Quest for the best : quality of colonoscopy and colorectal cancer diagnosis in clinical practice

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Quality of colonoscopy and colorectal cancer diagnosis in clinical practice

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Aan mijn ouders

Contents

1 General introduction

Colorectal cancer (CRC) is a major healthcare concern, affecting approximately 1.4 million new patients worldwide and causing 700,000 deaths each year.[1] In the Netherlands, annually 15,000 people are diagnosed with CRC, ranking the disease as third most common cancer and second most common cause of cancer-related mortality.[2] The majority of CRCs are now considered to arise from adenomatous polyps via a multistep genetic model, as proposed by Fearon and Vogelstein.[3,4] In addition, a significant proportion of CRCs can evolve from sessile serrated polyps via the serrated neoplastic pathway.[5]

The development of CRC from slowly progressing precursors offers the opportunity to (early) detect, intervene, and prevent cancer. In fact, CRC is most suitable for population wide screening.[6] A high quality colonoscopy will increase the detection of early CRC, subsequently decreasing the incidence of advanced CRC and reducing cancer-associated mortality.[7]

In the Netherlands, a nationwide fecal immunochemical test-based CRC screening program was initiated in January 2014.[8] Notably, the compliance to this screening program is as high as 71%.[9] To ensure the success of our program, next to high participation rates, a high quality of colonoscopy is essential to diagnose CRC, detect, and resect precancerous lesions and subsequently prevent CRC.[7,10] Unfortunately, over the past few years, the effectiveness of colonoscopy at reducing both the incidence[10,11] and mortality[7,12] of CRC was challenged. Despite a 76% to 90% reduction in the overall incidence of CRC,[11] colonoscopy seems to have limited effectiveness in preventing CRC of the proximal colon (<56%).[13-15] Numerous studies raised concern about the so-called *interval* or *postcolonoscopy* CRC, i.e. CRCs diagnosed after a colonoscopic examination during which no CRC was detected, which are predominantly located in the proximal colon.

Postcolonoscopy colorectal cancers

In the past, the terms interval CRC and postcolonoscopy CRC were used interchangeably, causing difficulties in the interpretation of outcomes and comparison across studies. The term *interval CRC* is suitable for screening and subsequent colonoscopy surveillance, where follow-up time intervals are clearly recommended. This term applies to screening with any test modality (fecal test, flexible sigmoidoscopy or colonoscopy). The term *postcolonoscopy CRC* refers to cancers diagnosed after a *colonoscopic* examination for screening, surveillance, or diagnostic indication.[16]

The incidence rate of postcolonoscopy CRC vary widely amongst studies, from 2.9% to 9.6% of the total number of CRCs diagnosed in a population[13,17-23] and from 1 in 130 to 1 in 1,000 colonoscopic examinations.[24] All in all, these studies demonstrate an overall protective effect of colonoscopy against CRC, albeit such effect seems to be limited in the proximal colon.[12,14]

Quality of colonoscopy

At the first glance, two key factors can explain the occurrence of postcolonoscopy CRC, namely *procedural factors* and *biologic features* of precursor lesions, associated with a faster progression to cancer.[25,26] Procedural factors, in particular the detection and complete endoscopic resection of precursor lesions play a dominant role. Several studies now demonstrate that the occurrence of postcolonoscopy CRCs is strongly dependent on the ability of the endoscopist to recognize precursor lesions.[24-28] The reasons why endoscopists may overlook such lesions are multifactorial: insufficient bowel preparation, inappropriate withdrawal time and technique,[29] but most likely insufficient knowledge and training on the recognition of such lesions. A better understanding of such factors is crucial for improving the quality of colonoscopic performance.

Ideally, postcolonoscopy CRC rates should be monitored in routine clinical practice as key patient outcome measures.[30, 31] Such monitoring is however difficult to conduct and requires time and resources. On the opposite, cecal intubation rate (CIR), adenoma detection rate (ADR) and mean adenoma per procedure (MAP) are much easier to monitor and provide reliable estimates for the quality of colonoscopy.[32] Not surprisingly, patients examined by colonoscopists with high ADR are less likely to develop postcolonoscopy CRC.[24,33] Even a minimal (1%) increase in ADR, can lead to 3% reduction of the risk for CRC,[34] justifying efforts to improve this quality measure. There is still a wide variation in performance between colonoscopists, with ADRs ranging from 9% to 59.8%.[29,35] However, little is known about the factors underlying such variability.[33,36,37] To optimize colonoscopy performance within our nationwide screening program, we need to clarify underlying factors and identify opportunities for improvement.[38]

Potential explanations for postcolonoscopy colorectal cancers

Few studies systematically examined potential explanations for postcolonoscopy CRC. In a study of 2,079 patients undergoing post-polypectomy surveillance, Pabby *et al.*[39] applied a structured algorithm to evaluate possible reasons for postcolonoscopy CRC. Based on the time elapsed from index colonoscopy to CRC diagnosis, tumor stage at diagnosis, and location at the site of a previously resected adenoma, postcolonoscopy CRCs were assigned to one of the following categories: incomplete examination, missed cancer, failed biopsy detection, incompletely resected lesion, or new cancer. The authors concluded 7 out of 13 CRCs were potentially avoidable being detectable at an earlier time. Following a similar rationale, two additional studies examined the most common explanations for postcolonoscopy CRC, suggesting procedural factors may be the main explanation.[23,40]

With the implementation of a CRC screening program, the number of CRC patients diagnosed will increase significantly in the near future. Therefore, also the quality of colonoscopy surveillance of patients under surveillance after colonic surgery for CRC, deserves attention. Moreover, since up to 4% of patients develop a second primary (i.e.

metachronous) CRC. In both cases – postcolonoscopy CRC and metachronous CRC – it is hypothesized that missed and incompletely resected polyps play an important role.[23,39,40] A subset of the metachronous CRC can be also related to non-compliance with surveillance recommendations.[41-43] A thorough analysis of the potential factors associated with postcolonoscopy and metachronous CRCs is essential to identify caveats in day-to-day colonoscopy practice and, ultimately, to improve its effectiveness. Such analysis can provide indications about the required improvements, i.e. endoscopic training, utilization of adequate equipment or a closer endoscopic surveillance in higher risk patient subgroups. More insight in the potential explanations and especially the role of procedural and biologic factors to the occurrence of these cancers may provide options to minimize the postcolonoscopy and metachronous CRC rates.

Biologic features

Although the majority of postcolonoscopy CRC might be attributable to missed or incompletely resected polyps, biologic factors are also thought to play a role. *Nonpolypoid (flat and depressed) colorectal neoplasms,* either conventional adenomas, or sessile serrated adenomas/polyps, may play a critical role herein.[44-46] Such lesions are often located in the proximal colon and have a subtle endoscopic appearance, rendering them easy to overlook, particularly during certain circumstances, i.e. suboptimal bowel preparation[47] or endoscopists who are not trained to recognize them.[47,48] In addition to a more challenging detection and treatment, some subtypes of nonpolypoid adenomas have been suspected to harbor a more aggressive biologic behavior.[49,50] The underlying molecular mechanisms are less understood. Few studies examined the contribution of biologic factors to postcolonoscopy CRC. Evidence at molecular level is sparse but suggests the involvement of the serrated neoplastic pathway with postcolonoscopy CRCs more likely to show microsatellite instability, CpG Island methylator phenotype, and BRAF mutations compared to prevalent CRCs.[10,51-54]

Aims and outlines of this thesis

In this thesis, we examined epidemiologic, clinical and histopathologic features of CRC. We studied the quality of colonoscopy performance and risk factors for the occurrence of (postcolonoscopy) CRCs in South-Limburg, the Netherlands prior to commencing the nationwide fecal test-based CRC screening program.

The first part (**Chapters 2-4**) of this thesis focuses on monitoring and reporting postcolonoscopy CRCs in routine clinical practice. **Chapter 2** is an overview on the current literature and potential explanations of the origin of these postcolonoscopy CRCs. In **Chapter 3**, we describe the prevalence and potential explanations of postcolonoscopy CRC in a population-based study in South-Limburg. In **Chapter 4** we

address the prevalence and most likely causes of interval CRC during surveillance after colon resection for CRC (metachronous CRCs). **Chapter 5** presents a proposal for standardizing the nomenclature for an interval CRC, as proposed by the Expert Working Group on "Right-Sided Lesions and Interval Colorectal Cancer" of the Colorectal Cancer Screening Committee, of the World Endoscopy Organization.

The second part (**Chapters 6-8**), discusses the contribution of technical performance and biologic factors to the occurrence of postcolonoscopy CRCs. **Chapter 6** examines the quality measures for colonoscopy performance in routine practice. **Chapter 7** analyzes clinicopathologic phenotypes of CRC in relation with tumor site. Special attention was payed to the macroscopic appearance and histopathology of CRC. **Chapter 8** presents a case report, suggesting potential implication of biologic factors in the genesis of postcolonoscopy CRC. Finally, in **Chapter 9** we discuss the main findings of this thesis and their potential implications for the colonoscopy practice and for future research in this area.

PhD thesis highlights

What is already known?

- Quality measures for colonoscopy are operator-dependent and vary considerably
- Up to 10% of the CRC patients had a colonoscopic examination within 5 years before the cancer diagnoses (i.e. postcolonoscopy CRC)
- Up to 4% of patients who underwent colonic resection for CRC develop a new CRC during surveillance (i.e. metachronous CRC)
- Adenoma detection rate varies considerably between endoscopists from 9 to 60%

What is not yet known?

- What is the contribution of missed and incompletely resected polyps to postcolonoscopy CRC in our practice in South-Limburg?
- What are key performance indicators in our colonoscopy practice?
- Did quality in performance of colonoscopy improve over time?

What are the aims of this thesis?

- To evaluate the postcolonoscopy CRC rate and etiology in our routine colonoscopy practice in South Limburg
- To evaluate the metachronous CRC rate and etiology in our practice
- To examine colonoscopic quality in daily clinical practice in South-Limburg

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PART I

Monitoring interval CRC in clinical practice

2

Interval colorectal cancers: What and why

Chantal M.C. le Clercq, Silvia Sanduleanu

Current Gastroenterology Reports 2014;16:375

Abstract

An increasing number of studies now indicate that colonoscopic examination is not perfect in preventing colorectal cancer (CRC), especially of the proximal colon. Several factors can be implicated in the occurrence of interval CRCs – further referred to as postcolonoscopy CRCs –, such as missed, incompletely resected lesions and newly developed cancers. Missed lesions represent by far the dominant cause of postcolonoscopy CRCs, with nonpolypoid (flat or depressed) neoplasms and sessile serrated polyps playing a significant role. Molecular events underlying progression of such lesions may further augment the cancer risk. In this article, we review the literature about postcolonoscopy CRC risk and the most common explanations. We discuss potential implications, paying special attention to improvements required in education and training.

Introduction

Colonoscopy is the primary or follow-up screening modality and the most common diagnostic procedure in the gastrointestinal endoscopy,[1,2] which implies *quality assurance* is vital. Over the past few years however, the medical community has been engaged in a spirited debate over the effectiveness of colonoscopy at reducing the incidence[3-5] and mortality[6,7] by colorectal cancer (CRC). Despite a 76% to 90% reduction in the overall incidence of CRC,[1] the effectiveness of colonoscopy in the proximal part of the colon seems to be limited, ranging from 0% to 56%.[3,4,8] Some patients are still diagnosed with CRC after a negative colonoscopic examination, which raise concerns about the quality of examination and may subsequently affect participation to surveillance. It is now evident that such events – referred to as *interval* or *postcolonoscopy* CRCs – are strongly operator-dependent and therefore preventable.[9,10] Understanding what the magnitude of this problem is, and why these cancers occur would be of great benefit, as it may help identify pitfalls in the current colonoscopy practice and subsequently deploy targeted measures, such as exposure to tailored educational and training programs. This approach will ultimately safeguard the quality and improve the effectiveness of colonoscopic examination.

In this review, we examine the incidence rates of postcolonoscopy CRCs, the factors implicated in their etiology, and discuss strategies which may be employed to fix them.

What are postcolonoscopy colorectal cancers?

Terminology

Postcolonoscopy colorectal cancers (PCCRCs) represent CRCs identified after a negative colonoscopy (i.e. an examination at which no CRC was detected). In the past, the terms *PCCRCs* and *interval CRCs* were used interchangeably, raising difficulties in the interpretation of outcomes and comparisons across studies. The term *interval CRC* seems to be in particular suitable for screening and subsequent surveillance, since such CRCs are identified *within* the time interval preceding the next recommended examination. The term *PCCRCs*, on the other hand, specifically describes those CRCs identified after a colonoscopic examination, whether in a screening or diagnostic setting. Since the latter term more accurately reflects the phenomenon studied in these studies, we will further refer as *postcolonoscopy CRCs*.[11]

Magnitude of the problem

A substantial body of evidence now indicates that incidence rates of PCCRCs vary largely, from 2.9% to 9.6% of the total number of CRCs diagnosed in a population[4,12-21] and from 1 in 130 to 1 in 1,000 colonoscopic examinations.[9,22,23] Together, these studies clearly demonstrate the protective effect of a colonoscopic examination against CRC, but consistently show its limitations in the proximal colon (Table 2.1).[3,4,6,8,24,25]

Taking a careful look to these data, several explanations may account for such variation, in particular differences in the definitions used for a PCCRC, or with regard to age, gender of the study populations and comorbidity, differences in methodological designs (prospective versus retrospective studies, employing administrative vs. clinical data), as well as differences in the endoscopic techniques and technologies applied, which have dramatically changed over the past years. Last but not least, the differences in educational background and proficiency of the participating endoscopists could explain such variation.

The definition of a PCCRC is rooted in the time interval from the baseline examination to subsequent diagnosis of CRC, which ranges from 6 to 60 months in the majority of studies,[6,12,14,16,19,21,24,26-29] but exceeds 10 years in others.[17,20] Recent modeling data, however, indicate the 'mean sojourn time' (ie, the estimated interval between the preclinical (screen)phase and the detectable period) may be longer, ranging from 4.5 to 5.8 years.[30] A shorter time interval may indeed result in underestimation of the PCCRC rates. For example, a study by Bressler *et al.*[24] based on insurance data and cancer registry in Ontario, Canada found an overall PCCRC rate of 3.4% when using an interval of 3 years, but a rate of 4.6% when extending the interval to 5 years.

With regard to the demographic features, it can be reasoned that younger ages[15,18,29] or a predominant female population[9] could have contributed, again, to underestimation of the overall PCCRC rates. Presence of comorbidity, such as cardio-vascular, pulmonary or diverticular disease, could have also affected the recommended frequency and effectiveness of colonoscopic examinations.[12,14,16,24,31]

With regard to methodology, a prospective vs. retrospective design could additionally affect the PCCRC rates: The majority of prospective studies were conducted in a trial setting,[7,32,33] by experienced endoscopists, and under 'ideal' clinical circumstances (nearly 100% completion rate, optimal bowel preparation), for which outcomes may not necessarily imply generalizability. Furthermore, such trials enrolled patients whose colon was allegedly 'free of residual neoplasia', and excluded those with recent resections of large flat/sessile polyps, implying possible selection bias leading to a somewhat more favorable outcome. For example, in a pooled analysis of 8 prospective trials, including 9,167 participants, with a median follow-up of 4 years, the observed rate of PCCRCs was low (0.6%, or 1.71 per 1,000 person-years follow-up).

Table 2.1 Overview of studies on postcolonoscopy colorectal cancers (PCCRCs)

Study	Study design	Number of patients with PCCRCs, mean age	Incidence	PCCRCs: risk factors and characteristics
le Clercq[19] 2014 The Netherlands	Population based, retrospective	147, 73yrs	147/5,107 = 2.9% of CRC pts	Older age, family history of CRC, diverticulosis, cardiovascular disease PCCRCs were more likely proximally located, small in size and had flat morphology (see also Table 2)
Robertson[18] 2014 USA	Pooled multicohort analysis	58, 67yrs	58/9,167 = 0.6% of participants	PCCRCs were likely the result of missed or incompletely resected lesions (see also Table 2)
Samadder[21] 2014 USA	Population based, retrospective	159	91/2,659 = 3.5% of CRC pts (6-36 months) or 159/2,659 = 6% (6-60 months)	Early stage, proximal location
Erichsen[20] 2013 Denmark	Population based, retrospective	982, 74yrs	982/38,064 = 2.6% of CRC pts	Female gender, comorbidities PCCRCs were more likely early stage, proximally located and contained mucinous histology
Brenner[17] 2012 Germany	Population based, case-control	78	78/1,945 = 4.0% of CRC pts	Female gender, proximal location
Cooper[16] 2012 USA	Population based, SEER-Medicare database, retrospective	4192	4,192/57,839 = 7.2% of CRC pts	Older age, more likely African-American, comorbidities, early stage, proximal CRC
Huang[28] 2012 China	Single center, retrospective	14, 59yrs	14/1,794 = 0.8% of pts undergoing colonoscopy	PCCRCs were likely the result of missed or incompletely resected lesions (see also Table 2)
Strock[15] 2011 Luxembourg	Single center, retrospective	19	19/8,950 = 0.2% of pts undergoing colonoscopy	Older age, no previous adenoma resection, size of suspected adenoma >6 mm
Horiuchi[29] 2011 Japan	Prospective colonoscopy cohort	9, 68yrs	9/3,212 = 0.3% of pts undergoing colonoscopy	Proximal colon, presence of small adenomas in the same colonic segment
Baxter[35] 2011 Canada	Population based, cancer registry	1260	1,260/14,064 = 9.0% of CRC pts	Endoscopist specialty and setting, distal PCCRC: older age, female gender, higher comorbidity score, proximal PCCRC: higher comorbidity score

Table 2.1 (continued)

Study	Study design	Number of patients with PCCRCs, mean age	Incidence	PCCRCs: risk factors and characteristics
Singh[14] 2010 Canada	Population based, cancer registry	388	388/4.883 = 7.9% of CRC pts	Prior colonoscopy with polypectomy, endoscopist specialty, year of CRC diagnosis, proximal CRC
Ferrández[27] 2010 Spain	Population based, retrospective	27	27/386 =7.0% of CRC pts	N/A
Leung[32] 2010 USA	Continued Follow-up Study, prospective	9, 71yrs	9/1.297= 0.7% of participants	History of advanced adenoma
Kaminski[9] 2010 Poland	Colonoscopy screening cohort, retrospective	42, 58yrs	42/45.026= 0.1% of participants	Low ADR of individual endoscopists
Matsuda[13] 2009 Japan	Observational, cohort study	13, 63yrs	13/5.309=0.2% of participants	Adenomas >6 mm or intramucosal cancer at initial colonoscopy
Kahi[67] 2009 USA	Colonoscopy screening cohort vs cancer registry, retrospective	7, 60yrs	7/715=1.0% of screenees	N/A
Lakoff[4] 2008 Canada	Population based, retrospective	1461	1.461/110.402 = 1.3% of pts undergoing colonoscopy	N/A
Imperiale[68] 2008 USA	Colonoscopy screening cohort, prospective	-	0 pts undergoing colonoscopy, after 5years follow-up	N/A
Lieberman[69] 2007 USA	Colonoscopy screening cohort, prospective	14	14/1.193=1.2% of screenees	N/A
Bressler[24] 2007 Canada	Claims-based administrative data, retrospective	430, 73yrs	430/12.487=3.4% of CRC pts	Older age, diverticular disease, proximal CRC; endoscopist specialty and setting
Farrar[12] 2006 USA	Single center, retrospective	45, 72yrs	45/830=5.4% of CRC pts	Proximal CRC; small size
Pabby[33] 2005 USA	Polyp Prevention Trial (PPT), prospective	13, 70 yrs	13/2.079=0.6% of participants	Etiology (see also Table 2)
Robertson[41] 2005 USA	3 chemoprevention trials, prospective	19, 65yrs	19/2.915=0.7% of participants	Older age, history of more adenomas
Leaper[70] 2004 New Zealand	Single center, retrospective	17, 71yrs	17/286 = 5.9% of CRC pts	Incomplete colonoscopy, poor bowel preparation, inadequate biopsy/interpretation

A few retrospective studies provided information on colonoscopic performance in a community-based environment.[12,19] Retrospective studies, however, raise questions about the quality and completeness of information (i.e. cecal intubation, adenoma detection rates, and withdrawal times), in particular when data are gleaned from administrative, claims-based records.[34]

In a population-based study of patients diagnosed with CRC in the South of Limburg, The Netherlands, from 2001 through 2010, in which colonoscopy and pathology records and data from the Netherlands Cancer Registry were reviewed, the authors identified a total of 5,107 patients with CRC.[19] Of these, 147 (2.9% of all CRC patients) had PCCRCs diagnosed on average 26 months after an index colonoscopy. In this study, PCCRCs were defined as CRC diagnosed within 5 years after an index-colonoscopy, in an attempt to maximize the confidence in capturing all PCCRC cases.

With regard to the experience and specialty of the practicing endoscopist, studies from Canada,[6,14,24] USA,[16,18,26,33] and Poland[9] consistently showed colonoscopies performed outside a hospital setting, by non-gastroenterologists, endoscopists with lower adenoma detection rates, lower volume of colonoscopies performed, or lower completion and polypectomy rates are likely associated with higher rates of PCCRCs.[9,14,24,26,35,36] Surprisingly, the PCCRC rates seemed to be fairly stable over time despite advances in endoscope technology and increased awareness, with an average of 1.8 PCCRCs diagnosed per 1,000 colonoscopies in the last decade,[19] indicating their etiology is incompletely understood and warrants further prospective investigation.[37]

Why do PCCRCs occur?

Briefly, two key factors, acting separate or in concert, may explain the occurrence of PCCRCs, namely *procedural factors* and *molecular underpinnings* of precursor lesions, associated with a faster progression to cancer.[10,38] Disentangling these groups of factors – although challenging – is of importance, as it may provide opportunities for improvements. A dominant role of the procedural factors clearly indicates the need for improvements at both technological and educational level. However, a few cases may not be sufficiently explained by procedural factors alone, suggesting additional involvement of the tumor biology.

Few studies systematically examined factors implicated in the etiology of PCCRCs (Table 2.2). In a seminal paper by Pabby *et al.*[33], the authors employed a structured algorithm to evaluate the reasons for PCCRCs in 2,079 patients with a history of one or more colorectal adenomas. Based on the time elapsed between the index colonoscopy and CRC diagnosis, the stage of the tumor at diagnosis and presence of a CRC at the site of a previous adenoma, the authors assigned each case of PCCRC to one of the following etiologic categories: incomplete examination, missed cancer, failed biopsy detection, incompletely resected lesion or new cancer. A number of studies have further built on this algorithm and tested such principles in various populations.[18,19,28,39] It should be mentioned, however, that such categorization, which is based on certain assumptions

will never be perfect, and needs further validation.[18,40] For example, distinction between a missed lesion or a newly developed cancer relies on assumptions regarding the *adenoma dwell time* and the *mean sojourn time*: Assuming progression from adenoma to invasive CRC takes more than 36 months, an advanced CRC detected <36 months after an index colonoscopy would be likely the result of a missed lesions, while a non-advanced CRC detected ≥36 months would be more likely a newly developed cancer.

Despite its imperfections, such categorization of the etiologic factors provides general estimates which may guide further improvements (i.e. endoscopic training, utilization of adequate equipment or a closer endoscopic surveillance in certain patient subgroups).

Table 2.2 Comparison of studies evaluating the etiology

Study	Study design	Number of PCCRCs	Missed lesions[a]	Incomplete resection[b]	New cancers[c]	Other/additional categories[d]	Location proximal vs. distal
Pabby, 2005[33] USA	Prospective trial	13	23%	31%	23%	23% failed biopsy	7 vs. 6
Huang, 2012[28] China	Population-based	14	36%	50%	14%	-	11 vs. 3
Robertson, 2014[18] USA	Prospective multicohort analysis	58	52%	19%	24%	5% failed biopsy	29 vs. 29
le Clercq, 2014[19] the Netherlands	Population-based	147	58%	9%	14%	20% inadequate surveillance/ examination	87 vs. 59

[a] Missed lesions: PCCRCs of any size or stage were diagnosed <36 months of the index colonoscopy or, in the case of advanced CRCs (size ≥2 cm and TNM stage III/IV), diagnosed in ≥36 months; no previous adenoma had to be found in the same segment at the index colonoscopy; [b] Incomplete resection: CRC diagnosed in the same anatomical segment as a previously resected adenoma; [c] Newly developed cancers: CRCs were detected ≥36 months after the index colonoscopy with none or one feature of advanced cancer (large size or advanced stage) and without a previous adenoma in the same segment; [d] Failed biopsy: cases occurring <1 year of the previous exam and in the same colonic segment as an adenoma and in which the endoscopist was suspicious that cancer may have been present; Inadequate surveillance/examination: incomplete colonic intubation, poor bowel preparation or inappropriate surveillance according to surveillance guidelines

Missed lesions

Undoubtedly, the operator-dependent performance with regard to detection of precursor lesions and effectiveness of resection are by far the most important factors in protecting against CRC.[9,38,39,41,42] Current data suggest 23% to 58% of the PCCRCs are attributable to missed lesions.[17-19,43] In the study by Pabby *et al.*[33], a PCCRC was ascribed to a missed lesion when a CRC of any size or stage was diagnosed <30 months and the respective colonic segment was free of any adenoma on index colonoscopy; or an advanced CRC (TNM-stage III-IV and size >2 cm) was diagnosed ≥30 months after an index colonoscopy. In the PLCO (Prostate, Lung, Colorectal, Ovarian Cancer Screening) trial, similar assumptions were employed to determine the etiology of interval CRCs after a screening sigmoidoscopy.[39] In a cohort of 77,447 participants, Schoen and colleagues found that out of a total of 977 CRC, 48.1% were not detectable, and 27.0% prevalent not

detected of which 20.5% due to missed lesions. The reasons why endoscopists may overlook some precursor lesions are probably multifactorial, with insufficient bowel preparation, suboptimal withdrawal time and technique,[44] but most probably gaps in knowledge and training of the endoscopist on the recognition of subtle appearing precursor lesions, such as nonpolypoid (flat or depressed) adenomas and sessile serrated adenomas/polyps.[23]

A key paper by Kaminski *et al.*[9], found adenoma detection rates (ADR) strongly correlate with the PCCRCs rates. Endoscopists with ADR in the lower ranges (e.g. <11%, 11-14.9% or 15-19.9%), had a 10-fold greater risk of PCCRCs than those with an ADR ≥20% (p=0.02). Whether the overall ADR is the ideal predictor of PCCRCs is questionable,[36] and additional studies are required to elucidate the precise relation between quality indicators in an individual or group practice and the subsequent PCCRC rates.[40] Next to ADR, the available infrastructure (i.e. quality of healthcare system, endoscopic equipment and training of the supportive personnel) as well as patient's education and compliance with screening may finally determine the PCCRC rates.

Nonpolypoid neoplasms and PCCRCs

For a long while underestimated in the western endoscopy practice, nonpolypoid (flat or depressed) colorectal neoplasms (NP-CRN)[45,46] are now recognized as a major contributor to the occurrence of PCCRCs. Such lesions have an inconspicuous endoscopic appearance, being more easily overlooked, especially under circumstances of suboptimal bowel preparation[47] and insufficient training.[48] Further compounding this issue, EMR and ESD resection techniques of large NP-CRNs are not yet standard care in all endoscopy centers.[49] Recognition and classification of NP-CRNs in the 'real-world' practice is indeed challenging and requires training. In a study at our institution, we first familiarized all endoscopists (faculty and trainees) on the diagnosis and endoscopic resection techniques of NP-CRNs.[45,46,48] Building on the *learning pyramid* by Miller,[50] we developed a systematic, stepwise training curriculum, comprising topic lectures, video-training, individualized feedback/supervision and interactive case discussions. We then embarked in a prospective study of 3,720 consecutive patients who underwent elective colonoscopy for diagnostic, screening or surveillance indications. In this cohort, the prevalence rates of adenomas, NP-CRNs and serrated polyps were 29.4%, 14.4% and 5.7%, respectively. We observed that proximal adenomas with high-grade dysplasia/early CRC were more likely to be diminutive in size or nonpolypoid in shape than the distal ones (76.3% vs. 26.2%, OR 9.2, 95% CI 4.5-19.2),[46] which may explain in part the disparity in effectiveness of colonoscopic examinations between the proximal versus distal colon. In line with these findings, a cross-sectional study by Gupta *et al.,*[51] in which 233,414 polyps from 142,686 patients were examined, found adenomas containing high grade dysplasia or adenocarcinoma were significantly smaller in the proximal vs. distal colon (OR 5.3, 95% CI 4.1-6.8). Few studies demonstrated the link between NP-CRNs and PCCRCs. In the experience of the authors, PCCRCs were also likely proximally located (OR 3.9, 95% CI 2.7-5.7), smaller in size (OR 0.8, 95% CI

0.7-0.9), and had more often a flat macroscopic appearance (OR 1.7, 95% CI 1.2-2.4) than prevalent cancers, suggesting potential origin from flat precursors.

Sessile serrated polyps and PCCRCs

Similar to NP-CRNs, sessile serrated adenomas/polyps (SSA/Ps) are, again, more difficult to recognize with variations in detection ranging from 3% to 9%.[52] In a study examining the endoscopic appearance of dysplastic or large, proximal non-dysplastic serrated lesions, nearly half of them had a nonpolypoid shape.[53,54] This finding might explain the large variation in detection rates among endoscopists,[55] and underscores the need for education and training to improve their detection.[54] A synchronous presence of advanced adenomas or certain risk profiles may aid in detection of SSA/Ps.[53,56]

Incompletely resected lesions

With regard to the effectiveness of polypectomy and its potential role in the occurrence of PCCRCs, 2.4% to 26% of PCCRCs seem to develop at the same anatomic location with a previous polypectomy. [9,12,33,57] Incomplete removal was defined as a cancer at the site of previous *adenoma*,[18,28,33] or a previous *advanced* adenoma.[19] In a study by Robertson *et al.*[41] based on 3 adenoma chemoprevention trials, 26% of PCCRCs developed in the same anatomic segment as a previous polypectomy, in line with a previous retrospective study[12] and a dietary polyp prevention trial.[33] Others found, however, lower rates of ineffective polypectomy (2.4%).[9] A recent study by Pohl *et al.*[57] found an overall 10.1% rate of incomplete polypectomies, even in the hands of experienced gastroenterologists. Incomplete resection was more likely in case of large (10-20 mm) than small (5-9 mm) lesions (17.3% vs. 6.8%, relative risk 2.1) and in case of SSA/Ps vs. adenomas (31.0% vs. 7.2%; relative risk 3.7).

New cancers

Very few data are available about the contribution of biologic factors to the genesis of PCCRCs, indicating such factors may be implicated in the etiology of 14% to 24% of the PCCRCs (Table 2.2). Evidence at molecular level is, however, sparse.[5,58-62] Higher prevalence of MSI and extensive DNA methylation were found in PCCRCs vs. prevalent CRCs: MSI 30.4% vs. 10.3% (p=0.003), CIMP 57% vs. 33% (p=0.004). It is worthwhile to mention, these studies were conducted on the same sample of 63 tumors, from a predominantly male population of veterans, underscoring the need for additional data.

It has been suggested that certain phenotypes of NP-CRN, in particular the lateral spreading tumors of non-granular type and the depressed lesions, are associated with a more aggressive biologic behavior.[63] These data are originating from Japan, but have been recently confirmed in the West: a study by Moss *et al.*[64] found that 31.8% of the depressed lesions and 15.3% of the lateral spreading tumors of non-granular type contain submucosal invasion at the time of diagnosis. Identification and accurate

classification of all NP-CRNs are therefore key to the understanding the biology of these lesions. In a meta-analysis by Voorham *et al.*[63] which spanned two decades of molecular research on NP-CRNs, the authors found that certain subtypes of NP-CRNs, in particular the lateral spreading tumors of nongranular type and the depressed neoplasms contain less often KRAS mutations (summary OR 0.3) and APC mutations (OR 0.4), but more often BRAF mutation (OR 2.2) than the protruded type. Furthermore, nonpolypoid neoplasms seem to harbor more often 5q loss, but less often APC and MSI than their polypoid counterparts, again supporting a distinct molecular pathway.[63,65]

Similar to NP-CRNs, some phenotypes of SSA/Ps are also associated with a more aggressive biologic behavior.[52] In a study of the molecular characteristics of 580 conventional adenomas and 419 serrated lesion, Burnett-Hartman *et al.*[66] found that SSA/Ps (and other large right-sided serrated lesions) harbor indeed more often mutant BRAF (55% vs. 1%), CIMP-high (26% vs. 1%), and methylated MLH1 (5% vs. 1%), features resembling the CIMP high, BRAF mutated CRCs. As the survival of patients with PCCRCs does not seem to differ from that of patients with prevalent CRCs, substantial differences in tumor biology seem unlikely.[20]

Summary and remarks

In summary, the etiology of PCCRCs is multifactorial, with missed or incompletely resected lesions as dominant factors.[18,19] Biologic features of precursor lesions leading to a faster progression may have an adjunctive role, albeit of lower significance. Nonpolypoid (flat or depressed) neoplasms and sessile serrated polyps, which are more challenging to detect and resect, and a proportion of which harbor molecular events associated with a more aggressive biologic behavior, are considered major contributors to PCCRCs. Education and training programs aiming to boost the quality of colonoscopic cancer prevention should pay additional attention to the accurate detection and effective resection of such lesions. Assuming colonoscopy will be always operator-dependent, efforts should be made to reduce the variation among endoscopists with regard to technical performance. A thorough registration of endoscopic findings (including photo-documentation) at index examination, quality indicators, as well as the characteristics of PCCRCs (time to diagnosis, clinicopathologic features) may help to identify most common etiologic factors. New developments in the molecular mechanisms underlying nonpolypoid carcinogenesis are awaited with great interest, as these may form the basis for personalized surveillance strategies in the future.

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3

Postcolonoscopy colorectal cancers are preventable: a population-based study

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Abstract

Objective

The quality of colonoscopy is key for ensuring protection against colorectal cancer (CRC). We therefore aimed to elucidate the etiology of postcolonoscopy CRCs (PCCRCs), and especially to identify preventable factors.

Methods

We conducted a population-based study of all patients diagnosed with CRC in South-Limburg, from 2001 to 2010. We used colonoscopy and histopathology records and data from the Netherlands Cancer Registry. We defined PCCRCs as cancers diagnosed within 5 years after an index colonoscopy. According to location, CRCs were categorized into proximal or distal from the splenic flexure and, according to macroscopic aspect, into flat or protruded. Etiologic factors for PCCRCs were subdivided into procedural related (missed lesions, inadequate examination/surveillance, incomplete resection), and biology related (new cancers).

Results

We included a total of 5,107 CRC patients, of whom 147 patients (2.9% of all patients, mean age 72.8 years, 55.1% males) had PCCRCs, diagnosed on average 26 months after an index colonoscopy. Logistic regression analysis, adjusted for age and gender, showed that PCCRCs were significantly more often proximally located (OR 3.92, 95%CI 2.71-5.69), smaller in size (OR 0.78, 95%CI 0.70-0.87) and more often flat (OR 1.70, 95%CI 1.18-2.43) than prevalent CRCs. Of the PCCRCs, 57.8% were attributed to missed lesions, 19.8% to inadequate examination/surveillance and 8.8% to incomplete resection, while 13.6% to newly developed cancers.

Conclusions

In our experience, 86.4% of all PCCRCs could be explained by procedural factors, especially missed lesions. Quality improvements in performance of colonoscopy, with special attention for the detection and resection of proximally located, flat precursors have the potential to prevent PCCRCs.

Introduction

Colorectal cancer (CRC) is a public concern, with 440,000 incident cases and 210,000 deaths in Europe each year.[1,2] Colonoscopy, with detection and removal of precursor lesions, substantially reduces both the incidence[3,4] of and mortality[5] by CRC, but its protective effect against proximal CRC lags behind.[6] A number of studies from Canada and the USA found incidence rates of postcolonoscopy colorectal cancer (PCCRC) ranging from 3.4% to 9.0% of all diagnosed CRCs, with a predominant proximal location.[7-10]

The majority of studies on PCCRCs relied on claims-based administrative data,[8-10] thus providing limited information about the contribution of procedural factors, i.e. completeness of colonoscopy, potentially missed or incompletely resected lesions. The macroscopic features of PCCRCs and especially the potential role of flat precursors in the development of PCCRCs, have been less studied.[11] In particular, non-polypoid (flat or depressed) adenomas can be more easily overlooked in routine practice,[12] are more challenging to resect,[13] and a subset of them have the potential to progress more rapidly to cancer.[14] A study by Farrar *et al.*, conducted in a veteran population, showed that PCCRCs are smaller in size and more often proximally located than prevalent CRCs, albeit the macroscopic appearance and etiology of these cancers has not been addressed in their study.[15]

Understanding of the etiology of PCCRC diagnosed in routine practice, and especially the contribution of procedural factors is of utmost importance, as these factors are amenable to correction through educational programs. In a population-based, multicenter study conducted in South-Limburg, we examined the incidence, clinicopathologic characteristics and etiology of PCCRCs diagnosed over a 10 year-period. Special attention was paid to the procedural factors, i.e. missed or incompletely resected lesions, as these are potentially avoidable.

Methods

Study population and design

We identified all consecutive patients who had been diagnosed with CRC in South-Limburg, the Netherlands, from January 1, 2001 to December 31, 2010. We excluded patients with hereditary CRC (i.e. Lynch syndrome or polyposis syndromes), inflammatory bowel disease or a previous history of CRC. As we particularly examined incidence rates and the etiology of PCCRCs in South-Limburg, we refrained from including external referrals.

Data were collected at 3 large-volume hospitals (one university and two non-university: Maastricht UMC, Atrium MC Heerlen, and Orbis MC Sittard) in South-Limburg. South-Limburg is located in the southeast of the Netherlands, between Germany and

Belgium, and has a narrow northern border with the rest of the Netherlands. The region has a total population of approximately 650,000 inhabitants and a low net migration rate of 0.8 per 1000 inhabitants per year.[16]

For the purpose of this study, we firstly retrieved all cases diagnosed with CRC using a nationwide digital pathology database (PALGA). We then reviewed digital clinical and histopathology records, including photographic documentation of the CRC resection specimens. We verified the validity and completeness of data using the Netherlands Cancer Registry. A high concordance exists between the pathology database and the Netherlands Cancer Registry.[17,18] The study was approved by the Institutional Review Boards of the participating hospitals and registered in the Netherlands Trial Registry: NTR3093 (www.trialregister.nl).

Definitions

We defined PCCRCs as CRCs which had been diagnosed within 5 years after an index-colonoscopy, while the remaining CRCs were classified as prevalent CRCs. Other authors considered a 3 year-interval in defining PCCRCs;[8-10, 19, 20] however, in our study, we preferred to extend this interval to 5 years, as the 'mean sojourn time', i.e. estimated interval between the preclinical (screen) phase and the detectable period[21,22] may vary with the tumor biology (i.e. growth rate), and for achieving highest confidence in capturing all PCCRCs.

To assign the most probable etiology to the identified PCCRCs, we built on an algorithm developed by Pabby *et al.*[23] and modified by Huang *et al.*[24] We assigned each case of PCCRC to one of the following categories: procedural factors (inadequate examination or surveillance, incomplete resection, or missed lesions), or tumor biology (newly developed cancers). *Inadequate examination* was defined as incomplete colonic intubation or poor bowel preparation. *Inappropriate surveillance* was defined according to the Dutch post-polypectomy surveillance guidelines.[25] *Incomplete resection* was defined as cancer diagnosed in the same anatomic segment as a previously resected advanced adenoma (e.g. ≥1 cm in size or containing high grade dysplasia or a villous component). *Missed lesions* were considered the main etiologic factor when PCCRCs of any size or stage were diagnosed ≤36 months of the index-colonoscopy, or in case of advanced CRCs (size ≥2 cm and TNM-stage III/IV) diagnosed ≥36 months; no previous advanced adenoma had to be found in the same segment at the index-colonoscopy. *Newly developed cancers* were CRCs detected >36 months after the index-colonoscopy; with none or one feature of advanced cancer (large size or advanced stage), and without a previous advanced adenoma in the same segment. Assignment to etiology was performed by two of the study investigators, and in cases of disagreement discussed until consensus was reached.

Colonoscopic procedure was considered complete when the endoscopist visualized and documented the cecal landmarks. Quality of bowel preparation was classified depending on the endoscopist estimation as sufficient (good or fair) or insufficient

(poor).[26,27] According to location CRCs were categorized into proximal or distal from the splenic flexure, and according to their macroscopic appearance into protruded (sessile or pedunculated) versus flat.[28,29] A tumor was considered flat when both the endoscopist and pathologist independently described it as having a non-exophytic, flat or depressed macroscopic appearance. In case of disagreement, the pathologist' estimation was considered leading. Size of CRCs was routinely measured and documented in the pathology reports. The specialty of endoscopist was subdivided into gastroenterologist and non-gastroenterologist (including gastrointestinal surgeon, general internist or nurse endoscopist).

Study endpoints and statistical analyses

The primary outcome measure was to evaluate the etiology of PCCRCs. Secondary outcome measures were to examine clinicopathologic characteristics of PCCRCS (i.e. location, size, macroscopic appearance, and histopathology). Subanalyses were performed according to setting (university vs. non-university, and gastroenterologist vs. non-gastroenterologist), as well as relation between tumor shape and stage at diagnosis.

Multiple logistic regression analyses, using age, gender, location, size, macroscopic appearance, mucinous histology, endoscopist specialty, and hospital setting, were used to identify potential risk factors for the occurrence of PCCRCs, with a minimum of 10 outcome events (i.e. PCCRC cases) per predictor variable, as a prerequisite.[30] To adjust for possible clustering within the same endoscopist, taking into consideration the variations in number of patients diagnosed with CRC per endoscopist, we used generalized estimating equations (GEE).[31] Differences in dichotomous variables were tested using the chi-square test or Fisher's exact test, where appropriate. Differences in numerical variables were examined by the independent-samples t-test. All odds ratios (ORs) were presented with 95% confidence intervals (CI). P-values ≤0.05 were considered statistically significant. Data were analyzed using the SPSS-program version 20.

Results

We identified a total of 5,701 patients who had been diagnosed with CRC in South-Limburg, from January 2001 to December 2010. Figure 3.1 depicts the flow-chart of the study. Of the 5,107 patients with 5,303 CRCs finally analyzed, 147 had undergone an index-colonoscopy within 5 years prior to the diagnosis and were considered PCCRCs, accounting for 2.9% of all diagnosed CRCs. The mean (SD) time between the index-colonoscopy and diagnosis of CRCs was 26.1 (16.3) months. Table 3.1 presents the clinical characteristics of patients with PCCRCs and prevalent CRCs. Patients with PCCRCs were significantly older, had more often diverticular disease, coronary artery disease, and a family history of CRC than those with prevalent CRCs.

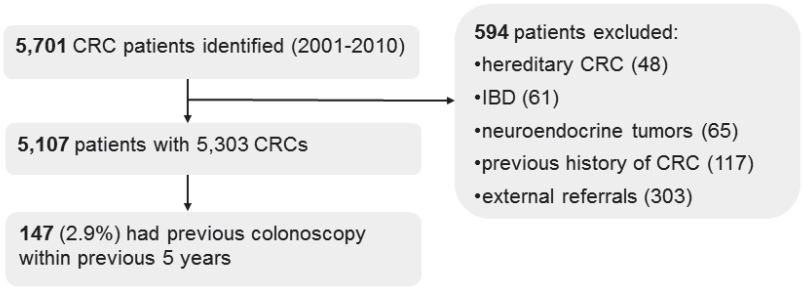

Figure 3.1 Study flowchart

Table 3.1 Basic characteristics of patients with postcolonoscopy colorectal cancers (PCCRCs) at the time of diagnosis versus those with prevalent CRCs

	PCCRC (n=147)	Prevalent CRC (n=4960)	p-value
Mean (SD) age (years)	72.8 (9.1)	69.9 (11.1)	<0.001
Male gender (%)	81 (55.1)	2667 (53.8)	0.750
Current or former smoker (%)	34 (23.1)	1167 (23.5)	0.911
Family history of CRC (%)	8 (5.4)	81 (1.6)	0.004*
Diverticulosis (%)	70 (47.6)	1258 (25.4)	<0.001
Coronary artery disease (%)	58 (39.5)	1177 (23.7)	<0.001

CRC, colorectal cancer; SD, standard deviation. Family history of CRC, i.e. one first-degree relative <50 yrs or at least 2 first-degree relatives 50-70 yrs; diverticulosis, i.e. presence ≥2 diverticula; coronary artery disease, i.e history of myocardial infarction, angina, congestive heart failure or severe arrhythmias, *Fisher's Exact Test

Index- and diagnostic colonoscopy in patients with PCCRCs

Indications for index-colonoscopy were symptoms (i.e. anemia or rectal blood loss) in 74.1%, post-polypectomy surveillance in 22.4%, and screening in 3.4% of cases. Of the 147 patients with PCCRCs, 57 had at least one adenoma (mean: 1.8; range 1-5), with 33 of them having at least one advanced adenoma, and 90 patients had no abnormalities at the index-colonoscopy.

Overall, 87.8% of PCCRC cases were diagnosed by colonoscopy, whilst 12.2% during surgery for acute bowel obstruction. Of the 129 patients endoscopically diagnosed with PCCRCs, 73.6% were symptomatic and 26.4% were asymptomatic at the time of diagnosis.

Clinicopathologic characteristics of PCCRCs and prevalent CRCs

As shown in Table 3.2, PCCRCs were significantly more frequently located in the proximal colon, were smaller in size, and more often had a flat macroscopic appearance than prevalent CRCs.

Table 3.2 Clinicopathologic characteristics and TNM stage of postcolonoscopy colorectal cancers (PCCRC) versus prevalent CRCs

	PCCRC (n=147)	Prevalent CRC (n=5156)	p-value
Proximal location* (%)	87 (60.0)	1634 (31.9)	<0.001
Mean (SD) tumor size* (cm)	3.7 (1.8)	4.4 (2.2)	<0.001
Flat macroscopic appearance* (%)	66 (45.2)	1379 (27.7)	<0.001
≥50% mucinous histology (%)	18 (12.2)	433 (8.4)	0.099
Differentiation* (%)			
Poor	36 (31.0)	1066 (24.4)	0.102
Moderate/well	80 (69.0)	3301 (75.6)	
TNM-stage* (%)			
Early	79 (55.6)	2499 (49.7)	0.162
I	41 (28.9)	1060 (21.1)	
II	38 (26.8)	1439 (28.6)	
Advanced	63 (44.4)	2531 (50.3)	
III	43 (30.3)	1233 (24.5)	
IV	20 (14.1)	1298 (25.8)	

CRC, colorectal cancer; SD, standard deviation. * Data on location, size, macroscopic appearance, differentiation and stage were unavailable in 1%, 10%, 3%, 16%, 3% of cases, respectively, due to retrospective study design

Multiple logistic regression analysis, adjusting for age and gender, showed that proximal location (OR 3.92, 95%CI 2.71-5.69), a smaller size (OR 0.78, 95%CI 0.70-0.87) and flat appearance (OR 1.70, 95%CI 1.18-2.43) were independent risk factors for PCCRCs (Table 3.3). As the macroscopic shape of the tumor may be rigorously classified (Paris classification) in early (T1) cancers only, we conducted a sensitivity analysis, showing that early (T1) PCCRCs are indeed more often flat than the early (T1) prevalent CRCs, e.g. 30.8% (8/26) vs.14.0% (68/486), p=0.040, age-adjusted OR: 2.78, 95% CI 1.16-6.68. Generalized estimating equations (GEE), adjusting for clustering within patients in case of synchronous CRCs, showed similar results (data not shown). We found no significant differences between PCCRCs and prevalent cancers with regard to presence of mucinous histology, degree of differentiation or TNM-stage at diagnosis.

Table 3.3 Multiple logistic regression analysis adjusting for age and gender to examine risk factors for postcolonoscopy colorectal cancers (PCCRC)

Postcolonoscopy vs. prevalent CRCs*	OR	95% CI	p-value
Proximal location (vs. distal)	3.92	2.71 - 5.69	<0.001
Size in cm (continuous)	0.78	0.70 - 0.87	<0.001
Flat appearance (vs. protruded)	1.70	1.18 - 2.43	0.004
≥50% mucinous histology (vs. <50%)	1.61	0.94 - 2.76	0.085
Specialty of endoscopist (gastroenterologist vs. non-gastroenterologist)	1.33	0.81 - 2.19	0.266
Hospital setting (university vs. non-university hospital)	1.22	0.82 - 1.83	0.333

CRC, colorectal cancer; OR, odds ratio; CI, confidence interval. *adjusted for age and gender

Etiology of postcolonoscopy colorectal cancers

In Figure 3.2 the etiology of PCCRCs is described. Of the 147 cases of PCCRCs, 29 (19.7%) were ascribed to inadequate examination (i.e. poor bowel preparation, n=8; incomplete colonoscopy, n=14) or non-compliance to recommended post-polypectomy surveillance intervals (n=7). Of the remaining 118 cases, 13 (8.8%) were attributed to an incomplete resection of an advanced adenoma, while 85 cases (57.8%) to missed lesions. Twenty cases (13.6%) were attributed to newly developed cancers. In Table 3.4, the etiology of PCCRCs is detailed in relation to the clinical characteristics. Of the 85 PCCRCs ascribed to missed lesions, 52 (63%) were proximally located, of which 29 (57%) were flat.

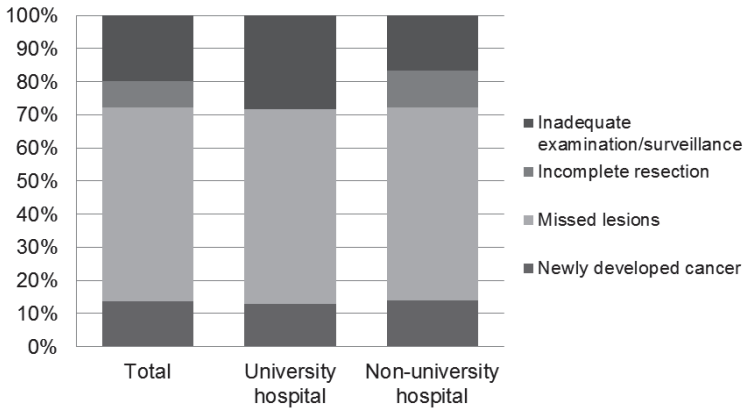

Figure 3.2 Etiology of postcolonoscopy colorectal cancers in a South-Limburg cohort

Table 3.4 Etiology of PCCRCs in relation to location and macroscopic appearance; data represent numbers (%) of patients

Etiology of 147 PCCRCs	Proximal colon			Distal colon		
	Total	Exophytic	Flat	Total	Exophytic	Flat
Inadequate examination/surveillance 29 (20%)	21 (72%)	14 (67%)	7 (33%)	8 (28%)	4 (50%)	4 (50%)
Incomplete resection 13 (9%)	3 (23%)	1 (33%)	2 (67%)	10 (77%)	8 (80%)	2 (20%)
Missed lesions * 85 (58%)	52 (63%)	22 (43%)	29 (57%)	31 (37%)	17 (55%)	14 (45%)
Newly developed cancer 20 (14%)	11 (55%)	6 (55%)	5 (45%)	9 (45%)	6 (67%)	3 (33%)

PCCRC, postcolonoscopy colorectal cancer; * Location was unknown in 2 cases and morphology in 1 case

Rates of PCCRCs in university vs. non-university hospitals and the relation to endoscopist specialty

Overall, incidence rates of PCCRCs did not differ significantly between the three hospitals (3.1% in the university vs. 2.6% and 3.0%, respectively, in the non-university hospitals, p=0.67). The proportions of inadequate procedure/surveillance, missed lesions and newly developed cancers were similar across the three hospitals. Incomplete resection of an advanced adenoma explained however some PCCRCs in the non-university hospitals, but none in the university hospital (12.0% vs. 0%, p=0.02, Fisher's Exact Test).

Index-colonoscopies were performed by 30 gastroenterologists and 9 non-gastroenterologists. The participating non-gastroenterologists were either gastrointestinal surgeons (n=6), general internists (n=2) and one specialized nurse endoscopist. We found no significant association between specialty of practicing endoscopists (i.e. gastroenterologist versus non-gastroenterologist), and the occurrence of PCCRCs using a multiple logistic regression model, adjusting for age and gender (OR 1.33, p=0.27). Generalized estimating equations (GEE) were used to examine a possible clustering of PCCRCs within the same endoscopist, and taking into consideration the variations in number of CRC patients each endoscopist contributed to this study, again no associations were found.

Time trends in diagnosis of CRC and PCCRC

As shown in Figure 3.3 the total numbers of colonoscopies gradually increased over the study period, with a slight increase in the number of diagnosed CRCs. Nonetheless, the number of diagnosed PCCRCs per 1000 colonoscopies remained stable with an average rate of 1.8 PCCRCs/1000 colonoscopies per year.

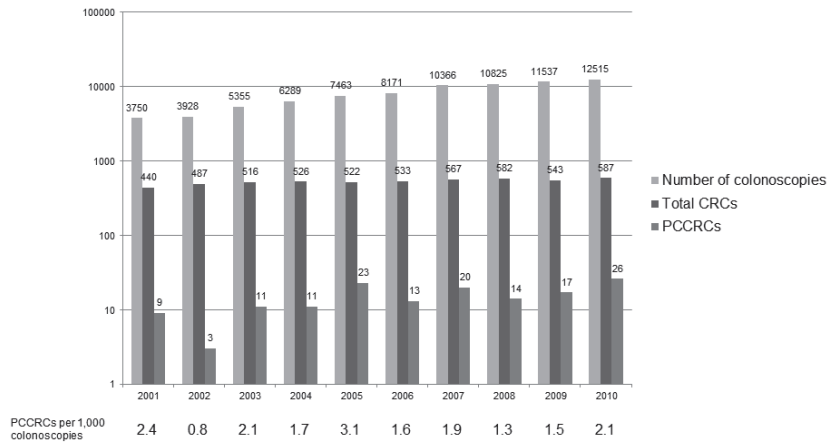

Figure 3.3 Time trends in diagnosis of CRC and PCCRC in a South-Limburg cohort

Discussion

In this study, we found that the vast majority (86%) of postcolonoscopy colorectal cancers would most probably have been preventable, being caused by missed, incompletely removed lesions, and inadequate examination or surveillance. Of note, we found that PCCRCs were more likely to be proximally located, smaller in size, and have a flat macroscopic appearance than prevalent CRCs, suggesting these could have originated from overlooked precursors at the index-colonoscopy. Taken together, these findings strengthen the importance of developing practical skills for accurate detection and resection of all precursor lesions, with special attention for small, flat, and proximally located lesions.

We found that procedural factors accounted for the majority of PCCRCs. A two-fold failure explained this finding, namely missed and incompletely removed lesions. With regard to the former, a number of studies now indicate that non-polypoid (flat or depressed) colorectal adenomas contribute to the development of PCCRCs, either due to overlooked lesions,[6,32,33] a more challenging resection,[34] or perhaps a more aggressive biologic behavior.[13,35] So far, information on clinicopathologic features and especially the macroscopic appearance of PCCRCs is scarce, as the vast majority of studies relied on registry-based, administrative data[6,8-10] and only a few were based on clinical data.[4,15,36] Our study is one of the few to examine the clinical features and potential explanations of PCCRCs, and is to our knowledge, the first non-Japanese study reporting that a substantial proportion of PCCRCs (31% of the early (T1) PCCRCs) and 45% of all diagnosed PCCRCs had a flat macroscopic appearance.

In line with previous studies, we found that PCCRCs are significantly smaller and more often proximally located than prevalent CRCs.[5,8,9,15] As these cancers were diagnosed relatively early after the index-colonoscopy (mean interval of 26 months), it is possible they originated from flat precursors. Early Japanese studies found a predominant proximal localization of the relatively uncommon, yet highly malignant depressed lesions,[37-39] suggesting these could partly explain the occurrence of PCCRCs.[40] In a prospective study at our institution, involving endoscopists who have been trained in the recognition of flat lesions,[41,42] we found that proximally located colorectal neoplasms are more often small and flat than the distal ones, thereby contributing to the limited effectiveness of colonoscopy in the proximal colon.

An additional finding of our study, is that incomplete polypectomy accounted for 8.8% of all PCCRCs. We specifically focused on the resection of advanced adenomas, as approximately up to 35% of these lesions may progress to cancer within 10 years.[43,44] In a study of 417 polyps, resected by experienced gastroenterologists, Pohl *et al.* found a comparable rate of incompletely resected adenomas (10.1%, 95%CI 6.9-13.3%).[34] Data on the potential impact of incomplete polypectomy on the occurrence of PCCRCs vary widely, ranging from 2.4%[27] to 26%.[45]

In the present study, we did not find a significant association between the occurrence of PCCRCs and the specialty of endoscopists or individual clustering of PCCRC cases.

This is in line with some,[15] but contradicts several other studies, showing that patients with PCCRCs are more likely to have undergone a colonoscopy by a non-gastroenterologist, i.e. family physician,[8,9] internist,[8] general surgeon[10,46] or in a non-hospital-based setting.[8] It is possible that relative homogeneity with regard to equipment, facilities used, and supportive personnel might explain such findings. Notably, in our study, missed lesions accounted for most of the PCCRCs, in both university and non-university setting, indicating opportunities for future improvements. In contrast, incomplete resection appeared to be more likely a cause of PCCRC in a non-university than university setting.

The incidence rate of PCCRCs in our study was 2.9% of all diagnosed CRCs, corresponding to 1.8 per 1000 colonoscopies. This rate is relatively low and consistent with previous data from the Netherlands,[36] thus conferring generalizability for our routine practice. It is, however, difficult to compare the outcomes of different studies with regard to incidences of PCCRCs, due to large variations in methodology, i.e. definition of PCCRCs, retrospective versus prospective design, and differences in populations examined.

In line with previous data,[8,9] we found that patients with PCCRCs were older and had substantial co-morbidity, such as cardiovascular disease or diverticular disease. It is plausible that insufficient bowel preparation, which is more common in older and fragile patients with co-morbidity, increases the risk of missing lesions.[47,48] In addition, colonoscopic examination of patients with diverticular disease, some of whom also harbor multiple adenomas[49] is more difficult and colonoscopy might be less effective in preventing cancer. Of note, patients with PCCRC in our study more likely had a family history of CRC than those with prevalent CRCs (5.4% vs. 1.6%). Although this observation is based on a small number of cases, it emphasizes the importance of a thorough family history taking and strict adherence to surveillance guidelines in higher risk groups.

Strengths of our study reside in the population-based design, and the use of clinical records and national databases, as well as use of predefined criteria to retrace the potential etiologic factors of PCCRCs. Our study has several limitations that need to be acknowledged. First, this study was retrospective in design, and hence the results and conclusions are based on the assumption of reliable data registration across the study period. We attempted to enhance reliability through meticulous documentation and by using validated national registries to reconstruct, as much as possible, the 'real-life scenario' underlying the development of PCCRCs. Although we realize that a prospective approach might have been the ideal setting, the relatively low rates of PCCRCs (i.e. 1.8/1000 colonoscopies per year in our endoscopy practice) would make it difficult to assemble a large prospective cohort. Second, although some PCCRCs were detected during surveillance, the majority of the patients were diagnosed due to symptoms. We therefore realize we could have underestimated the true incidence of CRCs, as slow growing cancers which had not yet become clinically overt, could have been missed. To minimize this potential bias, we extended the definition of PCCRCs to

cancers diagnosed within 5 years after an index-colonoscopy. Along with a large sample size, the long-term duration of this study might have mitigated this bias. Third, the precise classification of the shape of CRCs into flat or protruded is difficult, particularly in case of advanced CRCs, as the Paris classification[29] is in fact solely applicable to superficial neoplasms. We classified the macroscopic appearance of CRCs in our study based on descriptive data from both endoscopy and pathology records, including photographic documentation. We uniformly applied this definition to all postcolonoscopy and prevalent CRCs, making it less likely this factor would have greatly affected the outcome of the study. To mitigate potential bias in appreciation of the tumor shape, we also performed a sensitivity analysis in early-stage (T1) cancers, showing again that PCCRCs were more often flat than the prevalent CRCs. Fourth, our study focused on the contribution of procedural factors to the occurrence of PCCRCs, and their biologic features were not addressed. A few studies reported that PCCRCs are approximately fourfold more likely to be microsatellite instable and CIMP-high,[35, 50] compared with prevalent CRCs, suggesting a potential role of the serrated neoplastic pathway. None of these studies has been, however, large enough in size or biological scope and a comprehensive examination of the biology of PCCRCs is therefore awaited. This information may help the identification of subgroups of patients at higher risk for CRC, who may need intensive surveillance.[11]

In summary, in our experience, PCCRCs accounted for 2.9% of all diagnosed colorectal cancers, and the majority of them could be explained by missed or incompletely resected lesions, with a predominant proximal location and a flat macroscopic appearance. Systematic training of the endoscopists, with focus on detection and management of flat precursors has the potential to prevent postcolonoscopy colorectal cancers.

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Metachronous colorectal cancers result from missed lesions and non-adherence to surveillance

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Abstract

Background
Several studies examined the rate of colorectal cancer (CRC) developed during colonoscopy surveillance after CRC resection (i.e. metachronous CRC, mCRC), yet their underlying etiology is unclear.

Objective
To examine the rate and likely etiology of mCRCs.

Design and setting
Population based, multi-center study. Review of clinical and histopathology records, including data of the national pathology database and the Netherlands Cancer Registry. South-Limburg, the Netherlands.

Patients
Total CRC population diagnosed in South-Limburg from January 2001 to December 2010.

Main outcome measurements
We defined a mCRC as a second primary CRC, diagnosed >6 months after the primary CRC. Using a modified algorithm to ascribe likely etiology, we classified the mCRCs into cancers due to non-compliance with surveillance recommendations, inadequate examination, incomplete resection of precursor lesions (CRC in same segment as previous advanced adenoma), missed lesions or newly developed cancers.

Results
We included a total of 5,157 CRC patients, of whom 93 (1.8%) had mCRC, which were diagnosed on average (range) 81 (7-356) months after the initial CRC diagnosis. Of all mCRCs, 43.0% were attributable to non-adherence to surveillance advice, 43.0% to missed lesions, 5.4% to incompletely resected lesions, 5.4% to newly developed cancers and 3.2% to inadequate examination. Age- and gender-adjusted logistic regression analyses showed that mCRCs were significantly smaller in size (OR 0.8, 95%CI 0.7-0.9) and more often poorly differentiated (OR 1.7, 95%CI 1.0-2.8) than solitary CRCs.

Limitations
Retrospective evaluation of clinical data.

Conclusions
In this study, 1.8% of all CRC patients developed mCRCs and the vast majority were attributable to missed lesions or non-adherence to surveillance advice. Our findings underscore the importance of high quality colonoscopic examination to maximize the benefit of post-CRC surveillance.

Introduction

Colorectal cancer (CRC) continues to be an important health issue worldwide, with high incidence and mortality rates.[1,2] After CRC resection, patients are at risk for recurrent cancer and metachronous neoplasms of the colon, and thereby colonoscopy surveillance is recommended.[3-6] Although the updated society guidelines[7-10] include recommendations on the surveillance intervals after CRC surgery, the proportion of a second primary CRC - further referred to as *metachronous CRC* (mCRC) - did not decrease over the past decade, ranging from 1% to 4% of all CRC patients.[11-19] In the early '80s, Tornqvist *et al.* found that mCRCs account for 2.1% of all CRCs, in a cohort of curatively treated CRC patients.[11] Two decades later, Green *et al.* found 42 mCRC cases over 15,000 person-years of follow-up, corresponding to a proportion of 1.3%.[12] A recent study by Samadder *et al.,* spanning 30 years of cancer registry in Utah, showed that 1.6% of the CRC patients developed mCRCs.[20] Previous studies emphasized the importance of surveillance *frequency* to the detection of recurrent and mCRC after colonic surgery, but did not address the *quality* of colonoscopic examination. Information about the etiologic factors implicated in the genesis of mCRCs is lacking.

Studies addressing the potential etiology of postcolonoscopy CRCs in general, either in a population-based setting[21] or polyp prevention trials,[22,23] found that *missed* and *incompletely resected polyps* contribute to the occurrence of more than 75% of the postcolonoscopy CRCs. It is highly likely that besides non-compliance with surveillance recommendations,[13,19,20] such factors can also contribute to the occurrence of mCRCs.[21,23,24] The understanding of the etiologic factors implicated in the occurrence of mCRCs is essential to identify caveats in the day-to-day practice and, ultimately, to improve the effectiveness of post-CRC surveillance by colonoscopy.

We conducted a population-based, multicenter study of all CRC patients diagnosed in South-Limburg, the Netherlands, over a decade, aiming to evaluate the proportion, characteristics, and potential etiologic factors underlying the development of mCRCs.

Methods

Study population and design

We conducted a population-based retrospective study, using both the national pathology database (PALGA) and the Netherlands Cancer Registry. We retrieved medical information from all patients diagnosed with CRC in South-Limburg, the Netherlands, from January 1, 2001 to December 31, 2010. In combination, PALGA and the Netherlands Cancer Registry provide a full coverage of the CRC population in this area.[25,26] We merged clinical data from the cancer registries with clinical and histopathological records derived from hospital databases. We excluded patients with hereditary forms of CRC (i.e. Lynch syndrome or polyposis syndromes), inflammatory

bowel disease or neuroendocrine tumors. As we specifically examined the proportion and etiology of mCRCs diagnosed in South-Limburg, external referrals were also excluded. Unlike our previous study on postcolonoscopy CRCs in the same population,[21] in the current study we included patients with a prior history of CRC (e.g. mCRC cases). Data were collected at 3 large-volume hospitals in South-Limburg (one university: Maastricht UMC and two non-university: Atrium MC Heerlen and Orbis MC Sittard). This province is located in the south-eastern part of the Netherlands, between Germany and Belgium, and has a narrow northern border with the rest of the Netherlands. The region has a total population of approximately 650,000 inhabitants and a low net migration rate of 0.8 per 1000 inhabitants per year.[27]

Definitions

We defined mCRCs as a second primary colorectal adenocarcinoma diagnosed at least 6 months after the primary CRC diagnosis, and which was not a recurrence of the primary CRC, as previously described.[28] The remaining CRCs were classified as solitary CRCs.

To ascribe the most likely etiology, we employed similar criteria as those used for the evaluation of postcolonoscopy CRCs.[21-23] In particular, we assigned each case of mCRC to one of the following categories (I) Non-adherence to the recommended surveillance intervals, (II) Inadequate bowel examination, (III) Missed lesions, (IV) Incomplete polyp resection, or (V) Newly developed cancers based on the *time* elapsed from prior colonoscopy to mCRC diagnosis, the *findings* at prior colonoscopy and the *characteristics* of mCRC (e.g. location, stage at diagnosis, histopathology). To ascribe the most likely etiology, the following questions were answered in a stepwise fashion (Figure 4.1): a) Was the (colonoscopy) surveillance interval after primary CRC diagnosis correct? b) Was the last colonoscopy complete and the bowel preparation adequate? c) Was the CRC identified in same anatomic segment as a previously resected advanced adenoma? d) Was colonoscopy performed in the past 36 months negative for cancer? e) What was the tumor stage at diagnosis?

Metachronous CRCs were attributed to *non-adherence to surveillance* (owing to patient, clinician-dependent factors or shared decision) when intervals exceeded those recommended by the Dutch surveillance guidelines at that time (e.g. a clearing colonoscopy pre-operatively or within 3 months post-operatively, followed by surveillance colonoscopy at 3 years).[29,30] Subsequent surveillance interval was 6 years when 1-2 adenomas were found at the clearing colonoscopy, or 3 years when 3 or more adenomas were found.[29] *Inadequate examination* was considered the most likely cause in case of incomplete colonic intubation or poor bowel preparation. *Incomplete resection* was defined as cancer diagnosed in the same anatomic segment as a previously resected advanced adenoma (e.g. ≥1 cm in size or containing high grade dysplasia or a villous component). *Missed lesions* were considered the main etiologic factor when mCRCs of any size or stage were diagnosed ≤36 months of the last complete (surveillance)

colonoscopy, or in case of advanced CRCs (size ≥2 cm and TNM-stage III/IV) diagnosed >36 months; assuming that no advanced adenoma was found in the same segment at the last colonoscopy and the surveillance intervals were adequate. *Newly developed cancers* were considered those CRCs detected >36 months after the last complete colonoscopy; and with none or one feature of advanced cancer (size ≥2 cm or advanced stage); and occurring after adequate surveillance intervals; and in the absence of advanced adenomas in the same segment at previous examination. Assignment of the likely etiology was performed by two of the study investigators (CIC, SS), and in cases of disagreement, discussed until consensus was obtained.

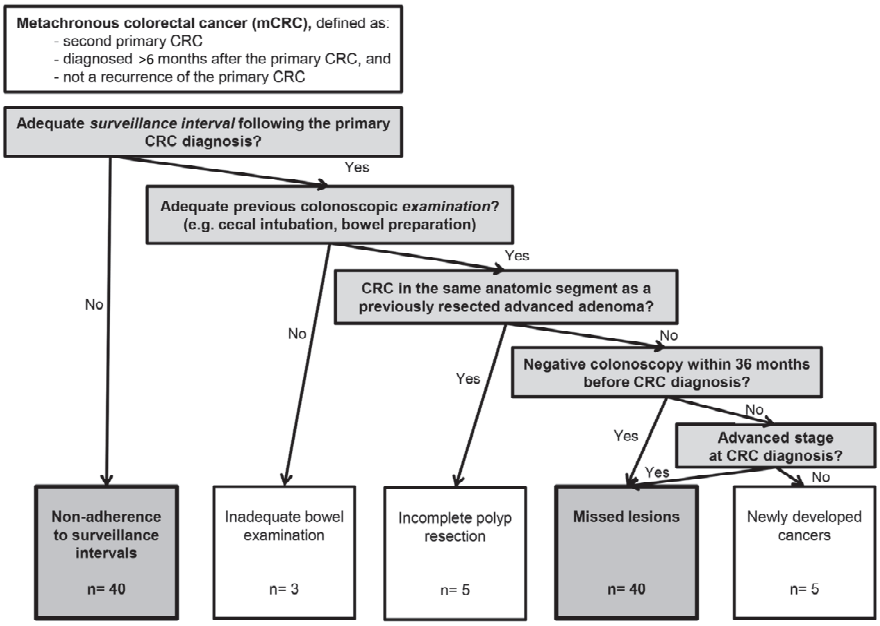

Figure 4.1 Algorithm employed to ascribe the etiology of metachronous (second primary) CRCs

Colonoscopy procedure was considered complete when the endoscopist visualized and documented the cecal landmarks or the surgical anastomosis (for those with right hemicolectomy). Quality of bowel preparation was classified as adequate (good or fair) or inadequate (poor) based on the endoscopist's estimation.[31,32] According to location, CRCs were categorized into proximal or distal from the splenic flexure, and according to their macroscopic appearance into protruded (sessile or pedunculated) versus flat.[33] A tumor was considered flat when both the endoscopist and pathologist independently described it as having a non-exophytic, flat or depressed macroscopic appearance. In case of disagreement, the pathologist's estimation was considered leading. Size of CRCs was routinely measured and documented in the pathology reports. According to

specialty, the endoscopists were subdivided into gastroenterologists and non-gastroenterologists (including gastrointestinal surgeon, general internist, or nurse endoscopist).

Study endpoints and statistical analyses

Endpoints of this study were: 1) to estimate the proportion of mCRC; 2) to compare the clinicopathologic characteristics of mCRC versus solitary CRCs and; 3) to examine the most likely etiology of mCRCs. We used multiple logistic regression analysis to identify potential features associated with mCRCs. Patient and tumor-related variables were included, with a minimum of 10 outcome events (i.e. mCRC cases) per predictor variable.[34] In case of multiple CRCs per patient, the most advanced CRC was included in the analyses. We conducted generalized estimating equations (GEE), accounting for clustering of (synchronous) CRCs within the same patient,[35,36] as a sensitivity analysis. Categorical variables are presented by number of CRCs or patients (%) and numerical variables by mean (SD). Differences in categorical variables were tested using the chi-square test or Fisher's exact test, where appropriate. Differences in numerical variables were examined by the independent-samples t-test. All odds ratios (ORs) were presented with 95% confidence intervals (CI). P-values ≤0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0. The study was approved by the Institutional Review Boards of the participating hospitals and registered in the Netherlands Trial Registry: NTR3093 (http://www.trialregister.nl).

Results

We identified a total of 5,701 CRC patients diagnosed between January 2001 and December 2010. Of these, 544 patients were excluded as shown in Figure 4.2. We finally analyzed 5,157 patients (mean age 70.0 years, 53.7% males) diagnosed with a total of 5,357 CRCs. Of these, 93 (1.8%) patients were diagnosed with a total of 98 mCRCs, of which two patients had synchronous CRCs during follow-up after CRC resection, one patient had 3 synchronous CRCs and one patient had two mCRCs subsequently diagnosed. The mean interval (range) between primary CRC and the diagnosis of mCRC was 81 (7-356) months. Of all mCRCs, 40.8% were diagnosed ≤36 months, while 59.2% were diagnosed >36 months after primary CRC diagnosis (Figure 4.3). Table 4.1 shows the baseline characteristics of patients with mCRCs and solitary CRCs. Patients with mCRCs were significantly older than those with solitary CRC (74 vs. 70 years, p<0.001). Women with mCRC had significantly more often a history of hysterectomy than those with solitary CRCs (37.8% vs. 23.8%, p=0.030). The majority of CRC patients were diagnosed by colonoscopy (94.6% of mCRC patients vs. 88.5% of solitary CRC patients, p=0.067), while the remaining CRCs were diagnosed during surgery for acute bowel obstruction.

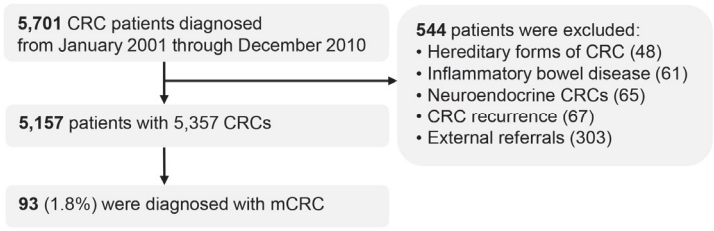

Figure 4.2 Study flowchart. CRC: colorectal cancer.

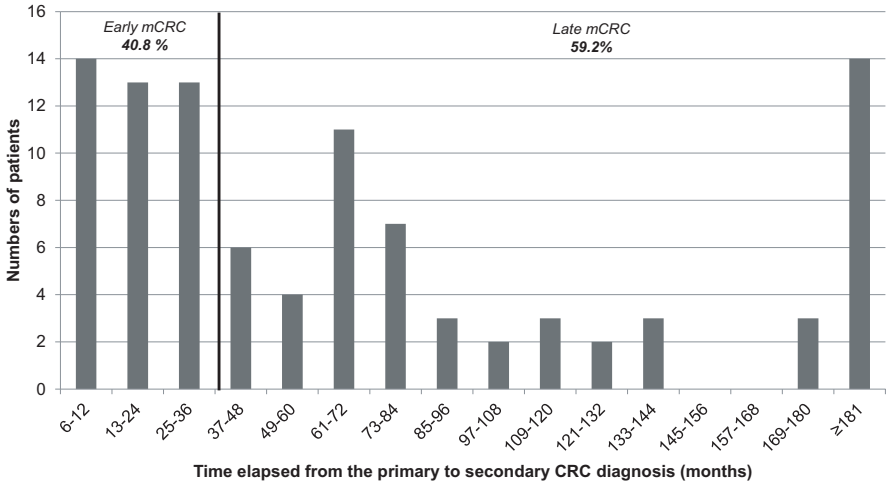

Figure 4.3 Time interval elapsed from the primary to metachronous (second primary) CRC diagnosis. CRC: colorectal cancer; mCRC: metachronous CRC.

Table 4.1 Clinical characteristics of patients with metachronous colorectal cancers (mCRCs) versus those with solitary CRCs

	mCRC (n=93)	Solitary CRC (n=5064)	p-value
Mean (SD) age (years)	74.2 (9.3)	70.0 (11.1)	<0.001
Male gender (%)	48 (51.6)	2722 (53.8)	0.682
Current or former smoker (%)	21 (22.6)	1189 (23.5)	0.839
Family history of CRC (%)	1 (1.1)	88 (1.7)	0.520*
Diverticulosis (%)	28 (30.4)	1311 (25.9)	0.324
History of hysterectomy (% of women)	17 (37.8)	558 (23.8)	0.030
Presence of synchronous CRCs	3 (3.2)	183 (3.6)	>0.999*
Coronary artery disease (%)	26 (28.0)	1225 (24.2)	0.401
Pulmonary disease (%)	6 (6.5)	466 (9.2)	0.362
Diabetes mellitus (%)	13 (14.0)	710 (14.0)	0.991
History of other cancer (%)	16 (17.2)	703 (13.9)	0.359

* Fisher's Exact Test. CRC, colorectal cancer; mCRC, metachronous CRC; SD, standard deviation. Family history of CRC, i.e. one first-degree relative < 50 yrs or at least 2 first-degree relatives 50-70 years; diverticulosis, i.e. presence of multiple diverticula; coronary artery disease, i.e history of myocardial infarction, angina, congestive heart failure or severe arrhythmias; pulmonary disease, chronic obstructive pulmonary disease or asthma; diabetes, i.e. diabetes mellitus treated with oral or insulin therapy; history of cancer, i.e, personal history of cancer other than CRC.

Clinicopathologic characteristics of metachronous CRCs versus solitary CRCs

Table 4.2 summarizes the clinicopathologic characteristics of mCRCs and solitary CRCs. mCRCs were significantly smaller in size, had more often a flat morphology, and were poorly differentiated than solitary CRCs. No significant differences were found between mCRCs and solitary CRCs with regard to location, tumor stage, and presence of mucinous histology. Age- and gender adjusted logistic regression analyses examining features associated with mCRCs, showed that mCRCs were significantly smaller in size (OR 0.82, 95%CI 0.72-0.94) and more often poorly differentiated (OR 1.70, 95%CI 1.04-2.77) than solitary CRCs. mCRCs also tended to have more often a flat macroscopic appearance than solitary CRCs (OR 1.52, 95%CI 0.95-2.41) (Table 4.3). Generalized estimating equations (GEE) conducted to adjust for clustering of CRCs within patients in case of synchronous CRCs provided similar results (data not shown). In a subgroup analysis including early stage (TNM I and II) CRCs only, mCRCs appeared to be more often flat than solitary CRCs (41.5% vs. 30.7% p=0.094).

Potential factors implicated in the etiology of metachronous CRCs

Figure 4.1 describes the potential etiologic factors of the mCRCs. Of all patients with mCRCs, 40 cases were attributable to non-adherence to surveillance recommendations, 3 to inadequate bowel examination (e.g. poor bowel preparation, n=1; incomplete colonoscopy, n=2), 5 to incomplete resection of an advanced adenoma, and 40 to potentially missed lesions. Five cases were considered to be newly developed cancers. In 11 out of the 40 cases (27.5%) attributable to potentially missed lesions, cancers were

diagnosed during the first post-operative colonoscopy. In addition, the mCRCs ascribed to missed lesions were significantly more often flat compared to those ascribed to other etiologies (61.5% vs. 28.8%, p=0.002). No significant differences were observed in potential causes of early vs. late mCRCs except for the newly developed cancers (which is expected due to the definitions used) (Supplementary Figure S4.1).

Table 4.2 Clinicopathologic characteristics of metachronous colorectal cancers (mCRC) versus solitary CRCs

	mCRC (n=98)	Solitary CRC (n=5259)	p-value
Proximal location* (%)	38 (38.8)	1702 (32.6)	0.194
Mean (SD) tumor size* (cm)	3.7 (2.1)	4.4 (2.2)	0.002
Flat macroscopic appearance* (%)	41 (42.7)	1434 (28.2)	0.002
≥50% mucinous histology (%)	7 (7.1)	445 (8.5)	0.642
Differentiation* (%)			0.039
Poor	28 (34.6)	1091 (24.6)	
Moderate/well	53 (65.4)	3351 (75.4)	
TNM-stage* (%)			0.199
Early	53 (56.4)	2549 (49.7)	
I	27 (28.7)	1092 (21.3)	
II	26 (27.7)	1456 (28.4)	
Advanced	41 (43.6)	2579 (50.3)	
III	15 (16.0)	1265 (24.7)	
IV	26 (27.7)	1314 (25.6)	

CRC, colorectal cancer; SD, standard deviation. * Data on location, size, macroscopic appearance, differentiation and stage were unavailable in 1%, 10%, 3%, 16%, 3% of cases, respectively

Table 4.3 Multiple logistic regression analysis to examine features associated with metachronous colorectal cancers (mCRC) in the study population

Metachronous vs solitary CRCs*	OR	95% CI	p-value
Age in years (continuous)	1.04	1.02 - 1.07	0.001
Size in cm (continuous)	0.82	0.72 - 0.94	0.004
Flat appearance (vs protruded)	1.52	0.95 - 2.41	0.078
Poor differentiation (vs moderate/well)	1.70	1.04 - 2.77	0.034

* per patient analyses. CRC, colorectal cancer; OR, odds ratio; CI, confidence interval

Metachronous CRCs according to hospital setting and endoscopist specialty

The proportion of patients diagnosed with mCRCs did not differ significantly between the three hospitals (2.3% in the university vs. 1.6% and 1.7%, in the non-university hospitals, p=0.317). Overall, the majority of both mCRCs and solitary CRC were diagnosed by gastroenterologists (70.5% of mCRCs and 81.5% of solitary CRCs). In the university hospital, mCRCs were more often diagnosed by non-gastroenterologists than in the non-university hospital (53.1% vs. 17.5%, p<0.001). Of the 93 patients with mCRCs, 17

(18.3%) were diagnosed with mCRC at the first colonoscopy after surgery, while 76 (81.7%) were diagnosed later during surveillance (>1 surveillance exam).

With regard to the relation between the hospital setting and etiologic factors, non-adherence to surveillance was more likely associated with mCRCs in the non-university hospital (50.0% vs. 27.6%, p=0.043, Supplementary Figure S4.2). No significant differences were found between the university and non-university hospitals with regard to the contribution of missed lesions to mCRCs (51.7% vs. 39.1%, p=0.253).

Discussion

In this population-based study, 43% of mCRCs were attributable to *missed lesions* during colonoscopic surveillance, while 43% to *non-adherence* to surveillance intervals (owing to patient, clinician-related factors or shared decision). Noteworthy, mCRCs were often small in size and had a flat macroscopic appearance. Our findings underscore that both the *frequency* and *quality* of colonoscopy are crucial to optimize the protection against cancer during post-CRC resection surveillance.

We evaluated and ascribed the potential etiology of individual mCRC cases using an algorithm previously applied for postcolonoscopy CRCs in average risk populations.[21-23,37] To our knowledge, this study is the first aiming to shed light on the main factors contributing to mCRCs. Based on clinical judgment that employs the time elapsed from prior colonoscopy to CRC diagnosis, the stage of the tumor at diagnosis and findings at previous colonoscopy, we ascribed the identified mCRCs to one of the following potential etiologies: non-adherence to surveillance intervals, inadequate bowel examination, incomplete polyp resection, missed lesions, or newly developed cancers. We found that 43.0% of the identified mCRCs were attributable to missed lesions and 5.4% to incompletely resected advanced adenomas.

A new finding of this study is that mCRCs likely have subtle macroscopic appearance, in particular more often flat morphology and smaller size than solitary CRCs. It is possible that flat appearing neoplasms have contributed to the occurrence of mCRCs in this study. Flat neoplasms are likely to be overlooked, especially under circumstances of suboptimal bowel preparation, insufficient awareness and gaps in education. The observed smaller size of mCRCs versus solitary CRCs could be also explained by closer surveillance of these patients. In line with previous studies evaluating the contribution of missed lesions to the occurrence of postcolonoscopy CRC in average-risk populations,[21,23] we found that missed lesions constitute the most common explanation of mCRCs. A significant proportion (40.8%) of mCRCs were diagnosed early (within 3 years) after the primary CRC diagnosis, suggesting again they could be the result of missed lesions.[38] Such increased risk for mCRC during the first three years after CRC resection is in alignment with previous data.[19,20,39]

Similarly consistent with previous findings, our data indicate there is room for improvement in the practical application of post-CRC resection surveillance

recommendations.[17,19,40] Forty-three percent of the mCRCs in our study were attributable to non-adherence to the recommended surveillance intervals. Several reasons can underlie this non-adherence, including clinician-, patient-related factors, or most likely a shared decision making. The mCRC patients in our study were older (mean age 74.2 years) and often had comorbidities (e.g. 28% had cardiovascular disease), factors that could drive the decision to cease colonoscopic surveillance, in line with the Dutch post CRC-resection surveillance guideline.[29] As our study is retrospective in nature, and hence lacks such level of clinical detail, we combined the patient- and clinician-related factors under the term 'non-adherence'. Of note, 30% of the patients with mCRCs also had diverticular disease and 38% a history of hysterectomy, conditions which are known to increase the technical difficulty of colonoscopic procedure and the likelihood to miss lesions. At the time of the study, Dutch guidelines did not strictly recommend a follow-up colonoscopy at 1 year after the surgical resection.[30] Accountability for organizing and providing colonoscopic surveillance was not formalized by sending out reminders or phone calls. Several studies evaluated the *frequency* of surveillance in patients at risk for recurrent or mCRC, supporting the need for follow up examination at 2-3 years after surgical resection.[41-43] However, most of these studies ignored the importance of the *quality* of examination. Recent data challenged the quality of colonoscopic performance by non-gastroenterologists.[44-46] Insufficient experience, especially on the detection and resection of subtle appearing lesions can limit the effectiveness of colonoscopy to prevent CRC. In a study using administrative data of 14,064 patients from Ontario, Baxter *et al.* found that endoscopist's specialty (non-gastroenterologist) and setting (non-hospital-based colonoscopy) were likely associated with a greater risk of postcolonoscopy CRC.[44] In the Netherlands, the majority of colonoscopies (>80%) are performed by gastroenterologists.[47] Although traditionally, a significant proportion of post-CRC resection surveillance colonoscopies were performed by colorectal surgeons, which was also the case of this study, in particular in the university hospital.

An additional finding of our study was that mCRCs more likely contain poor differentiation than solitary CRCs. Along the same lines, others found that mCRCs are more often featured by mucinous histology and microsatellite instability.[39] An association with a family history of CRC was also reported.[20,39] Taken together, these findings suggest potential involvement of distinct biologic factors, including the newly described serrated neoplastic pathway.[48] Little is known on the molecular make-up of mCRCs. A comprehensive evaluation may help to identify subgroups of patients at higher risk to develop mCRC, and in whom closer surveillance is beneficial.

Overall, 1.8% of all CRC patients diagnosed in this study developed mCRC, a proportion comparable with that described by others.[13,19,20,49] No significant differences were found between the university and non-university hospitals in this respect, albeit a slightly higher overall rate of mCRC was noted in the university hospital (2.3% vs. 1.6% and 1.7%). This may be explained by the fact that the university hospital also acts as referral center, with potentially more complex pathology. The comparable rates of mCRCs across the three hospitals most probably reflect the similarities with regard to

infrastructure, surveillance protocols, and the ongoing educational exchanges. Of note, we observed differences between the university and non-university hospitals with regard to the potential etiologic factors for mCRCs: non-adherence to surveillance was the most common explanation for mCRCs in the non-university hospitals, while missed lesions in the university hospital. Again, differences in the specialty of the endoscopists (e.g. gastroenterologists versus colorectal surgeons) responsible for the colonoscopic surveillance of the post-CRC resection patients could partially explain such observations. For example, more difficult CRC cases owing to comorbidities or complicated primary CRC resection likely underwent surveillance in the university center. Circumstances such as comorbidity or complicated primary CRC resection could be associated with poor bowel preparation and a greater likelihood to miss lesions. Non-gastroenterologists who performed a significant proportion of surveillance colonoscopies in the university hospital could be also less experienced in the detection and resection of flat lesions and might have overlooked them. Presently, the colonoscopic surveillance after CRC resection at the university hospital is under the responsibility of gastroenterologists.

Strengths of this study include the population-based setting and the use of clinical records in conjunction with a validated nationwide cancer registry.[25] The population is well characterized and reconstructs the real-world scenario in a large gastrointestinal endoscopy practice. We attempted to disentangle the etiologic factors implicated in the occurrence of each mCRC case by applying a structured algorithm which was previously employed for the evaluation of postcolonoscopy CRCs.[21,22] In doing so, we aimed to establish potential improvements in the post-CRC resection surveillance practice. Several limitations need, however, to be acknowledged: this is a retrospective evaluation of clinical data. Hence, the results are dependent on the reliability of data registration across the study period and some cases of mCRC could have been missed when diagnosed in other hospitals, in case of relocation or death. Asymptomatic *mCRC* cases, who were not yet diagnosed before December 31, 2010, were not captured in our study. As this also applies to the asymptomatic cases of solitary CRC it is unlikely that the overall rate of mCRCs (1.8%) or the ascribed etiology would be significantly altered. We applied the same length of time of retrospective observation (from birth to CRC diagnosis) to all 5,157 CRC patients included, which further strengthens our data. Furthermore, validated national registries (e.g. the pathology database and Netherlands Cancer Registry) were used, and given the low migration rate of the population in South-Limburg, it is, again, unlikely that missed cases could significantly change the outcomes and conclusions of our study.[25-27] In 18% of mCRCs, the cancers were diagnosed during the first surveillance colonoscopy after the primary CRC diagnosis, synchronous CRC cannot be ruled out.[38] By using the Moertel criteria for defining mCRC,[28] the proportion of mCRCs in our study is however comparable with previous data.[5,19,20,28] We also acknowledge that information on the quality indicators such as the adenoma detection rate, cecal intubation rate and withdrawal time at individual endoscopist level was not available. This would be of additional value for the evaluation of mCRC occurrence, as studies demonstrated an association between the individual endoscopist performance

and the occurrence of postcolonoscopy CRC.[32,44,50] Last, our study did not specifically address the biologic features of mCRCs. Such information, in particular on the potential involvement of the serrated neoplastic pathway might be beneficial to identify subgroups of patients at higher risk for CRC.

The results of this study indicate that improvements are required in both university and non-university endoscopy practice, to maximize the effectiveness of post-CRC surveillance by colonoscopy. Performance by experienced gastroenterologists, who are proficient in the detection and endoscopic resection techniques of colorectal neoplasms, is a key factor. As missed lesions and the non-compliance to surveillance equally contribute to both early and late mCRCs, current guidelines should not only focus on the *frequency* of colonoscopic surveillance, but also the *quality* of examination. Studies on the effectiveness of post-CRC colonoscopic surveillance need to monitor and report on quality indicators (e.g. completeness of colonoscopy, adenoma detection rate, bowel preparation). Potential benefits of including image-enhanced endoscopy techniques in patients after CRC resection need further evaluation. Automatic personal invitation systems may help to secure the adherence to surveillance recommendations.

In conclusion, in this population-based study including 5,157 CRC patients, and which spanned a 10 year period, we found that metachronous CRCs accounted for 1.8% of all CRCs identified. Missed lesions and non-adherence to the advised surveillance intervals were the most likely explanations for the occurrence of mCRCs. Gastrointestinal societies guidelines need to consider both the frequency and quality of colonoscopic examination when advising on surveillance intervals after CRC resection.

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Supplementary figures

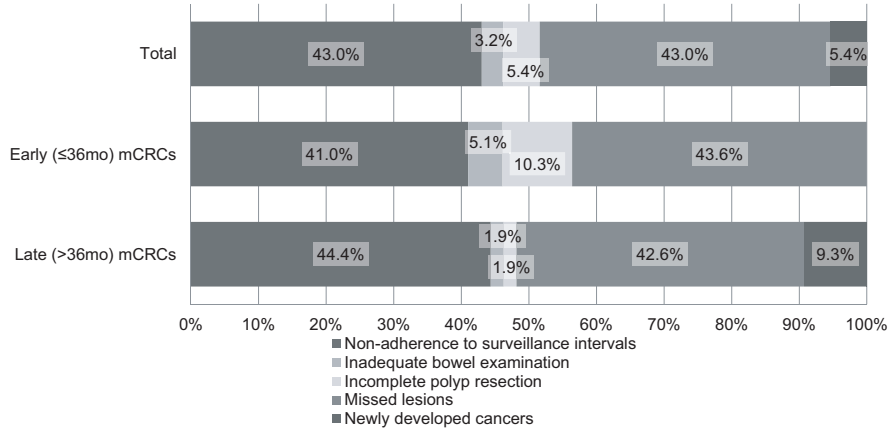

Figure S4.1 Potential etiologic factors of early vs. late metachronous CRCs in the studied population

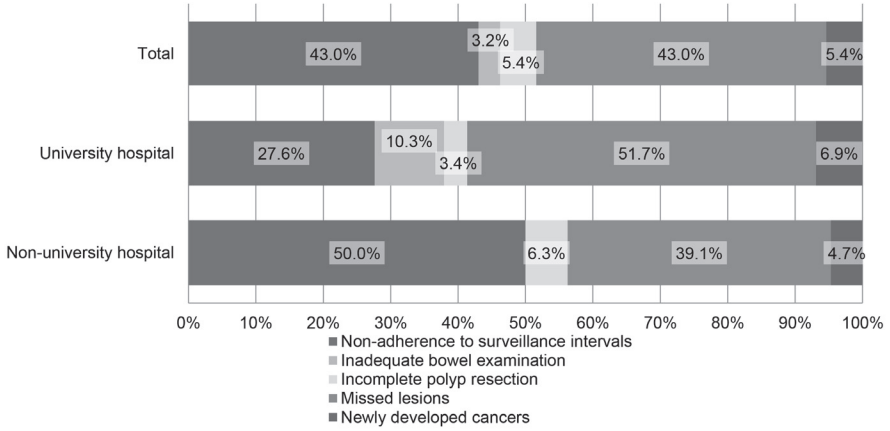

Figure S4.2 Potential etiologic factors of metachronous CRCs in the studied population

5

Definition and taxonomy of interval colorectal cancers: a proposal for standardizing nomenclature

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Abstract

Objective

Interval colorectal cancers, i.e. cancers occurring after a negative screening test or examination, are an important indicator of the quality and effectiveness of colorectal cancer (CRC) screening and surveillance. In order to compare incidence rates of interval CRCs across screening programs, a standardized definition is required. Our goal was to develop an internationally applicable definition and taxonomy for reporting on *interval CRCs*.

Design

Using a modified Delphi process to achieve consensus, the Expert Working Group on *interval CRC* of the Colorectal Cancer Screening Committee of the World Endoscopy Organization developed a nomenclature for defining and characterizing interval CRCs.

Results

We define an *interval CRC* as a 'colorectal cancer diagnosed after a screening or surveillance exam in which no cancer is detected, and before the date of the next recommended exam'. Guidelines and principles for describing and reporting on interval CRCs are provided and clinical scenarios to demonstrate the practical application of the nomenclature are presented.

Conclusions

The Working Group on *interval CRC* of the World Endoscopy Organization endorses adoption of this standardized nomenclature. A standardized nomenclature will facilitate benchmarking and comparison of interval CRC rates across programs and regions.

Introduction

As evidence accumulates demonstrating the effectiveness of colorectal cancer (CRC) screening[1-7] and population screening is increasingly adopted as a public health initiative worldwide, interest in *interval CRCs,* or cancers occurring after a negative screening or surveillance exam is growing. While no screening test will ever be perfect, the frequency of failures is a marker of the quality and effectiveness of a screening program. Minimizing the occurrence of interval CRCs is important for assuring the *quality* of a screening program. Better measurement of interval CRCs will enable screening programs to identify performance gaps that can be addressed to improve effectiveness.

Although observational studies indicate that colonoscopy and polypectomy are associated with a reduction in the incidence of[8-10] and mortality from[10-12] CRC, there is a large operator-dependent variability in the quality of examinations,[13-16] which likely contributes to variable effectiveness of colonoscopy, especially in the proximal colon.[17-19] Likewise, the sensitivity and specificity of fecal tests in detecting colorectal neoplasms vary.[20] In order to compare the effectiveness of programs and tests, a standard definition for quality measures such as interval CRCs is needed. For example, reports on interval CRC have included in their definition cancer diagnosed from <3 years, to <5 years, to <10 years to an unlimited time after index colonoscopy.[21-24] Lack of consistency in the definition of interval CRC precludes meaningful comparisons across studies and programs, and hinders progress towards understanding and addressing their causes.

The Expert Working Group on *interval CRC* of the Colorectal Cancer Screening Committee of the World Endoscopy Organization reviewed the previously used definitions of interval CRCs with the goal of developing a nomenclature for defining interval CRCs, to facilitate benchmarking and comparison of interval CRC rates across studies and programs internationally. Our goal was to develop a definition that could be applied after screening or surveillance exams. Using a modified Delphi process to develop and achieve consensus, we offer a standardized nomenclature for interval CRCs, and a practical guideline for determining and reporting on interval CRCs.

Methods

Membership of the Consensus Panel

Criteria for eligibility to the Consensus Panel were: (1) demonstrated knowledge/ expertise by previous or current research on *interval CRCs*, peer-reviewed publications in the field or participation in national or regional guideline development; (2) wide geographical representation (including Europe, North America, Australia); (3) diversity of training expertise (including gastroenterology, pathology, epidemiology, and public health). The Consensus Panel comprised 8 members, who were identified by the World Endoscopy Organization (WEO) chairs through invitation.

Literature review

We conducted an electronic search on PubMed and Cochrane databases using the following keywords: Colorectal Neoplasms [Mesh]; colorectal cancer; colorectal cancer screening; interval colorectal cancer; post colonoscopy colorectal cancer; fecal immunochemical test; FIT; guaiac fecal occult blood test; gFOBT; FOBT; fecal occult blood test; stool test; Colonoscopy [Mesh]; colonoscopy; negative colonoscopy; Sigmoidoscopy [Mesh]; sigmoidoscopy; negative sigmoidoscopy. Searches were limited to English language articles published in the preceding 10 years (from January 2004 to January 2014). Relevant studies included those in which identification of interval CRCs and estimation of rates were primary or secondary goals. We also reviewed original studies on the effectiveness of screening (with any test modality) in reducing the incidence of CRC. We obtained information on interval CRCs from national and regional CRC surveillance guidelines.[25-31] To maximize the output of our search, we retrieved additional articles extracted from the reference list of the reviewed articles. We examined the effect of the definition used for an interval CRC, after screening or surveillance exams, on the estimated rates of these outcomes. Secondary goals were to identify salient features of interval CRCs (e.g. time to diagnosis, anatomic location, cancer stage at diagnosis and histology), as well as their putative etiology (e.g. missed, incompletely resected polyps or biologic factors associated with a more rapid progression). We excluded studies in persons with hereditary CRC syndromes or inflammatory bowel disease.

Modified Delphi process

To develop and achieve consensus on a standardized nomenclature for *interval CRCs*, the Consensus Panel used a modified Delphi process.[32] The Delphi process encompasses a stepwise approach, including: (1) summarizing the literature and rating the quality of evidence; (2) developing consensus statements; (3) achieving consensus through in-depth discussions and subsequent voting. After a systematic literature review by two of the authors (SS, ClC), narrative summaries were circulated to the members of the Consensus Panel and frank discussion and debate were encouraged. During four meetings (Digestive Disease Week 2013, May 2013, Orlando, FL; World Congress of Gastroenterology 2013, Sept 2013, Shanghai; United European Gastroenterology Week 2013, Sept 2013, Berlin; and the Digestive Disease Week 2014, May 2014, Chicago, IL) and nine teleconferences, the Consensus Panel analyzed and rated the evidence. An analytic, case-based approach was used to maximize participation and provide a framework for developing the nomenclature. Subsequently, two of the authors (SS, RES) drafted a list of statements and circulated it electronically. In total, three sets of consensus statements were defined: The first set (statements 1 to 10) aimed to ensure consistency regarding knowledge and view about the current literature in particular the definitions employed for interval CRCs, study methodology, incidence rates, and the potential etiologic factors. For each statement, a summary of the current evidence, rating

according to the GRADE methodology[33] and discussion of the areas of uncertainty and controversy were included. A second set (statements 11 to 16) aimed to define criteria for standardizing the nomenclature. The third set (validation set) tested the level of agreement between the Consensus Panel members on the nomenclature, in a series of 12 clinical examples. Each member was asked to consider the evidence to support or refute the statements and to rate it on a Likert scale ranging from 1 to 5: (1), accept completely; (2), accept with minor reservation; (3), accept with major reservation; (4), reject with reservation; and (5), reject completely. The first vote was conducted electronically and simultaneously for the entire Consensus Panel, without explanation or justification of each statement. Feedback was then obtained from all members. The results and the comments were subsequently evaluated by two authors (SS, RES). Consensus was considered to be achieved when >80% of the voting members indicated "accept completely" or "accept with reservation", and refuted when >80% of the voting members indicated "reject completely" or "reject with reservation". Finally, a teleconference was organized to review the evidence with respect to each statement that reached consensus and discuss again those statements that did not reach consensus on the first voting. A second vote was held following the teleconference. All members of the consensus process were given ample opportunity for input into the final wording of the consensus document. The final document was peer reviewed by the WEO Chairs and approved, in accordance with the WEO Publication Policy.

Results

Literature review on interval CRCs

The membership of the Consensus Panel agreed that the nomenclature currently employed for interval CRCs varies considerably, hindering comparison across studies. Supplementary Table S5.1 presents the consensus statements and the corresponding levels of evidence and agreement between the Panel members. In this section, we detail the definitions used and their effect on interval CRC rates.

Interval CRC after a colonoscopy

In 1997, Haseman *et al.*[34] described a series of 47 cases of CRC diagnosed within 3 years after a colonoscopy; 27 of them were considered missed cancers, while 20 cases were likely the result of an incomplete colonoscopy. Performance of colonoscopy by a non-gastroenterologist was associated with greater odds for an interval cancer (OR 5.46, 95% CI 2.94-9.77). Since then, gastroenterology specialists around the world have extensively addressed the magnitude of this problem and its putative explanations. In Tables 5.1a and 5.1b key studies estimating rates of interval CRC after colonoscopy in different populations are summarized.

The members of the Consensus Panel acknowledged striking differences in the definition of an interval CRC: in particular the minimum time elapsed from the baseline

colonoscopy to diagnosis of an interval cancer ranged from 6 to 60 months in the majority of studies,[11,17,18,35-41] but exceeded 10 years in others.[24,42] For example, in a study by Bressler *et al.* in Ontario, Canada, the overall proportion of interval CRCs after colonoscopy was 3.4% when including cancers diagnosed within a 3-year interval of a negative exam versus 4.6% when extending the interval to 5 years.[17] Epidemiologic models indicate the 'mean sojourn time' for cancer (e.g, the estimated interval between the asymptomatic (screening) and the symptomatic phase) may be longer than previously assumed, ranging from 4.5 to 5.8 years.[43] A time cut-off of three years may underestimate the proportion of interval CRCs. A 3-year cut-off will likely capture interval CRCs after missed lesions, but may miss those due to slower growing precursor lesions.[39,44,45]

As detailed in Tables 5.1a and 5.1b, the reported *proportions of interval CRC vary* greatly, ranging from 0.8% of colonoscopic examinations[46] to up to 9% of all diagnosed CRCs.[19] However, the number of interval CRCs/number of colonoscopic examinations performed is not comparable to number of interval CRCs/total number of CRCs. Studies from Ontario and Manitoba, employing claims-based administrative data, found that proportions of interval CRC within three years after prior colonoscopy ranged from 3.4% to 9.0%.[17-19,47]These studies could not include details on the quality of the baseline colonoscopy, such as cecal intubation rate or adenoma detection rate (ADR). In a Polish colonoscopy-based screening program, Kaminski *et al.* found a rate of 42 interval CRCs among 45,026 subjects during 188,788 patient-years of follow-up.[48] Endoscopists' adenoma detection rate was significantly associated with the risk of interval CRC (Hazard Ratio: 12.5, 95% CI: 1.5-103.4 for ADR of 15.0% to 19.9% versus ≥20%, p=0.02). Endoscopists who performed a lower number of colonoscopies were excluded, which may underestimate the total number of interval CRCs in the population. In a recent study, using data from an integrated health care delivery system in the USA, the adenoma detection rate was inversely associated with the risks of interval CRC, advanced-stage interval CRC, and fatal interval CRC.[49]

The Consensus Panel also agreed there was a wide variation in the methodological evaluation of interval CRCs across studies, including retrospective,[17,23,36,37,48,50-52] prospective,[21,22,38,40,44,53,54] programmatic versus opportunistic screening, use of claims-based administrative data[18,22,36,45,47] versus clinical records,[23,24,37,39,42] as well as differences in study populations (age-group included and proportion of men, inclusion of average- versus higher-risk groups; and screening versus surveillance settings). Methodological variation likely influenced the reported proportions of interval CRCs. For example, the study by Kaminski *et al.* included persons aged 40 to 66 years, 35.7% of whom were men. The study by Singh *et al.* included persons aged 50 to 80 years, 57.5% of whom were men.[18,48] As CRC is associated with older age and male sex, inclusion of a significant proportion of younger women would reduce interval CRC rates. Rigorous documentation of the clinical characteristics of the included populations is important for comparisons of interval CRC rates across studies.

Table 5.1a Overview of studies on interval CRCs after colonoscopy in asymptomatic populations, showing that variation in the definitions used for an interval CRC affects the estimated rates

Studies	Definition iCRC	Design	Outcomes	Stage of CRC I-II vs. III-IV	Location of CRC Prox vs. dist	Risk factors/possible etiology
Brenner[24] 2012 **Germany**	1-10 yrs after negative colonoscopy	Population-based; 1,945 CRC cases; 2,399 controls	433 screen detected vs. 78 iCRCs	Screen detected: 282 vs. 149 iCRCs: 39 vs. 39	Screen detected: 167 vs. 243 iCRC 44 vs. 32	Predictors of iCRCs
Strock[23] 2011 **Luxembourg**	All CRCs after index colonoscopy	Retrospective; 8,950 pts after screening CS	19 iCRCs in 47,725 person-years follow-up	Not specified	iCRC: 6 vs. 13	N/A
Kaminski[48] 2010 **Poland**	CRC diagnosed between screening and surveillance examination	Retrospective; 45,026 pts in colonoscopy screening program	CRC incidence; 42 iCRCs in 188,788 person-years of follow-up	Not specified	iCRC: 12 vs. 25	Association ADR of individual endoscopists
Matsuda[22] 2009 **Japan**	<36 mo	Observational; cohort study; NPS; 5,309 pts	Incidence of advanced neoplasms after CS: 13 iCRCs within 3 yrs	iCRC: 12 vs. 1	iCRC: 5 vs. 8	Macroscopic appearance (5 depressed, 2 flat)
Kahi[51] 2009 **USA**	Not defined	Retrospective; screening cohort of 715 patients vs. SEER data	5 screen detected; 7 iCRCs in 10,492 person-years follow-up	Screen detected 5 vs. 0 iCRC: 4 vs. 3	Screen detected 2 vs. 3 iCRC: 6 vs. 1	N/A
Lieberman[21] 2007 **USA**	<5yrs after screening colonoscopy	Prospective; 3,121 screenees	1.7 per 1,000 person-years follow-up	iCRC: 10 vs. 4	iCRC: 7 vs. 7	N/A

CRC, colorectal cancer; iCRC, interval CRC; ADR, adenoma detection rate; N/A, not applicable

Table 5.1b Overview of studies on interval CRCs after colonoscopy in a mix of symptomatic and asymptomatic populations, showing that variation in the definitions used for an interval CRC influences the estimated rates

Studies	Definition iCRC	Design	Outcomes	Stage of CRC I-II vs. III-IV	Location of CRC Prox vs. dist	Risk factors/possible etiology
Corley[49] 2014 USA	6mo-10 yrs after colonoscopy	Retrospective, population-based, 314,872 colonoscopies 712 pts with iCRC	712 iCRC in 927,523 person-years FU; 8.2% of all CRCs were iCRCs	iCRCs: 457 vs. 255	iCRC: 427 vs. 267 (18 unknown)	Inverse association between ADR and risk of iCRC, advanced iCRC and fatal iCRC
le Clercq[39] 2014 The Netherlands	< 5yrs	Retrospective, population-based, 5107 pts with CRC	147/5,107 = 2.9% iCRCs	Sporadic CRC: 2,499 vs. 2,531 iCRC: 79 vs. 63	Sporadic CRC: 1,634 vs. 3,522 iCRC: 87 vs. 59	Predictors of iCRCs
Erichsen[42] 2013 Denmark	1-5yrs	Retrospective, 982 pts with iCRC vs. 358 pts with colo>10yrs vs. 35,704 pts with sporadic CRCs	982/38064 = 2.6% iCRCs	Sporadic CRC: 12,995 vs. 17,982 iCRC: 377 vs. 414	Sporadic CRC: 9,782 vs. 23,979 iCRC: 441 vs. 433	Predictors of iCRCs
Cooper[36] 2012 USA	6-36 mo	Retrospective; SEER-Medicare database with 57,839 CRC patients	7.2% had prior colo 53,647 detected CRC 4192 iCRCs	Screen detected: 29172 vs. 18,778 iCRCs: 2,444 vs. 1291	Screen detected: 25,870 vs. 17,921 iCRC: 2,851 vs. 819	N/A
Huang[38] 2012 China	<5 yrs	1,764 pts with adenomas under surveillance	14/1,794 iCRCs= 0.78% = 2.9 cases per 1,000 person-years follow-up	iCRCs: 9 vs. 4	iCRC: 11 vs. 3	Possible etiology
Horiuchi[40] 2011 Japan	<60mo after negative colo	Prospective FU cohort of 3,212 pts with negative CS	9 iCRCs within 5 yrs	iCRC: 7 vs. 2	iCRC: 6 vs. 3	N/A
Baxter[19] 2011 Canada	7- 36 mo	Observational study of 14,064 CRC patients	Incidence iCRC: 9.0% of all diagnosed CRCs	Not specified	iCRC: 676 vs. 584	N/A
Leung[54] 2010 USA	Average 41 mo; range 11-83 mo	Prospective; Continued Follow-up Study (PPT)	9 CRCs over 7,626 person-years observation (1.2/1,000 PYO)	iCRC: 7 vs. 2	iCRC: 8 vs. 1	Risk factors and possible etiology
Ferrández[52] 2010 Spain	<36 mo	Retrospective; 16,866 colonoscopy reports	386 CRC pts of whom 27 (7.0%) had prior CS	Not specified	iCRC: 6 vs. 21	N/A
Singh[18] 2010 Canada	6-36 mo	Population based study of 4,883 CRC patients	Incidence of iCRC: 388 (7.9%) had prior CS	iCRC 70 vs. 67	iCRC: 225 vs. 147	Risk factors

Table 5.1b (continued)

Studies	Definition iCRC	Design	Outcomes	Stage of CRC I-II vs. III-IV	Location of CRC Prox vs. dist	Risk factors/possible etiology
Lakoff[47] 2008 Canada	>6 mo	110,402 pts with neg colo; 14 yr FU Control: general population	1,461 iCRCs 1.3% (n=1,461) of cohort-patients develop CRC vs. 2.2% of controls	Not specified	Controls: 19,056 vs. 33,195 iCRC: 610 vs. 443	N/A
Imperiale[68] 2008 USA	<5 yrs	2,436 with negative CS, 5 yr FU	No iCRCs diagnosed	N/A	N/A	N/A
Bressler[17] 2007 Canada	6-36 mo	Retrospective. Claims-based administrative data; 31,074 CRC patients	12,487 had prior colo Detected: 12,057 New/missed: 3.4% (n=430)	Not specified	Detected: 3,827 vs. 8,422 New/missed: 238 vs. 192	Risk factors
Farrar[37] 2006 USA	<60 mo	Retrospective; 830 CRC pts; 45 iCRCs vs. 90 sporadic CRCs	iCRC incidence: 5.4% of all diagnosed CRCs	Sporadic: 52 vs. 38 iCRC: 30 vs. 15	Sporadic: 26 vs. 64 iCRC: 23 vs. 22	Possible etiology
Pabby[44] 2005 USA	CRC detected during surveillance at year 1 or year 4	Prospective; 2,079 pts with 5,810 PY of observation (PPT)	13 iCRC cases (2.2/1,000 person-yrs observation)	iCRC: 8 vs. 5	iCRC: 7 vs. 6	Possible etiology
Robertson[53] 2005 USA	Any cancer diagnosed after a clearing colonoscopy	Prospective; 2,915 pts, mean FU: 3.7yrs (3 chemoprevention trials)	19 CRCs in 2,915; 1.74/1,000 incidence.	iCRC 16 vs. 3	iCRC 10 vs. 9	Possible etiology
Leaper[50] 2004 New Zealand	>6wks	Retrospective; pts undergoing CS	17 of 286 (5.9%) were missed by CS	iCRC: 10 vs. 7	iCRC 13 vs. 4	Possible etiology

CRC, colorectal cancer; iCRC, interval CRC; N/A, not applicable

Only a few investigators have examined predictors of interval CRCs, such as endoscopists' specialty,[17,18,48] hospital vs. non-hospital setting,[17] or a family history of CRC.[9,54] Few applied a structured algorithm to estimate the underlying etiology.[38,44] In a study of 2079 subjects enrolled in a polyp prevention trial, Pabby *et al.*[44] sought to estimate the proportion of interval CRCs due to procedural factors versus aggressive tumor biology. Using an algorithm, the authors estimated that 13 persons in 5810 person-years of follow-up developed interval CRCs, with 54% (n=7) being "avoidable" (3 missed and 4 incompletely resected polyps). Others found that *procedural factors* (e.g. incomplete colonoscopy, suboptimal bowel preparation, missed or incompletely resected lesions) could have made an even greater contribution to the occurrence of interval CRC (71% to 86%).[38,39,45] Missed lesions, which may explain over 50% of interval CRCs.[38,39,45] are difficult to distinguish from newly developed CRCs, since classification and distinction rely on assumptions regarding the 'mean sojourn time'[44] of adenomas evolving into cancer. Describing a cancer as missed is impossible to prove, since it is impossible to prove a precursor lesion was present when it was not initially detected. Studies examining the molecular characteristics of interval CRCs, such as those demonstrating higher rates of microsatellite instability and CpG island methylator phenotype (CIMP)-high status[10,55,56] may help to improve classification of interval CRCs by better defining the biological characteristics of tumors more likely to rapidly progress.

Few studies contain details about the process for interval CRC identification and the method used for estimating rates. For example, in the study by Farrar *et al.*,[37] the proportion of interval CRC was calculated as follows: *Proportion of interval CRC* = (Number of persons with CRC who had a previous colonoscopy 6-60 months prior to CRC diagnosis) / (Total number of persons with CRC identified), resulting in a proportion of 5.4%. Other authors[17,18,36] used a different approach: *Proportion of interval CRC* = (Number of persons with CRC who had a previous colonoscopy 6-36 months prior to CRC diagnosis) / (Total number of persons with CRC identified), resulting in proportions of 3.4%,[17] 5.4%,[18] and 7.2%, respectively.[36] The time cut-off in including a cancer as an interval CRC affects the overall proportion. If the cut-off had been 3 months instead of 6 months, or if diagnoses up to 60 months were included, the final proportions would have been altered.

Interval CRCs after flexible sigmoidoscopy (FS)

There is a wide variation in the definition of an interval CRC after a FS, as detailed in Table 5.2. Although 4 high-quality randomized controlled trials of FS are available,[4,5,57,58] definitions of interval CRC after FS lack uniformity and the estimated rates are again not comparable.

FS-based screening, with subsequent colonoscopy in case of a positive examination, is associated with incidence rates of interval CRCs ranging from 0.3 to 0.9 per 1000 FS exams, corresponding to higher and lower rates of adenoma detection, respectively.[59] Others have reported crude numbers of interval CRCs.[5,57,58]

Table 5.2 Overview of studies on interval CRCs after flexible sigmoidoscopy (FS)

Studies	Definition iCRC	Design	Outcomes	Stage of CRC I-II vs. III-IV	Location of CRC proximal vs. distal	Risk factors/ possible etiology
Schoen 2012[58] USA	Screen detected: <12mo of positive FSG; Not detectable: stage I-II and >30 mo; or stage III-IV >48 mo; Prevalent nondetected: stage I-II detected <30 mo or stage III-IV <48 mo	PLCO multicenter trial; 77,447 intervention group	CRC Incidence 977 CRCs: 243 screen detected 470 not detectable 264 prevalent nondetected	Screen detected: 184 vs. 59 Prevalent not detected: 95 vs. 169 Not detectable: 256 vs. 214	Screen detected: 46 vs. 197 Prevalent not detected: 171 vs. 93 Not detectable: 310 vs. 158	Possible etiology
Segnan 2011[5] Italy	Not specifically detailed	RCT; 17,136 intervention group of which 9,911 attenders; 17,136 controls	CRC incidence and mortality Intervention group: 251 CRCs Controls: 306 CRCs	Screen detected: 78 vs. 48; Not screened: 61 vs. 64; Control: 154 vs. 152	Screen detected: 55 vs. 71; Not screened: 44 vs. 81; Control: 108 vs. 198	N/A
Atkin 2010[4] UK	Not specifically detailed	Multicenter RCT; screening cohort; 40.674 intervention group, vs. 113.195 control group	CRC Incidence and mortality Intervention group: 706 CRCs; Controls 1,818 CRCs	Not specified	Intervention: 311 vs. 386; Controls: 628 vs. 1192	N/A
Hoff 2009[57] Norway	Post-screen detected CRCs	RCT screening cohort; 13,653 screened vs. 41,092 controls	CRC incidence: 33 screen detected CRC; 38 post screen detected CRC; 52 non-attenders; 362 controls	Screen detected: 20 vs. 11; Post screen detected: 6 vs. 29; Non-attenders: 7 vs. 38; controls: 62 vs. 262	Screen detected: 9 vs. 24; Post screen detected 27 vs.11; controls: 145 vs. 217	N/A

CRC, colorectal cancer; iCRC, interval CRC; N/A, not applicable ; PLCO, Prostate, Lung, Colorectal, and Ovarian trial

Analyses on the etiology of interval CRCs are few.[58,59] In the Prostate, Lung, Colorectal, and Ovarian (PLCO) FS Trial, the authors classified CRCs into three categories: 1) *screen-detected* (within 12 months of a positive finding on FS); 2) *not detectable* (early-stage CRCs identified >30 months or advanced CRCs identified >48 months after a negative screening FS); or 3) *prevalent, not-detected* (early-stage CRCs identified <30 months and advanced CRCs identified <48 months after a negative screening FS). Over 11 years of follow up, the proportion of screen-detected, not detectable, and prevalent not-detected CRC was 24.9%, 48.1% and 27.0%, respectively.[58] Among prevalent not detected lesions, 35.6% were attributed to patient non-compliance, 43.9% to the limitations of FS relative to colonoscopy, and 20.5% (n=54) to missed lesions.

Interval CRC after a fecal test

Unlike interval CRCs after endoscopic examination, there is greater uniformity in the definition of an interval CRC after fecal testing (Table 5.3). The most common definition used was "CRC detected after a negative fecal occult blood screening test and before the next invitation is due". However, the studies used various tests (gFOBT vs. FIT), at different frequency (yearly or biennially) and at different cut-off concentrations for a positive fecal occult blood test, in diverse populations. Lack of standardization in the reporting units for FIT (e.g. micrograms of hemoglobin per gram of feces) may have also contributed to differing results.[60] Only a few studies have examined *interval CRCs* after multiple rounds of fecal occult blood testing.[61-63]

In a study of 3616 screening participants,[62] the authors found that 10 of a total of 39 CRCs (25.6%) identified after two rounds of fecal testing were interval CRCs: nine following a negative FIT or gFOBT and one following a negative colonoscopy. In an evaluation of the National Health Service Bowel Cancer Screening Programme in England, in 534,411 participants, 192 of 1336 CRCs (14.4%) identified were interval CRCs, all of them following a negative gFOBT.[64]

Proposed nomenclature for interval CRCs

Following a critical appraisal of the literature, the Consensus Panel defined key principles for creating a standardized nomenclature. A substantial agreement was achieved between the Panel members with regard to the definition and classification of *interval CRCs*, as detailed in Supplementary Table S5.1.

Table 5.3 Overview of studies on interval CRCs after fecal testing

Studies	Definition iCRC	Study population/ design	Outcomes/ Results	Stage of CRC (I-II vs. III-IV)	Location of CRC (proximal vs. distal)	Predictors /possible etiology
***van Roon[63] 2013 The Netherlands FIT**	After negative FIT/gFOBT/colo, but within screen interval	Average-risk screening population	29 screen-detected 3 iCRC	Screen detected: 23 vs. 6 iCRC 2 vs. 1	Not described	Yes, limited
Denters 2012[62] The Netherlands gFOBT/FIT	After negative FIT/gFOBT, but within screen interval	3616 subjects average-risk screening population	29 screen detected (20 1st round;9 2nd round); 10 iCRCs	Screen detected 18 vs. 11 iCRCs: 5 vs. 5	Screen detected 9 vs. 20 iCRCs: 3 vs. 7	N/A
Scholefield 2012[69] UK gFOBT	Between screening rounds	RCT, 153,850 subjects, screening population	236 screen detected; 173 iCRCs <2yrs	Screen detected 168 vs.68 iCRCs: 78 vs. 94	Not described	N/A
Gill 2012[64] UK gFOBT	After a negative FOBT or screening colo and before next invitation	Prospective; 1336 CRC pts Screening population	322 screen-detected; 192 interval; 311 non-uptake (declined screening); 511 control (diagnosed before screening)	Screen detected: 206 vs. 110 iCRC: 87 vs. 100 non-uptake: 130 vs. 167 control: 221 vs. 275	Screen detected: 69 vs. 253 iCRC: 64 vs. 128 non-uptake: 106 vs. 205 control:153 vs. 358	N/A
Crotta 2012[70] Italy FIT	<2 yrs after negative FIT	2959 pts; screening population	8 screen detected; 5 iCRCs	Screen detected: 4 vs. 4 iCRCs: 1 vs. 4	Not described	Yes, limited
de Wijkerslooth 2012[71] The Netherlands FIT	After negative FIT but within screening interval	1,256 average-risk pts; screening population	7 screen detected 1 iCRC	Screen detected: 6 vs. 1 iCRC 1 early.	Screen detected: 2 vs. 5 iCRC: 1 distal.	N/A
Morris 2012[72] UK FOBT	After a negative screening test and before next invitation	76,943 CRC pts (retrospective)	2213 screen-detected; 623 iCRC; 1760 non-uptake; 72437 controls	Screen detected: 1131 vs. 992 iCRC: 211 vs. 412 Non-uptake: 577 vs. 1183; Controls: 24706 vs. 29320	Screen detected: 416 vs. 1628 iCRC: 223 vs. 352 Non-uptake: 518 vs. 1103; Controls: 21779 vs. 43871	N/A
Rozen 2012[73] Israel FIT	Not clearly described	1,630 subjects; screening population	20 screen-detected 5 during FU	Overall, 18 vs. 7	Overall, 10 vs. 15	Yes

Table 5.3 (continued)

Author/ Year/ Country	Definition iCRC	Study population/ design	Outcomes/ Results	Stage of CRC (I-II vs. III-IV)	Location of CRC (proximal vs. distal)	Predictors /possible etiology
Steele 2012[61] **UK** **gFOBT**	<2 yrs after neg gFOBT Missed cancer: <2 yrs after neg colo following pos FOBT	304,245 subjects invited for screening	1st round: 351 screen-detected; 193 iCRC; 2 missed; 2nd round: 208/213/4; 3rd round: 139/229/2	Screen detected: 462 vs. 201 iCRC 252 vs. 279	Screen detected: 136 vs. 506 iCRC 201 vs. 422	N/A
***Levi 2011[74]** **Israel** **FIT vs. gFOBT**	Missed cancer: CRC not detected by FIT/gFOBT	Group A, FIT, 1,224 subjects Group B, gFOBT, 2,266 subjects	FIT, 6 gFOBT, 8 iCRC, 5	Not specified	FIT: 3 vs. 3 gFOBT: 3 vs. 5 iCRC: 2 vs. 3	N/A
Zorzi 2011[75] **Italy** **FIT**	After a negative screening test and before next invitation	267,789 pts with negative screening exam	Screen detected: 748 iCRCs: 126	iCRC: 37 vs. 48	iCRC: 37% vs. 64%	Yes
***Lisi 2010[76]** **Italy** **gFOBT vs. colo**	Not clearly described	Average-risk screening population gFOBT, 1,149 CS, 414	FOBT, 1 CS, 2	Not specified	Not specified	N/A
***Hol 2010[77]** **Netherlands** **gFOBT vs. FIT, vs. FS**	Not clearly described	Average-risk screening population 2351 gFOBT, 2,975 FIT, 1,386 FS	FOBT, 6 FIT, 14 FS, 8	FOBT: 3 vs. 3 FIT: 12 vs. 2 FS: 6 vs. 2	Not specified	N/A
Paimela 2010[78] **Finland** **gFOBT**	After negative gFOBT	52,998 screening participants vs. 53,002 controls	66 screen-detected; 35 iCRC; 27 non-uptake; 99 controls	Screen-detected: 34 vs. 32; iCRC: 14 vs. 21; non-uptake: 6 vs. 21; controls: 38 vs. 61	Screened: 36 vs. 84 Controls: 20 vs. 65	Yes, limited
Faivre 2004[79] **France** **gFOBT**	After negative gFOBT and before next invitation	91,199 screening participants vs. controls	196 screen-detected; 285 iCRC; 218 non-uptake; 696 control	Screen detected: 142 vs. 54; iCRC: 164 vs. 121; non-uptake: 107 vs. 111; Controls: 361 vs. 335	Not specified	N/A
Kronborg 2004[3] **Denmark** **gFOBT**	Within 2 yrs after negative FOBT	30,762 screening participants vs. 30,966 controls	199 screen-detected; 239 iCRC; 306 non-uptake; 874 controls	Screen detected: 72 vs. 127 iCRC: not specified controls: 99 vs. 775	Not specified	N/A

* Studies comparing different screening modalities. CRC, colorectal cancer; iCRC, interval CRC; gFOBT, guaiac-based fecal occult blood test, FIT, fecal immunologic test

Definition of an interval CRC

The Expert Working Group on *interval cancers* of the Colorectal Cancer Screening Committee, World Endoscopy Organization defines an interval CRC as a *'colorectal cancer diagnosed after a colorectal screening examination or test in which no cancer is detected, and before the date of the next recommended exam'.* This definition is derived from the IARC (International Agency for Research on Cancer) definition of interval cervical cancer, which is defined as an 'invasive cancer diagnosed in an attender after a negative screening; and before the next invitation to screening was due' (IARC Handbooks of Cancer Prevention; Cervix Cancer Screening).[65]

In the framework of an organized screening program, systematic reporting of: 1) S*creen-detected* CRCs, defined as cancers diagnosed *within* the screening program and, at a defined period after a positive screening test/examination; and 2) *Non-screen detected* CRCs, which can include *interval CRCs*, as defined above, and cancers in individuals who are not compliant with screening, is recommended (Figure 5.1).[66] *Interval CRCs*, by definition, do not apply to those who are not compliant with screening, since there can not be an interval CRC if the individual did not undergo initial testing. The proposed nomenclature applies to screening (with any modality) and colonoscopy surveillance. A CRC diagnosed during colonoscopy surveillance, but *before* the date of the next recommended exam will qualify as *interval CRC*. When the screening interval is not provided, standard intervals should be employed (such as 2 years for FIT/gFOBT, 5 years for FS and 10 years for CS). In the circumstance of a once only screening program, since no repeat exam is recommended, there is no opportunity for an interval cancer.

In order to apply the definition of an *interval CRC* in an organized, reproducible manner, the Consensus Panel recommends the following principles regarding classification:

1. Designation of the test/examination that preceded the diagnosis of cancer

Interval CRC rates should be reported with the designation of the test that preceded the subsequent diagnosis of cancer.

For example, within a FIT screening program: a CRC after a negative FIT screening test but before the next FIT is due, would be designated as a "FIT interval CRC". Likewise, within a colonoscopy (CS) screening program: a CRC after a negative screening CS but before the next recommended procedure would be designated as a "CS interval CRC".

2. Designation of the test/examination to which an interval CRC should be attributed

The screening test to which an interval CRC is attributed, should refer to the most recent, most comprehensive examination performed prior to cancer diagnosis. For example a cancer after a positive FIT screening test and a subsequent negative colonoscopy (but before the interval for the next FIT is due) would be considered a colonoscopy (CS) interval CRC and not a FIT interval CRC.

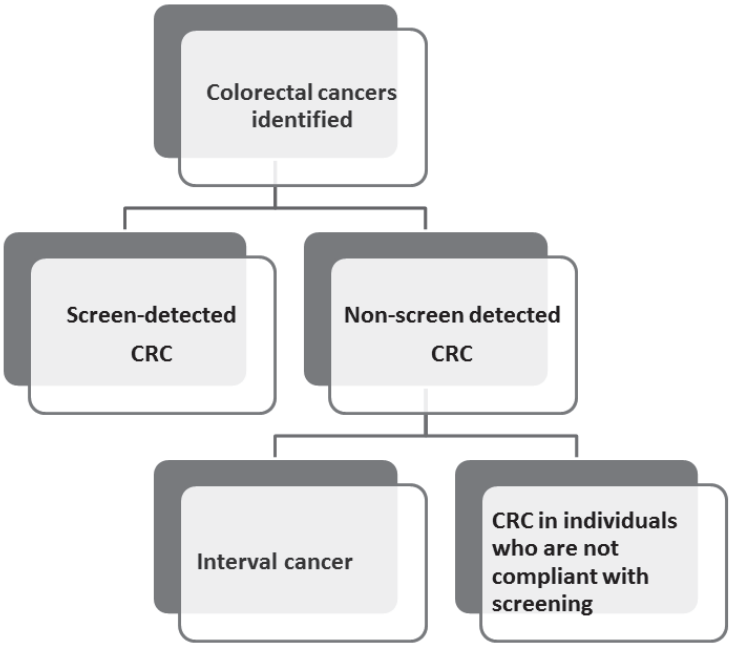

Figure 5.1 Proposed nomenclature for classification of CRCs. The nomenclature applies to screening (with any modality) and colonoscopy surveillance

3. Designation of the context in which the interval cancer arose

Screen-detected and non-screen detected cancers can be reported in the context of the program which led to diagnosis, e.g. FIT biennial screening, primary CS, or FS-screening. In the case from principle 2, though a CS interval cancer, the context was that of a program of FIT testing, so this cancer can be designated as a "CS interval cancer (within a FIT screening program)." In the case of a CS interval CRC, the context can be further described, such as an interval CRC within a screening program or following opportunistic screening.

4. Numeric calculation and reporting of interval CRC rates

Ideally, screen-detected and non-screen detected cancers should be reported as numbers per 100,000 person-years of observation.[44] This measure reflects the observed person time at risk and accounts for loss to follow-up. In contrast, reporting rates per 1000 persons invited to participate (intention-to-screen) may preclude accurate comparisons because of variability in participation. The European guideline for quality assurance in CRC screening and diagnosis[67] recently recommended a comprehensive approach to interval CRC rates calculation, adjusting for the CRC incidence in the background population, as well as age- and sex-specific variations.

5. Minimum data set

The Consensus Panel recommends inclusion of the following data for the documentation of interval CRCs: demographic features (age, sex) of the affected subject and the overall population, the indication for the procedure (e.g. screening, surveillance exam, or symptoms), the initial test employed (e.g. gFOBT, FIT, FS, CS), the context in which the test was performed (e.g. organized screening program versus opportunistic screening), the recommended surveillance interval (where applicable), the upper age limit for screening (where applicable), the time elapsed from the screening test to CRC diagnosis, and the location, the histopathology, and the cancer stage at diagnosis of the CRC. In the case of FIT screening, the test characteristics should be included, in particular the type of test (including type of buffer) and the analytic measurement device. If referring to a quantitative FIT device, the cut-off concentration for a positive test in microgram hemoglobin/gram feces should be included.

Practical application of the nomenclature

Table 5.4 shows examples of case scenarios with the attached *interval cancer* classification, to demonstrate the practical application of the nomenclature. Substantial agreement was obtained among the membership of the Consensus Panel when evaluating these cases. Supplementary Table S5.2 presents samples of minimum data sets corresponding to the previous clinical case scenarios.

Notable features of the proposed nomenclature should be acknowledged. First, the IARC definition of *interval cancers* has been extended to CRC arising during colonoscopy surveillance. To ensure consistency with the IARC nomenclature, the Consensus Panel restricted the definition to ‘invasive cancer’ and did not include advanced or non-advanced adenoma. Because there is international variation in the recommended timing of repeat screening and surveillance exams, the nomenclature preserved the term “recommended exam” in the definition.

Table 5.4 Case examples illustrating the practical applicability of the nomenclature

Case	Description	Nomenclature	Level of agreement
1	60 yr old female participates in a *biennial FIT* screening program. The first FIT screening episode is negative. The second FIT screening episode is negative. The third FIT screening episode is positive. Subsequent colonoscopy detects a CRC.	FIT screen-detected cancer	1=100%; 2=0%; 3=0%; 4=0%; 5=0%
2	57 yr old male participates in a *biennial FIT* screening program. The first FIT screening episode is negative. One year later, he develops rectal blood loss for which colonoscopy is performed showing a CRC in the rectosigmoid.	FIT interval cancer (*within* a FIT screening program)	1=100%; 2=0%; 3=0%; 4=0%; 5=0%
3	64 yr old male, participates in a *biennial FIT* screening program. The first FIT screening episode is positive. Colonoscopy shows no abnormalities. A recommendation is made to participate again in the FIT program, after 10 years. A colonoscopy performed 4 years later, due to rectal blood loss, reveals a cancer in the rectosigmoid colon.	CS interval cancer (*within* a FIT screening program)	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%
4	69 yr old male participates in a *primary colonoscopy* screening program. Baseline colonoscopy shows no abnormalities, and repeat screening colonoscopy is recommended after 10 years. However, 6 years later he undergoes colonoscopy due to a iron deficiency anemia, which reveals a cancer of the cecum.	CS interval cancer (*within* a CS screening program)	1=100%; 2=0%; 3=0%; 4=0%; 5=0%
5	55 yr old male participates in a once in 5 years *FS-screening program*. Baseline FS shows no abnormalities. However, a colonoscopy performed 3 years later due to rectal blood loss shows a cancer in the rectosigmoid colon.	FS interval cancer (*within* a FS screening program)	1=100%; 2=0%; 3=0%; 4=0%; 5=0%
6	60 yr old male participates in a *biennial FIT* screening program. The first FIT screening episode is positive. Subsequent colonoscopy shows 2 small adenomas, for which a repeat colonoscopy is recommended after 5 years. However, 3yrs later a colonoscopy is performed due to rectal blood loss, which shows a cancer in the rectosigmoid colon.	CS interval cancer (*within* a FIT screening program)	1=100%; 2=0%; 3=0%; 4=0%; 5=0%

Table 5.4 (continued)

Case	Description	Nomenclature	Level of agreement
7	75 yr old male participates in a primary *colonoscopy* screening program. Baseline colonoscopy detects 8 adenomas, which are removed, with 2 of them containing high-grade dysplasia. Surveillance colonoscopy is recommended after 3 years. The patient experiences a coronary event and postpones the examination. Two years later (5 years from the initial colonoscopy), a repeat colonoscopy is performed due to symptoms, which shows a CRC.	This is NOT an interval CRC, because the detection occurred beyond the recommended interval for repeat testing.	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%
8	75 yr old male participates in a primary *colonoscopy* screening program. Baseline colonoscopy detects 6 adenomas, which are removed, with 2 of them containing high-grade dysplasia; surveillance colonoscopy is recommended after 3 years. Two years later a colonoscopy is performed due to rectal blood loss, which shows a cancer in the rectosigmoid colon.	CS interval cancer (*within* a CS screening program)	1=100%; 2=0%; 3=0%; 4=0%; 5=0%
9	60 yr old female participates in a 5-yearly *FS-screening program*. Baseline FS examination shows 1 small rectal adenoma, which is removed. Subsequent colonoscopy shows no additional neoplasms; surveillance colonoscopy is recommended after 5-10 years. Four years later a colonoscopy is performed for obstructive symptoms, showing a cancer in the rectosigmoid colon.	CS interval cancer (*within* a FS screening program)	1=100%; 2=0%; 3=0%; 4=0%; 5=0%
10	55 yr old male participates in a once in 5 year *FS screening program*. FS shows no abnormalities. Three years later a colonoscopy is performed due to iron deficiency anemia, which shows a cancer in the ascending colon.	FS interval cancer *(within* a FS screening program)	1=100%; 2=0%; 3=0%; 4=0%; 5=0%
11	58 yr old male underwent a screening colonoscopy - recommended by his general practitioner (opportunistic screening), which showed no abnormalities. A repeat colonoscopy is advised after 10 years. Four years later a colonoscopy is performed because of rectal bleeding, showing a cancer in the sigmoid colon.	CS interval cancer (following opportunistic CS screening)	1=100%; 2=0%; 3=0%; 4=0%; 5=0%
12	55 yr old male underwent a screening colonoscopy (opportunistic screening) showing 2 tubular adenomas in the sigmoid colon, for which a surveillance colonoscopy is recommended after 5 years. Three years later he is noted to be iron deficient and colonoscopy demonstrates a cancer in the ascending colon.	CS interval cancer (following opportunistic CS screening)	1=100%; 2=0%; 3=0%; 4=0%; 5=0%

*level of agreement: 1, accept completely; 2, accept with minor reservation; 3, accept with major reservation; 4, reject with reservation; and 5, reject completely

This means that interval cancer rates may vary by local or regional practice due to variation in when exams should be repeated. Thus, clear documentation of the recommended dates for a repeat exam must be included. The proposed nomenclature provides general principles for determining and reporting interval CRCs. Complex situations can arise which will prove challenging (e.g. multiple FIT screening episodes, single FS screening followed by FIT biennially, etc). Finally, identification of interval CRCs requires resources to support organized, systematic reporting. Better insight into the underlying biologic processes driving interval CRC formation and a more extensive understanding of the endoscopic performance characteristics associated with interval CRC will facilitate reduction of their occurrence. Future work will aim to develop criteria for adjudicating the causes of interval CRCs during screening and surveillance (e.g. missed, incompletely resected or rapidly progressive neoplasms).

In conclusion, principles for defining and categorizing interval CRCs after screening or colonoscopy surveillance exams, and a proposed nomenclature are presented. Clinical scenarios, to demonstrate the practical application of the nomenclature, are provided. The Expert Working Group encourages adoption of this standardized nomenclature. A standardized nomenclature will facilitate benchmarking and comparison of interval CRC rates across programs and regions internationally.

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Supplementary tables

Table S5.1 Consensus Statements pertaining to current knowledge on interval CRCs (Statements 1-10) and criteria for developing a standardized nomenclature (Statements 11-16)

Statements	Level of agreement*	Quality of evidence
There is heterogeneity in the definition of an *interval CRC* after colonoscopy and the estimated rates are not comparable.	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%	Moderate
Frequency of interval CRC after colonoscopy varies.	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%	Moderate
There is wide methodological variation in the study of *interval CRC* after colonoscopy, affecting comparison of the estimated rates.	1=100%; 2=0%; 3=0%; 4=0%; 5=0%	Moderate
It is difficult to determine the precise contribution of *procedural* versus *biological* factors to the occurrence of *interval CRCs* after colonoscopy.	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%	Moderate
The process employed for calculating proportions of *interval CRC* varies, limiting comparison of the estimated rates.	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%	Moderate
There is heterogeneity in the definition of an *interval CRC* after flexible sigmoidoscopy (FS).	1=100%; 2=0%; 3=0%; 4=0%; 5=0%	Moderate
Incidence rates of *interval CRCs* after FS vary.	1=100%; 2=0%; 3=0%; 4=0%; 5=0%	Moderate
It is difficult to determine the precise contribution of *procedural* versus *biological* factors in the occurrence of *interval CRCs* after FS.	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%	Moderate
Variation exists in definition of an *interval CRC* after screening using fecal occult blood testing.	1=100%; 2=0%; 3=0%; 4=0%; 5=0%	High

Table S5.1 (continued)

Statements	Level of agreement*	Quality of evidence
Proportions of *interval CRCs* identified after screening by fecal occult blood tests vary.	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%	Moderate
A cohesive, universal definition for *interval CRCs* will reduce variation in reported incidence rates and allow rigorous comparison of outcomes.	1=100%; 2=0%; 3=0%; 4=0%; 5=0%	
Definition of *interval CRCs* should be ideally derived from International Agency for Research on Cancer (IARC) definitions, to ensure consistency with international nomenclature.	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%	
To facilitate benchmarking, the nomenclature should be generally applicable to screening, with *all* modalities.	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%	
The nomenclature should be applicable to screening and to colonoscopy surveillance.	1=87.5%; 2=12.5%; 3=0%; 4=0%; 5=0%	
The nomenclature should facilitate reporting on *interval CRCs*, in an organized, reproducible manner.	1=100%; 2=0%; 3=0%; 4=0%; 5=0%	
Following the identification of an *interval CRC*, a minimum data set should be documented, that specifies the important characteristics of an *interval CRC*.	1=100%; 2=0%; 3=0%; 4=0%; 5=0%	

*level of agreement: 1, accept completely; 2, accept with minor reservation; 3, accept with major reservation; 4, reject with reservation; and 5, reject completely

Table S5.2 Samples of minimum data sets corresponding to the clinical case scenarios illustrated in Table 5.4

Case 2 - FIT *interval CRC* (*within* a FIT screening program)

- **Patient characteristics**: 57 year old male, at average-risk for CRC
- **Program characteristics**: biennial FIT screening program, age 55 to 75 yrs; first FIT screening episode
- **Screening test characteristics**: test system (e.g. OC Sensor, OC Diana), at a cut-off concentration of 100 µg Hb/g feces
- **Follow-up advice**: FIT after 2 years
- **Interval CRC characteristics**: cT2N0M0 rectosigmoid adenocarcinoma, identified 1 year after the first FIT screening episode

Case 4 - CS *interval CRC* (*within* a CS screening program)

- **Patient characteristics**: 69 year old male, at average-risk for CRC
- **Program characteristics**: colonoscopy screening program, baseline colonoscopy exam
- **Follow-up advice**: repeat colonoscopy after 10 years (date of the next recommended exam and the upper age limit for screening should be specified)
- **Interval CRC characteristics**: cT1N0M0 adenocarcinoma of the cecum, identified 6 years after the baseline colonoscopy
- **Lesions identified at baseline colonoscopy** (if available): None
- The **quality** of the baseline colonoscopy exam (if available), namely the cecal intubation, adenoma detection and polyp resection rates of examining physician, quality of bowel preparation, withdrawal time, etc.

Case 5 - FS *interval cancer* (*within* a FS screening program)

- **Patient characteristics**: 55 yr old male, at average-risk for CRC
- **Program characteristics**: 5-yearly FS-screening program, baseline FS exam
- **Follow-up advice**: repeat FS after 5 years (date of next recommended exam and the upper age limit for screening should be specified)
- **Interval CRC characteristics**: cT1N0M0 rectosigmoid adenocarcinoma, identified 3 years after the baseline FS
- **Lesions identified at baseline FS exam** (if available): None.
- The **quality** of the baseline FS exam (if available), namely the adenoma detection and polyp resection rates of examining physician, quality of bowel preparation, etc.

PART II

Interval CRC: technical performance or biology?

6

Temporal trends and variability of colonoscopy performance in a gastroenterology practice

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Abstract

Background and study aim

Quality measures for colonoscopy are operator-dependent and vary considerably. It is unclear whether quality measures change over time. In this study, we examined variations to quality measures across colonoscopists and practices.

Patients and methods

We reviewed colonoscopy and histopathology records from 3 large-volume (1 university and 2 non-university) hospitals, in South-Limburg, the Netherlands. Data from colonoscopists performing at least 100 procedures per year were examined. Patients with inflammatory bowel disease, hereditary colorectal cancer (CRC), prior history of CRC or colon resection were excluded. We examined variations amongst colonoscopists with regard to adjusted cecal intubation rate (ACI), adenoma detection rate (ADR), advanced ADR, mean adenoma per procedure (MAP), proximal ADR, non-polypoid ADR, and serrated polyp detection rate, over three time periods (2007, 2010 and 2013). Inter-colonoscopist variation was calculated using coefficients of variation (CV).

Results

A total of 23 colonoscopists performing 6,400 procedures were included. Overall, the mean ACI, ADR, MAP and proximal ADR improved significantly over time from 91.9%, 22.5%, 0.37 and 10.2% in 2007 to 95.3%, 25.8%, 0.45 and 13.4%, respectively in 2013 ($p<0.05$). The inter-colonoscopist variability in ADR decreased from 37% in 2007 to 15% in 2013 ($p<0.05$). In 2007 and 2010, quality measures were significantly higher in the university vs. non-university hospitals, but no significant differences were found anymore in 2013.

Conclusions

In our routine colonoscopy practice, core quality measures improved over time through decreased variability among colonoscopists. Our findings suggest that awareness and continuous training improvement can effectively change the quality outcomes.

Introduction

Many studies raised concerns about the effectiveness of colonoscopy for the prevention of colorectal cancer (CRC) in routine practice. Colonoscopy is regarded as the reference standard for the detection of (pre)cancerous lesions and their resection. Quality measures for colonoscopy, such as adenoma detection rate (ADR) and the cecal intubation rate are key indicators of the effectiveness of the procedure to detect and prevent CRC.[1] Patients of colonoscopists with an ADR less than 20% have greater likelihood to develop postcolonoscopy CRC than those of colonoscopists with ADR >20% (HR: 12,5; 95%CI: 1.5-103.4).[2] Notably, each 1% increase in ADR can result in a 3% reduction of the risk for CRC.[3] Likewise, patients of colonoscopists with a high polyp resection rate are less likely to develop postcolonoscopy CRC.[4]

Although targets for ADR have been proposed already for more than one decade,[5] a wide variation in performance exists between colonoscopists, with ADRs ranging from 9% to 59.8%.[6,7] Studies about quality measures for colonoscopy in relation with the background specialty (gastroenterologist vs. non-gastroenterologist) and setting (hospital vs. non-hospital) are few.[4,8] A comprehensive evaluation of the quality measures in this context is lacking.

A number of studies examined the effect of different interventions (e.g. incentives or financial consequences) on the performance of colonoscopy in the day-to-day practice. Unfortunately, none of such interventions proved to be effective. In a prospective, community-based study, Shaukat *et al.* examined the effectiveness of five targeted educational interventions on ADR, finding no significant improvements.[9] A systematic review (including 7 published studies and 10 abstracts) by Corley *et al.* found, again, that all interventions aiming to enhance the colonoscopist's performance were not successful.[10] Understanding of the factors affecting colonoscopy performance will provide opportunities for targeted educational programs.[11] Few studies examined time-dependent variability for quality measures.[12] Evaluating such trends helps to identify systemic factors that can stimulate or hinder performance. Furthermore, comparing institutions and individual colonoscopists with regards to performance measures helps to identify gaps in education and practical skills and to close them. We hypothesized that overall, variability in performance of colonoscopy fell significantly over the past years. The aim of this study was to examine time-trends for quality measures in colonoscopy in our region, and compare such measures among colonoscopists and across practices.

Patients and methods

Study design and population

We reviewed colonoscopy records from elective colonoscopies performed by 23 colonoscopists at three large-volume hospitals (one university and two non-

university), in South-Limburg, the Netherlands. South-Limburg is a province with a total population of approximately 650,000 inhabitants. There is a close interaction between the three hospitals within the framework of clinical care and GI endoscopy training.

We randomly selected three samples of 100 consecutive colonoscopies for each colonoscopist, starting from January 2007, January 2010, and January 2013, respectively. Participating colonoscopists were experienced gastroenterologists, internists or trainees under close supervision who met the following criteria: 1) performed at least 100 colonoscopies per year and 2) participated in at least two of the three time periods of this study. In the Netherlands a nationwide fecal immunologic test-based CRC screening program was initiated in January 2014.[13] Quality certification of participating colonoscopists is a prerequisite. This includes monitoring of quality measures (i.e. adjusted cecal intubation rate, adenoma detection and polyp resection rates) in a sample of 100 consecutive colonoscopies – the reason for which we used this cut-off. We excluded colonoscopies performed in patients aged <18 years, with inflammatory bowel disease, hereditary forms of CRC, a history of CRC, or colon resection. In patients who underwent two colonoscopies during the study period, we only evaluated colonoscopic data from the first (most extensive) procedure.

The study was approved by the Institutional Review Boards of the participating hospitals and registered in the Netherlands Trial Registry: NTR3093 and NTR4844 (http://www.trialregister.nl).

Colonoscopy

Patients received 2 to 4 L of polyethylene glycol solution for bowel preparation. We reviewed prospectively collected digital colonoscopy and histopathology reports. Colonoscopic examinations were documented by using a standardized reporting system, including digital photographic documentation. Indication for colonoscopy (e.g. screening, surveillance or diagnosis), documentation of cecal intubation, quality of bowel preparation, presence, location, size, and shape of the identified neoplasms, as well as simultaneous colon pathology (e.g. diverticular disease) were collected. Colonoscopy was considered complete when the colonoscopist documented the cecal landmarks in the colonoscopy report. Quality of bowel preparation was classified depending on the colonoscopist's estimation as sufficient (good or fair) or insufficient (poor).[14] According to location, the identified neoplasms were classified as proximally (cecum to splenic flexure) or distally (descending colon to rectum) located in the colon. Shape was classified using the Paris classification.[15] We defined *non-polypoid* colorectal neoplasms as lesions with a height less than half the diameter. We defined an advanced adenoma as any adenoma ≥10 mm in size, containing villous components or high grade dysplasia. We categorized serrated polyps according to the WHO into hyperplastic polyps, traditional serrated adenomas, or sessile serrated adenomas with or without dysplasia. Digital histopathology records of all resected neoplasms were collected and examined by gastrointestinal pathologists.

Definitions of quality indicators

Adenoma detection rate (ADR), advanced ADR (A-ADR), non-polypoid ADR (NP-ADR), proximal ADR (P-ADR) were defined as proportion of colonoscopies where at least one (advanced / non-polypoid / proximal) adenoma was detected. Serrated polyp detection rate (SPDR) was the proportion of colonoscopies where at least one serrated polyp (hyperplastic polyp, sessile serrated adenoma or traditional serrated adenoma) was detected. Polyp resection rate (PRR) was the proportion of colonoscopies were polyps were resected. The mean adenoma per procedure (MAP) was calculated by dividing the total number of adenomas by the total amount of procedures. Adjusted cecal intubation rate (ACI) was defined as the cecal intubation rate adjusted for poor bowel preparation, benign or malignant stenosis and severe diverticular disease.[16]

Statistical analysis

Primary outcome of this study was to determine quality measures for colonoscopy, i.e. mean rate of ACI, ADR, A-ADR, MAP, p-ADR, NP-ADR, SPDR and PRR in a group of 23 colonoscopists. First, detection rates per colonoscopist were calculated. Second, differences in mean (standard deviation, SD) detection rates per year were tested using paired-samples t-test. We quantified the inter-colonoscopist variation per year using coefficients of variation (CV) for the detection rates, where CV = 100% x standard deviation (SD) / mean. For the comparison of the CVs of detection rates between 2007 and 2010 or 2013, we first log-transformed the detection rates and then tested the difference in SD of the log-transformed data between two study years. As detection rates are repeatedly measured for the same colonoscopist over time, the detection rates are dependent and Pitman's test for comparing variances of correlated samples was used. This test is based on calculating the correlation between difference and mean scores.[17] Differences in mean detection rates between university vs. non-university hospitals over time were assessed by independent-samples t-test. P-values ≤0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0.

Results

Patient characteristics

We examined 8,383 consecutive colonoscopies performed by 23 colonoscopists at three participating centers. Colonoscopies performed in patients with inflammatory bowel disease, a history of CRC or hereditary CRC syndromes were excluded from the final analyses (Figure 6.1). Table 6.1 summarises the main characteristics of the study subjects. The mean (SD) age was 59.1 (15.8) years and 44.9% were male. Subjects included at the three institutions had similar distribution of demographic features.

Indications for colonoscopy were symptoms, surveillance or screening in 85.3%, 10.0% and 4.7% of the cases, respectively. Overall, a total of 3,365 polyps were found, of which 2,433 were adenomas and 922 serrated polyps (859 hyperplastic polyps, 52 sessile serrated adenomas, 11 traditional adenomas).

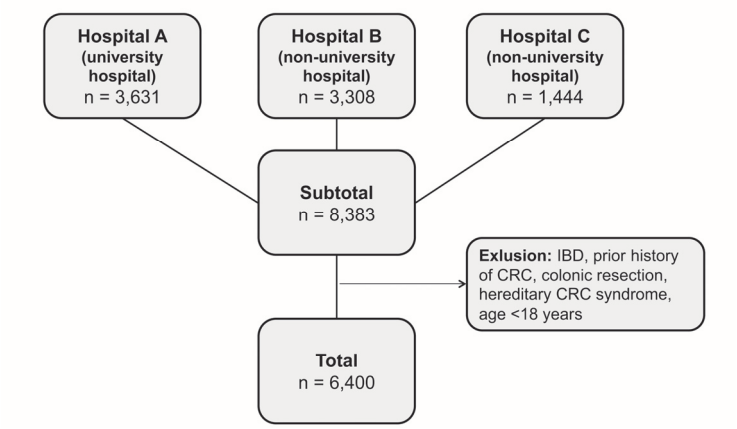

Figure 6.1 Study flowchart. n, number of colonoscopies analyzed

Table 6.1 Characteristics of the study subjects included at the three participating hospitals

	Total	Hospital A (university)	Hospital B (non-university)	Hospital C (non-university)
Colonoscopies (N)	6400	2700	2600	1100
Gender, % Male	44.9	44.2	45.7	42.6
Mean age (SD)	59.1 (15.8)	59.1 (16.0)	58.9 (15.8)	59.8 (15.6)
Polyps (N)	3362	1697	1220	445
Adenomas (N)	2443	1293	831	319
CRC (N)	287	113	130	44
Indication for colonoscopy:				
Symptoms %	85.3	81.6	90.3	82.5
Surveillance %	10.0	11.5	6.5	14.2
Screening %	4.7	6.9	3.2	3.3

Per patient one colonoscopy was analysed; SD, standard deviation; Polyps, including both adenomas and serrated polyps; CRC, colorectal cancer

Variation of quality measures among colonoscopists

A total of 6400 colonoscopies performed by 23 colonoscopists were examined (hospital A: n=10, hospital B: n=9, hospital C: n=4). Of them, 17 were gastroenterologists, 3 internists (with colonoscopy experience) and 3 gastroenterology trainees. The number of years of endoscopy practice ranged from 2 to 30 years and the average number of

procedures performed per year from 100 to 1000 procedures. Mean ADR and polyp resection rate (PRR) varied considerably across the participating colonoscopists (Figures 6.2 and 6.3). For example, the ADR ranged from 6% to 38% in 2007 and from 19% to 35% in 2013. Notably, the variability in ADR between colonoscopists significantly declined over time: the coefficients of variation (CV) for the ADR decreased significantly from 37% in 2007 to 23% in 2010 and 15% in 2013 (Figure 6.4). The CVs for MAP, SPDR and PRR show significant reduction over time.

Variation in quality measures between university and non-university hospital

Overall, the ACI, ADR and MAP were 92.9%, 23.2%, and 0.39, respectively. As shown in Table 6.2, the ACI, ADR, MAP, P-ADR, SPDR and PRR were all significantly greater in 2013 versus 2007. Table 6.3 shows the variation in quality measures between practices according to the year of colonoscopy. In 2007 and 2010, mean ADR, MAP, P-ADR, NP-ADR, SPDR and PRR were all significantly higher in the university versus non-university hospitals. In 2013, no significant differences were observed anymore in quality measures between university and non-university hospitals.

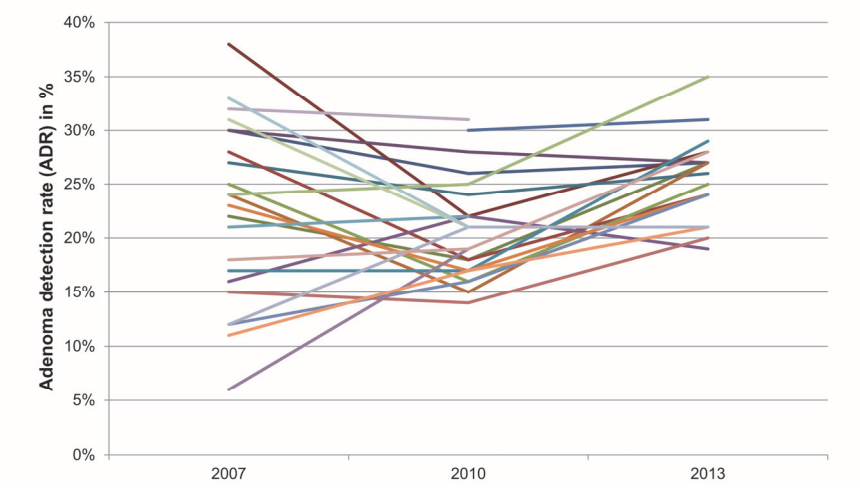

Figure 6.2 Variation of adenoma detection rates among 23 colonoscopists.
5 of the 23 colonoscopists operated during 2 out of 3 time periods, resulting in some intermittent lines

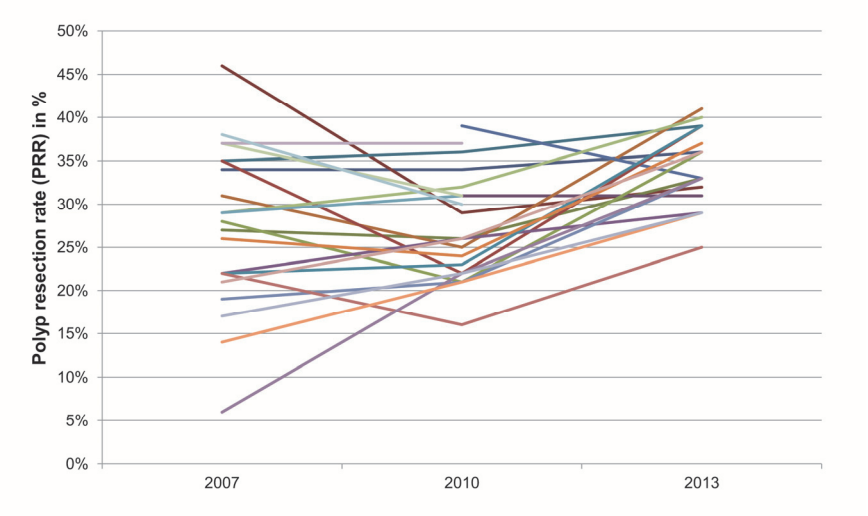

Figure 6.3 Variation of polyp resection rates among 23 colonoscopists.
5 of the 23 colonoscopists operated during 2 out of 3 time periods, resulting in some intermittent lines

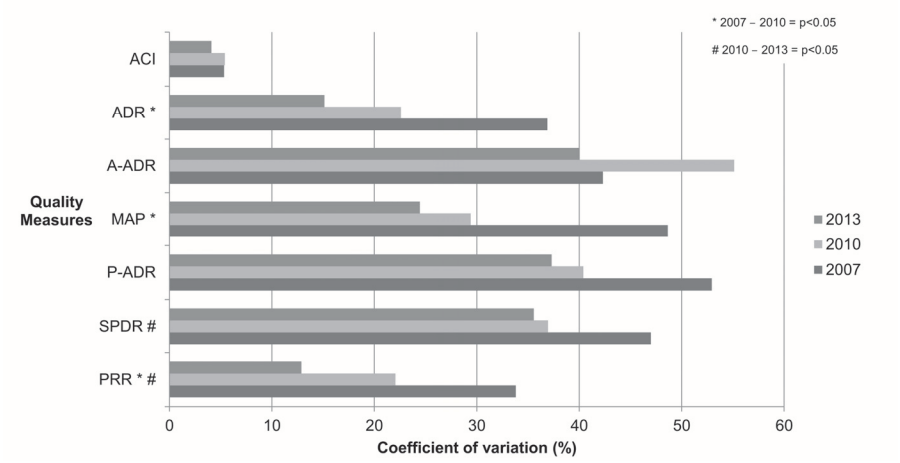

Figure 6.4 Variation of quality measures among 23 colonoscopists.
ACI: adjusted cecal intubation (adjusted for poor bowel preparation, benign or malign stenosis and severe diverticular strictures), ADR: adenoma detection rate, MAP: mean adenoma per procedure, A-ADR: Advanced ADR e.g. adenoma ≥1 cm in size or containing high-grade dysplasia or a villous component, P-ADR: proximal ADR, SPDR: serrated polyp detection rate, PRR: polyp resection rate

Table 6.2 Variation in quality measures for colonoscopy over time

	Overall Mean (±SD)	2007 Mean (±SD)	2010 Mean (±SD)	2013 Mean (±SD)	2010 vs 2007 (p-value)	2013 vs 2010 (p-value)	2013 vs 2007 (p-value)
ACI %	92.9 (4.1)	91.9 (4.9)	92.4 (5.0)	95.3 (3.9)	0.789	0.028	0.028
ADR %	23.2 (4.7)	22.5 (8.3)	20.8 (4.7)	25.8 (3.9)	0.188	<.001	0.022
A-ADR %	9.2 (2.5)	10.4 (4.4)	7.8 (4.3)	9.0 (3.6)	0.055	0.190	0.259
MAP	0.39 (0.11)	0.37 (0.18)	0.34 (0.10)	0.45 (0.11)	0.171	<.001	0.037
P-ADR %	11.1 (3.6)	10.2 (5.4)	9.9 (4.0)	13.4 (5.0)	0.655	0.001	0.043
NP-ADR %	2.8 (2.4)	2.2 (2.7)	3.2 (2.9)	3.2 (2.9)	0.078	0.853	0.202
SPDR%	10.8 (3.1)	10.0 (4.7)	9.2 (3.4)	13.5 (4.8)	0.312	<.001	0.005
PRR %	29.8 (5.3)	27.8 (9.4)	27.2 (6.0)	34.2 (4.4)	0.448	<.001	0.001

SD: Standard deviation, ACI: adjusted cecal intubation (adjusted for poor bowel preparation, benign or malign stenosis and severe diverticular strictures), ADR: adenoma detection rate, A-ADR: advanced ADR (adenoma ≥1 cm in size or containing high-grade dysplasia or a villous component), MAP: mean adenoma per procedure, P-ADR: adenoma proximal to splenic flexure, NP-ADR: nonpolypoid ADR, SPDR: serrated polyp detection rate, PRR: polyp resection rate

Table 6.3 Quality measures in university vs non-university hospitals

	2007			2010			2013		
	University hospital n=1000 mean (±SD)	Non-University n=1200 mean (±SD)	p value	University hospital n=1000 mean (±SD)	Non-University n=1300 mean (±SD)	p value	University hospital n=700 mean (±SD)	Non-University n=1200 mean (±SD)	p value
ACI %	90.9 (4.2)	92.6 (5.3)	0.427	91.2 (5.1)	93.2 (5.0)	0.348	95.9 (1.8)	94.9 (4.8)	0.626
ADR %	29.7 (4.8)	17.5 (6.4)	<.001	23.6 (5.2)	18.7 (3.1)	0.010	27.6 (1.6)	24.8 (4.6)	0.079
A-ADR %	12.2 (3.5)	9.2 (4.6)	0.091	8.5 (4.5)	7.2 (4.2)	0.495	8.9 (2.9)	9.0 (4.1)	0.936
MAP	0.52 (0.08)	0.27 (0.14)	<.001	0.43 (0.09)	0.27 (0.06)	<.001	0.48 (0.06)	0.43 (0.12)	0.287
P-ADR %	15.1 (4.3)	6.8 (2.9)	<.001	12.5 (2.2)	7.9 (4.0)	0.003	14.9 (3.1)	12.5 (5.8)	0.339
NP-ADR %	4.0 (3.1)	1.0 (1.3)	0.022	4.6 (2.5)	2.1 (2.8)	0.033	4.3 (3.0)	2.5 (2.8)	0.206
SPDR %	13.3 (3.5)	7.6 (4.1)	0.003	12.0 (1.8)	7.1 (2.8)	<.001	13.1 (5.6)	13.7 (4.5)	0.825
PRR %	35.8 (5.2)	22.3 (7.5)	<.001	31.8 (4.6)	23.6 (4.3)	<.001	35.0 (3.8)	33.8 (4.9)	0.568

n: number of colonoscopies analysed, ACI: adjusted cecal intubation (adjusted for poor bowel preparation, benign or malign stenosis and severe diverticular strictures), ADR: adenoma detection rate, A-ADR: advanced ADR (adenoma ≥1 cm in size or containing high-grade dysplasia or a villous component), MAP: mean adenoma per procedure, P-ADR: adenoma proximal to splenic flexure, NP-ADR: nonpolypoid ADR, SPDR: serrated polyp detection rate, PRR: Polyp Resection Rate. Differences in categorical variables were tested using the chi-square test and numerical variables were tested using independent sample t-test.

Discussion

In this study of a large colonoscopy practice from the Netherlands, core quality measures, in particular the overall adenoma detection rate, proximal adenoma detection rate and mean adenoma per procedure improved significantly over the past years. Importantly, the variability between colonoscopists regarding ADR decreased significantly, from 37% in 2007 to 15% in 2013. We hypothesize that such improvements in quality of colonoscopy performance over time are the result of greater awareness and continuous training.

In the Netherlands, a nationwide fecal immunologic test-based CRC screening program was started in January 2014. The main goal is to reduce the annual mortality by approximately 50%. The observed participation rate and diagnostic yield after the first year are much higher than previously expected.[13] Given the high expectations of the screening participants, quality of colonoscopy performance is of utmost importance to ensure the success of our program. Many studies showed that, even in highly experienced colonoscopy services, moderate variation exists between colonoscopists regarding their ability to detect colorectal adenomas and serrated polyps.[12,18] For example, a study of 6,681 screening colonoscopies performed by 15 colonoscopists showed that the ADR varied from 17% to 47%.[19] A more recent study from the same group found, again, variation amongst colonoscopists regarding ADR, ranging from 16% to 46%.[20]

Understanding what factors drive the ADR in clinical practice can help to close gaps in colonoscopy training and tailor educational programs. Such information is, however, sparse and controversial. In a community-based study, Shaukat *et al.*[9] found that planned, systematic, interventions, e.g. ADR monitoring, personal feedback and even financial consequences have limited effect on the ADR. In contrast, Coe *et al.*[21] found that compared with untrained senior colonoscopists, staff colonoscopists who followed an educational intervention program achieved greater ADRs (47% versus 35%) in their patients.

Our current study shows a significant improvement of quality measures over time: the overall ADR increased significantly from 22.5% in 2007 to 25.8% in 2013 and the variation in ADR among colonoscopists decreased significantly. A significant decrease of the coefficients of variation over time was also observed, confirming such improvements. The reduction in variability among colonoscopists in our study likely results from improved performance of those in the lower performance range: of the 8 colonoscopists having ADRs <20% in 2007, 6 improved their performance in 2013. It is reasonable to assume that improved awareness and sustained training (which are partly driven by technological progress) can explain such changes. In the quality assurance era, the traditional, apprenticeship-based model for learning colonoscopy must be changed. Attention has now shifted towards monitoring the *quality* of procedures, not only the *volume*. Changing paradigms in colonoscopy training starts with implementation of structured educational programs, to develop both cognitive and practical skills, followed

by ADR assessment in practice.[22] Innovative and effective training tools (web-based learning, videos, cases) are now available and should be implemented to update knowledge and skills.[5,21,23]

An original finding of this study is the significant reduction of variability in performance across practices. Variation was found over time between ADRs in non-university versus university hospitals: 17.5% versus 29.7% in 2007, 18.7% versus 23.6% in 2010, while no significant differences were found anymore in 2013 (24.8% versus 27.6%). Homogeneity in performance within an endoscopy practice is a critical step to professionalize colonoscopy practice. It may reflect the cumulative effect of many factors: efforts to optimize bowel preparation,[24] withdrawal time and technique, a better recognition of the subtle appearing non-polypoid (flat and depressed) colorectal neoplasms and sessile serrated polyps, and quality of colonoscopic equipment. In 2008, a training program was implemented at our university hospital, aiming to upgrade colonoscopy performance, with focus on the detection and resection of non-polypoid colorectal neoplasms.[25,26] In the current study, the non-polypoid colorectal neoplasm detection rates were higher in the university versus non-university hospitals, albeit such variation also decreased over time.

The explanation for the observed reduction in variation between hospitals remains unclear. Intuitively, the existing close collaboration between colonoscopists at the three institutions, both in terms of patient care, education, and endoscopy training can partly explain this. There is cross-interdisciplinary interaction, trainee exchanges, shared educational activities, and continuous learning environment, facilitating dissemination of knowledge and practical skills. Such continuous interaction can increase homogeneity in performance of colonoscopy. In contrast to other studies showing a large variation in cecal intubation rate between practices, ranging from 77% to 97%,[27] in our study cecal intubation rate was comparable between hospitals.

We examined a large spectrum of intraprocedural quality measures: ACI, ADR, MAP, P-ADR, NP-ADR and SPDR. The reliability of ADR as a single quality indicator was recently challenged.[7] Foremost of which its potential susceptibility to 'gaming' and inability to distinguish between colonoscopists who detect only one adenoma per procedure ('one and done') versus those finding multiple adenomas.[18,28] In this respect, MAP could better estimate detection skills. A study of 42,817 participants in the faecal occult blood test-based CRC screening program from France[29] proposed the benchmark for MAP at 0.6. Our study performed in a predominantly (85%) diagnostic population found a lower MAP (0.45 in 2013), but MAP showed a similar improvement over time as ADR and a decrease in variation among colonoscopists.

It has been shown that compared with the distal colon, the effectiveness of colonoscopy to detect and prevent CRC of the proximal colon lags behind. With that in mind, we specifically studied the variability in detection of proximal adenomas, and particularly of non-polypoid colorectal neoplasms and serrated polyps, a significant proportion of which are proximally located. Continuous improvement of detection and resection of such neoplasms, even small steps, matter. A study by Corley *et al.*, involving 136 gastroenterologists performing over 300,000 colonoscopies showed that ADRs

varied markedly, from 7.4% to 52.2%.[3] Each 1% increase in ADR in that study reduced the risk of CRC by 3%. Furthermore, the authors estimated that an increase of ADR from <19% to 34-53% can prevent one interval CRC over the next 10 years for every 213 colonoscopies performed. In a population-based study in South-Limburg, we found that the postcolonoscopy cancer rate (i.e. CRCs diagnosed from 6 to 60 months after a previous colonoscopy) was roughly 2 in 1000 colonoscopies, and did not significantly differ across the same three practices described in this study.[30]

Some distinct features of this study need to be acknowledged. Our study was conducted in a large gastroenterology practice in South-Limburg, where nearly all colonoscopists are gastroenterologists or GI fellows under close supervision – hence, the study results provide estimates of colonoscopy performance indicators in a gastroenterology practice. Our data help to identify opportunities for improvement when rolling out a nationwide screening program. For example, the need for additional training on detection and resection of non-polypoid neoplasms and serrated polyps. To better understand the pace of quality improvement, we evaluated key quality measures at different moments in time, at different hospitals and performed by colonoscopists with different numbers of years of practice and different volume of procedures performed per year. Next to standard methods for calculating quality measures, we also used coefficients of variation. Such approach provides more robust estimates of variance, thereby strengthening the conclusions of this study. Our study has, however, several limitations. We included colonoscopists who performed at least 100 colonoscopies in each of the three study periods. Quality certification for CRC screening in the Netherlands also requires monitoring of quality measures in a consecutive sample of 100 procedures. Ideally, to generate reliable data, a sample of 500 colonoscopies must be examined.[31] We examined consecutive colonoscopies performed for diagnosis, screening or surveillance. Age, sex, and indication for colonoscopy were comparable across practices, thereby allowing meaningful comparison. Unarguably, such quality measures can help to determine standards for general colonoscopy practice, but cannot be generalized to a screening population. As demographic features and indication for colonoscopy significantly affect ADR, reporting quality measures needs stratification.[26,28] Although more qualitative changes have been implemented in our colonoscopy practice over time, it is unlikely that the observed reduction in variability between practices and between colonoscopists results from technological advancement alone and/or improvement of bowel preparation – such factors were not subject to major changes within this time period, and especially did not differ between practices. We assume that *colonoscopist*-driven changes in performance of colonoscopy, in particular a greater motivation and focus on quality improvement represent the dominant factor. A large multicenter study from the UK (Quality Improvement in Colonoscopy study), showed that a combination of measures (e.g. withdrawal time >6 minutes, use of butylscopalamine, position change during colonoscopy to optimize exposure of the mucosa and rectal retroflection) leads to a measurable improvement of the adenoma detection rates.[32]

In conclusion, this study of a large-volume gastroenterology practice showed that

quality measures, in particular overall adenoma detection rate, proximal adenoma detection rate and mean adenoma per procedure significantly improved over time. Variability in ADR amongst colonoscopists and practices decreased, likely due to better performance of those in the lower performance range. Monitoring of quality metrics can form the basis for meaningful interventions to continuously improve our practice.

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7

Clinicopathologic features of proximal versus distal colorectal cancers: results from a 10-year population-based survey in the Netherlands

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Submitted

Abstract

Background and study aim

Colonoscopy is less effective in reducing incidence of and mortality from proximal versus distal colorectal cancer (CRC). Aim of this study was to examine the clinicopathologic characteristics of proximal versus distal CRCs.

Methods

We conducted a population-based study of all patients diagnosed with CRC in South Limburg, the Netherlands, from January 2001 to December 2010. We used digital colonoscopy, histopathology reports and medical records, a national pathology database (PALGA) and data from the Netherlands Cancer Registry. Patients with hereditary forms of CRC, IBD, and unknown CRC localization were excluded. CRCs were categorised into proximal or distal from the splenic flexure, according to macroscopic aspect, into flat or protruded, and according to stage into early (TNM I) and advanced (TNM II, III or IV).

Results

We included a total of 5,126 patients (mean age 70.0 years, 53.8% males) with 5,365 CRCs. Of all patients, 1679 (32.8%) had proximally located CRC, these were more likely women (54.4% vs. 42.3%, p<.001) of older age (72.0 vs. 69.1 years, p<.001) than those with distal CRC. Logistic regression analysis after adjusting for age, sex and TNM stage showed that proximal CRCs were significantly more often flat, larger in size, more like poorly differentiated and contained mucinous histology. Cox regression analysis adjusted for age, sex and stage, showed no significant difference in survival between proximal and distal CRCs.

Conclusions

In this study, proximal CRCs showed distinct biological features and shape compared to distal colorectal cancer. These findings strengthen the hypothesis that differences might exist in the biologic mechanisms underlying carcinogenesis in the proximal versus distal colon.

Introduction

Colonoscopy is the gold standard technique to diagnose colorectal cancer (CRC), to detect and resect precursor lesions and subsequently prevents CRC and reduces CRC related mortality.[1,2] Unfortunately, several studies indicate that colonoscopy is less effective in reducing CRC related incidence and mortality in the proximal colon compared to the distal colon.[3-5] More specifically, postcolonoscopy (interval) CRCs are found, predominantly in the proximal colon and are mainly the result of missed lesions or incomplete resected adenomas.[6-8] These proximal postcolonoscopy CRCs more often show smaller size and flat macroscopic appearance.[8] When analysing precursor lesions, also differences in polyp shape between colonic sites have been observed: proximal adenomas with high-grade dysplasia/early CRC were more likely to be diminutive in size or nonpolypoid in shape than the distal ones and therefore easier to be missed compared to distal adenomas.[9,10] The characteristics of proximal lesions result into procedural difficulties to detect and resect precursor lesions and may contribute to the disparity in effectiveness of colonoscopic examinations between the proximal versus distal colon.

In addition, a distinct biological behaviour may also contribute to morphological differences between proximal and distal colorectal neoplasms. It has been hypothesized that CRC develops differently in the proximal versus distal colon, following distinct pathways. The embryological origin of the proximal vs. distal colon (midgut vs. hindgut) may contribute,[11] adjacent to environmental factors, for example the protective effect of physical activity on proximal lesions, while red meat consumption is predominantly a risk factor for distal lesions.[12] At the molecular level, differences in gene expression patterns are found.[13,14] Proximal CRCs are more frequently associated with microsatellite instability, distal CRCs with chromosomal instability.[15]

The underlying differences in macroscopic appearance and in clinicopathological features in relation to patient characteristics between proximal and distal CRCs have not fully been elucidated. Two studies from Japan suggest an association between flat macroscopic appearance and proximal CRCs.[16,17] In the Western population a relation between CRC location and shape has only occasionally been evaluated in average risk populations, with a predominance of polypoid lesions in the left sided colon.[18]

To optimize screening, surveillance and colonoscopic quality, especially in the proximal colon, more detailed insight is needed about the clinical and endoscopic appearance difference between proximal and distal CRCs.[19] We hypothesize that proximal CRCs in general, show more subtle macroscopic appearance, in line with proximal precursor lesions and postcolonoscopy CRCs. Hence the primary aim of this study was to examine the clinicopathologic characteristics of proximal versus distal CRC, with special attention for tumor shape. Second, we aimed to examine the association of patient characteristics such as age, gender and comorbidity to tumor site and finally to patient's survival.

Methods

Study population and design

The study population was described previously in our studies on postcolonoscopy[8] and metachronous[20] CRC. To summarize: we identified all patients diagnosed with CRC in South-Limburg, the Netherlands, between January 1, 2001 and December 31, 2010. We excluded CRC cases diagnosed elsewhere (second opinions or referrals), patients with hereditary CRC (i.e. Lynch syndrome or polyposis syndromes) or inflammatory bowel disease. Unlike our previous studies,[8,20] in the current study we excluded patients with unknown CRC localization. Data were collected at 3 large-volume (1 university and 2 non-university) hospitals in South-Limburg (Maastricht UMC+, Atrium-Orbis MC locations Heerlen and Sittard). South-Limburg is located in the southeast of the Netherlands, between Germany and Belgium, and has a narrow northern border with the rest of the Netherlands. The region has a total population of approximately 650,000 inhabitants and a low net migration rate of 0.8 per 1000 inhabitants per year.[21] For the purpose of this study, we firstly retrieved all cases diagnosed with CRC by using a nationwide digital pathology database (PALGA) and cross-linked it with the Netherlands Cancer Registry to ensure the validity and completeness of information.[22,23] We then reviewed digital clinical (i.e. location, size, macroscopic appearance of tumors) and histopathology records, including photographic documentation of the CRC resection specimens. The study was approved by the Institutional Review Boards of the participating hospitals and registered in the Netherlands Trial Registry: NTR3093 (www.trialregister.nl).

Definitions

Proximal CRCs were defined as CRCs located between the cecum and the splenic flexure and distal CRCs as CRCs located in descending colon, sigmoid or rectum. According to stage, CRCs were categorized into early (TNM I) and advanced (TNM II, III or IV), and according to the macroscopic aspect, into protruded (sessile or pedunculated) versus flat (non-polypoid or depressed). A tumor was considered flat when both the endoscopist and pathologist described it as having a non-exophytic, flat or depressed macroscopic appearance. In case of disagreement, the pathologist's estimation was considered leading. Size of CRCs was routinely measured and documented in the pathology reports. Family history of CRC was defined according to Dutch guidelines, as patients with at least 3-fold increased risk for CRC, namely those with i) $\geq$1 first degree relative with CRC diagnosed <50 year or ii) $\geq$2 first degree relatives with CRC diagnosed between 50-70 year or iii) 1 first degree and 1 second degree relative with CRC diagnosed <70 year.[24]

Study endpoints and statistical analyses

In this study we examined patient and tumor characteristics of proximal versus distal CRCs. We particularly examined potential risk factors at patient level (i.e. age, sex, presence of comorbidities or family history of CRC) and at tumor level (i.e. size, shape, stage, and differentiation).

We used multiple logistic regression analysis to identify potential features associated with proximal CRCs compared to distal CRCs. All significant patient-related and tumor-related variables from univariable analyses were included in the multivariable analysis. In case of multiple (synchronous or metachronous) CRCs per patient, the most advanced CRC was included in the analyses. We conducted sensitivity analyses including only those patients with single CRCs and no prior history of CRC.

Categorical variables are presented by number of patients or CRCs (%) and numerical variables by mean (±standard deviation (SD)). Differences in categorical variables were tested by using the chi-square test. Differences in numerical variables were examined by the independent-samples t-test. To assess the difference in survival times, we used Kaplan-Meier curves and cox-regression analysis adjusting for age, sex, and TNM stage at diagnosis. All odds ratios (ORs) were presented with 95% confidence intervals (CI). Data were analyzed by using IBM Statistical Package for Social Sciences (SPSS) for Windows, Version 22.0 (IBM Corp., Armonk, NY).

Results

From January 2001 to December 2010, 5,701 patients have been diagnosed with CRC in South-Limburg. We excluded patients with hereditary CRC (n=48), inflammatory bowel disease (n=61), neuroendocrine tumors of the colon (n=65), CRC recurrence (n=67), unknown tumor localization (n=31), or external referrals (n=303) (Figure 7.1). The remaining 5,126 patients (mean age (SD): 70.0 (11.1), 53.8% men), were diagnosed with 5,365 CRCs, of them 1,679 (32.8%) had at least one proximally located CRC and 3,447 (67.2%) distally located CRC. In Table 7.1 the clinical characteristics of patients with proximal and distal CRCs are given. Patients with proximal located CRCs in general were significantly older, with female predominance and had significantly more often (family) history of CRC, diverticulosis, coronary artery disease or lung disease than those with distal CRCs.

Tumor characteristics of proximal vs. distal CRCs

At the time of diagnosis, proximal CRCs were significantly larger, contained more often poorly differentiated and mucinous histology than distal CRCs. In addition, proximal CRCs were less often diagnosed at an early stage than distal CRCs. The early staged CRCs (stage I) located in the proximal colon, were more likely to have a flat macroscopic appearance than the distal CRCs (38.7% vs. 27.7%, p=0.003) (Table 7.2). These

findings were confirmed in logistic regression analysis including all significant univariate variables. It shows that proximal CRCs were larger (OR 1.21, 95% CI 1.16-1.25), more likely poorly differentiated (OR 1.46, 95% CI 1.25-1.71) and more often contained mucinous histology (OR 1.98, 95%CI 1.56-2.51) than distal CRCs (Table 7.3). In addition, at the time of diagnosis proximal CRCs were less often at early stage (OR 0.51, 95%CI 0.42-0.63) compared to distal CRCs. Sensitivity analyses including only those patients with single CRCs and no prior history of CRC showed similar results (data not shown).

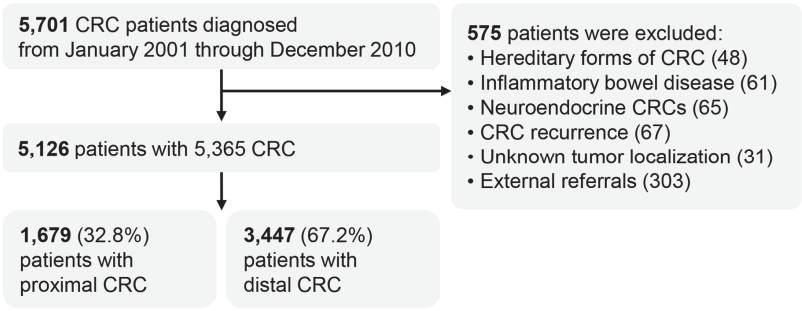

Figure 7.1 Study flowchart. CRC, colorectal cancer

Table 7.1 Patient characteristics of proximal versus distal CRCs

	Proximal (n=1,679)	**Distal** (n=3,447)	**p-value**
Mean age in years (SD)	72.0 (10.6)	69.1 (11.1)	<0.001
Female sex (%)	913 (54.4)	1457 (42.3)	<0.001
Current or former smoker (%)	372 (22.2)	827 (24.0)	0.145
Family history of CRC (%)	20 (1.2)	69 (2.0)	0.037
Personal history of CRC (%)	24 (1.4)	24 (0.7)	0.011
History of other cancer (%)	244 (14.5)	469 (13.6)	0.368
Diverticulosis (%)	539 (32.1)	794 (23.0)	<0.001
Coronary artery disease (%)	460 (27.4)	782 (22.7)	<0.001
Lung disease (%)	176 (10.5)	296 (8.6)	0.028
Diabetes (%)	225 (13.4)	493 (14.3)	0.383

CRC, colorectal cancer; SD, standard deviation. Family history of CRC: one first-degree relative aged <50 y or ≥2 first-degree relatives aged 50-70 y; Diverticulosis: presence of multiple diverticula; Coronary artery disease: history of myocardial infarction, angina, congestive heart failure, or severe arrhythmias; Lung disease: chronic obstructive pulmonary disease or asthma; Diabetes: diabetes mellitus treated with oral or insulin therapy; History of cancer: personal history of cancer other than CRC

Table 7.2 Clinicopathologic characteristics and TNM stage of proximal CRCs versus distal CRCs

		Proximal (n=1,679)	Distal (n=3,447)	p-value
Mean tumor size (SD) (cm)*		5.1 (2.3)	4.1 (2.0)	<0.001
Flat macroscopic appearance (%)*		465 (28.7)	951 (28.3)	0.750
of early (TNM-stage I) CRCs		70 (38.7)	228 (27.7)	0.003
≥50% mucinous histology (%)		220 (13.1)	213 (6.2)	<0.001
Differentiation (%)*	Poor	480 (32.2)	606 (21.2)	<0.001
	Moderate/well	1010 (67.8)	2252 (78.8)	
TNM-stage (%)*	I	183 (11.1)	819 (24.6)	<0.001
	II-IV	1461 (88.9)	2515 (75.4)	

CRC, colorectal cancer; SD, standard deviation. *Data on size, macroscopic appearance, differentiation, and stage was unavailable in 10%, 3%, 15%, 3%, respectively, of cases due to retrospective study design

Table 7.3 Logistic regression analysis to examine features associated with proximal CRCs vs. distal CRCs

Proximal CRCs vs. distal CRCs	OR	95% CI	p-value
Age at diagnosis (continuous)	1.02	1.01-1.03	<0.001
Female sex (vs. male)	1.65	1.43-1.90	<0.001
Positive family history of CRC	0.73	0.42-1.29	0.285
Personal history of CRC	2.57	1.24-5.31	0.011
Presence of diverticulosis	1.60	1.37-1.87	<0.001
Positive history of coronary artery disease	1.20	1.01-1.41	0.037
Positive history of lung disease	1.42	1.12-1.79	0.004
Size in cm (continuous)	1.21	1.16-1.25	<0.001
Flat macroscopic appearance (vs. protruded)	1.22	1.05-1.42	0.011
≥50% mucinous histology (vs. <50%)	1.98	1.56-2.51	<0.001
Poor differentiation (vs. moderate/well)	1.46	1.25-1.71	<0.001
TNM-stage I (vs. advanced II,III,IV)	0.51	0.42-0.63	<0.001

CRC, colorectal cancer; OR, odds ratio; CI, confidence interval

Survival and time trends in diagnosis

Stage specific cox regression analyses adjusted for age and sex, showed no significant difference in survival of patients with proximal CRCs versus distal CRC (Figure 7.2, Hazard Ratio: 1.07, 95%CI 0.99-1.17, p=.10). Figure 7.3 shows that the number of both proximal and distal CRCs gradually increased over the studied period, while the ratio between proximal and distal CRC remained stable.

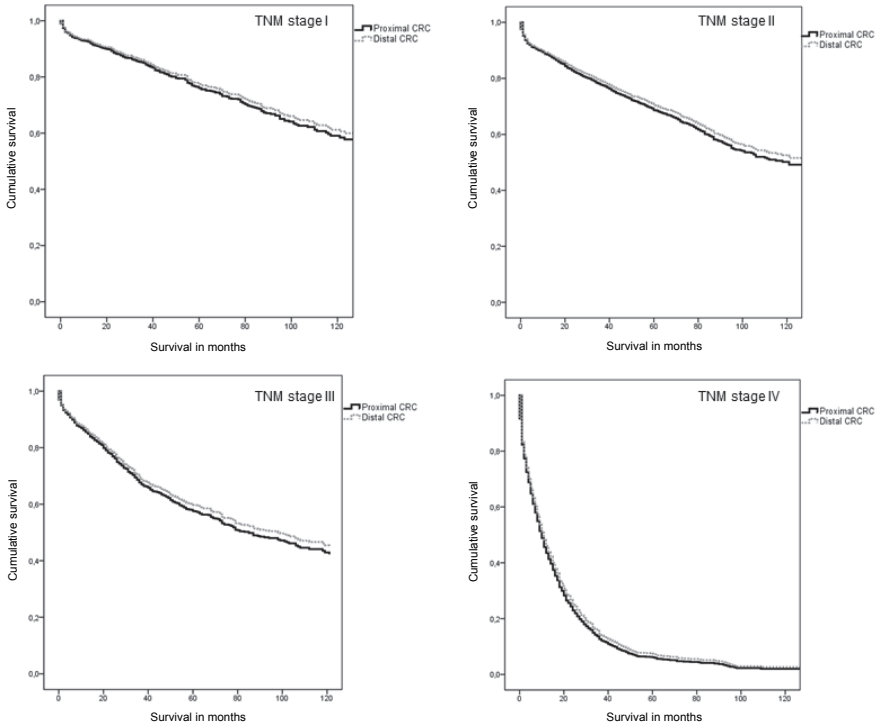

Figure 7.2 Stage specific survival. Cox regression analysis, age and sex adjusted

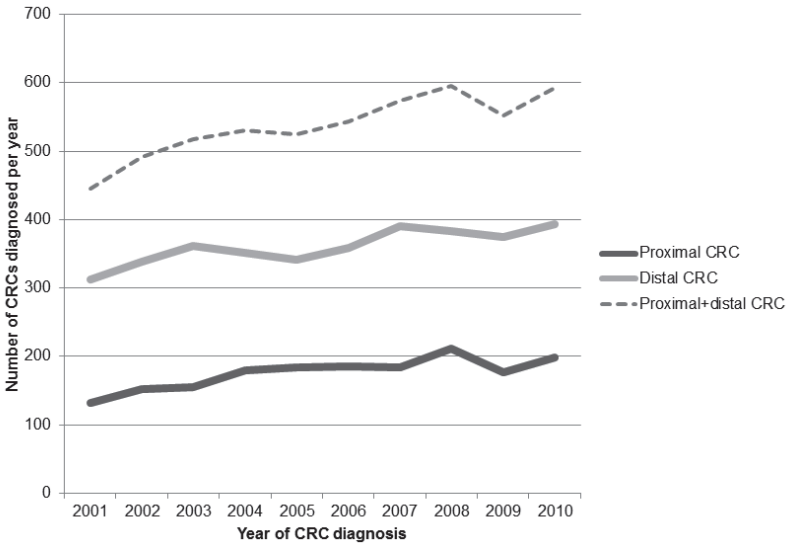

Figure 7.3 Time trends in diagnosis of proximal and distal CRCs in a South-Limburg cohort

Discussion

In this large population-based study, we found that proximal CRCs have distinct clinicopathologic features compared to distal CRCs. Thirty-three percent of patients had a CRC located in the proximal colon, these tumors are more often poorly differentiated, contain more often mucinous histology and occur more likely in older women. These pronounced differences in clinicopathologic features of proximal vs. distal CRCs may point to separate biological pathways. Despite pronounced clinicopathologic differences, survival of patients with proximal vs. distal CRCs was comparable, when corrected for age, sex and stage.

We observed that proximal CRCs show a distinct biological phenotype with larger tumors containing mucinous histology and poor differentiation, independent from tumor stage. These findings are in line with other studies[17,25-27] and point to involvement of the serrated neoplastic pathway. Serrated colorectal cancers typically display microsatellite instability and CpG island methylator phenotype (CIMP)-high.[28] Overall, in proximal CRCs microsatellite instability is often seen, whereas in distal CRCs more chromosomal instability is seen.[29-33] Precursor lesions derived from the serrated pathway are more often located proximally and show nonpolypoid appearance.[28] In addition, also conventional adenomas located in the proximal colon are more often nonpolypoid and contain high-grade dysplasia compared to precursor lesions located in the distal colon.[10] Our data show that proximal stage I CRCs – either derived from the serrated neoplastic pathway or via the conventional adenoma-carcinoma sequence – have significantly more often flat macroscopic appearance compared to distal CRCs, rendering them more difficult to detect.[34] Since the macroscopic shape (Paris classification) of a tumor may change in more advance stages, reliable conclusions of shape can be drawn in early CRCs only. Two studies from Japan showed an association between flat shape and proximal CRCs.[16,17] In a prospective colonoscopy study, Konishi *et al.* found submucosal depressed type CRCs were more often proximal located compared to distal, with 17% vs. 5%.[16] Nawa and co-authors analysed data from a Cancer Registry including 34 hospitals and found within 3552 CRCs, flat-type early CRCs was more often proximally located compared to distal (44% vs. 25%, $p<0.01$).[17] Our study is one of the few studies outside Japan where morphology of proximal versus distal CRCs was examined in an average risk population.[15] We clearly demonstrate flat tumor macroscopic appearance, in addition to size, is an important feature of proximal CRCs (OR 1.22, 95%CI: 1.05-1.42). Overall, more insight into the macroscopic appearance in relation to the exact biological pathway between proximal and distal CRCs is necessary to design more effective screening and surveillance strategies.

We confirm previous findings that proximal CRCs are more prevalent in women and also in older patients with more prevalent comorbidities.[11,25,33] In a German multicenter study by Benedix *et al.* evaluating 17,641 CRC patients, the authors found 55% of patients with proximal CRC were women vs. 46% of patients with distal CRC, furthermore they found the women were 4.5 years older than men when diagnosed with

proximal CRCs.[27] The potential explanations could be related to both biological as well as environmental factors. Proximal CRCs become symptomatic (i.e. blood loss, weight loss, change of bowel habit) at a later stage, resulting in a later tumor detection, the difference of age distribution, in combination with larger tumors.[25] On the other hand, detection of CRC in older, frailer patients with comorbidities, a prior history of CRC, and less sufficient bowel preparation is more difficult and lesions or CRC might be missed. These patient characteristics in combination with subtle (flat) tumor appearance, could partly explain the overrepresentation of proximal CRCs within postcolonoscopy CRCs.[6]

Several studies have pointed to the importance of tumor location as a prognostic marker[13,35] but this has not been confirmed by others,[27,36] who even suggest improved survival of patients with stage II proximal CRC and impaired survival for those with stage III proximal CRC compared to stage-matched patients with distal CRCs.[37] Over the past years, multiple studies suggest there is an overall shift towards the proximal colon in CRC diagnosis. It is hypothesized that potential factors involved in this shift, include aging of the population, influence of environment such as physical activity or red meat consumption and systematic screening.[15,38] In our study of predominantly symptomatic patients in a non-screening setting, we did not observe a left to right side CRC shift (Figure 7.3), however, the period of ten years observation might be too short to observe such a shift. The overall increase in annual numbers of CRC detection in our stable population of South-Limburg is in line with similar observations by others.[15,21,38] However, the proportion of proximal vs. distal CRCs in our population remained constant. In addition, we did not observe significant differences in survival when corrected for age, sex and stratified for tumor stage.

Strengths of this study include the population-based setting and the use of clinical records in conjunction with a validated nationwide cancer registry.[22] The population is well-characterized and reconstructs the real-world scenario in a large GI endoscopy practice. We increased the accuracy of data by verifying all charts individually. However, some limitations need to be acknowledged. This is a retrospective evaluation of clinical data. Hence, the results are dependent on the reliability of data registration across the study period. By using validated national registries (e.g., the pathology database and The Netherlands Cancer Registry), and given the low migration rate of the population in South-Limburg,[21] it is unlikely that missed cases could change significantly the outcomes and conclusions of our study. By analyzing patients with proximal and distal CRCs, in this study we included patients with a history of CRCs and with multiple (synchronous or metachronous) CRCs. Thus a patient could have had both proximal and distal CRC and by using the most advanced tumor for analyses, this could bias the results. However, by conducting sensitivity analysis including only patients with single CRCs, the results were comparable. Thus, we chose to use the current overview of our data, representing the real-world scenario. Finally, at this stage, besides the histopathological characteristics we do not have additional information on the exact molecular tumor profile of these CRCs. In a recent pooled analysis of three studies involving metastatic disease, the authors showed differences in gene expression between the proximal and distal colon.

Right-sided tumor location was independent of mucinous histology or BRAF mutational status, a negative prognostic marker.[13] However, this study was based on metastatic disease and it is unknown whether these observed differences apply to primary resected tumors. This information may help to further distinguish subgroups of patients who might benefit from more intense post polypectomy or post-CRC surveillance.

In conclusion, in this population-based study including 5,126 patients diagnosed with CRC, 33% of patients had proximal CRC. These proximal cancers showed distinct features both at patient and tumor level compared to distal CRCs, suggestive of a distinct biology. More specifically, in comparison with distal CRCs, proximal CRCs in general were related to poorly differentiation, mucinous histology and flat macroscopic appearance, which support the hypothesis that proximal CRCs are at risk of being missed due to subtle appearance.

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8

Understanding the biologic behavior of sessile serrated adenomas/polyps

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Letter to the Editor

With great interest we read the recent article by Tinmouth *et al.* in this Journal, adding evidence on the importance of accurate detection, classification and complete endoscopic resection of sessile serrated adenomas/polyps (SSA/Ps) to avoid the occurrence of postcolonoscopy colorectal cancers (PCCRCs).[1] The biologic behavior of SSA/Ps is sparsely understood. Here, we present the case of a patient who developed a PCCRC 4 years after a colonoscopy with removal of a SSA/P with dysplasia.

A 77-years old woman underwent colonoscopy due to microcytic anemia (Hb, 4.1 mmol/L, MCV, 69 fL), showing a 40 mm large, flat growing adenocarcinoma (pT3N0M0) in the proximal ascending colon (Figure 8.1a-c). Her family history was positive for CRC (one sister, older age), for which three colonoscopies have been performed in the past, showing a small adenoma only. The most recent colonoscopy (51 months prior to CRC diagnosis, at age 73-years), identified 3 polyps which were all removed, as follows: in the proximal ascending colon, a 3 mm SSA/P with dysplasia removed by cold biopsy (Figure 8.1d); in the distal ascending colon, a 3 mm sessile tubular adenoma with low-grade dysplasia removed by cold biopsy, while in the transverse colon, an 8 mm sessile tubulovillous adenoma with high-grade dysplasia was found and removed by snare polypectomy). Given the age and general condition, surveillance was not recommended.

It is known that over 75% of PCCRCs result from missed or incompletely resected lesions.[2,3] In a smaller proportion of cases, biologic factors associated with a faster progression play a role.[4] A stepwise clinical judgment, evaluating the time to diagnosis and clinicopathologic features of the tumor, can help to estimate the potential etiology of PCCRCs.[2,3,5] Using such algorithm, as detailed elsewhere,[2] we consider this case likely illustrates a newly developed cancer – albeit incomplete resection of the initially identified sessile serrated polyp or a missed lesion cannot be excluded. The histologic features of the tumor (i.e. serration and mucinous differentiation) support the involvement of the serrated neoplastic pathway.[6] With the advent of technology, SSA/Ps are nowadays increasingly recognized in the day-to-day endoscopy practice.[7] The subtlety of their endoscopic appearance (i.e. nearly half of them have a flat morphology),[8] implies the need for training to increase the proficiency in detection and resection. The take-home message of this case is two-fold: comprehensive endoscopic characterization of precursor lesions at index-examination and PCCRCs, including extensive photodocumentation is crucial to retrace, as far as possible, the likely etiology of PCCRCs.[9] Accurate histologic classification of serrated polyps and close surveillance after resection of SSA/Ps are likely beneficial.[6]

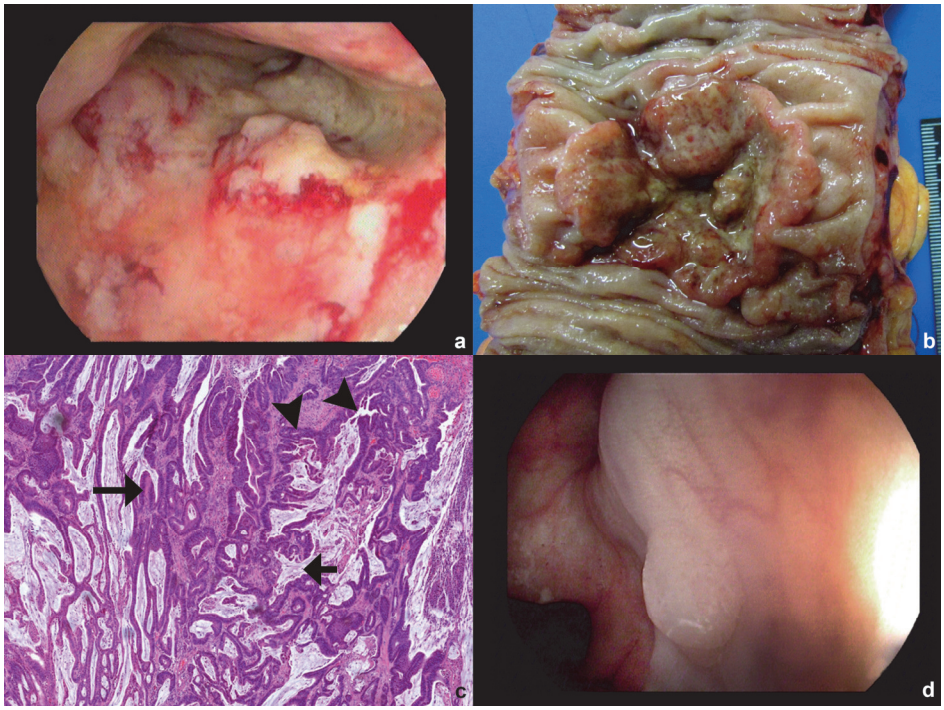

Figure 8.1 Clinicopathologic features of a colorectal cancer identified 51 months after a colonoscopy. Colonoscopy (**a**) and the resection specimen (**b**) showed a flat appearing tumor, with a central depression, which was located in the ascending colon. Histopathology (**c**) indicated a pT3N0M0 adenocarcinoma which displayed serration (arrowhead), mucinous differentiation (short arrow) and eosinophilia (long arrow), features suggesting the involvement of the serrated neoplastic pathway. At previous colonoscopic examination completion was documented and the bowel preparation was adequate. In the proximal ascending colon a 3 mm polyp was found (**d**) and removed by cold biopsy. Histopathology showed a SSA/P with cytologic dysplasia

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9

General discussion

Colonoscopy is one of the most commonly performed endoscopic procedures worldwide, serving for diagnosis of colorectal and ileal diseases, screening for colorectal cancer (CRC) and surveillance. In the Netherlands, around 200,000 colonoscopies are performed each year for regular care and this number will increase by 80,000 when the nationwide CRC screening program has been fully implemented.[1] Over the past decade, continuous efforts have been directed towards optimizing the quality and safety of colonoscopy. Although far from perfect, colonoscopy still remains the gold standard for diagnosis of colorectal (pre)neoplasms and for treatment of colorectal lesions. There is now compelling evidence that the majority of *postcolonoscopy colorectal cancers* result from limitations in the technical performance of colonoscopy. In-depth analysis of such technical factors is critical to maximize the effectiveness of colonoscopy in clinical practice. A small proportion of the postcolonoscopy CRCs can be associated with biological factors operating alone or in combination with technical factors.

In this thesis, we investigated the contribution of missed, incompletely resected lesions, and biological factors associated with a more rapid growth, to *postcolonoscopy CRCs* in a large population-based gastroenterology practice from South-Limburg, the Netherlands. A better understanding of such factors will permit to target training resources to ensure the success of our nationwide screening program. In **Chapter 1** we have reviewed the existing literature. Aims and outlines of the various chapters have been stated in **Chapter 1**.

Monitoring interval CRC in clinical practice

Definitions and taxonomy

In **Chapter 2** we evaluated the current studies on the incidence and on most common causes of postcolonoscopy CRCs. We observed a wide variation amongst studies with regard to the postcolonoscopy CRC rate, from 2.9% to 9.6% of all diagnosed CRCs and from 1 in 130 colonoscopies to 1 in 1,000 colonoscopies (**Table 2.1**). A systematic review and meta-analyses showed that approximately 1 in 27 CRCs (3.7%) are still postcolonoscopy CRCs.[2] We should bear in mind that the heterogeneity among the studies was high, precluding definition of international standards.[3] Such heterogeneity was several-fold: regarding the demographic characteristics of the populations, study methodology, but most importantly the definitions used for an *interval CRC* (**Chapter 2**). The Expert Working Group on 'Right-sided lesions and interval cancers' of the Colorectal Cancer Screening Committee of the World Endoscopy Organization proposed an international standardized nomenclature for an *interval CRC*, which applies to colorectal cancer screening irrespective of the test modality used and to colonoscopy surveillance (**Chapter 5**). In this framework, all CRCs diagnosed can be classified into screen-detected cancers and non-screen detected cancers, which can be interval CRC or cancers due to general factors, such as in patients who are not compliant with screening

(**Figure 5.1**). This nomenclature has been adopted by the Dutch National Institute for Public Health and the Environment and was applied to monitor and report on interval CRC within the nationwide CRC screening program in the Netherlands.[1]

Cancer diagnosis by colonoscopy

A uniform terminology is the first step in speaking the same scientific language to ultimately unravel the magnitude of the problem and the main causes of postcolonoscopy CRCs. The next step is to evaluate current limitations in colonoscopy performance which may affect cancer prevention in routine clinical practice. To this end, we conducted a population-based study of all 5,701 patients diagnosed with CRC over a 10 year period in South-Limburg. We retrieved clinicopathological records at three large-volume (one university and two non-university) hospitals and cross-linked these data with the validated Netherlands Cancer Registry and the national pathology database (PALGA).[4,5] All digital clinical and histopathology records were reviewed, as well as photo-documentation of resected CRC specimens.

We defined postcolonoscopy CRCs as colorectal cancers diagnosed within five years after an index colonoscopy. In **Chapter 3** we described that postcolonoscopy CRCs account for 2.9% of all diagnosed CRCs in our region, which seems to be in the lower range.[2] Importantly, in our experience, over 65% of the postcolonoscopy CRCs were attributable to missed or incompletely resected polyps. These findings are in line with a recently published pooled multicohort analysis of 8 studies by Robertson *et al.*[6] showing that over 70% of cases were missed or incomplete resected adenomas.

Besides, in our CRC cohort, metachronous CRCs - defined as a second primary CRC, diagnosed >6 months after the primary CRC, represented 1.8% of all diagnosed CRCs (**Chapter 4**). Similar to postcolonoscopy CRCs, a significant proportion of these metachronous cancers were associated with missed (43%) and incompletely resected (5%) polyps, while the remainder were attributable to non-compliance with surveillance guidelines (43%), newly developed cancers (5%) or inadequate bowel preparation (3%).

The lessons learned from this large, population-based study spanning one decade of colonoscopy experience in the period preceding the start of the nationwide screening program, are of utmost value. Such information improves our understanding of the gaps that still exist with respect to knowledge and colonoscopy skills and provide clues for interventions. Our data indicate that there is considerable room for improvement. For example, a substantial proportion of the postcolonoscopy CRCs (**Chapter 3**) and metachronous CRCs (**Chapter 4**) were flat (in particular the early tumors). We assume that flat precursor lesions, which are only recently recognized in Western colonoscopy practice,[7] have resulted in limited effectiveness of colonoscopic cancer prevention. A targeted educational program is now running at our university hospital in Maastricht aiming to reduce the incidence of postcolonoscopy CRCs by training on diagnosis and treatment of nonpolypoid (flat and depressed) colorectal neoplasms.[8,9]

Potential explanations for postcolonoscopy colorectal cancer

Next to the proportion of postcolonoscopy CRC in our practice and their clinicopathologic characteristics, we evaluated the potential explanations, i.e. the 'etiologic factors'. To compare our data with existing studies, we applied a previously described algorithm by Pabby *et al.*[10] to evaluate the potential causes of interval CRC (**Figure 9.1**).[6,11] The following factors were taken into consideration: the time elapsed from prior colonoscopy to cancer diagnosis, the findings at prior colonoscopy, and the tumor characteristics (e.g., location, stage at diagnosis, histopathology). We realize that this algorithm is, although uniformly applied, logical, and consistent,[12] not perfect because it is based on assumptions.[13] For example a lesion that is diagnosed within 36 months may not be missed but may possibly be a new lesion that has rapidly developed from normal mucosa. On the other hand, underestimating the adenoma dwell time (time from adenoma to carcinoma)[14] may overestimate those deemed to be new cases and falsely lower the number of cases classified as missed. Nevertheless, studies applying such algorithm consistently found that missed lesions represent the dominant cause of postcolonoscopy CRC.[6,10,11,15-17]

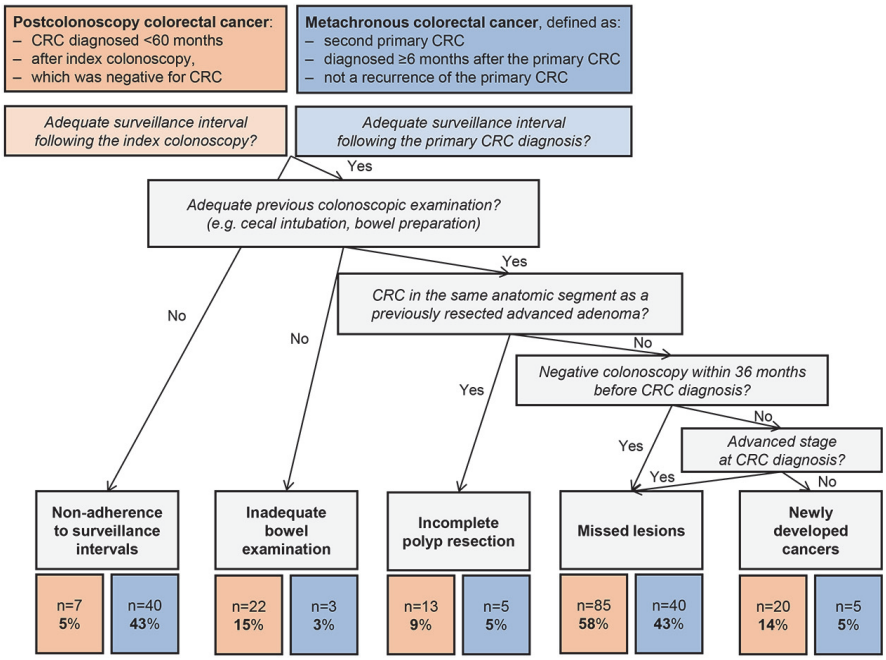

Figure 9.1 Algorithm to evaluate the potential cause of postcolonoscopy and metachronous colorectal cancers.

To summarize, this thesis shows that a significant proportion of CRC developed after a previous colonoscopy or previous surgery for CRC, can be prevented by improvement of the quality in performance of colonoscopy.

Interval colorectal cancer: technical performance or biology?

Although the majority of postcolonoscopy and metachronous CRCs are attributable to missed lesions (**Chapters 3, 4**), biologic factors are also thought to play a role.[18] It is plausible that postcolonoscopy CRCs are the result of a mix of technical and biologic factors. For example, as mentioned in the previous section of this chapter, the nonpolypoid colorectal neoplasms are more challenging to diagnose and resect endoscopically. In addition, a subgroup of them contains molecular features associated with a more aggressive biologic behavior.

Quality of colonoscopy

In an attempt to correlate the postcolonoscopy CRC rate with colonoscopic quality measures amongst individual colonoscopists, we examined a total of 6,400 colonoscopies performed by 23 endoscopists over 3 time periods in South-Limburg (**Chapter 6**). We compared the quality in performance of colonoscopy in our gastroenterology practice with international standards.[19] We found that the core quality measures in this group of colonoscopists improved significantly over the past years, in particular the mean adenoma detection rate (ADR), proximal adenoma detection rate and mean adenoma per procedure. For example, the overall ADR increased significantly from 22.5% in 2007 to 25.8% in 2013. Importantly, the variability among colonoscopists regarding ADR decreased significantly from 37% in 2007 to 15% in 2013. A significant decrease of the coefficients of variation over time was also observed, confirming such improvements.

Quality measures for colonoscopy have been recommended already since more than one decade.[20] Many studies including ours showed that wide variations exist among endoscopists regarding quality in colonoscopy performance in daily practice.[21-24] It is thought that endoscopists with a lower ADR more likely overlook polyps, especially the subtle appearing (flat and depressed) lesions, which are common in the proximal colon. Moreover, the ADR has been shown to be an important predictor of postcolonoscopy CRCs.[25,26] A landmark paper by Corley *et al.* showed a range in mean ADR from 7.4% to 52.5% among 136 gastroenterologists performing a total of 314,872 colonoscopies. The authors identified 712 postcolonoscopy CRCs and found colonoscopists with the highest ADRs had an adjusted hazard ratio for diagnosis of postcolonoscopy cancer of 0.52 (95%, CI 0.39-0.69) compared to colonoscopists with the lowest ADRs.[27]

The protective effect of colonoscopy against CRC appears to be influenced by the specialty of endoscopists. Amongst others,[6,28-31] Singh *et al.*[32] demonstrated that

colonoscopy performed by a gastroenterologist provides better protection against death from proximal CRC, while this was not found for colonoscopies performed by endoscopists from other specialties. In our studies (**Chapters 3, 4**), we could not observe such differences, most likely because of the relative small number of non-gastroenterologists among endoscopists in the Netherlands and in South-Limburg.

Biologic factors

Although the majority of postcolonoscopy CRCs are attributable to missed or incompletely resected polyps (**Chapter 3**), biologic factor may impact the outcome of colonoscopy as well. Nonpolypoid (flat and depressed) colorectal neoplasms, either conventional adenomas or sessile serrated adenomas/polyps, are now increasingly recognized as an important contributor to postcolonoscopy CRC.[33,34] Such an example is illustrated in **Chapter 8**. A patient with a history of multiple colonoscopies for adenomas developed a postcolonoscopy CRC 4 years after removal of a sessile serrated adenomas/polyp with dysplasia. By applying the algorithm previously described (**Figure 9.1**), this case was classified as a newly developed cancer. Interestingly, this tumor was located in the proximal colon and showed flat morphology (**Figure 8.1b**), features by which CRCs are more easily missed and a combination of procedural and biology related factors could be involved.

Still little is known about the contribution of the various forms of serrated polyps to colorectal carcinogenesis.[35] The majority are considered harmless hyperplasic polyps, while sessile serrated adenomas/polyp with and without dysplasia, and traditional serrated adenomas are (pre)malignant in potential.[36] According to Burgess *et al.* sessile serrated adenomas/ polyps with cytologic dysplasia are considered a triple threat for interval CRC.[37] These lesions are rapidly progressive, evade detection through their subtle shape, and are difficult to resect because the endoscopist may resect only the dysplastic component resembling a conventional adenoma, leaving the unrecognized surrounding nondysplastic component. As a consequence, large variation exists among colonoscopists in the detection of serrated polyps.[21,38] However, in addition, pathologists might fail to recognize sessile serrated adenomas/polyps with dysplasia if they disregard or overlook serrated histology in what appears to be a conventional adenoma or if they receive only the dysplastic nodule in an incompletely resected specimen.[39,40] Therefore, colonoscopists and pathologists should continuously cooperate in optimizing training in the recognition, removal and classification of all types of colorectal neoplasms.

As described in **Chapter 2**, microsatellite instability, CpG Island Methylator Phenotype (CIMP), and BRAF mutations are more often associated with postcolonoscopy CRCs than prevalent CRCs.[18,41-45] These characteristics have typically been associated with the serrated neoplastic pathway[46] but appear also to be related to the *proximal* colon. It has been suggested that CRC can be roughly divided into two different subtype: namely proximal and distal CRC.[47] Proximal and distal neoplasms show distinct epidemiological, clinical, histological and molecular characteristics.[33,48] In a

previous study at our institution, we found that proximal colorectal neoplasms with advanced histology are more frequently small in size or have a nonpolypoid appearance than the distal ones.[33] Similar findings were reported in a study from the USA.[48] Overall, nonpolypoid precursor lesions show distinct molecular features than their polypoid counterparts, such as lower APC mutation rate or more often 5q loss.[49-51] Especially the lateral spreading tumors of non-granular subtype and the depressed lesions seem to be associated with a more aggressive biologic behavior.[51]

In **Chapter 7** of this thesis, we have investigated the site-specific differences in clinicopathological characteristics of CRCs. We hypothesized that proximal CRCs in general show distinct features compared to distal CRCs, in line with proximal precursor lesions and postcolonoscopy CRCs. Overall, proximal CRCs were more common in older patients, especially women. Right-sided cancers were larger in size, more like poorly differentiated, and contained mucinous histology. Despite these tumor features, survival analyses showed no significant difference in survival between patients with proximal and distal CRCs. Taken together, these data support the assumption of biological differences between proximal and distal CRCs. It therefore seems likely, that in addition to endoscopist performance (i.e. in detection and resection of subtle but relevant neoplasms in the proximal colon) biological factors may in part explain the disparity between proximal and distal colon with regard to colonoscopic cancer prevention.[52,53]

Implications for the clinical practice and suggestions for future research

Information on the molecular profile of the postcolonoscopy CRCs identified in our population-based cohort would be of great value to differentiate the contribution of chromosomal instability and the serrated neoplastic pathway to postcolonoscopy CRCs. Progress in understanding the molecular biology of postcolonoscopy and interval CRC will help to clarify the contribution of newly described molecular pathways to colorectal carcinogenesis, i.e. the role of nonpolypoid (flat and depressed) adenomas and sessile serrated adenomas/polyps. It will also clarify the contribution of well-known syndromes (i.e. serrated polyposis syndrome, Lynch syndrome) to postcolonoscopy CRC, so it might be beneficial for identifying subgroups of patients at higher risk for CRC. At this stage, such molecular analyses are underway.

Monitoring of interval CRCs during screening programs is of paramount importance to guarantee both quality and effectiveness of screening. Such data are now underway in several countries.[1, 54-56] Due to the relatively low rates of postcolonoscopy CRC (i.e. in our experience 1.8/1,000 colonoscopies per year, **Chapter 3**), observation of large cohorts over long time periods is required to generate robust estimates. By now, data from large observational, case-control studies indicate that the majority of postcolonoscopy CRCs are preventable, a key-finding of this thesis.[6,11,57,58] Training in recognition and treatment of nonpolypoid neoplasms seems to be a useful intervention to

minimize the postcolonoscopy CRC rate,[9] further prospective studies in screening setting should confirm this observation. For the time being, lessons learned from these clinical studies are of importance for the success of our nationwide screening program. A highly effective program will increase the motivation of patients and endoscopists to participate. After the first year of screening for CRC in the Netherlands, promising data showed that the observed participation rate and diagnostic yield are higher than previously estimated (participation rate: 71% vs. 60%; CRC diagnosis: 8% vs. 6%).[1] On the long term, this screening program should result in more early CRC detection and less CRC related mortality, ideally minimizing the interval CRC rate to nearly zero.

As outlined in this thesis, it became clear that low quality colonoscopy can result in overlooking polyps, especially the nonpolypoid colorectal neoplasms, favoring the development of postcolonoscopy and metachronous CRC. Therefore, efforts should be made to optimize the use of colonoscopic resources. First, uniformity in terminology and categorization of colorectal neoplasms should be adopted in clinical practice, to allow comparison between studies. Ideally, each postcolonoscopy CRC diagnosed in daily practice should be identified and subject to scrutiny to provide feedback to endoscopists. Colonoscopists need to pay special attention to update their knowledge and skills in endoscopic diagnosis and resection techniques. Overall, a multidisciplinary approach with joint educational programs and close collaboration between gastroenterologists, pathologists, surgeons and oncologists will improve quality of colorectal cancer care. Such strategy will professionalize the practice of colonoscopy and maximize the benefits of screening. Future research will elucidate the biologic behavior of postcolonoscopy CRCs to possibly develop tailored management and follow-up strategies for patients at higher risk for CRC.

Key messages of this thesis

What are the new findings?

- In our experience, nearly 3% of the patients diagnosed with CRC had a previous negative colonoscopy in the 5 years prior to CRC diagnosis. Also 2% of the patients with a history of CRC developed a new CRC during colonoscopic surveillance after surgery.
- Postcolonoscopy CRCs are more often proximally located in the colon, small in size and have a flat macroscopic appearance. The majority of postcolonoscopy CRCs are attributable to procedural factors: missed lesions (58%), inadequate examination/surveillance (20%) or incomplete resected lesions (9%). Thus, most postcolonoscopy CRCs seem to be preventable.
- Metachronous CRCs are also small in size and often poorly differentiated. The majority of metachronous CRCs are attributable to missed lesions (43%), non-compliance with surveillance advice (43%) and incomplete resected lesions (5%). Both more intensive and high quality of colonoscopy can help to prevent CRC during surveillance after colonic surgery for CRC.
- Proximal and distal CRCs have different macroscopic and biological characteristics, suggesting a difference in the underlying carcinogenesis pathways.
- Flat appearing (early) CRCs are overrepresented among postcolonoscopy and metachronous CRCs and are more prevalent in the proximal colon, which suggests that nonpolypoid (flat and depressed) colorectal neoplasms play an important role.

How might these results impact clinical practice in the future?

- Uniformity in terminology, methodology and endpoints is the first step to compare outcomes between studies.
- Next, monitoring of interval CRC rate during screening programs is critical to maximize both quality and effectiveness.
- Examination of each case of interval CRC using a structured approach is important to provide feedback to the medical community and our patients.
- Technical factors still have a dominant role in the occurrence of postcolonoscopy CRC. Every single improvement in colonoscopy training is worthwhile and needs full consideration.
- A better understanding of the biologic factors associated with CRC will increase the overall knowledge and pave the way towards optimized diagnosis, prevention and treatment of the disease.

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Addendum

Summary

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer-related mortality in the Netherlands. Colonoscopy is the primary or follow-up screening modality for CRC diagnosis, which implies *high quality* is of critical importance. Gaps in colonoscopic performance should be identified and tailored strategies should be developed to optimize the effectiveness of colonoscopy in cancer prevention.

In this thesis, we aimed to investigate epidemiologic, clinical, and histopathologic features of CRC diagnosed in South-Limburg, The Netherlands. We specifically studied the quality of colonoscopy performance and risk factors for the occurrence of (postcolonoscopy) CRCs.

In the first part of this thesis, we focus on monitoring and reporting postcolonoscopy CRCs in routine clinical practice. **Chapter 1** summarizes the main goals of this thesis. In **Chapter 2**, we reviewed the current literature on postcolonoscopy CRC risk and the most common explanations of the origins of postcolonoscopy CRCs. Worldwide, up to 10% of all CRC patients previously underwent a colonoscopic examination (i.e. postcolonoscopy CRC). Comparison across studies showed large heterogeneity in the definitions used for a postcolonoscopy CRC (e.g. definitions range from 6 months to 36 months, from 6 months to 60 months, and even 120 months after a colonoscopy). Furthermore, the methodology applied to calculate postcolonoscopy CRC rates varies substantially within studies. Several factors have been associated with the occurrence of postcolonoscopy CRCs. Foremost, missed, incompletely resected lesions and newly developed cancers. Missed lesions are thought to represent a major cause of postcolonoscopy CRCs, with nonpolypoid (flat or depressed) neoplasms and sessile serrated polyps likely playing a significant role. Molecular events underlying progression of such lesions may further augment the cancer risk. We conclude that education and training programs aiming to improve the quality of colonoscopic cancer prevention should pay additional attention to the accurate detection and effective resection of such subtle lesions.

To evaluate the postcolonoscopy CRC rate and the underlying factors in our endoscopy practice, we conducted a population-based multi-center study in South-Limburg (**Chapter 3**). We included all newly diagnosed patients with CRC from 2001 to 2010. We reviewed colonoscopy and histopathology records and the Netherlands Cancer Registry data. We defined postcolonoscopy CRCs as cancers diagnosed within 5 years after an index-colonoscopy. A total of 5,107 CRC patients were included, of whom 147 patients (2.9%) had postcolonoscopy CRC. Logistic regression analysis, adjusted for age and gender, showed that postcolonoscopy CRCs were significantly more often proximally located (OR 3.92, 95%CI 2.71-5.69), smaller in size (OR 0.78, 95%CI 0.70-0.87), and more often flat (OR 1.70, 95%CI 1.18-2.43) than prevalent CRCs. When evaluating the etiologic factors, we found that the majority were related to procedural factors, namely 57.8% were attributed to missed lesions, 19.8% to inadequate examination/surveillance, and 8.8% to incomplete resection, while only 13.6% seemed to be associated to biologic factors leading to more rapid cancer progression (new cancers). All in all, our findings

indicate that quality improvements in performance of colonoscopy, with special attention for the detection and resection of proximally located, flat precursors should be prioritized to prevent cancer.

In the study described in **Chapter 4**, we investigated the interval CRC rate and the most likely explanations for metachronous CRCs (cancers detected during surveillance after colonic resection for CRC). This has been examined in the same study population described in Chapter 3. We defined a metachronous CRC as a second primary CRC, diagnosed ≥6 months after the primary CRC. We classified the potential explanations into: cancers due to non-compliance with surveillance recommendations, inadequate examination, incomplete resection of precursor lesions (CRC in same segment as previous advanced adenoma), missed lesions or newly developed cancers. We found that 93 (1.8%) of the 5,157 CRC patients were diagnosed with a metachronous CRC. Age- and gender-adjusted logistic regression analyses showed that metachronous CRCs were significantly smaller in size (OR 0.8, 95%CI 0.7-0.9) and more often poorly differentiated (OR 1.7, 95%CI 1.0-2.8) than solitary CRCs. Of all metachronous CRCs, 43.0% were attributable to non-adherence to surveillance advice, 43.0% to missed lesions, 5.4% to incompletely resected lesions, 5.4% to newly developed cancers, and 3.2% to inadequate examination. This study shows again, that the vast majority of metachronous CRCs are attributable to missed lesions or non-adherence to surveillance advice, and hence can be prevented. Our findings emphasize the importance of both more intensive and high quality colonoscopic examination to maximize the benefit of post-CRC surveillance.

In many studies the terms *postcolonoscopy* and *interval* CRCs are used interchangeably, raising difficulties in the interpretation of outcomes and comparisons across studies. The term interval CRC is applicable for screening and subsequent surveillance, since such CRCs are diagnosed within the time interval preceding the next recommended examination. The term postcolonoscopy CRCs, on the other hand, specifically describes those CRCs identified after a colonoscopic examination, either performed for screening, surveillance or diagnostic indication. **Chapter 5** presents a proposal for standardizing the definition and taxonomy for an interval CRC. Using a modified Delphi process, the Expert Working Group on interval CRC of the Colorectal Cancer Screening Committee of the World Endoscopy Organization developed a nomenclature for defining and characterizing interval CRCs. An interval CRC is a '*colorectal cancer diagnosed after a screening or surveillance exam in which no cancer is detected, and before the date of the next recommended exam*', in line with international nomenclature on interval cancer (e.g. cervical cancer, breast cancer). A standardized nomenclature will facilitate benchmarking and enable to compare interval CRC rates across programs around the world.

In the second part of this thesis, we discuss the contribution of technical performance and biologic factors to the occurrence of postcolonoscopy CRCs. In **Chapter 6**, we have examined quality measures for colonoscopy performance in routine practice. It is known

that quality measures for colonoscopy are *operator-dependent* and vary considerably. Adenoma detection rate varies strongly between endoscopists from 9 to 60%. We evaluated variations in quality indicators across colonoscopists and practices in South-Limburg. We reviewed colonoscopy and histopathology records from three large-volume hospitals (1 university and 2 non-university hospitals). Data from colonoscopists performing at least 100 procedures per year were examined. A total of 23 colonoscopists performing 6,400 procedures were included. Overall, the mean adjusted cecal intubation rate (ACI), adenoma detection rate (ADR), mean adenoma per procedure (MAP), and proximal ADR improved significantly over time from 91.9%, 22.5%, 0.37, and 10.2% in 2007 to 95.3%, 25.8%, 0.45, and 13.4%, respectively in 2013 ($p<0.05$). The inter-colonoscopist variability in ADR decreased from 37% in 2007 to 15% in 2013 ($p<0.05$). In 2007 and 2010, quality measures were significantly higher in the university vs non-university hospitals, but no significant differences were found anymore in 2013. Taken together, these data indicate that in routine colonoscopy practice, core quality measures and indicators improved over time through decreased variability among colonoscopists and in particular improved performance of the less optimal performing colonoscopists. Our findings underscore the importance of awareness and continuous training to optimise colonoscopic performance in daily practice.

In **Chapter 7** we have analyzed the clinicopathologic phenotypes of CRC in relation to tumor site. We evaluated proximal and distal CRCs in our population-based cohort. For the purpose of this study, we included a total of 5,126 patients with 5,365 CRCs. Of all patients, 1679 (32.8%) had proximally located CRC. Proximally located CRC were identified more often in women (54.4% vs 42.3%, $p<.001$) of older age (72.0 vs 69.1 years, $p<.001$) than distal CRC. Logistic regression analysis adjusting for age, sex, and TNM stage showed that proximal CRCs were significantly more often flat (OR 1.22, 95%CI 1.05-1.42), larger in size ((OR 1.21, 95% CI 1.16-1.25), more like poorly differentiated (OR 1.46, 95% CI 1.25-1.71), and contained mucinous histology (OR 1.98, 95%CI 1.56-2.51). Cox regression analyses adjusted for age, sex, and stage, showed no significant difference in survival between proximal and distal CRCs. Thus, we concluded that proximal CRCs showed distinct biological features and shape compared to distal colorectal cancer. Our findings support the hypothesis that differences might exist in the biologic mechanisms underlying carcinogenesis in the proximal versus distal colon.

In **Chapter 8**, we present a case of postcolonoscopy CRC and discuss the potential explanations. Such approach may be used in clinical practice to understand the reasons for postcolonoscopy CRC and identify room for potential improvement.

In summary, the studies described in this thesis have assessed the quality of colonoscopic performance in a large gastroenterology practice in the Netherlands. We identified modifiable factors associated with postcolonoscopy CRCs (missed polyps, incompletely resected polyps and non-compliance to surveillance recommendations). Uniformity in terminology and categorization of colorectal neoplasms are crucial to allow meaningful comparison between studies. Ideally, each postcolonoscopy CRC diagnosed

in daily practice should be identified and the potential causes should be analyzed to provide feedback to endoscopists. Such strategy will optimize the practice of colonoscopy and maximize the benefits of our nationwide screening program.

Nederlandse samenvatting

Darmkanker, ofwel colorectaal carcinoom (CRC), is een van de meest voorkomende vormen van kanker. Jaarlijks wordt er bij 14.000 mensen in Nederland CRC gediagnosticeerd en het staat daarmee op de derde plaats van meest voorkomende vormen van kanker. Daarnaast is het de tweede oorzaak van aan kanker gerelateerde sterfte. Darmkanker ontstaat uit voorstadia (poliepen) die langzaam uitgroeien tot kanker. Wanneer men tijdig een poliep detecteert en verwijdert, kan men in principe CRC voorkómen. Om deze reden is CRC geschikt voor screening.

In januari 2014 is men in Nederland gestart met bevolkingsonderzoek naar darmkanker. Dit onderzoek wordt uitgevoerd door middel van een ontlastingsonderzoek op bloedsporen die darmkanker of poliepen kunnen afgeven. Wanneer de uitkomst van deze test ongunstig is, wordt vervolgens een coloscopie verricht. Een coloscopie (onderzoek van de darm middels een flexibele slang met een klein lampje en een camera aan het uiteinde) heeft als doel poliepen en kanker op te sporen en indien mogelijk te verwijderen. Een kwalitatief goed uitgevoerde coloscopie is essentieel voor adequate en effectieve bescherming tegen CRC.

Helaas toont recent onderzoek aan dat de coloscopie niet altijd perfect is in het detecteren van poliepen of kanker. Bij sommige mensen wordt er binnen vijf jaar na een coloscopie toch CRC gevonden. Deze kankers worden *postcoloscopie CRCs* of *interval CRCs* genoemd. Het is nog onduidelijk wat de oorzaak van deze kankers is. Zijn ze het gevolg van suboptimaal onderzoek doordat een endoscopist een poliep mist tijdens coloscopie of deze niet goed verwijderd heeft? Of is een agressief biologisch gedrag de verklaring, doordat de poliepen/kankers sneller groeien of een ander uiterlijk hebben en daardoor gemist worden?

Om antwoord op deze vragen te krijgen, hebben we ons in dit proefschrift gericht op de epidemiologische, klinische en histopathologische kenmerken van CRCs gediagnosticeerd bij patiënten uit Zuid-Limburg. We bestudeerden in het bijzonder de kwaliteit van de coloscopie en risicofactoren voor het ontstaan van (postcoloscopie) CRCs. Meer kennis over het ontstaan van deze postcoloscopie kankers is van groot belang aangezien een succesvol bevolkingsonderzoek op darmkanker gekenmerkt dient te zijn door hoge kwaliteit van de coloscopieën en een zeer laag percentage postcoloscopie/interval CRCs.

In het eerste deel van dit proefschrift hebben we ons gericht op de monitoring en mogelijke verklaring van postcoloscopie CRCs in de klinische praktijk. **Hoofdstuk 1** beschrijft de belangrijkste doelen van dit proefschrift: de incidentie en de etiologie van postcoloscopie en metachrone (tweede primaire) CRCs en de associatie met kwaliteit van coloscopie. In **hoofdstuk 2** hebben we een overzicht gegeven van de huidige literatuur over postcoloscopie CRC en de meest voorkomende verklaringen over oorzaak van deze carcinomen. Wereldwijd werd een incidentie van postcoloscopie CRC gevonden tot wel 10% van alle darmkanker patiënten. Deze patiënten hadden een coloscopie ondergaan binnen vijf jaar voordat de diagnose kanker werd gesteld en bij deze coloscopie werd geen kanker gezien. De diverse studies waren in hoge mate heterogeen wat betreft de definitie van een postcoloscopie CRC, de studie opzet en

patiëntkarakteristeken. Verschillende factoren werden geassocieerd met het ontstaan van deze postcoloscopie CRCs, zoals gemiste poliepen, incompleet verwijderde laesies of nieuw gevormde carcinomen. Men denkt dat gemiste poliepen een van de meest belangrijke verklaring is voor postcoloscopie carcinomen, waarbij vlakke poliepen of de zogenaamde 'geserreerde' poliepen een mogelijke precursor laesie zijn. Specifieke aandacht en training in de detectie en adequate resectie van dergelijke subtiele laesies, zal de kwaliteit van coloscopie ten goede komen.

In **hoofdstuk 3** beschrijven we onze populatiestudie naar alle patiënten gediagnosticeerd met CRC in Zuid-Limburg (Maastricht, Heerlen, Sittard) tussen januari 2001 en december 2010. Hiervoor werden de nationale pathologie database (PALGA) en de Nederlandse Kankerregistratie gebruikt. Postcoloscopie CRC werd gedefinieerd als "*een CRC gediagnosticeerd binnen 5 jaar na een complete coloscopie",* waarbij destijds geen kanker werd gediagnosticeerd. Etiologie (verklaring) van postcoloscopie CRCs werd onderverdeeld in procedure gerelateerde factoren (gemiste poliepen, inadequate procedure/surveillance of incomplete poliep verwijdering) en biologie-gerelateerde (nieuw gevormde kanker). In totaal zijn er 5.107 patiënten met darmkanker gediagnosticeerd, waarvan 147 patiënten (2,9%) met een postcoloscopie CRC werden gediagnosticeerd. Logistische regressie analyses, gecorrigeerd voor leeftijd en geslacht, toonden dat postcoloscopie CRCs significant vaker in het rechter deel van de dikke darm (proximale colon) voorkwamen (OR 3,92, 95%CI 2,71-5,69), kleiner waren (OR 0,78, 95%CI 0,70-0,87) en vaker een vlak (non-polypoid) uiterlijk vertoonden (OR 1,70, 95%CI 1,18-2,43) dan de overige CRCs. Van de postcoloscopie CRCs werd 57,8% toegeschreven aan gemiste poliepen, 19,8% aan inadequate procedure/surveillance en 8,8% aan incomplete poliep resectie, terwijl er in 13,6% sprake was van nieuw gevormde kanker. Concluderend vonden we dat 86,4% van alle postcoloscopie CRCs het gevolg van procedure gerelateerde factoren, in het bijzonder gemiste laesies. Het verbeteren van de coloscopie kwaliteit, met specifieke aandacht voor detectie en verwijdering van vlakke poliepen gelegen in het rechter deel van de dikke darm, kan bijdragen aan het voorkomen van postcoloscopie (interval) CRCs en daarmee het optimaliseren van de Nederlandse darmkanker screening.

Hoofdstuk 4 behandelt de incidentie en etiologie van tweede primaire darmkankers, ook wel metachrone CRCs genoemd. Dit zijn CRCs in patiënten die reeds een voorgeschiedenis van CRC hebben en onder surveillance zijn na resectie van het eerdere carcinoom. Om dit te onderzoeken gebruikten we dezelfde populatie als in hoofdstuk 3 beschreven, met daarbij alle patiënten die een voorgeschiedenis van CRC hadden. We hebben een metachrone CRC gedefinieerd als een tweede primaire CRC, gediagnosticeerd ≥6 maanden na de primaire CRC. De etiologie werd toegeschreven met een aangepast algoritme zoals we dat ook in hoofdstuk 3 hebben toegepast. We maakten onderscheid tussen kankers die te wijten waren aan het niet-naleven van surveillance aanbevelingen, incomplete coloscopie, incomplete poliep resectie, gemiste laesies of nieuw gevormde kanker. Op een totaal van 5.157 CRC patiënten, bleken 93 patiënten (1,8%) metachrone CRCs te hebben. Leeftijd en geslacht gecorrigeerde

logistische regressie-analyses toonden dat metachrone CRCs beduidend kleiner waren (OR 0,8, 95% CI 0,7-0,9) en vaker slecht gedifferentieerd waren (OR 1,7, 95%CI 1,0-2,8) dan overige CRCs. Van alle metachrone CRCs was 43,0% toe te schrijven aan het niet-naleven van surveillance, 43,0% betrof gemiste laesies, 5,4% incompleet verwijderde poliepen, 5,4% nieuw ontwikkelde kanker en in 3,2% betrof het een incomplete coloscopie. Deze studie toonde aan dat de meerderheid van metachrone CRCs toe te schrijven bleek aan gemiste laesies of het niet-naleven van surveillance. Waardoor ook deze bevindingen onderstrepen het belang van zowel de frequentie van coloscopieën als kwaliteit van het coloscopisch onderzoek om de post-CRC surveillance te optimaliseren.

Zoals blijkt uit de bevindingen in hoofdstuk 2, worden in de huidige literatuur de termen *postcoloscopie* en *interval* CRC door elkaar gebruikt. Hierdoor bemoeilijkt het de vergelijking en interpretatie van de resultaten van de diverse studies. De term interval CRC lijkt in het bijzonder geschikt te zijn voor screening en de daaropvolgende surveillance, aangezien dergelijke CRC geïdentificeerd zijn binnen het tijdsinterval vóór het volgende aanbevolen onderzoek (ontlastingstest of darmonderzoek). De term postcoloscopie CRCs beschrijft specifiek die CRCs geïdentificeerd na coloscopie of dit nu in een screening of diagnostische setting is. **Hoofdstuk 5** beschrijft het voorstel voor de nomenclatuur en de internationaal geldende definitie van een interval CRC. De 'Expert Working Group on interval CRC' van de Colorectal Cancer Screening Committee van de World Endoscopy Organization' ontwikkelde een nomenclatuur voor het definiëren en karakteriseren van interval CRC. We definiëren een interval CRC als een 'colorectaal carcinoom gediagnosticeerd na een screening of surveillance onderzoek waarin geen kanker wordt ontdekt, en vóór de datum van de volgende aanbevolen onderzoek'. De Werkgroep onderschrijft het gebruik van deze gestandaardiseerde nomenclatuur waardoor het ontwikkelen van benchmarks en vergelijking tussen studies, screening programma's en landen mogelijk wordt.

In het tweede deel van dit proefschrift hebben we ons gericht op de bijdrage van technologische en biologische factoren bij het ontstaan van postcoloscopie CRC. In **hoofdstuk 6** beschrijven we onze studie naar de kwaliteit van coloscopie in de dagelijkse Zuid-Limburgse praktijk. Het is bekend dat kwaliteitsindicatoren zoals de adenoma detection rate (ADR) sterk variëren tussen de verschillende endoscopisten van wel 9% tot 60%. In deze studie richtten we ons op de verschillen in kwaliteit tussen endoscopisten en ziekenhuizen gedurende 3 verschillende tijdperiodes. We onderzochten coloscopie en histopathologie gegevens van de drie ziekenhuizen in Zuid-Limburg. Hiervoor includeerden we de bevindingen van endoscopisten die tenminste 100 coloscopieën per jaar uitvoerden. Van deze endoscopisten werden de eerste 100 coloscopieën van in 2007, 2010 en 2013 onderzocht. In totaal analyseerden we 6.400 procedures uitgevoerd door 23 endoscopisten. Over het geheel genomen verbeterden de gemiddelde coecum intubatie rate (ACI), ADR, mean adenoom per procedure (MAP), en proximale ADR aanzienlijk over de tijd, van 91,9%, 22,5%, 0,37 en 10,2% in 2007, tot 95,3%, 25,8%, 0,45 en 13,4% in 2013 ($p<0,05$). De inter-endoscopist variatie in ADR

daalde van 37% in 2007 tot 15% in 2013 (p<0,05). Kortom, deze studie toonde aan dat in de huidige dagelijkse coloscopie praktijk de kwaliteit verbeterde in de loop van de tijd, met name door een daling in de variatie tussen endoscopisten. Onze bevindingen suggereren dat bewustwording over kwaliteitsindicatoren en aanvullende training, effectief zijn in het verbeteren van de kwaliteit en opbrengst van coloscopieën.

Hoofdstuk 7 toont de karakteristieken van CRC in relatie tot de locatie van het carcinoom. We vergeleken proximale (rechtzijdige) en distale (linkszijdige) CRCs in ons Zuid-Limburg cohort. Ten behoeve van deze studie werden de gegevens van 5.126 patiënten met 5.365 CRCs vergeleken. Van alle patiënten hadden 1.679 (32,8%) een proximaal CRC. Dit betrof vaker vrouwen (54,4% versus 42,3%, p<0,001) met een oudere leeftijd (72,0 jaar versus 69,1 jaar, p<0,001) dan bij distale CRCs. Logistische regressie-analyse gecorrigeerd voor leeftijd, geslacht en TNM stadium bleek dat proximale CRCs significant vaker vlak waren (OR 1,22, 95%CI 1,05-1,42), groter in omvang (OR 1,21, 95%CI 1,16-1,25), slecht gedifferentieerd (OR 1,46, 95%CI 1,25-1,71), en mucineuze histologie bevatten (OR 1,98, 95%CI 1,56-2,51). Cox regressie analyses gecorrigeerd voor leeftijd, geslacht en het stadium, toonden geen significant verschil in overleving tussen patiënten met proximale of distale CRCs. Concluderend tonen proximale CRCs duidelijke verschillende biologische kenmerken ten opzichte van distale colorectale carcinomen. Deze resultaten versterken de hypothese dat verschillen kunnen bestaan in de biologische mechanismen die ten grondslag liggen aan het ontstaan van kanker in het proximale versus distale colon.

In **hoofdstuk 8** illustreren we de mogelijke implicatie van biologische factoren in het ontstaan van postcoloscopie CRC aan de hand van een casus. Een 77-jarige vrouw ontwikkelde een postcoloscopie CRC 4 jaar na een coloscopie met verwijdering van een sessile serrated adenoma/poliep (SSA/P) met dysplasie. Het stapsgewijze klinische algoritme, rekening houdend met de tijd tot diagnose en histologische kenmerken van het carcinoom - zoals beschreven in hoofdstuk 3 - toonde dat dit postcoloscopie CRC een "nieuw ontwikkelde kanker" betrof. De histologische kenmerken van de tumor (dat wil zeggen het geserreerde aspect en mucineuze differentiatie) ondersteunen de betrokkenheid van de geserreerde neoplastische pathway. Deze casus toont het belang van nauwkeurige endoscopische karakterisering van precursor laesies tijdens een index coloscopie en de karakteristieken van postcoloscopie CRC. Op deze wijze kunnen we de mogelijke oorzaak van postcoloscopie CRC trachten te achterhalen. Nauwkeurige histologische classificatie van geserreerde poliepen en adequate surveillance na resectie van SSA/Ps is essentieel.

Concluderend, tonen de studies beschreven in dit proefschrift dat hoge kwaliteit van coloscopie essentieel is om de ontwikkeling van postcoloscopie en metachrone CRC te voorkomen. Specifieke aandacht voor de subtiele precursor laesies, de vlakke poliepen is daarbij van belang. Uniformiteit in de nomenclatuur en etiologie van colorectale carcinomen is cruciaal om de vergelijking tussen studies mogelijk te maken. Idealiter zou bij elke postcoloscopie CRC gediagnosticeerd in de dagelijkse praktijk, de mogelijke

oorzaak moeten achterhaald en teruggekoppeld worden aan de endoscopist. In het algemeen zal de multidisciplinaire benadering met gezamenlijke onderwijsprogramma's en nauwe samenwerking tussen maag-darm-leverartsen, pathologen, chirurgen en oncologen de kwaliteit van colorectale kanker zorg verbeteren. Een dergelijke strategie zal de kwaliteit van coloscopische darmkankerpreventie en screening verder optimaliseren.

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Valorisation

Dutch universities have three main tasks: to educate at an academic level, to conduct scholarly research and to ensure that research findings impact society.[1] Valorisation is the term that governmental and university policymakers use to denote the process of "translating academic wisdom to societal benefit." This chapter is intended to translate the scientific findings of this thesis into applicable prospects for society. This thesis provides relevant new aspects and views on quality of colonoscopy and on colorectal carcinogenesis relevant for several stakeholders: first to patients, but also to health care providers and organizations involved in developing guidelines.

As described in **Chapter 1**, colorectal cancer (CRC) had a major impact worldwide also in The Netherlands, where annually 15,000 patients are diagnosed with the disease.[2] This number will even increase with the start of the fecal test based population based nationwide CRC screening program.[3] In view of this screening program, the quality of colonoscopy is key since all patients with an unfavourable fecal test result will undergo colonoscopy. Herein colonoscopy is our best available modality to detect CRC. Although generally considered as the golden standard, colonoscopy is not and cancers are being missed at colonoscopy. Suboptimal colonoscopy quality will decrease the benefit of screening programs both from a clinical and financial perspective. It is important to inform patients also about the limitations of colonoscopy. Even in experienced hands, it is not a 100% perfect diagnostic and therapeutic method. Thus, apart from being informed about the risk of perforation and bleeding during colonoscopy, a patient should also be informed about the value of the technique and the potential risk of postcolonoscopy (interval) CRCs.

In order to evaluate the current colonoscopic quality in South-Limburg, the Netherlands prior to commencing CRC screening, we conducted several studies in regional collaboration that have described in **Chapters 3, 4, 6** and **7**. The findings of these studies, first of all, show the quality at baseline is already of adequate standard, with low incidence rates of postcolonoscopy CRC (i.e. 2/1,000 colonoscopies or 2.9% of all CRC patients) and metachronous CRC compared to other studies[4,5] and with colonoscopic quality indicators who meet international standards.[6] These data are reassuring and in general should be available for patients, community and the various stakeholders. Second, the cases in which CRC was missed (i.e. postcolonoscopy CRC cases) were most likely related to procedural factors. These procedural factors are amendable for improvement by training of the endoscopist, by adhering to surveillance guidelines and by strengthening the importance of adequate bowel preparation to patients. The results on the origin of postcolonoscopy CRC and recommendations described in **Chapter 3**, are cited and distributed among patients,[7] health care providers,[3] organizations involved in developing guidelines,[8] and among scientist.[9-11] More importantly, the results are incorporated into new Dutch guidelines on colonoscopy surveillance[8] and national training modules such as the e-learning module for certification of endoscopists in the bowel cancer screening program.[3]

The results on colonoscopic quality described in this thesis form the basis for CRC screening in South-Limburg. With the implementation of e-learning module with specific attention for the detection of nonpolypoid lesions, the colonoscopic quality will further improve within the screening program, in our region but also nationwide in the Netherlands. Monitoring of each 'failure', with use of uniform nomenclature (**Chapter 5**) and evaluation of the potential origin of these missed CRCs, will further improve overall quality.

In addition this thesis presents more detailed insight on the colonoscopic quality of patients with a history of CRC. These patient will undergo lifelong colonoscopic surveillance in order to detect recurrences or metachronous CRCs. The results described in **Chapter 4** show the quality of colonoscopic surveillance in this group of patients is open for improvement. The incidence of metachronous CRC was relatively low compared to other studies,[5] but it was not zero. The majority of these metachronous CRCs are related to missed lesions and to non-adherence to surveillance guidelines. Therefore, in 2013, in the Netherlands a new guideline has been published for the surveillance of CRC survivors, underscoring the importance of quality colonoscopy in this group of patients.[8]

Prior the start of the studies described in this thesis, the main research question was whether postcolonoscopy CRCs were related to technology (procedural factors) or merely biology (new cancers). Over time, exploring the data in more detail, it became evident to us and others,[12,13] that the main explanation of postcolonoscopy CRCs is technology (in fact: missed lesions) . In contrast, some studies showed a difference in molecular make-up of postcolonoscopy CRCs compared to prevalent CRCs,[14,15] leaving room for debate. The data described in this thesis point towards a combination of factors: both technology and biology related. We have shown postcolonoscopy CRCs are missed lesions in 58% of cases. These cancers show subtle (flat and small) morphology and are located primarily in the proximal colon, factors by which they are easily missed, but also factors related to different carcinogenesis such as the involvement of the serrated pathway. By analysing each postcolonoscopy cancer case thoroughly, including DNA mutation analyses, we will further unravel the roles of technology, biology and its combination.

In short, the data presented in this thesis emphasize the high quality of the Dutch colonoscopy practice. We have pointed to potential causes for the occurrence of postcolonoscopy cancers as the majority were related to avoidable causes that provide room for improvement. These improvements (with specialo attention to the detection and removal of right sided located flat polyps, quality of bowel preparation, compliance with the surveillance guidelines) have already been incorporated into local, national and international guidelines and e-learning modules. In the future, the results on incidence, etiology of postcolonoscopy, interval, and metachronous CRCs occurring within the

screening program, will further increase our knowledge and understanding of the disease. Especially the knowledge on the role of its biology will shed light on colorectal carcinogenesis in the near future.

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2012 UEGW travel grant for UEG Week 2012
2011 Best of Digestive Disease Week (DDW) 2011 ‘Interval colorectal cancers frequently have subtle macroscopic appearance: a 10 year-experience in an academic center’.
2014 Academische Incentive Maastricht UMC 'Exploring the molecular secrets of postcolonoscopy colorectal cancer

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Curriculum vitae

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Chantal Marie Christine le Clercq was born on May 19th, 1986 in Nijmegen, The Netherlands. She graduated from secondary school at the Elzendaal College in Boxmeer in 2004 and continued with medical school at Maastricht University. She was an active member of student association Circumflex and she interrupted her studies between 2006 and 2007 to be a permanent board member. During her medical training, she accomplished clinical and scientific traineeships at the Division of Gastroenterology and Hepatology, Maastricht University Medical Center (supervisor Dr. S. Sanduleanu), where the work presented in this thesis was initiated. Part of the work presented in Chapter 3 was awarded "Best of Digestive Disease Week 2011'. From September 2011 to August 2015, Chantal worked as a PhD student affiliated to the Division of Gastroenterology and Hepatology of Maastricht University Medical Center, the Department of Internal Medicine of Zuyderland Medical Center, and GROW, School for Oncology & Developmental Biology, Maastricht University (Promotor: Prof.dr. A.A.M. Masclee, copromotor: Dr. S. Sanduleanu). In October 2015, she received the 'Maag Lever Darm Stichting' Award for data presented in this thesis. From September 2015, she started her gastroenterology fellowship under supervision of Dr. J. Buijs (internal medicine, Zuyderland Medical Center), Dr. C.M. Bakker (gastroenterology, Zuyderland Medical Center) and Prof.dr. A.A.M. Masclee (gastroenterology, Maastricht University Medical Center).

Dankwoord

‘Man sieht nur, was man weiß’ *J.W. von Goethe*

In de zoektocht naar het beste, moet men weten wat men zou kunnen aantreffen. Wanneer men het colon (dikke darm) onderzoekt, weet dan van het bestaan van vlakke, kleine, rechtszijdige poliepen en zoek niet alleen naar de gesteelde poliepen. Wanneer men Teatro Colón bezoekt, weet dan dit een prachtig plafond bezit, kijk omhoog, niet alleen naar het podium. Wanneer u dit proefschrift leest, weet dan dat vele mensen hebben bijgedragen. Het is het resultaat van duurzame samenwerking en teamwork binnen verschillende disciplines, van een grote groep mensen, zichtbaar of meer op de achtergrond. Allen wil ik daarvoor danken en enkele in het bijzonder. Allereerst dank aan de patiënten die hun medewerking hebben verleend aan ons onderzoek.

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