A single-centre analysis of post-colonoscopy colorectal cancer

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Abstract

Patients and methods: **A prospective registration of patients with colorectal cancer and a colonoscopy within the last 10 years. We tried to classify these post-colonoscopy colorectal cancers (PCCRCs) by most reasonable explanation and into subcategories suggested by the World Endoscopy Organization (WEO) and calculated the unadjusted PCCRC rate.**

Results: **47 PCCRCs were identified. The average age at diagnosis of PCCRC was 73 years. PCCRCs were more located in the right colon with a higher percentage of MSI-positive and B-RAF mutated tumours. The average period between index colonoscopy and diagnosis of PCCRC was 4.2 years. Sixty-eight % of all PCCRCs could be explained by procedural factors. The mean PCCRC-3y of our department was 2.46%.**

Conclusions: **The data of our centre are in line with the data of the literature from which can be concluded that most post-colonoscopy colorectal cancers are preventable. The PCCRC-3y is an important quality measure for screening colonoscopy. Ideally all centres involved in the population screening should measure the PCCRC-3 y annually, with cooperation of the cancer registry and reimbursement data provided by the Intermutualistic Agency (IMA).** (Acta gastroenterol. belg., **2021**, 84, **401-405**).

Key words: colonoscopy, screening, interval.

Introduction

Colorectal cancer (CRC) is the third most common form of cancer worldwide and the second leading cause of cancer-related deaths (1,2). Colonoscopy is performed routinely for CRC screening, follow-up of other abnormal screening tests, workup of signs and symptoms of gastrointestinal disease, and surveillance after CRC and polyp removal (3,4).

Post-colonoscopy colorectal cancers (PCCRCs) are a small but clinically important subset of CRC that refer to cancers that are diagnosed after a prior colonoscopy in which no cancer is diagnosed. The pathogenesis of PCCRC is likely multifactorial, including cancers and precursor adenomas that are missed or incompletely excised at colonoscopy or unique molecular pathways. Several patient factors (female gender, diverticulosis) and endoscopist factors (non-gastroenterologist physician, rural facility, low adenoma detection rate) have emerged as risk factors for PCCRC. However also certain tumour characteristics associated with PCCRC have suggested that there could be underlying molecular differences in the development of these cancers (5,6,7).

Three main pathways of tumorigenesis are described for CRC. First the conventional adenoma pathway where early events include mutations in APC and KRAS and results in aneuploidy and microsatellite instability. Second the microsatellite instable (MSI) pathway that includes Lynch syndrome CRC as well as 15% of sporadic CRCs, and third the serrated polyp pathway that accounts for 10-15% of sporadic CRCs and is exemplified by CpG island methylation (CIMP-high) and BRAF-mutation (5,7).

Terminology and definitions

PCCRCs can be subcategorized into true interval cancers, this means those identified before the next recommended screening or surveillance examination, and non-interval cancers (8).

The term interval cancer is primarily a screening and surveillance term. Its precise definition is a CRC diagnosed after a colorectal screening examination or test in which no cancer is detected and before the date of the next recommended examination. From a screening program perspective a cancer found at a subsequent screening colonoscopy is a screening "success" and not an interval cancer by definition. But from a colonoscopy quality point of view study of these procedures is worthwhile as there might have been a missed opportunity to identify a cancer or precancerous lesion at the time of the prior exam (9).

On the other hand many colonoscopy procedures, particularly diagnostic procedures, do not result in a recommendation for a further colonoscopy and therefore there is no "interval".

These non-interval cancers may be further subcategorized into those that occur at (type A) or after (type B) a recommended screening or surveillance interval and those where no subsequent screening or surveillance procedure was recommended (type C).

Determining the precise etiology of a PCCRC is challenging (3). Categorization of PCCRCs according to their most plausible explanations should be used to facilitate quality assurance work or research. We followed the proposal of the WEO (4,5) on PCCRC with categorization into 5 categories and one modifying statement: 'deviation from the planned management

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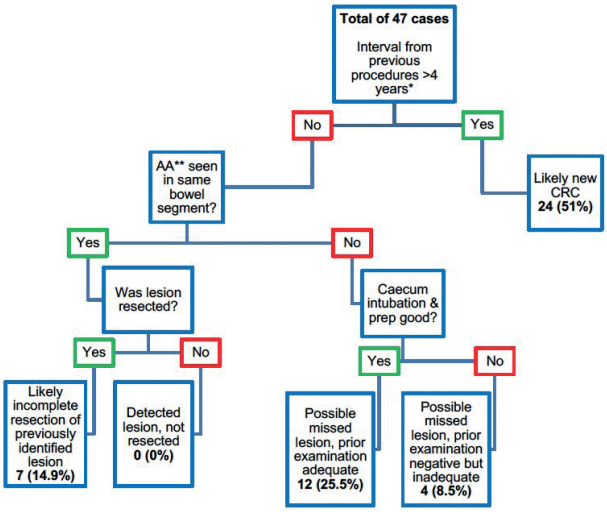

Figure 1. — Root cause analysis: most plausible PCCRC explanation (9).

pathway'. The cutoff in this algorithm is 4 years after the index colonoscopy (Fig. 1).

The PCCRC rate of a colonoscopy service determines its efficacy in detecting and preventing cancer and should therefore be considered as the principal measure of quality in colonoscopy, driving performance improvement within the service. For quality assurance purposes, a standardized method to calculate an unadjusted PCCRC rate may be used to permit the benchmarking of services. This unadjusted PCCRC rate should be calculated as the number of PCCRCs divided by the total of the number of PCCRCs plus the number of detected cancers, expressed as a percentage. The PCCRC rate is calculated based on the date the person had the colonoscopy, with the term detected cancer being used to describe cancers diagnosed by the colonoscopy or within 6 months of the date of the colonoscopy, and the term PCCRC used to describe cancers beyond 6 months of the date of the colonoscopy. For consistency and to permit benchmarking it was suggested that as a minimum the PCCRC rate should be reported for an interval of 3 years (6-36 months; PCCRC-3y). Ideally the PCCRC rate-1y, PCCRC-5y, and PCCRC-10y should also be calculated (9).

Methods

Study Design

In 2014 a prospective registration was started in our department: every patient with CRC and a colonoscopy within the last 10 years was registered after the multidisciplinary team meeting (MDT) discussing the treatment of the patient. Patients with a carcinoma in situ and anal cancers were excluded.

Yearly more than 5000 colonoscopies are performed in our regional teaching hospital. All colonoscopies were done by one of the seven gastroenterologists.

Medical records and colonoscopy reports were reviewed to assess indication of last prior colonoscopy, quality of bowel preparation, completeness of examination, findings at examination and advice for re-evaluation. A pathological examination was performed to detect the presence of MSI, RAS- and BRAF-mutations in near all PCCRCs.

Additionally, we tried to classify the PCCRCs by most reasonable explanation and into the above mentioned subcategories and we calculated the unadjusted PCCRC rate.

Bias

The calculation of PCCRC rates is complex and calculation requires theoretically a collaborative approach within a multidisciplinary health care system, including cancer registries. Here we propose our own data, without data of official cancer registries. However, we are quite sure about the near completeness of our data: our hospital is a rather large regional centre with a minimal spontaneous transfer of patients to other hospitals for colonoscopy and colorectal cancer treatment. Also, we included two patients where index colonoscopy was done in our hospital and PCCRC diagnosis was made in another hospital.

Statistics

Unpaired t-test is used to calculate potential differences between groups with normal variation. The chi-square test of independence is used to analyze the frequency table formed by two or more categorical variables.

Results

During the 6 years of data collection 807 colorectal cancers were diagnosed, of which 47 (5.82%) were classified as PCCRC (colonoscopy within the last 10 years) and 760 (94.18%) as detected cancer (data on these detected cancers were not analysed).

The report of the index colonoscopy was consulted retrospectively. This colonoscopy was completed with caecal intubation in 100% of the examinations. Preparation was mentioned as very bad in 4 (8.5%), moderate in 6 (12.8%) and good in the remaining 37 patients. Boston bowel preparation scale (BBPS) was only registered systematically in our ward from 2016 onwards (10). A polyp or carcinoma was detected at index colonoscopy in 36 patients (77%): three patients had a malignant lesion (two malignant T1 polyps, one a more advanced carcinoma) and 33 patients had polyps (24 adenomatous polyps, 9 serrated lesions). Four patients had already a colorectal carcinoma in their medical history. In the small proportion of patients were BBPS was mentioned during the index colonoscopy, no relation at all could be detected between less prepared segment and location of the tumour during second colonoscopy.

The indications for the second colonoscopy were post-polypectomy surveillance in 25.5%, screening in 14.9%

Table 1. — **Stage PCCRCs at diagnosis according to the American Joint Committee on Cancer (UICC) TNM system, 7th edition**

Stage	PCCRCs	%	Mean interval (years)
I	23	48,93	3,87 [0,56 - 9,08]
II	6	12,77	3,85 [2,93 - 5,27]
III	13	27,66	5,37 [1,90 - 9,31]
IV	5	10,64	3,12 [1,06 - 6,42]

and symptoms in 59.6%. Most reported symptoms were iron deficiency anaemia (13/28=46%) and rectal blood loss (6/28=21%).

The average age at diagnosis of PCCRC was 73 years (52-87 years) and did not differ significantly from average age of all CRC. There was a slight majority of women: 53.2%.

In PCCRC, tumours were more likely to be located in the right colon (57.1%) as compared to the left colon (42.9%). Tumours in the transverse colon were considered right sided tumours.

Nearly half of the PCCRCs were stage I carcinoma at the time of diagnosis, but also nearly 40% stage III or IV (table 1).

In 15 out of 45 cases in which data on MSI was determined (33.3%), the tumour exhibited MSI. Fourteen (93.3%) of the tumours that exhibited MSI were located in the right colon and 1 (6.7%) in the left colon (p=0.0012). In three of these patients (6.4% of all patients included) the diagnosis of Lynch syndrome was confirmed by genetic examination. This was not known prior to diagnosis of PCCRC.

BRAF-mutations were found in 13 patients (37.1% of determined cases). Twelve (92.3%) of the tumours with BRAF-mutation were right-sided tumours (p=0.011). RAS-mutations were found in 8 patients (17.8%). Of these patients 4 (50.0%) had a right-sided tumour and 4 had a tumour located in the left colon (p=0.86).

The average period between index colonoscopy and diagnosis of PCCRC was 4.2 years (0.56-9.31 years). One case was found within the first year of colonoscopy, 7 cases within the first 2 years, 19 within the first 3 years and 31 within the first 5 years. Sixteen cases were diagnosed after a 5 year time interval. There was no significant difference between interval of right sided (4.2 ± 1.6 years) and left sided (3.7 ± 1.7 years) locations (p=0.08). The interval time for MSI-positive and MSI-negative tumours was 5.0 ± 1.6 and 3.8 ± 1.6 years respectively (p=0.047). CRC associated with the 3 Lynch syndrome patients had a shorter interval period with a mean of 3.1 years (number too low for statistical comparison). There was no difference in detection of PCCR for different members of staff (taking there activity in years in the ward into account) (p=0.38).

PCCRC subcategories

All PCCRCs were classified in interval type and non-interval type A, B and C (table 2).

Table 2. — **PCCRC subcategories**

PCCRC subcategories				
Interval type	Non-interval type			Total cases
	Type A	Type B	Type C	
9	14	12	12	47
19,15%	29,79%	25,53%	25,53%	100,00%

Most possible explanation – root cause analysis

A root cause analysis was performed for all PCCRCs, and also separately for the PCCRCs with exclusion of likely new CRCs using the WEO definition. PCCRC was detected more than 4 years following the index colonoscopy in 24/47 cases (51%). These cases are thus classified as likely new CRC (5). Of the remaining 23 true PCCRs, 12 (52.2%) were categorized as truly missed lesions following adequate preparation. Two of these had a post cancer diagnosis of Lynch syndrome. Four of the PCCRCs (8.5%) were possible missed lesions because of inadequate preparation for previous colonoscopy.

Of all the 47 PCCRCs in our cohort there was a deviation from the planned follow-up in 12 (25.5%) of them. Of the true PCCRCs following WEO definition, 2 out of 23 (8.7%) deviated from the planned follow-up.

If we would assume the PCCRCs classified as 'new CRC with no deviation from planned pathway' are because of biology-related factors, we could say that 68.1% (32/47) of all PCCRCs could be explained by procedural – and thus preventable – factors and only 31.9% (15/47) by biology-related factors (Table 3).

Table 3. — **Most possible explanation for all CRC and with likely new CRC (>4 yrs past first colonoscopy) excluded**

Most possible explanation		All PCCRCs	Likely new CRC excluded
Total cases of PCCRC		47 (100%)	23 (100%)
Possible missed lesion, prior examination adequate		12 (25.5%)	12 (52.2%)
Possible missed lesion, prior examination negative but inadequate		4 (8.5%)	4 (17.4%)
Detected lesion, not resected		0 (0%)	0 (0%)
Likely incomplete resection of previously identified lesion		7 (14.9%)	7 (30.4%)
Likely new CRC		24 (48.9%)	/
	Deviation from the planned management pathway	9 (19.2%)	/
	No deviation from the planned management pathway	15(31.9%)	/
Deviation from the planned management pathway		*12 (25.5%)*	*2 (8.7%)*

Unadjusted PCCRC rate

Unadjusted PCCRC rate was calculated following the definition of WEO Consensus Statements. PCCRC-3y was 2.46% (Table 4). PCCRC-1y and PCCRC-5y were calculated similarly and were 0.14% and 3.99% respectively.

Table 4. — **PCCRC-3y**

	Total CRC	Detected cancer	PCCRCs	%
2014	169	167	2	1,18
2015	142	139	3	2,11
2016	116	114	2	1,72
2017	126	121	5	3,97
2018	139	137	2	1,44
2019	115	110	5	4,35
Total	807	788	19	2,35
Mean				**2,46**

Conclusion

In October 2013 a colorectal cancer screening program with iFOBT was implemented in Flanders (11). After a positive test a colonoscopy was proposed. However, till now there is no centralized colonoscopy quality registry in Belgium.

BBPS, caecal intubation rate, adenoma detection rate and withdrawal time are traditionally considered as quality measures of colonoscopy (14). However, the above mentioned parameters are only surrogates of the true outcome that matters most to patients, that is a post-colonoscopy cancer (9).

The data of our centre are in line with the data in literature: more right-sided PCCRCs and more MSI-positive and B-RAF mutated tumours. Although the majority of the patients had early stage (I-II) cancer, almost 40% of the PCCRCs were advanced (stage III-IV). Eighty % of the patients had polyps or a cancer at index colonoscopy (6,12,13).

The average period between index colonoscopy and PCCRC was 4.2 years. As demonstrated previously, intervals between colonoscopies in Belgium are shorter than suggested by guidelines (14). Although minor differences between European and US guidelines, they agree that in case of a qualitative good bowel preparation and the presence of only small hyperplastic polyps in rectum or sigmoid, surveillance colonoscopy is recommended after 10 years in the absence of a strong genetic predisposition (3). If we proposed a surveillance colonoscopy after 5 years, most PCCRC's would nevertheless be diagnosed earlier then the proposed date. Because 80% of the PCCRC's had (pre)neoplastic lesions at index colonoscopy, the risk of a PCCRC with a normal colonoscopy is very small (15,16).

Twenty-five % of the PCCRCs were type B, in which the PCCRC was diagnosed after the proposed surveillance interval. The question arises how we can improve the follow-up of proposed surveillance.

Our results are similar to previous studies, from which can be concluded that most post-colonoscopy colorectal cancers are preventable. In our study 68% of all PCCRCs could be explained by procedural factors and 32% by biology-related factors (1,12,15,17,18).

In a retrospective analysis E. Macken calculated the PCCRC rate in Belgium for the period 2002-2010, also using the WEO recommendations (11,19). The mean PCCRC rate was 7.4%. Benchmarks need to be set for minimum acceptable standards and aspirational targets. These benchmarks have not been defined for PCCRC-3y rates. In an English cohort study the 25% centile from the range of unadjusted PCCRC-3y was 5.5%. A minimum standard of up to 5.5% and an aspirational target of up to 3.6% could be applied as quality standards (20,21). The mean PCCRC-3y of our department was 2.46%.

A limitation of our study is that no direct statistical comparison could be made between the 47 identified PCCRCs and the other 760 'detected cancers'. Withdrawal time and bowel cleansing using the BBPS score were not systematically registered. It is also nearly impossible, if there is no link with cancer registries and registrations of colonoscopies, to identify all PCCRC cases and to notify the service where the index colonoscopy was performed

There are opportunities for improved colonoscopy performance, for using cancer appearing after a negative colonoscopy as an important benchmark for quality, and for standardizing methodologies to allow more direct comparisons between services. The PCCRC-3y, as proposed in the WEO Consensus Statements (9), is probably a good quality indicator. However to implement this and make comparison between services possible with reliable data, a national colonoscopy registry is necessary.

Nearly seven years after the start of the colorectal screening program, it is time for the implementation of such a colonoscopy registry.

Conflict of interest: none.

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