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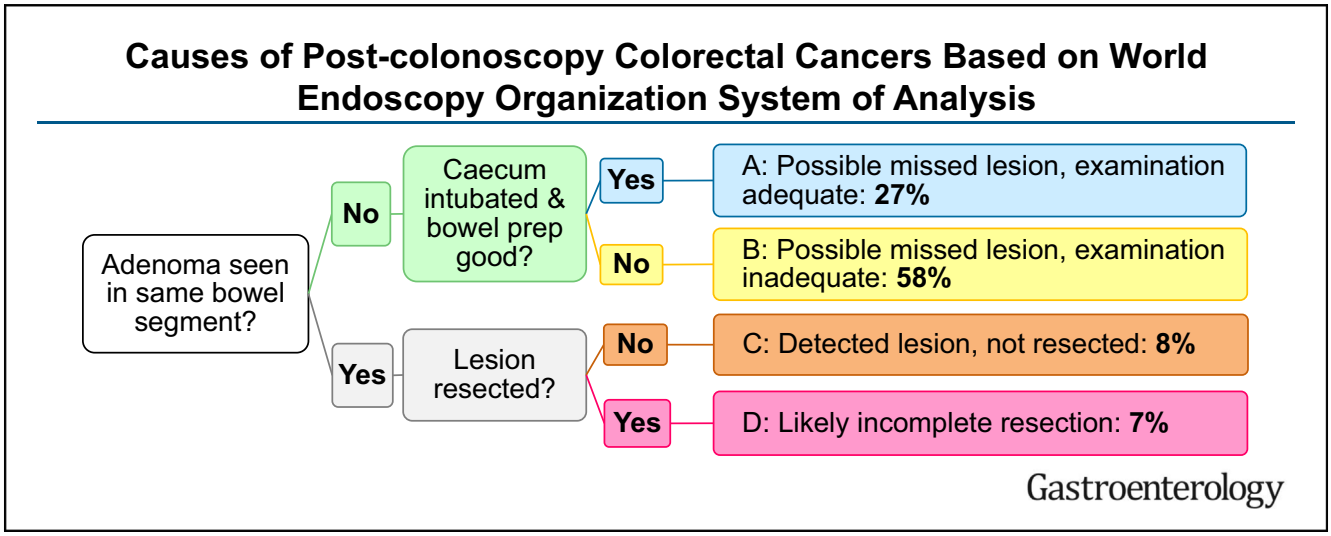
Causes of Post-Colonoscopy Colorectal Cancers Based on World Endoscopy Organization System of Analysis

Rebecca Anderson,[1] Nicholas E. Burr,[2,3] and Roland Valori[1]

[1]Gloucestershire Hospitals NHS Foundation Trust, Gloucester, United Kingdom; [2]The Mid Yorkshire Hospitals NHS Trust, Pinderfields General Hospital, Wakefield, United Kingdom; and [3]Cancer Epidemiology Group, Institute of Cancer & Pathology and Institute of Data Analytics, University of Leeds, United Kingdom



BACKGROUND & AIMS: Postcolonoscopy colorectal cancer (PCCRC) is CRC diagnosed after a colonoscopy in which no cancer was found. A consensus article from the World Endoscopy Organization (WEO) proposed an approach for investigating and categorizing PCCRCs detected within 4 years of a colonoscopy. We aimed to identify cases of PCCRC and the factors that cause them, test the WEO system of categorization, quantify the proportion of avoidable PCCRCs, and propose a target rate for PCCRCs detected within 3 years of a colonoscopy that did not detect CRC. **METHODS:** We performed a retrospective analysis of 107 PCCRCs identified at a single medical center in England from January 1, 2010, through December 31, 2017 using coding and endoscopy data. For each case, we reviewed clinical, pathology, radiology, and endoscopy findings. Using the WEO recommendations, we performed a root-cause analysis of each case, categorizing lesions as follows: possible missed lesion, prior examination adequate; possible missed lesion, prior examination inadequate; detected lesion, not resected; or likely incomplete resection of previously identified lesion. We determined whether PCCRCs could be attributed to the colonoscopist for technical or decision-making reasons, and whether the PCCRC was avoidable or unavoidable, based on the WEO categorization and size of tumor. The endoscopy reporting system provided performance data for individual endoscopists. **RESULTS:** Of the PCCRCs identified, 43% were in high-risk patients (those with inflammatory bowel disease, previous CRC, previous multiple large polyps, or hereditary cancer syndromes) and 66% were located distal to the hepatic flexure. There was no correlation between postcolonoscopy colorectal tumor size and time to diagnosis after index colonoscopy. Bowel preparation was poor in 19% of index colonoscopies, and only 36% of complete colonoscopies had adequate photodocumentation of completion. Development of 73% of PCCRCs was determined to be affected by technical endoscopic factors, 17% of PCCRCs by administrative factors (follow-up procedures delayed/not booked by administrative staff), and 27% of PCCRCs by decision-making factors. Twenty-seven percent of PCCRCs were categorized as possible missed lesion, prior examination adequate; 58% as possible missed lesion, prior examination inadequate; 8% as detected lesion, not resected; and 7% as incomplete resection of previously observed lesion; 89% were deemed to be avoidable. **CONCLUSIONS:** In a retrospective analysis of PCCRCs, using the WEO system of categorization, we found 43% to occur in high-risk patients; this might be reduced with more vigilant surveillance. Measures are needed to reduce technical, decision-making, and administrative factors. We found that 89% of PCCRCs may be avoidable. If half of avoidable PCCRCs could be prevented, the target rate of 2% for the PCCRC-3y (cancer diagnosed between 6 and 36 months after index colonoscopy) benchmark would be achievable.

Keywords: Colon Cancer; Etiology; Cohort; Recurrence.

CLINICAL AT

Colonoscopy is the reference standard investigation for prevention and diagnosis of colorectal cancer (CRC). However, sometimes CRC is diagnosed after a colonoscopy that has not found cancer. These CRCs are called postcolonoscopy colorectal cancers (PCCRCs),[1] a term recently endorsed by the World Endoscopy Organisation (WEO).[2]

There is now an extensive literature exploring factors contributing to PCCRCs and interval cancers that is both exemplified and well summarized by Tollivoro et al.[3] Most of these studies have used linked datasets, or case-control design to identify factors associated with PCCRCs, such as right-sided cancers, older patients, polymorbid patients, female sex, diverticular disease, previous surgery, previous/family history of CRC, cancer biology, and endoscopist factors (eg, adenoma detection rate [ADR] and colonoscopy volume). These studies benefit from large numbers, making it possible to demonstrate statistically significant associations. However, they do not provide the detail required to understand exactly what led to the PCCRC. As such, advice to services of how to reduce PCCRCs is general, remote from the real world, and will therefore have relatively little impact.[4–6]

In contrast, there is a smaller literature that reviews individual cases. These studies often have small numbers,[7–9] or there is case selection limiting their generalizability.[10] For example, the largest study of this type drew patients from 8 large randomized controlled trials.[10] All these trials had significant exclusion criteria, most excluding patients with the highest risk of PCCRC: previous cancer, the very young or very old, inflammatory bowel disease (IBD), comorbid patients, and patients with high-risk family history. In contrast, the study of Samadder et al.[7] was population based (covering 85% of the population of Utah) and included a review of 36 charts.

The Joint Advisory Group on Gastrointestinal Endoscopy requires endoscopy services to identify PCCRCs, perform root-cause analysis, and introduce improvements to reduce PCCRC rates.[11,12] The WEO consensus recommends services review their PCCRCs "to determine the most plausible explanation for the PCCRC," and it made recommendations for investigators to follow.[2] The intention was to provide a guide and bring consistency so that future reports could be compared and contrasted. The WEO recommended 2 different PCCRC intervals. A 6- to 48-month interval for quality improvement based on case review on the basis that the "most plausible explanation" for cancers appearing after 48 months is "likely new cancer." A shorter, 6- to 36-month interval (PCCRC-3y) was proposed for quality assurance or benchmarking.[2] The WEO group recognized that their recommendations needed to be tested.

With this, and the limitations of previous studies in mind, the aim of this study was to apply the WEO recommendations in a well-defined and stable population to

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Post-colonoscopy colorectal cancer (PCCRC) is CRC diagnosed after a colonoscopy in which no cancer was found. We used the World Endoscopy Organization (WEO) methodology for determining the etiology of PCCRCs and categorizing them.

NEW FINDINGS

In an analysis of PCCRCs detected over an 8-year period, we found 89% to be avoidable, based on WEO criteria, and 43% to occur in high-risk patients. Causes included possible missed lesion, adequate colonoscopy (27%); possible missed lesion, inadequate colonoscopy (58%); detected, unresected lesion (8%); and incomplete resection of detected lesion (7%).

LIMITATIONS

Earlier cases had less complete documentation and some measures, such a bowel preparation quality, were subjective. The center is a tertiary referral center for complex polypectomy, which may influence categorization.

IMPACT

We identified factors that can be addressed to reduce rates of PCCRC at a local level. We propose aiming for a rate of fewer than 2% of PCCRCs within 3 years of a colonoscopy.

- Perform a route-cause analysis for each PCCRC case appearing in the 6- to 48-month interval
- Define factors that lead to PCCRCs
- Categorize PCCRCs using the WEO method
- Determine the strengths and limitations of the WEO methodology
- Determine what proportion of PCCRCs are preventable and propose a target for PCCRC-3y rates
- Make recommendations of how to reduce PCCRC rates

Methods

Clinical Setting

The study identified and reviewed PCCRCs at Gloucestershire Hospitals over an 8-year period. Gloucestershire Hospitals

Abbreviations used in this paper: **ADR, adenoma detection rate; BCSP, bowel cancer screening programme; CIR, cecal intubation rate; CRC, colorectal cancer; IBD, inflammatory bowel disease; ICD-10, International Classification of Diseases, 10th Revision; MDT, multidisciplinary team; PCCRC, postcolonoscopy colorectal cancer; PCCRC-3y, cancer diagnosed between 6 and 36 months after index colonoscopy; PDR, polyp detection rate; PICI, performance indicator of cecal intubation; WEO, World Endoscopy Organisation.**

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is the principal provider of health care services to the county of Gloucestershire, England (population 628,000), which has a slight preponderance of people aged >65.[13] The endoscopy service is delivered from 4 sites. The service has a single governance structure, integrated electronic reporting system,[14] and 1 group of colonoscopists provides all the colonoscopies (6000–7000 procedures/year). The service participates in the National Bowel Cancer Screening Programme (BCSP) and has delivered colonoscopy training courses since 1999.[15]

Case Selection

Using International Classification of Diseases, 10th Revision (ICD-10) codes for malignant neoplasm of the colon (ICD-10 C18.0-C18.9), rectosigmoid (ICD-10 C19), rectum (ICD-10 C20), and anus (ICD-10 C21), all CRCs (January 1, 2010 to December 31, 2017) in which a colonoscopy had been performed in the preceding 6 to 48 months were identified from the hospital clinical database. A 6- to 48-month interval was chosen in accordance with the WEO guideline for case review. All adult patients older than 18 were included. Cases within 6 months of a cancer diagnosis, appendiceal cancers (ICD-10, C18.1), neuroendocrine tumors, and squamous cell cancers of the anus (ICD-10, C21) were excluded.

Benchmarking data for the most contemporary (all colonoscopy for years 2011–2013) PCCRC-3y rates was obtained from the UK Colorectal Cancer Intelligence Hub's colorectal cancer data repository (CORECT-R). This hub links cancer registry and routinely collected hospital data (including colonoscopies) to identify PCCRCs and calculate rates.[16] Data were available for all colonoscopy providers in England and PCCRC-3y rates were ranked in deciles.

Data Collection

For each case, the clinical record, pathology, radiology, endoscopy electronic systems, and printed Polaroid photographs were reviewed to collect data required by the WEO method[2] (Figure 1). There is a minimum dataset for pathology reporting of cancer in England, including exact size of the tumor. For patients who had multiple colonoscopies, that closest to cancer diagnosis was regarded as the "index" colonoscopy. However, data from earlier colonoscopies were also collected.

Root-Cause Analysis

A root-cause analysis (using the WEO categorization) was undertaken for each PCCRC. The categorization involves a 3-step process, which looks at the index colonoscopy in relation to the location of the cancer. It has 4 categories (labeled A to D).

Step 1: Was an adenoma seen in the subsequent cancerous bowel segment at index colonoscopy?

If No, proceed to Step 2; if Yes, proceed to Step 3.

Step 2: Was the cecum intubated and bowel preparation good at index colonoscopy?

If Yes, PCCRC is categorized as "A": possible missed lesion, examination adequate.

If No, PCCRC is categorized as "B": possible missed lesion, examination inadequate.

Step 3: Was the lesion resected?

If No, PCCRC is categorized as "C": detected lesion, not resected.

If Yes, PCCRC is categorized as "D": likely incomplete resection.

An adequate colonoscopy was defined as a complete procedure with adequate bowel preparation. Completion was deemed adequate if there was a photograph of the ileocecal valve, appendiceal orifice, or terminal ileum. During the study period, image capture was limited to Polaroid photographs and relatively few pictures were taken, therefore 1 clear photograph was considered sufficient. The reporting system had a compulsory field for preparation with 3 options: "Good," "Satisfactory," or "Poor." "Good" and "Satisfactory" were deemed adequate.

A "lesion" was defined, as per the WEO, as an advanced adenoma >1 cm and/or with villous component and/or with high-grade dysplasia.

Clinical records were reviewed to identify key management decisions, patient preferences, and deviations from management plans, for example, if a repeat procedure was recommended but not booked within the specified time period (or not at all), or the patient defaulted on an appointment.

Survival

To account for lead-time bias, survival should be calculated from the date of index colonoscopy and not PCCRC diagnosis; however, there is an additional potential bias: immortal time bias.[5] Patients with PCCRC must survive in the interval between index colonoscopy and the diagnosis of PCCRC to be available for survival analysis. For example, if a patient has a false negative colonoscopy at time 0, and then dies for an unrelated reason at 1 year (before being diagnosed with PCCRC) he or she will not be included in PCCRC mortality data calculated from the index colonoscopy. This would lead to falsely improved survival times in PCCRC cases. To avoid this "immortal time" bias, and to provide direct comparison with the results of the Belgium PCCRC study,[5] survival was calculated in patients still alive at 3 years and 4 years after index colonoscopy

Avoidability

The default position of the WEO categorization is that PCCRCs are avoidable, but this is not always the case. The authors made a judgment as to whether a PCCRC was avoidable or unavoidable. Small PCCRCs were categorized as unavoidable on the basis that if growing by <5 mm/year they would not have been present at the index colonoscopy. For example, a PCCRC <20 mm found at 48 months was deemed unavoidable. Submucosal lesions resulting from local recurrence of cancer were also deemed unavoidable.

In the NHS, all cancers must be discussed at multidisciplinary team (MDT) meetings before treatment, including all cases with potential malignant pathology. In certain cases, the patient may be deemed too unwell to proceed with further investigations/treatment of/for their precancerous pathology. Cases were deemed unavoidable if the patient declined recommended follow-up, or the MDT felt their comorbidities precluded them from further investigation. All other PCCRCs were deemed avoidable based on contributory

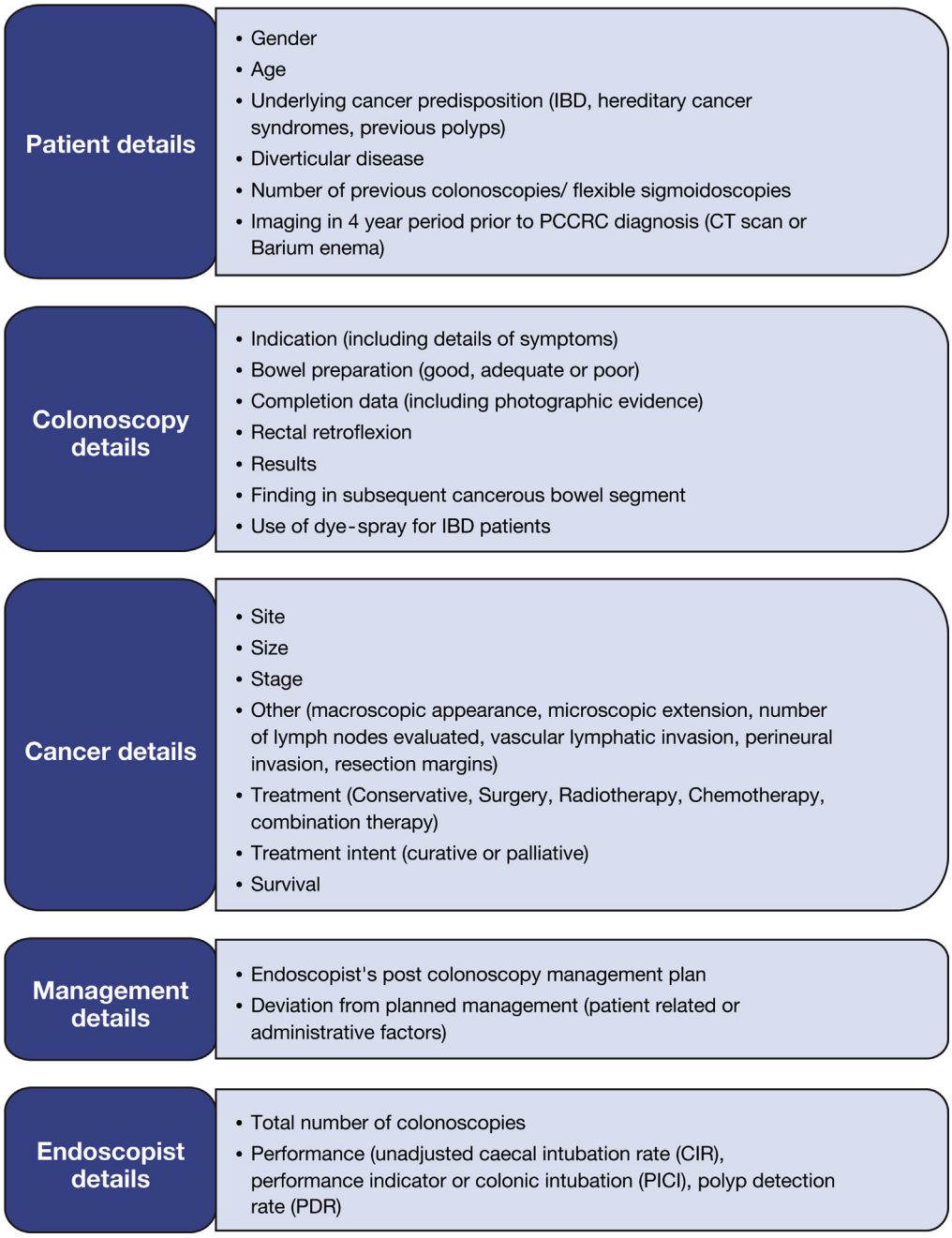

Figure 1. Data collected for each PCCRC. CT, computed tomography.

and modifiable technical, decision-making, and/or administrative factors.

Attribution

The authors concluded the PCCRC could be attributed to an individual colonoscopist for both technical and decision-making reasons on the basis that a colonoscopy is more than just a technical procedure. Thus, a PCCRC was deemed attributable in 1 or more of the following situations:

1. A PCCRC developed after a negative colonoscopy (excluding very small PCCRCs), irrespective of adequacy, on the basis a cancer or precursor lesion was missed.
2. The colonoscopist did not arrange further investigations after an inadequate colonoscopy or one in which potential precursor lesions were observed but not treated.
3. The colonoscopist did not state a timeframe, or recommended too long a timeframe, for repeat procedures.

The PCCRC was not deemed attributable in 1 or more of the following situations:

1. Small PCCRCs (growing at <5 mm/year).
2. PCCRCs in which the colonoscopist had requested prompt and appropriate further investigations that were not booked within the stated timeframe (or at all) by the administrative team.

3. When the decision about further procedure(s) lay with another clinician.

For the purpose of exploring the relationship between performance measures (such as cecal intubation rate [CIR]) and PCCRCs, a "technically attributable" rate for each individual was calculated that excluded decision-making factors. For each colonoscopist who had performed >200 procedures, the rate of PCCRCs per 1000 colonoscopies was calculated by dividing the number of PCCRCs that could be attributed to them for technical reasons, divided by the number of colonoscopies they had performed at Gloucestershire Hospitals during the study period. A PCCRC was felt to be technically attributable to a colonoscopist if it was incomplete (or lacked sufficient evidence of completion), or otherwise adequate but where a lesion was likely missed or incompletely excised.

Endoscopist Performance Data

The endoscopy reporting system provided performance data for individual endoscopists including polyp detection rate (PDR), CIR, sedation usage, and nurse-assessed comfort scores. The data enable calculation of the Performance Indicator of Cecal Intubation (PICI), a composite measure of intubation, patient comfort, and use of midazolam sedation.[17] ADR is not routinely collected.

Statistics/Correlations

A scatterplot was produced to show the correlation between tumor size and delay to diagnosis. Scatterplots were produced to illustrate the relationship of technically "attributable" rates of PCCRC/1000 colonoscopies to numbers of procedures, PDR, CIR, and PICI. Only colonoscopists who had performed >200 procedures were included. Pearson's correlation was performed where visual inspection suggested asymmetry.

Analyses were performed using Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA) and STATA v15 (StataCorp LP, College Station, TX).

Ethics

The project was registered as an audit with the hospital's Quality Improvement Department, and endorsed by the local Caldicott Guardian, an individual responsible for protecting the confidentiality of people's health and care information, and making sure it is used properly.[18]

Results

A total of 61,110 colonoscopies were performed in Gloucestershire Hospitals between January 2006 and July 2017 with an unadjusted PCCRC-3y rate of 4.7% (95% confidence interval 3.15%–6.25%), which was in the top decile of all colonoscopy services in England. A total of 129 potential PCCRCs were identified in the study period. Hospital records were unavailable in 9 early cases. Thirteen cases were excluded, leaving 107 cases for final analysis (Figure 2).

Patient Details

Fifty-five (51.4%) PCCRCs occurred in male patients. Age range at index colonoscopy was 37 to 87 (mean 71.1, median 71). Delay between index colonoscopy and PCCRC diagnosis ranged from 6 to 47 months (mean 24.9 months, median 24 months). Sixty-eight PCCRCs were diagnosed between 6 and 36 months (2.27/month) and 29 between 36 and 48 months (2.42/month).

Nine (8.4%) PCCRCs were diagnosed in patients with IBD, and 4 (3.7%) in patients with hereditary cancer syndromes (one familial adenomatous polyposis, 3 Lynch syndrome). Thirty patients (28%) had undergone previous resection for CRC. Five patients (4.7%) were noted to have multiple polyps on previous examinations. One of these patients had 2 subsequent PCCRCs. Forty-six patients (43%) had concurrent diverticular disease.

Twenty-six patients (24.3%) underwent more than 1 colonoscopy in the 6- to 48-month period (maximum 4). Fifteen patients (14%) underwent 1 or more flexible sigmoidoscopies in addition to their colonoscopy. Fifty patients (46.7%) had radiographic imaging (computed tomography scan/barium enema) in the 6- to 48-month period preceding CRC diagnosis.

Cancer Details

PCCRC locations were cecum (15, 14%), ascending (15, 14%), hepatic flexure (5, 4.7%), transverse (18, 16.8%), splenic flexure (4, 3.7%), descending (4, 3.7%), sigmoid (12, 11.2%), rectosigmoid junction (3, 2.8%), rectum (27, 25.2%), and anastomosis (1, 0.9%). In 3 cases (2.8%), the cancer location was ambiguous. Stage at diagnosis was I (34, 31.8%), II (34, 31.8%), III (26, 24.3%), and IV (13, 12.1%) (Figure 3). Tumor size was recorded in 95 (88.8%) of 107 PCCRCs, ranging from 1 to 200 mm in maximum diameter. The 1-mm cancer was identified in a polyp removed endoscopically. There was no correlation between delay to diagnosis and tumor size or staging (Figure 4).

Treatment for PCCRCs was surgery (67, 62.6%), chemotherapy (4, 3.7%), radiotherapy (2, 1.9%), combination therapy (20, 18.7%), polypectomy (5, 4.7%), transanal endoscopic microsurgery (3, 2.8%), and nil (6, 5.6%). Treatment intent was curative in 86 (80.4%) of 107 cases and palliative in 21 (19.6%) of 107 cases.

Immortal time bias and lead-time bias were accounted for by ignoring deaths within 3 and 4 years of the index colonoscopy[5,19]: 1-year survival at 3 and 4 years from index colonoscopy was 76 (80%) of 95 and 59 (69.4%) of 85, respectively.

Index Colonoscopy Details

Indication for colonoscopy included symptoms (43, 40.2%), surveillance for previous CRC (24, 22.4%), surveillance of polyps/post polypectomy (16, 15%), IBD surveillance (9, 8.4%), hereditary cancer surveillance (4, 3.7%), BCSP (7, 6.5%), previous abnormal investigation (3, 2.8%), and planned polypectomy (1, 0.9%). Anemia and rectal bleeding were the commonest indications in symptomatic patients.

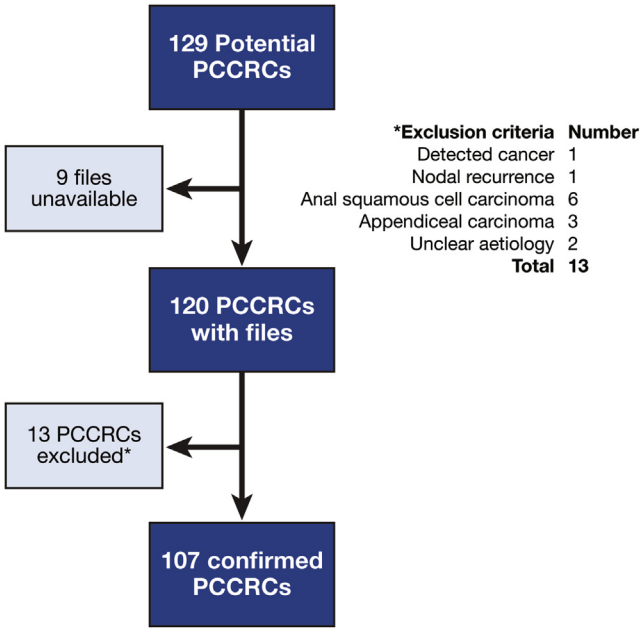

Figure 2. Identification of PCCRCs and *exclusions.

Two reports omitted quality of preparation. Of the remaining 105, bowel preparation was good in 73 (69.5%) cases, satisfactory in 12 (11.4%), and poor in 20 (19.0%). In 9 (45%) of 20 cases with poor preparation no repeat/alternative investigations were arranged and there was no record of an explicit decision for repeat colonoscopy or another test.

There was no electronic image capture during the study period. Photographs were printed, attached to a paper report, and filed in the patient record. Therefore, to assess for photodocumentation of completion, the original endoscopy report (with attached photographs) needed to be reviewed. In 7 cases, the endoscopy report could only be accessed electronically and photodocumentation of completion could not be verified. All 7 colonoscopies were reported as complete and PCCRC locations were transverse (1, 14.3%), descending (1, 14.3%), and rectum (5, 71.4%).

Overall, 98 (91.6%) of 107 colonoscopies were reported as complete. In comparison, the overall unadjusted CIR over the period was 95.6% (rates are not adjusted for any reason including poor preparation or stricture). Reasons for noncompletion were poor bowel preparation (2, 22.2%), diverticulosis (2, 22.2%), stricture (2, 22.2%), looping (1, 11.1%), otherwise difficult procedure (1, 11.1%), and patient discomfort (1, 11.1%). Two (22.2%) of 9 incomplete cases were referred for repeat colonoscopy and 4 (44.4%) of 9 for imaging. The remaining 3 (33.3%) had no further investigations and no documentation of decisions relating to repeat procedures. Photodocumentation of completion was not sought for these procedures, as the colonoscopist recognized the noncompletion.

Of the remaining, adequate photodocumentation was found in 33 (36.3%), inadequate (ie, not clearly showing the ileocecal valve, terminal ileum, or appendiceal orifice) in 13 (14.3%) cases, and 45 (49.5%) had no photodocumentation (ie, the colonoscopist had not taken a photograph).

Completion was deemed important in PCCRCs developing proximal to, and including, the hepatic flexure. Eleven (31.4%) of 35 of the colonoscopies of patients with PCCRCs in these locations were complete with adequate photodocumentation (Table 1); however, 4 of these cases had poor bowel preparation. It is appreciated that it is possible, especially with looping in the sigmoid, the splenic flexure may not be reached. In this circumstance, completion should be deemed important in PCCRCs proximal to, and including, the splenic flexure. In our service, >95% of procedures are done with use of the Olympus (Tokyo, Japan) ScopeGuide, making it less likely that the colonoscopist fails to appreciate that the splenic flexure has not been passed. However, we appreciate that lack of photodocumentation may have been important in some PCCRCs proximal to the splenic flexure or even, possibly, ones more distally.

Rectal retroflexion was documented (in the report or in a photograph) in 16 (15%) cases. Retroflexion was deemed important in PCCRCs developing in the rectum or rectosigmoid (30 cases). The rectosigmoid was included, as retroflexion may be a surrogate marker of careful inspection of the distal colon. Original reports (and any associated photographs) could not be located in 5 (16.7%) of 30 rectal or rectosigmoid cases, so retroflexion could not be verified. Of the remaining 25, only 6 (24%) had undergone retroflexion (Table 1).

Of the 100 cases with a paper colonoscopy report (and any photographs), issues were identified in 90 (90%) cases with 1 or more of the following: poor preparation, incomplete procedure, inadequately documented completion, or lack of rectal retroflexion. Only 10 (10%) index colonoscopies were complete, with adequate photodocumentation, retroflexion, and good bowel preparation. This demonstrates that even in the context of an established endoscopy reporting system there is room for improvement in documentation.

Findings reported at index colonoscopy were as follows: normal (14), diverticulosis (31), polyp(s) (65), inflammation/colitis (7), strictures (3), and cancer (4). Findings in the subsequent cancerous segment were as follows: normal (51, 52.3%), diverticulosis (11, 11.3%), polyp(s) (31, 32%), inflammation/colitis (3, 3%), and stricture (1, 1%). The subsequent cancerous segment was not reached in 7 (77.8%) of 9 of the incomplete colonoscopies. The cancerous segment was ambiguous in 3 (2.8%) cases.

IBD Patients

Chromoendoscopy was used in 1 (11.1%) of 9 patients with IBD. One patient who did not have chromoendoscopy had segmental biopsies. Bowel preparation was poor in 4 (44.4%) of 9 and active disease was present in 6 (66.7%) of 9. All colonoscopies were reported as complete, but 4 (44.4%) of 9 had inadequate photodocumentation of completion. Four (44.4%) of 9 cancers were located in the rectum and none of these patients underwent retroflexion.

Endoscopist Data

During the study period, 36 colonoscopists had performed >200 procedures (277– 4424). A decision was made as to whether a PCCRC developed because of technical factors, decision-making factors, and/or administrative factors. A total of 78 (72.9%) of 107 were found to have contributing technical factors. There was no correlation between an individual's technically "attributable" PCCRC rate and the number of procedures they performed, or their CIR or PDR. There was, however, a statistically significant correlation ($P < .05$) between PCCRC rate and the PICI[17] (Figure 5).

Other Influential Factors

Administrative issues affected 18 of 107 cases (in which follow-up procedures were either delayed, or not booked by administrative staff). In 2 of 107 cases, an active decision to not further investigate was taken by the endoscopist or team (in view of patient age/comorbidities). In 4 of 107 cases, the patient did not attend or declined recommended follow-up against medical advice.

In 29 of 107 cases, the decision-making of the endoscopist likely influenced the development of the PCCRC, such as an unexplained decision to not repeat the colonoscopy after inadequate bowel preparation.

WEO Categorization

Seven PCCRCs (6.5%) could not be categorized because the original report/photographs could not be located. Twenty-seven (27%) PCCRCs were categorized as possible missed lesion, prior examination adequate (A); 58 (58%) PCCRCs were categorized as possible missed lesion, prior examination negative but inadequate (B); 8 (8%) PCCRCs were categorized as detected lesion, not resected (C); and 7 (7%) PCCRCs were categorized as likely incomplete resection of previously identified lesion (D) (Figure 6). If any polyp, regardless of WEO definition, was observed in the subsequent cancerous segment and included, the rates are A: 23%; B: 54%; C: 12% and D 11% (Figure 6).

After detailed review by the authors, 95 of 107 PCCRCs were deemed avoidable and 12 of 107 unavoidable. The unavoidable cases were the 5 small PCCRCs, 1 submucosal lesion related to anastomotic recurrence, 4 cases of patient decision to not undergo further investigation, and 2 cases of MDT decision to not investigate further in unwell patients (one with widely metastatic gynecological malignancy, the other with extreme frailty).

Discussion

This study identified all PCCRC-4y cases, over an 8-year period, within a single endoscopy service. A total of 107 cases were subjected to a root-cause analysis to identify contributing and avoidable factors. It is the first to report use of WEO methodology for classifying PCCRCs. Unlike the only other similar large study[10] ours is population-based and has not excluded important groups that are at particular risk of PCCRC. If the exclusion criteria (extremes of age, comorbidity, and preexisting colon pathology) used in the study of Robertson et al[10] had been used in ours, 70% of our patients would have been ineligible. A small percentage of colonoscopy (estimated at <5%) done outside the NHS was not captured by our study.

Despite Gloucestershire Hospitals' status as a national colonoscopy training center and its low unadjusted PCCRC-3y rate of 4.7% during the study period, the analysis shows opportunities for preventing PCCRC, suggesting PCCRC-3y rates could, in ideal circumstances, be reduced to very low levels, perhaps 1% to 2%. In settings with fewer high-risk patients, PCCRC-3y target rates should be even lower.

Patient Factors Associated With PCCRC

Patient factors can be subdivided into those that put patients at risk of PCCRC because of underlying biology and those that adversely affect the quality of colonoscopy, such as diverticular disease or comorbidities. This distinction is justified because the 2 categories require different solutions, but sometimes there is overlap. For example, in IBD there is a biology-related increased risk and it is more difficult to assess the colon if there is inflammation. In patients with

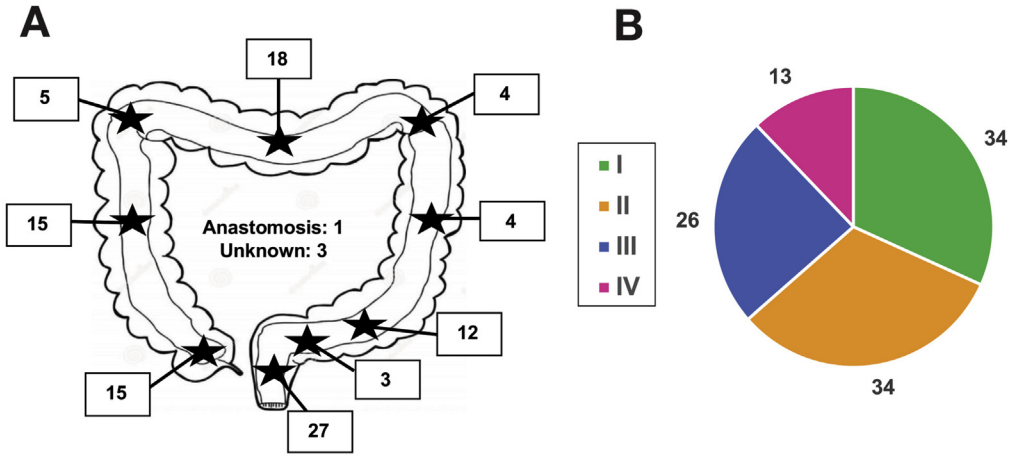

Figure 3. Illustration of (*A*) location and (*B*) staging of PCCRCs.

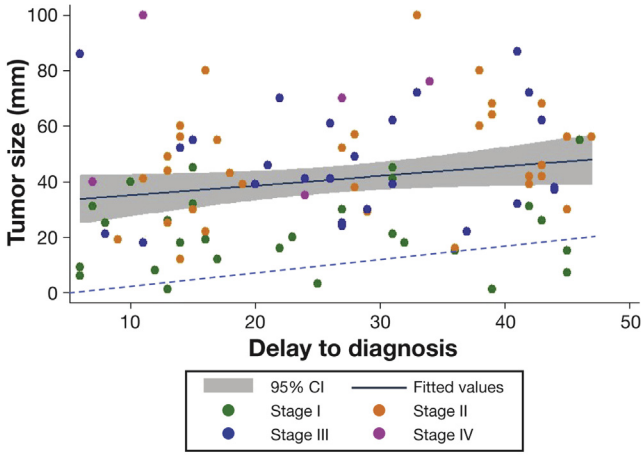

Figure 4. Relationship of PCCRC size and interval between index colonoscopy and diagnosis. NOTE. PCCRC size could be verified in 95 cases (range 1–200 mm). The 200-mm PCCRC was removed for scale. Broken line depicts a growth rate of 5 mm/year. CI, confidence interval.

diverticular disease, the colonoscopy may be technically challenging and visualization more difficult.

A high proportion of PCCRCs occurred in patients with known colonic pathology or excess risk. Twenty-six patients (24.3%) had more than 1 colonoscopy in the 4 years before PCCRC diagnosis. Although multiple colonoscopies appear to be a "red flag," they may reflect other risk factors. We propose, based on our findings and other literature,[20–23] that a subgroup of patients is identified as having unstable or "hot" colons. We define a "hot" colon as one with previous CRC, multiple previous large polyps, IBD, or hereditary cancer syndromes. Of the 107 cases reviewed, 46 (43.0%) fit into one of these categories and have, by our definition, a "hot" or unstable colon. These findings explain some of the database literature but enable a more focussed approach to preventing PCCRCs. For example, in cases with previous CRC resection, early colonoscopy will identify a high-risk subset with multiple lesions that need early repeated colonoscopy, perhaps even 6-monthly until it is clear the patient is in a lower-risk category. Other studies have suggested using fecal immunochemical testing after colonoscopy to identify patients at high risk of CRC, or alternatively patients at low risk who do not need surveillance.[24] In addition, performing molecular testing may identify patients with undiagnosed Lynch syndrome and increased risk of further CRC.[25]

Table 1. (A) Illustration of the Relationship of Adequately Documented Cecal Intubation and Importance of Completion in Relation to Position of the PCCRC and (B) Illustration of the Relationship of Rectal Retroflexion and Importance of Retroflexion in Relation to Position of the PCCRC

	Complete with adequate photo		
A	Yes	No	Total
Completion important			
Yes	11	24	35
No	21	41	62
Total	32	65	97
	Retroflexion done		
B	Yes	No	Total
Retroflexion important			
Yes	6	19	25
No	10	62	72
Total	16	81	97

NOTE. Table excludes 3 cases in which PCCRC location was ambiguous and 7 cases in which photographs could not be located.

More intense surveillance of high-risk groups will increase demand for endoscopy, and this may lengthen waits. However, in the context of higher-quality colonoscopy, surveillance offers less benefit than previously thought. Recently revised UK guidelines reflect this and will lead to a substantial reduction in colonoscopy surveillance workload.

Ideally, surveillance of high-risk patients should be done by the best-performing colonoscopists (possibly on dedicated lists as occurs in the English BCSP),[26] adopting longer withdrawal times and, where appropriate, using optimal techniques/technologies to identify precursor lesions. Long and difficult procedures may lead to inattention and failure to identify smaller precursor lesions. After lengthy polypectomy procedures, it may be appropriate to repeat the colonoscopy within 6 months to identify missed lesions. Patients with IBD present a different challenge because IBD surveillance may not be able to prevent cancer entirely. If so, then IBD-related PCCRC within surveillance time frames is inevitable.

Our findings indicate a need for further studies to identify the most effective way to manage these patients and determine whether PCCRC can be prevented in these groups.

The finding of more PCCRCs in high-risk groups is in line with the large database and case-control literature. This means that PCCRC-3y rates for colonoscopy services, the potential for improvement, and target rates will differ depending on case mix. The WEO has recommended use of unadjusted rates for benchmarking. However, the consensus statement fails to point out that although it is appropriate to use unadjusted rates for comparisons between jurisdictions where the effect of case mix is evened out, it is inappropriate to use unadjusted rates to make comparisons between institutions. Services that are less likely to offer colonoscopy to high-risk groups should therefore have a lower target PCCRC-3y rate.

Cancer Characteristics

PCCRC incidence, location, and size (varying from 1–200 mm) did not correlate with delay from index colonoscopy to diagnosis. There was a relatively high proportion of stage I cancers (31.8%), supporting the assumption that some PCCRCs were precursor lesions at index colonoscopy and thus amenable to prevention. There may be exceptions: 5 patients had very small PCCRCs and it is possible that there

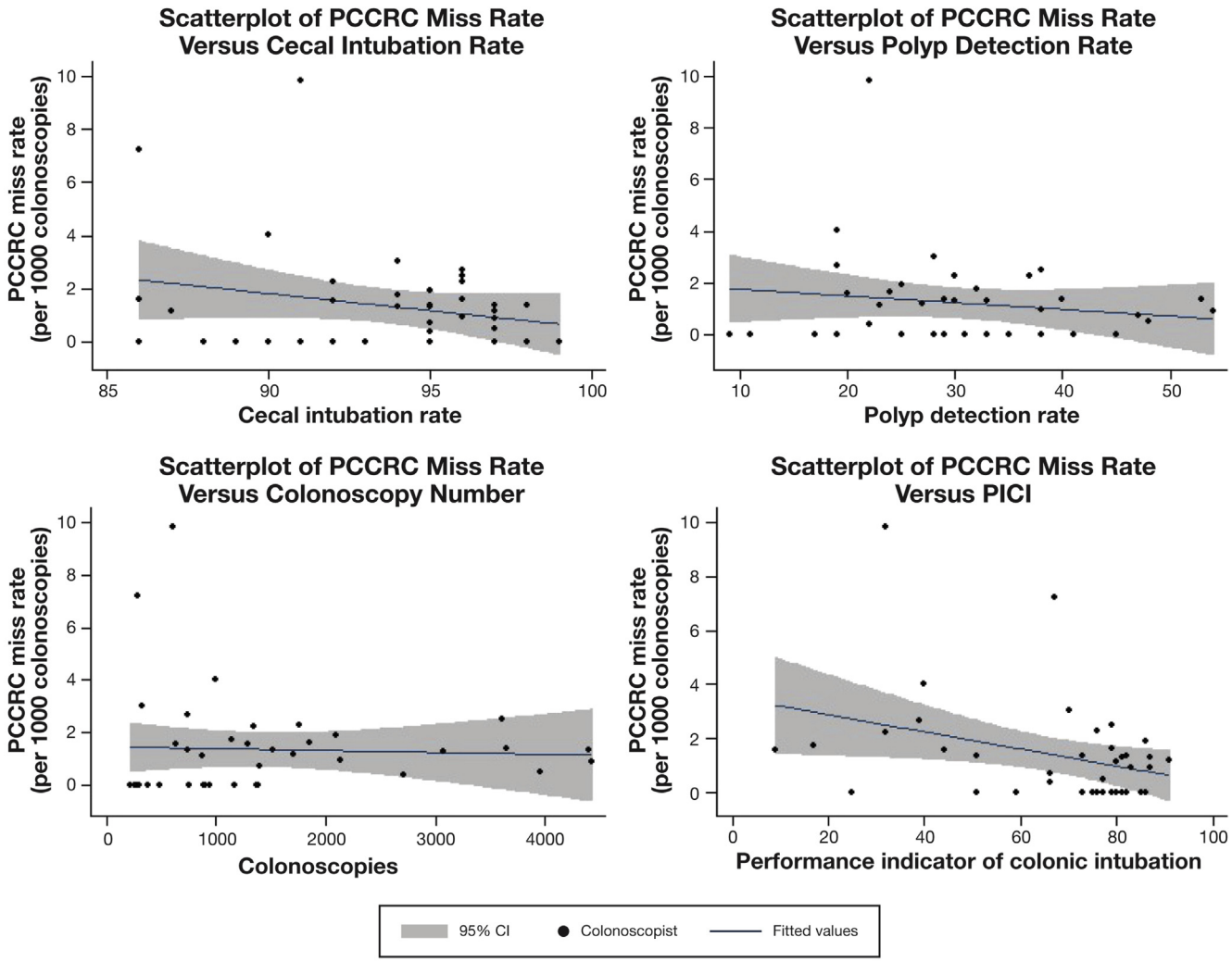

Figure 5. Scatterplots of "technically attributable" PCCRCs in relation to CIR, PDR, overall colonoscopy volume, and PICI. Note. Statistically significant correlation seen for PICI ($P < .05$). Other plots showed no significant correlation. CI, confidence interval.

was no precursor lesion visible at the time of the index colonoscopy. On the other hand, these small cancers could have been slow-growing tumors in polyps. Whether there were precursor lesions or not, these tumors were likely asymptomatic (effectively found opportunistically or with surveillance) and were all stage I, carrying a good prognosis. It is proposed that future guidance considers a tumor growth rate (we suggest 5 mm/year) that absolves the service or individual from responsibility for very small PCCRCs.

In contrast to other studies,[7] we did not find an excess of PCCRCs in the right colon. This may be a sample size issue or reflect the quality of the service manifest by high rates of completion and low rates of PCCRC.

Index Colonoscopy Factors Associated With PCCRC

Bowel preparation was inadequate in 19.0% of index colonoscopies compared with a rate of 5.4% in the service overall. A potential weakness is that a recognized bowel preparation scale was not used, and the rating of inadequacy may have been different had one been used. However, in cases of inadequate preparation, there was no documented decision in 45% of cases to repeat the procedure, arrange alternative investigations, or an explicit statement that further investigation was not appropriate. We strongly advise colonoscopists (or the responsible clinician) to arrange a repeat investigation if bowel preparation is considered inadequate, or to explain and document the rationale not to investigate further in the patient record. Poor documentation makes clinicians and services more vulnerable to litigation.

The requirement to retroflex in the rectum is relatively new. Of 100 cases with available photographs, rectal retroflexion was documented in 16%. Although rectal retroflexion will not have prevented all rectal PCCRCs, it is a significant shortcoming. Rectal retroflexion might be a proxy indicator for adequate visualization of the rectum (as is withdrawal time for ADR). Rectal retroflexion (and photodocumentation) should be, like photographic evidence of the cecum, a key performance metric.

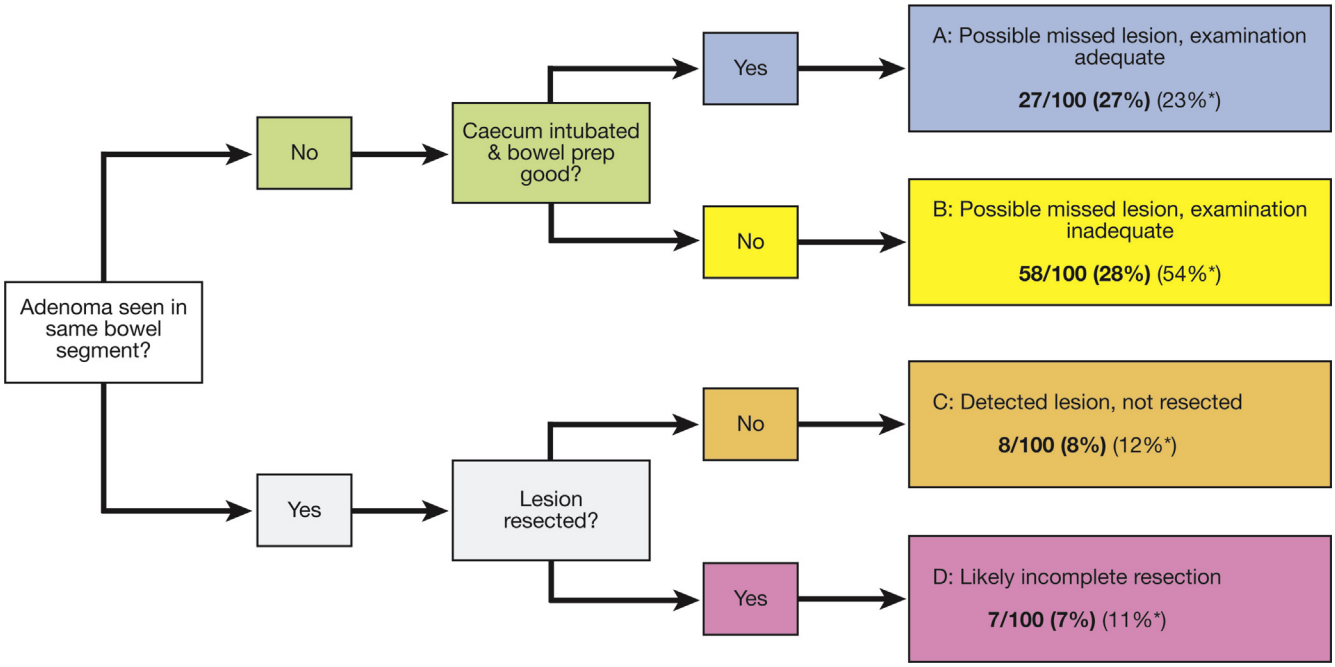

Figure 6. Categorization of PCCRCs using WEO method. NOTE. 7 cases uncategorizable as photographs were unavailable. Figures in bold indicate percentage of cancers in each category. Percentages with (*) are those if the algorithm included all previously visualized polyps/lesions.

Only 33 (36.3%) of 91 "complete" colonoscopies with available original report and photographs had adequate photographic evidence of completion. This reflects a lack of appreciation of the importance of cecal photographs and incomplete provision of the necessary equipment in the early period. Photodocumentation of the cecum is now a key performance metric in all guidelines. With electronic image capture, there is no excuse for not obtaining adequate photographs. A judgment was made as to whether lack of adequate photographs (and therefore possible incomplete colonoscopy) was relevant to the PCCRC. Assuming photographic evidence of completion to be relevant in PCCRCs located at, or proximal to the hepatic flexure, only 11 (31.4%) of 35 PCCRCs had adequate photodocumentation.

Chromoendoscopy was used in 1 (11.1%) of 9 index colonoscopies for PCCRCs developing in patients with IBD. Chromoendoscopy may not be possible if the preparation is poor or there is active disease (7 of 9 of our cases), and surveillance and interpretation of biopsies may be problematic if there is active colitis. These findings emphasize the need for adequate documentation, in this instance why dye spray was not used, why random biopsies were not taken, or why procedures were not repeated if they were compromised by active inflammation. Our endoscopy service is reorganizing IBD surveillance to overcome the shortcomings identified in this review.

Endoscopist Factors Associated With PCCRC

A decision was made as to whether a PCCRC could be attributed to the responsible endoscopist. Attribution was deemed secondary to technical factors, decision-making factors, or both. In our cohort 78 (72.9%) of 107 PCCRCs were thought to arise, in part, because of technical factors and 29 (27.1%) of 107 because of, with the benefit of hindsight, unwise decisions about follow-up.

In our study, an individual's technically "attributable" PCCRC rate was not associated with numbers performed, CIR, or PDR. However, there was an association with a new measure,[17] the PICI. Achieving this indicator requires cecal intubation with minimal sedation and a comfortable patient. High PICI may be a marker of diligence and less likelihood of missing lesions that lead to PCCRC. However, we recognize more studies of the relationship of PICI and PCCRC are required.

Other Influential Factors

Patients scheduled for surveillance procedures are a lower priority than symptomatic or screened patients and often wait beyond their due date, but for a small number, a delay becomes important. In this study, 18 of 107 cases were affected by administrative delays in surveillance or planned therapeutic procedures. Scheduling staff cannot judge urgency and it is the responsibility of endoscopists and referring clinicians to be clear whether a patient is in a high-risk category. In the United Kingdom, there is a requirement for administrative and clinical review of all surveillance cases before scheduling when high-risk patients are flagged so their procedures are not delayed.

Some PCCRCs developed after a positive decision, either by the CRC MDT or an informed patient, not to pursue further investigations or therapy. Although these were theoretically avoidable, they are not attributable to a colonoscopist or decision-maker.

Utility of the WEO Categorization

In this cohort, 85% were deemed, according to the WEO categorization, to be possible missed lesions after a negative colonoscopy; 15% were related to a previously seen lesion (either resected or not resected). The low number of incompletely resected lesions in this cohort (7%) may be explained by the hospital being a referral center for polypectomy and a low threshold locally for referring larger and/or complex polyps to endoscopists trained to excise them.

However, a flaw in the WEO categorization may explain the finding. To be categorized C or D requires the lesion in the affected segment to be an advanced adenoma, defined as a polyp larger than 1 cm, and/or villous and/or containing high-grade dysplasia. In 13 cases, a polyp had been seen at index colonoscopy, but could not be categorized as an advanced adenoma because of the following:

1. The polyp was <1 cm or its size was unclear on the endoscopy report
2. The polyp was not excised/retrieved; therefore, it was not possible to assess for villous component or high-grade dysplasia
3. There was discrepancy between the location of the polyp and the subsequent cancer, when it was clear the index colonoscopist was unsure of his or her position within the colon
4. A stricture (rather than a polyp) was diagnosed at index colonoscopy, but not biopsied and subsequently was found to be cancerous

There were cases in which PCCRCs appeared to develop from incompletely resected sessile serrated lesions that did not fulfil the WEO lesion definition and were therefore categorized as A or B PCCRCs rather than D. If all polyps in the affected segment were included, the proportion of C or D lesions would be higher. The new rates would be A = 23% (27%), B = 54% (58%), C = 12% (8%), D = 11% (7%).

Other flaws in the categorization relate to the omission of information from previous colonoscopies, relevance of completion for distal lesions, omission of rectal retroflexion in adequacy criteria, and other factors, such as malfunctioning equipment (Supplementary Material). Our data also highlight that many PCCRCs are related to nontechnical factors and suggest that to be clear about how to reduce PCCRCs, these be categorized as follows:

1. Patient factors
2. Administrative process factors
3. Clinical decision-making factors

The WEO modifying statement of "deviation from the planned management pathway" is insufficiently detailed to enable accurate classification (examples in the Supplementary Material).

Recommendations

Recommendation 1: Learning From Local Experience: Identifying and Reviewing PCCRCs

This study has illustrated how a WEO-based review of PCCRCs can lead to an in-depth understanding of PCCRCs and avoidable factors amenable to mitigation. Although the lessons learned are likely to be applicable to most endoscopy services, inevitably there will be differences in other settings. Moreover, sustained improvement is more likely if changes are based on local learning. Thus, we strongly support the recommendations of the WEO and the requirements of the Joint Advisory Group on Gastrointestinal Endoscopy to identify and review PCCRCs. In a moderate-sized endoscopy service performing 6000 to 10,000 colonoscopies per year, this will yield 10 to 20 cases per year (depending on rates of cancer in the service). Each endoscopist should receive feedback on their PCCRCs and lessons learned from others to identify areas for improvement.

Many services will find it difficult to identify all PCCRCs. We recommend systems are developed to link cancer registries with registrations of colonoscopy (however they are captured) to identify PCCRC cases and notify the service where the index colonoscopy was performed. This will ensure all PCCRCs are captured, and remove a significant barrier (identifying cases) to services wanting to review cases.

Recommendation 2: Identify and Manage High-Risk Patients

In this study cohort, 43% of PCCRCs occurred in high-risk patients, justifying a tailored approach to surveillance in this group. Once identified, these patients should have regular endoscopic surveillance (possibly supported by periodic fecal immunohistochemistry testing), perhaps more frequently than current guidance advises. These surveillance procedures should never be delayed, extra time should be allocated, and the procedure should probably be done by the best-performing colonoscopists using the most appropriate lesion recognition enhancement techniques. Early repeat procedures should be considered after lengthy index colonoscopies where multiple/large polyps were resected. Patients should be warned that lesions may be overlooked during long and difficult procedures, and an early second look to review the resection site(s) and check for missed lesions within 6 months is justified.

There is a need for research into the optimal protocols for high-risk patients and how these are delivered to a predefined standard.

Recommendation 3: Decision-Making, Documentation, and Follow-up

Inadequate decision-making and poor documentation played a key role in some PCCRCs. Endoscopists (and/or responsible clinicians) are advised to consider and document the following:

1. Whether the preparation was adequate and the investigation complete
2. Whether a repeat colonoscopy is required:
   a. If yes: when it should be scheduled
   b. If no: the reason and what investigation (if any) is recommended
3. Who is responsible for arranging and reviewing the repeat procedure and/or investigations
4. Whether the patient was involved in decision-making

Failure to follow this guidance will leave individuals and services vulnerable to litigation. We recommend follow-up of inadequate/incomplete procedures is subject to audit.

Recommendation 4: Recommendations to the WEO Categorization

On the basis of this study, we recommend some adaptations to the WEO categorization:

1. Rectal retroflexion and malfunctioning or inadequate equipment should be mandatory elements of colonoscopy adequacy.
2. Small cancers (to be defined) should be excluded from analysis on the basis that they are unlikely to have been detectable at index colonoscopy and are unlikely to have a significant impact because they are likely to be early-stage disease.
3. There should be more flexibility regarding the definition of "advanced adenoma," particularly if a lesion was seen at index colonoscopy but not biopsied.
4. If a patient has undergone more than 1 colonoscopy, the previous colonoscopies/flexible sigmoidoscopies should be reviewed to identify if a precursor lesion was seen in the cancerous segment before the index colonoscopy. If a lesion was seen previously, this should influence the categorization of the PCCRC.

Greater clarity is needed with respect to "deviation from the planned management pathway." This should be subdivided into decision-making factors (patient choice/clinical factors, such as comorbidity) or administrative factors (failure to book repeat procedure at recommended interval). There should be 2 further categories: "E" (patient choice/comorbid) and "F" (administrative issues).

Gathering and reviewing the entire WEO data set will be too time-consuming for most endoscopy services. It is recommended the WEO create an abbreviated version for everyday use, reserving the complete data set for academic studies.

Finally, the WEO should reconsider use of unadjusted PCCRC-3y rates for benchmarking purposes: there are instances when there should be adjustment of PCCRC-3y rates.

Summary and Conclusions

This is the largest, population-based study into PCCRC causation to date and the first to use and critique the WEO categorization. It builds on the findings of Robertson et al[10] with a sample of patients that has not excluded important high-risk groups, thereby providing a picture of why PCCRCs occur that is more generalizable to other settings. It provides rich learning of factors that lead to PCCRC and indicates that much of PCCRC can be avoided.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.12.031.

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Author names in bold designate shared co-first authorship.

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Correspondence
Address correspondence to: Roland Valori, MBBS, Gastroenterology, Great Western Road, Gloucester, GL1 3NN, United Kingdom of Great Britain and Northern Ireland. e-mail: roland.valori@nhs.net; fax: +44 3004226892.

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Author contributions: RA, NEB, and RV conceived and drafted the study. RA and RV collected all data. RA, NEB, and RV analyzed and interpreted the data. RA, NEB, and RV drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

Conflicts of interest
This author discloses the following: Roland Valori is co-director of AnderVal Ltd, an endoscopy training company. The remaining authors disclose no conflicts.

Supplementary Material

There were several cases in which the PCCRC could not easily be categorized because of shortcomings in the WEO categorization.

Examples, and recommendations for improvement, are detailed as follows:

1. Definition of advanced adenoma

Patient A had an index colonoscopy 6 months before PCCRC diagnosis. Multiple polyps were seen, including a cancerous lesion, which was biopsied. A 9-mm polyp in the rectum was not biopsied in view of the biopsy forceps being used to biopsy the sigmoid cancer. After CRC resection, the patient had a repeat colonoscopy, at which point the rectal polyp was resected. This was a CRC (and therefore a PCCRC). It is clear that the PCCRC developed from the rectal lesion, which was not resected at index colonoscopy. The PCCRC was labeled as an A (possible missed lesion, prior examination adequate), because of its size, but if the definition of "lesion" included 9-mm polyps, this would have been a C (detected lesion, not resected).

2. Previously observed lesions

There is some confusion when a patient has had multiple colonoscopies. For example: Patient B had a colonoscopy 43 months before PCCRC diagnosis where a proximal transverse colon cancer was diagnosed. In addition, there was a complex sessile polyp in the cecum and a 15-mm sessile polyp in the proximal descending colon. Only the transverse cancer was biopsied. The patient underwent hemicolectomy. A CRC follow-up colonoscopy (index colonoscopy) commented only on diverticular disease (not the cecal or descending polyp). Twenty-six months later the patient presented with a 61-mm descending colon PCCRC that most likely developed from the previously seen polyp. This information would be missed if only the index (or most recent) colonoscopy is reviewed. This case was categorized as an A (possible missed lesion, prior examination adequate), but if the previous colonoscopy had been taken into account, it would have been categorized as a C (detected lesion, not resected).

3. Relevance of cecal intubation

Another problem with the WEO categorization is with the definition of "adequacy." The method deems adequacy as one in which the bowel preparation was adequate and there was evidence of cecal intubation. However, evidence of cecal intubation could be considered only relevant in right-sided cancers. For example, in case C, a patient underwent index colonoscopy for diarrhea, which found only diverticulosis. Bowel preparation was good. Twenty-seven months later, a PCCRC was diagnosed in the rectum. Index colonoscopy bowel preparation was good but there was no photographic evidence of cecal intubation, therefore the procedure was categorized as a B. Clearly cecal intubation is less important in this case because of the distal position of the CRC.

4. Omission of rectal retroflexion in categorization

There is a significant omission within the methodology with regard to exclusion of rectal retroflexion. For example, in case D, a patient had index colonoscopy for IBD surveillance, which showed no active disease. The procedure was complete with good bowel preparation. Twenty-seven months later the patient presented with a 58-mm rectal PCCRC. The index colonoscopy did not mention retroflexion in the rectum, which would have been possible as there was no active disease. According to the WEO categorization, this was an A (possible missed lesion, prior examination adequate). If retroflexion was part of the adequacy criteria for rectal lesions this would be a B (possible missed lesion, prior examination inadequate).

5. Other adequacy factors

There are other factors that could render the index colonoscopy inadequate. For example, in case E, the index colonoscopy was undertaken as part of the BCSP, with a 240 series Olympus colonoscope. The colonoscopist commented that the images were flashing throughout the procedure and that the mucosa appeared unduly red. Twenty-seven months later, a 25-mm PCCRC was diagnosed within the rectum. This clearly was an inadequate procedure and should be labeled as such. According to the categorization, however, this was an A (possible missed lesion, prior examination adequate).

6. Patient factors

Patients also influence development of PCCRC, and the categorization does not account for this. For example, in case F, an index colonoscopy was completed as part of the BCSP. It was complete, with adequate photodocumentation, rectal retroflexion, and good bowel preparation. A 4-mm tubular adenoma polyp with low-grade dysplasia was seen in the rectum and the patient was referred for Transanal Endoscopic Microsurgery. She declined this for fear of developing fecal incontinence. Thirty-one months later she presented with a 21-mm rectal PCCRC. In this instance, the PCCRC is an A (possible missed lesion, prior examination adequate) (note that it is not a C because it does not fulfil the WEO lesion criteria). However, a precursor lesion was seen and correct management proposed, therefore it should be labeled as PCCRC solely because of a deviation from the planned management pathway due to patient factors. It should not be attributable to the index colonoscopist.

7. Administrative factors

Nonclinical administrative factors can also influence PCCRC development. For example, in case G, an index colonoscopy was completed for familial adenomatous polyposis surveillance, at which time multiple polyps were seen, as well as ascending colon and sigmoid colon CRCs. The patient underwent subtotal colectomy but was advised by the colonoscopist to undergo an early flexible sigmoidoscopy of the rectal stump to further assess the

rectal polyps. The follow-up flexible sigmoidoscopy was not booked until 14 months afterward, and then the patient had 3 examinations of the rectal stump within 6 months, with rectal PCCRC being diagnosed at the last of these. This is labeled as an A (none of the rectal lesions was biopsied at index colonoscopy, and their size was not recorded so it cannot be a C). However, a precursor lesion was seen and correct management proposed. Therefore, it should be labeled as PCCRC solely because of deviation from the planned management pathway due to administrative factors. It should not be attributable to the index colonoscopist.

8. Decision-making factors

Finally, the decisions made by responsible colonoscopist can influence PCCRC development. In case H, a patient had an index colonoscopy for IBD surveillance. It was complete with adequate photodocumentation, but the bowel preparation was poor. No active decision was taken to repeat the colonoscopy in view of the poor bowel preparation and inability to use chromoendoscopy. A 49-mm ascending colon PCCRC was diagnosed at repeat surveillance colonoscopy 13 months later. This case was clearly attributable to both poor preparation and a poor decision to not repeat the procedure, and this should be reflected in the categorization.