion of the endoscopist performing the procedure.
9. A small tattoo is placed 3cm distal to the resection site.
10. Tissue resection specimens are collected and processed for histologic evaluation in a standard fashion.
11. Total procedure time is recorded commencing at scope introduction until all specimens have been collected and full withdrawal is completed.
12. Technical aspects of the procedure are recorded during the procedure or directly thereafter using a standardized form.
13. Usual post-colonoscopy care is recorded
14. Patients will be blinded for the treatment they receive. They will however be informed regarding the amount, size and location of polyps removed as well as the follow-up arrangements and possible adverse events.
15. Histology results are recorded on follow-up datasheet, and communicated to the patient via the referring physician.
16. 14 Days following their procedure patients are contacted to assess any procedure related adverse events including unscheduled medical care or readmissions.
17. All patients will undergo a surveillance colonoscopy performed as per current guidelines at 6 months (SC1) and 18 months (SC2) following the index procedure.
18. During surveillance colonoscopy the resection scar will be carefully interrogated using high definition white-light and NBI.
19. If macroscopic recurrence of adenoma is present at the site of the scar (endoscopic assessment) biopsies will be obtained to confirm and the lesion will be re-resected using the cold avulsion snare tip soft coag (CAST) technique [29].
20. If no macroscopic recurrence is present standard biopsies of the resection site will be obtained to confirm endoscopic findings.
21. The identifiable information will be safely stored at Westmead Hospital at the Endoscopy Unit and the recorded data will be processed in Westmead as well.

6. SUBJECT ENROLLMENT AND RANDOMISATION

6.1. Recruitment

The Westmead Hospital Endoscopy unit is a tertiary referral centre for endoscopic tissue resection. All patients who have been referred for endoscopic resection will be recruited

6.2. Eligibility criteria

6.2.1. Inclusion criteria

- Any patient undergoing colonoscopy who is older than 18 years of age, has a written consent for trial participation and has at least one LSL meeting to the following description:
  - Localisation in the colon or rectum
  - Benign adenomatous surface features (Kudo III / IV, JNET 2a)
  - Granular or non-granular topography
  - Paris classification 0-IIa/IIb +/- Is
  - If present, sessile component may be no greater than 10mm in size.
  - Polyp size ranging from 15 to 40mm

6.2.2. Exclusion criteria

- Current use of antiplatelet (excluding aspirin) or anticoagulants which have not appropriately been interrupted according to the guidelines.
- Known bleeding disorder or coagulopathy.
- Pregnancy
- History of inflammatory bowel disease
- Previously attempted or otherwise non-lifting lesions
- Endoscopic features suggestive of submucosal invasion (Kudo Vi/n, JNET 2b / 3) or concurrent CRC
- Lesions involving the ileocaecal valve (ICV) or the anorectal junction (ARJ)

6.3. Randomisation and blinding

Computer generated randomization of patients will occur the moment an eligible lesion is encountered. The research nurse will perform the randomization and thereafter disclose the treatment arm to the endoscopist. Treatment allocation applies only to the one lesion for which randomization was performed. The applied treatment will be disclosed to the patient only after the assessment and documentation of any delayed events by the research nurse has taken place at 14 days post procedure. Future lesions detected during follow-up may be randomized separately if meeting the inclusion criteria, but will otherwise be subject to standard treatment as per clinical protocol.

6.4. Voluntary participation

Trial participation is entirely voluntary, and declining to do so should have no consequences with regard to the standard of care delivered. All investigators are required to express this to participants.

6.5. Study withdrawal

All participants have the right to withdraw from the study at any time, and for whatever reason without consequences for further treatment. Alternatively, investigators may exclude the patient from the study at any time if this is in the patient's interest. Participants that have withdrawn from trial will be asked if their collected data thus far may be used for analysis.

It is anticipated that with appropriate explanation and reassurance the rate of withdrawal will not exceed 5%. Withdrawals will be recorded so that final analysis with intention to treat is still possible.

6.6. Trial Closure

Interim analysis is planned for 12 months after commencing, or when half of the number of patients in both groups has been successfully recruited. Should the interim analysis reveal a marked difference in outcomes the trial will be discussed with the WSLHD/HREC. If one method is deemed significantly better as compared to the other, the trial may be closed due to ethical conflict of denying patients the better treatment. If the interim analysis reveals a significant difference in safety, which we do not anticipate, the less safe method will also be considered as harmful to patients, and the trial may be closed.

6.7. Continuation of therapy

If the interim analysis shows no differences in outcome or differences are minimal to moderate, the trial will be completed as planned.

7. STUDY VISITS AND PROCEDURES SCHEDULE

7.1. Procedures

The intervention will be performed during the index colonoscopy. Subsequent surveillance colonoscopies will happen according to current guidelines [30]. SC1 will be planned at 6 months- and SC2 at 18months following the index procedure. At surveillance colonoscopy polyp recurrence may be detected and treated.

7.2. Visits

Histology results will be discussed with either the referring physician or in the gastrointestinal clinic as per standard practice, requiring no additional study visits. The trial nurse or research fellow will contact participants by telephone 14 days following each procedure to assess any procedure related adverse events or unscheduled medical care.

8. CLINICAL AND LABORATORY ASSESSMENTS

The polyps will be measured against an open snare of known size and classified based on validated classification systems of superficial neoplastic lesions [31], [32]. The resected specimens will be histologically examined. Biopsies taken from the margin are to be examined separately in order to assess the presence of residual adenomatous tissue.

9. ADVERSE EVENT REPORTING

9.1. Definitions

Adverse event (AE): Any untoward event that does not necessarily have a causal relationship with the treatment. These may be expected.

Serious Adverse event (SAE): An event resulting hospitalisation, death, life threatening event, persistent disability

Serious Unexpected Suspected Adverse Reaction (SUSAR): An SAE which is probably related to the drug and is unexpected. This assessment is made after unblinding of data to judge causality.

9.2. Assessment and Documentation of Adverse Events

The data collection sheet has a dedicated column for recording the type, nature, description and severity of adverse events. Adverse events will be recorded during the baseline procedure and in recovery after the procedure. Delayed adverse events will be assessed by a research nurse during the 14-day post procedure follow-up telephone call. The assessment will be conducted independent of the investigators using a standardized questionnaire. All adverse events will be reported to the study coordinator.

9.3. Patient Safety Monitoring

To monitor patient safety an independent endpoint adjudication committee (EAC) will be appointed. The EAC will consist of two unaffiliated experts in the field. All adverse events will be reported to the EAC by the study coordinator. The EAC has access to unblinded patient data and will review all adverse events prior to the interim analysis. These will then be adjudicated according to the adverse events classification as listed in the protocol. Interim analysis will be performed by a blinded independent statistician who will report back to the study coordinator and the EAC.

10. STATISTICAL METHODS

10.1. Sample size estimation

Based on previously published recurrence rates of 7% in conventional EMR treatment of lateral spreading adenomas over 20mm [13], and 11% and 22% in cold snare EMR treatment of lateral spreading adenomas over 10mm and 20mm respectively [26], the total sample size required to achieve 80% power to detect a twofold superiority in recurrence rate of conventional EMR vs. cold snare EMR (7% vs. 14% respectively), at the 5% level of significance (two-sided test) is calculated at 600 patients (300 in each treatment arm), provided the recurrence rate in the cold snare EMR arm is 14% or greater

10.2. Statistical analysis plan

The collected information is outlined in the attached ACE datasheets (see appendices). The data will be entered in an Excel file and analysed using the statistical software SPSS. Chi-squared tests will be used to test for pairwise association between categorical variables. Multiple logistic regression will be used to investigate the joint effects of wire type and other potential risk factors in secondary analyses. Statistical support will be provided by Dr. Karen Byth, statistician.

10.3. Interim analysis

A Safety Data Monitoring Committee (SDMC) will conduct an interim analysis when half the number of patients needed has been recruited. If these preliminary results indicate statistically significant differences between the two treatment arms, measures will be taken to ensure best clinical practice and patient safety.

11. DATA MANAGEMENT600

11.1. Data Collection (see Appendices for detailed information)

- Patient characteristics: will be obtained from the patient, from the referral letter, or from the Medical Record.
- Procedural aspects: will be assessed immediately after the colonoscopy.
- Pathology report: will be collected from the electronic patient file.
- Adverse events: will be reported after the procedure and after 30 days via the research nurse's phone call.

11.2. Data Storage

Data will be stored **de-identified data** on an online web portal and will be entered by the study investigator/registrar/study nurse. The web portal is secured by the latest security technology (strong protocol (TLS 1.2), a strong key exchange (ECDHE_RSA with P-256), and a strong cipher (AES_256_GCM)) and access is via a non-publicly available link and secure password login. Study participants will be identified on this data collector by a study number only. No name, date of birth, medical record number, address details or any other personally identifiable information will be uploaded. The format of the data collector is in-line with the data collection form for this study. We will maintain a key to re-identify the database in a locked office accessible only to the investigators. This key will only be combined with the de-identified data on the closed intranet

of the hospital/institution at which this data was collected. It will not be possible to identify participants on the online portal.

11.3. Study Record Retention

Data will be securely stored for 5 years post publication. Afterwards, the paper-based forms will be shredded and put into a confidential bin. Electronically stored data will be deleted (including back-ups).

12. ADMINISTRATIVE ASPECTS

12.1. Confidentiality

All data will anonymously be analysed. Individual participant information or identifying information will not be published.

12.2. Independent HREC Approval

The trial will only proceed with official approval form WSLHD HREC, Scientific Study Committee and the chief executive of WSLHD.

12.3. Modifications of the protocol

The study protocol is subject to modification if a deficiency or improvement in the protocol is realised in time. Any modifications will be forwarded to WSLHD HREC.

12.4. Participant reimbursement

There will be no reimbursement for participation in the trial.

12.5. Financial disclosure and conflicts of interest

None.

13. USE OF DATA AND PUBLICATIONS POLICY

The data collected in this trial are property of the study investigators. The collected and analysed data will be used for publication in international peer-reviewed journals and for presentation at gastroenterology, surgery and/ or endoscopy meetings.

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