STUDY PROTOCOL

The Cap-Assisted Resection Margin Assessment (CARMA) technique after polyp resection: a prospective feasibility study of a “novel” approach to reduce polyp recurrence

Document date: 14 October 2021

NCT number: not yet assigned

PROJECT TEAM ROLES AND RESPONSIBILITIES

Principle Investigator:

Dr Alexander Huelsen Katz, Gastroenterologist, Department of Gastroenterology and Hepatology, Princess Alexandra Hospital

Additional Investigators:

Dr Zaki Hamarneh, Gastroenterologist, Department of Gastroenterology and Hepatology, Princess Alexandra Hospital

Dr Prabha Selvanathan, Gastroenterology Principal House Officer, Department of Gastroenterology and Hepatology, Princess Alexandra Hospital

Other Collaborators:

Dr Jennifer Borowsky, Anatomical Pathologist, Department of Anatomical Pathology, Pathology Queensland, Princess Alexandra Hospital

Dr Caroline Cooper, Anatomical Pathologist, Department of Anatomical Pathology, Pathology Queensland, Princess Alexandra Hospital

Research Site: Princess Alexandra Hospital

RESOURCES

No additional resources or funding are required for this observational study.

BACKGROUND

Colorectal cancer forms 11 per cent of new cancer diagnoses in Australia each year and contributes to 11 per cent of cancer-related deaths annually (1). Colonoscopic removal of polyps is an important and well-established tool in the prevention of colorectal cancers (2-5). However, high polyp recurrence rates after endoscopic resection, with resultant development of interval cancers, remains a problem (6-16). In fact, some studies report polyp recurrence rates as high as 48 per cent, and post-colonoscopy interval cancers may account for up to 27 per cent of all colorectal cancers (6-16). This most commonly stems from unrecognised incomplete polyp resection, especially at the margin of the resection site, with recent studies finding residual adenoma in up to 13 per cent of rim biopsies after removal of small polyps (12-13). This risk is seen across all types of polyps and all methods of polyp resection, though factors such as larger polyp size and sessile serrated lesions have been associated with a higher risk of recurrence (13). Studies to date have also found significant variability in rates of achieving clear margins between different endoscopists (12,17)

Thus, a standardised endoscopic technique is needed that will allow endoscopists to consistently achieve a clear margin of resection, independent of the method of polyp resection used. This should reduce the recurrence rate of polyps in general, as well as reducing the heterogeneity of polyp recurrence rates between endoscopists, leading to an overall reduced risk of interval cancers.

We believe the Cap Assisted Resection Margin Assessment (CARMA) technique will address this problem. This novel technique focuses on a standardised assessment of the resection margin after endoscopic polypectomy utilising available standard high-definition video endoscopes with imaging features including narrow band imaging (NBI) and magnification endoscopy. We hypothesise that normal colonic mucosa can be identified at the resection margin and differentiated from residual polyp tissue with this technique, thus allowing confirmation of a complete polyp resection.

This prospective study aims to evaluate the CARMA technique, primarily looking at the rate of achieving a clear resection margin. Secondary outcomes that will be examined include sensitivity and specificity of the CARMA technique for residual polyp detection, frequency of residual polyp prior to use of the CARMA technique, time required for CARMA technique assessment, incomplete resection rate with the CARMA technique, the effect of hot and cold snare use on rates of achieving clear resection margins in polyps larger than 10mm, the effect of hot and cold snare use on rates of polyp recurrence, and the effect of polyp size on recurrence rates.

We expect that the CARMA technique will be effective in confirming a clear resection margin (without residual polyp tissue).

PROJECT DESIGN

Research project setting

This study will be conducted at a single centre, Princess Alexandra Hospital. Procedures will be performed by up to three endoscopists at this study centre.

Methodological approach

This study aims to evaluate the use of the CARMA technique for the endoscopic resection of 60-100 polyps. In order to assess the applicability of this technique to polyps of various types and sizes, this will include polyps < 10mm (conventional adenomas or sessile serrated adenomas), sessile serrated adenomas > 10mm and conventional adenomas > 10mm.

All colonoscopies will be performed using high-definition video colonoscopes with distal cap attachment. The distal cap attachment is made from clear silicone and extends 2-4mm beyond the distal endoscope tip which includes the camera chip. It serves as a space holder between the camera chip and the mucosa allowing a consistent in focus assessment of the area of interest.

<u>1) Initial assessment</u>

Polyps will first be resected using standard resection techniques; this forms the control group of the study. Polyps < 10mm will be resected with cold snare without lifting. Sessile serrated adenomas > 10mm will undergo piecemeal resection with cold snare after lifting. Conventional adenomas > 10mm will be resected either with hot or cold snare, using lifting and single ("en bloc") resection or piecemeal resection technique, at the endoscopist's discretion. Mucosal lifting will be performed with a standard endoscopic needle injector and a standard solution of gelofusine, methylene blue and adrenaline 1:100 000 which is injected into the submucosal space underneath the lesion to reduce thermal or mechanical injury to the deeper tissue layers during resection.

Once standard polyp resection and assessment of the polypectomy site without magnification is completed, the CARMA technique will be applied; this forms the intervention group of the study. This will involve an assessment of the entire polypectomy margin using cap assisted magnification endoscopy with the ability to also use NBI (at the endoscopist's discretion) and documentation of any residual polyp noted. If residual polyp is noted, the scope channel will be flushed and cleared, and the abnormal margin will be resected with a cold snare, with the sample collected in a separate specimen pot labelled "residual margin". Once this is complete, the scope channel will again be flushed and cleared. A 2-3mm safety margin of the entire polypectomy rim will be resected, with this sample collected in a separate specimen pot labelled "normal margin". A single tattoo may be placed to mark the polypectomy site, to allow for accurate identification of the site when evaluating for recurrence at the time of re-assessment.

2) Follow-up assessment

Patients will undergo repeat colonoscopy as per national colonoscopic polyp surveillance guidelines at which time we will also re-assess for polyp recurrence. At the time of repeat colonoscopy, a picture and, if needed, a biopsy at the polypectomy site will be used to confirm clearance. Any residual polyp will be resected as per standard colonoscopy practice.

Participants

This study aims to evaluate the resection of 60-100 polyps, with a maximum of two polyps evaluated from each individual patient. Thus, it is expected that 50-60 participants will be enrolled in this trial. The study aims to assess 20 polyps < 10mm with resection not well-visualised (conventional adenomas or sessile serrated adenomas), 20-40 polyps that are > 10mm and endoscopically in keeping with sessile serrated adenomas, and 20-40 polyps that are > 10mm and endoscopically in keeping with conventional adenomas.

Given that this is a pilot feasibility study, power calculations have not been used to determine the sample size. In discussion with our biostatistical support service, it was felt that observation of 60-100 polypectomies would be adequate to demonstrate the ability of the CARMA technique to identify normal colonic mucosa without any residual polyp tissue at the resection margin.

Inclusion criteria:

- any polypectomy (though only a maximum of two polyps from one individual participant)

Exclusion criteria:

- polyps less than 10mm which were resected under endoscopic view with a definite > 1mm clear margin
- scar site recurrence polyps
- polyps with endoscopic evidence of invasion
- pedunculated polyps
- pseudopolyps
- participants who will not be available for follow up endoscopy

Participant recruitment

Participants for this study will be recruited from patients booked for routine diagnostic and surveillance colonoscopies at the study centre over a maximum 18-month period. The study endoscopists will review their booked procedure lists 1-2 weeks in advance and identify any patients booked for colonoscopies. Patients will be contacted by a member of the study team by phone at this stage to offer involvement in this study and address any initial queries they may have regarding the study. If the patient is agreeable to participating in the study, a copy of the Patient Information and Consent form (described below) will be posted to the patient to allow them time to peruse the information and discuss the study with their family or health care providers if required. On the day of the patient's procedure, they will be reviewed by the member of the study team performing the procedure to confirm their willingness to participate in the study, address any queries or concerns, and complete the consent process if they choose to proceed.

Provision of information to participants and consent

Patients will have already received standard information materials regarding colonoscopy and preparation for their colonoscopy at the time that their procedure was booked, as is routine practice for all patients undergoing colonoscopy at the study centre. A Patient Information and Consent form has been created specifically for this study and will be provided to patients enrolling in this study, in addition to the study institution's standard information materials and consent form for colonoscopy. In the study-specific Patient Information and Consent form, the CARMA technique and rationale for this study are outlined in simple language. The form explains that the initial polyp resection occurs using standard polypectomy techniques, and the CARMA technique is then applied to meticulously examine the polypectomy margin to identify residual polyp tissue which can then be resected. The form outlines that the use of a cap, endoscopic magnification and tattoo placement are all accepted and established techniques for polypectomy, and all devices and materials to be used (snares, needles, tattoo, lift) are standard TGA-approved equipment already used at the study centre. The form also explains that the resection of any residual polyp found is a required and standard practice, and will not add additional risk to the procedure. Similarly, the form explains that the resection of a safety margin is in keeping with standard best practice to avoid polyp recurrence, and does not increase risk of bleeding, perforation, or other complications, nor does it significantly increase procedure time (with time required for the CARMA assessment and technique anticipated

to be less than one to two minutes). The form also explains that the requirement for repeat colonoscopy for assessment for polyp recurrence is standard practice and will be arranged as per national colonoscopy polyp surveillance guidelines. Participation in this study will be strictly voluntary, with patients having the option to withdraw from the study at any point.

Research Activities

The expected project duration is 18 months for the initial assessments and 5 years for the follow up assessments. Participant commitment to this study will only involve their initial colonoscopy and repeat colonoscopy for assessment for recurrence, the latter which will be scheduled as per national colonoscopy polyp surveillance guidelines.

Outcome measures

Primary outcome:

- Rate of achieving a clear resection margin using the CARMA technique

Secondary outcomes:

- Sensitivity and specificity of the CARMA technique for residual polyp detection
- Frequency of residual polyp without CARMA assessment (control group)
- Incomplete resection rate with use of CARMA technique
- Incomplete resection rate with use of the CARMA technique in polyps > 10mm with hot snare
- Incomplete resection rate with use of the CARMA technique in polyps > 10mm with cold snare
- Residual polyp rate after CARMA technique with hot snare
- Residual polyp rate after CARMA technique with cold snare
- Time required for application of the CARMA technique with < 10mm
- Time required for application of the CARMA technique with > 10mm polyps
- Polyp recurrence rate for < 10mm polyps
- Polyp recurrence rate for > 10mm polyps

Data Collection

Patient information collected from their electronic medical record will include age, gender and indication for colonoscopy. Information collected at each participant's initial colonoscopy, from the procedure report and histology results, will include number of polyps resected, polyp size, Paris and NICE classifications of polyps, polyp resection technique used (use of hot or cold snare, and use of lifting, en bloc resection or piecemeal resection), time taken for application of the CARMA assessment/technique, and histological diagnosis. Information collected at each participant's repeat colonoscopy, from the procedure report and histology results, will include endoscopic impression of recurrence and histological confirmation of recurrence from scar biopsy.

Data Management

A unique patient identification number will be assigned to each patient and will serve as the patient's identifier for the study, with all patient data stored and collected under this number. De-identified patient information and study data will be stored in a password-protected electronic data collection form (in a Microsoft Excel spreadsheet), which will be saved in the study centre's computer system. Any hard copies of source notes containing identifiable medical information will be stored in a locked office area in the study centre. Identifying information will not be shared with any other institutions. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing of patient data. Investigators and research staff will assure that patient anonymity is strictly maintained and that patient identifiers are protected from unauthorised parties. Study data will be stored for a maximum of 15 years, after which any electronic records will be deleted from the study centre's computer system and any paper records will be destroyed through a confidential waste disposal service.

Data Analysis

The primary outcome of rate of achieving clear resection margins, as well as the secondary outcomes of frequency of residual polyp and incomplete resection rate, will be calculated using simple frequencies and percentages. Standard calculations will be used to determine the sensitivity and specificity of the CARMA technique for residual polyp detection. The effect of polyp size and resection technique on polyp recurrence rates, incomplete resection rates and time required for application of the CARMA technique will be analysed using an unpaired student's *t* test.

Data Linkage

Nil applicable

RESULTS, OUTCOMES AND FUTURE PLANS

For patients enrolled in this study, as per usual practice at the study centre, a copy of their individual procedure report will be sent to the patient's general practitioner and referring physician, and the patient can obtain the results of their colonoscopy through them. The patient can also request the discuss their procedure findings with the treating endoscopist immediately following their procedure if they wish, as is standard practice in the study centre's endoscopy unit.

With regards to the study findings, given the outcomes of the study will be analysed as grouped data, it is unlikely that the study findings will be meaningful or relevant to the individual patient's clinical management; thus, there are no plans to return the research results to patients enrolled in the study. We aim to present the results of this study at national and international scientific meetings, and publish the analysed data in a peer-reviewed medical journal.

There are no plans for further use of the data from this project once this study is complete.

REFERENCES

1. Cancer Australia. Bowel cancer (Colorectal cancer) in Australia statistics [Internet]. Canberra, ACT: Australian Government; 2020 October 20 [cited 2021 May 23]. Available from: https://www.canceraustralia.gov.au/affected-cancer/cancer-types/bowel-cancer/bowel-cancer-colorectal-cancer-australia-statistics.

2. Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375(9726):1624-33.

3. Holme Ø, Løberg M, Kalager M, Bretthauer M, Hernán MA, Aas E, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. Jama. 2014;312(6):606-15.

4. Holme Ø, Schoen RE, Senore C, Segnan N, Hoff G, Løberg M, et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. Bmj. 2017;356:i6673.

5. Lin JS, Piper MA, Perdue LA, Rutter CM, Webber EM, O'Connor E, et al. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2016;315(23):2576-94.

6. Farrar WD, Sawhney MS, Nelson DB, Lederle FA, Bond JH. Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol. 2006;4(10):1259-64.

7. le Clercq CM, Bouwens MW, Rondagh EJ, Bakker CM, Keulen ET, de Ridder RJ, et al. Postcolonoscopy colorectal cancers are preventable: a population-based study. Gut. 2014;63(6):957-63.

8. Moss A, Williams SJ, Hourigan LF, Brown G, Tam W, Singh R, et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. Gut. 2015;64(1):57-65.

9. Robertson DJ, Lieberman DA, Winawer SJ, Ahnen DJ, Baron JA, Schatzkin A, et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. Gut. 2014;63(6):949-56.

10. Kang DK, Park SB, Kim HW, Kang DH, Choi CW, Kim SJ, et al. Long-term outcomes and surveillance timing of patients with large non-pedunculated colorectal polyps with histologically incomplete resection in endoscopic resection. Surgical endoscopy. 2021.

11. Knabe M, Pohl J, Gerges C, Ell C, Neuhaus H, Schumacher B. Standardized long-term follow-up after endoscopic resection of large, nonpedunculated colorectal lesions: a prospective two-center study. The American journal of gastroenterology. 2014;109(2):183-9.

12. Pedersen IB, Bretthauer M, Kalager M, Løberg M, Hoff G, Matapour S, et al. Incomplete endoscopic resection of colorectal polyps: a prospective quality assurance study. Endoscopy. 2021;53(4):383-91.

13. Pohl H, Srivastava A, Bensen SP, Anderson P, Rothstein RI, Gordon SR, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology. 2013;144(1):74-80.e1.

14. Belderbos TD, Leenders M, Moons LM, Siersema PD. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. Endoscopy. 2014;46(5):388-402.

15. Singh S, Singh PP, Murad MH, Singh H, Samadder NJ. Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. The American journal of gastroenterology. 2014;109(9):1375-89.

16. Samadder NJ, Curtin K, Tuohy TM, Pappas L, Boucher K, Provenzale D, et al. Characteristics of missed or interval colorectal cancer and patient survival: a population-based study. Gastroenterology. 2014;146(4):950-60.

17. Klein A, Tate DJ, et al. Thermal ablation of mucosal defect margins reduces adenoma recurrence after colonic endoscopic mucosal resection. Gastroenterology. 2019 Feb;156(3):604-613.