Colonoscopy Surveillance After Colorectal Cancer

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Colonoscopy Surveillance After Colorectal Cancer: the Optimal Interval for Follow-Up

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Abstract

Purpose Patients who have undergone curative surgery for colorectal cancer are at risk of developing a metachronous colorectal tumour or anastomotic recurrence. The aim of this study was to determine the incidence of recurrent colorectal cancer in a cohort of patients who participated in a colonoscopy surveillance programme.

Methods This single-centre retrospective observational cohort study included patients who underwent curative surgery for colorectal cancer between 2005 and 2015. All reports of postoperative colonoscopies were retrieved to calculate the incidence rates of recurrence and metachronous colorectal cancer.

Results Of 2420 patients, 1644 (67.9%) underwent at least one postoperative colonoscopy and 776 (32.1%) did not. In 1087 patients, colonoscopy was performed in the first 18 months after surgery, which detected 34 (3.1%) instances of metachronous colorectal tumours or anastomotic recurrence. Thirty-three additional patients were also diagnosed with recurrent colorectal cancer, but the tumours were detected by other diagnostic modalities or detected perioperatively, rather than by colonoscopy.

Conclusions Patients with a history of colorectal cancer have an increased risk for a second colorectal tumour. Therefore, we recommend a colonoscopic surveillance programme with the first colonoscopy performed 1 year after curative surgery, which is in accordance with national guidelines.

Keywords Surveillance · Colonoscopy · Colorectal cancer · Follow-up

Introduction

Patients who have undergone a colorectal resection because of malignancy have a higher risk of developing a metachronous colorectal tumour. These tumours can involve either a second primary colorectal cancer (CRC) or anastomotic recurrence. In the current literature, the reported incidence rates of metachronous CRC after previous curative resection are between 0.6 and 9% [1, 2]. The risk of second primary tumour is approximately 2.5% within the first 5 years [3]. There are

studies that show increasing incidence of metachronous tumours with time in general population and in patients with specified genetic predisposition [4, 5]. However, other studies show that the risk of developing metachronous CRC is highest within the first 2 to 3 years after diagnosis [6–8]. Mulder et al. found a cumulative incidence rate of metachronous CRC of 1.1% after 3 years. This is 1.4 times the incidence rate of CRC in the Netherlands [2]. Therefore, Dutch guidelines were adapted in 2014 to advise that the first colonoscopy surveillance should occur approximately 1 year after curative resection rather than at 2 to 3 years. However, this is a recommendation based on weak evidence [8]. This recommendation complies with international guidelines, which clearly state that a follow-up colonoscopy is indicated after surgery for CRC [9–12]. However, the guidelines differ regarding the time interval for monitoring the colon and rectum both for the first postoperative colonoscopy and for subsequent colonoscopies. Furthermore, some studies suggest that early endoscopy does not contribute to the detection of recurrence or metachronous tumours [13–15]. The intervals for prearranged follow-up colonoscopies vary among

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different clinics and institutions, with both overuse and underuse being reported after resection for CRC [16, 17]. In general, patients who have undergone surgical resection for stage I–III and/or intentional curable stage IV CRC are potential patients for surveillance colonoscopy. Patients with stage IV CRC that is unresectable for cure are generally not candidates for surveillance, because of the poor survival benefit. Preoperative colonoscopy can be incomplete due to tumour obstruction or be absent in some patients. These patients mostly present with an acute bowel obstruction requiring emergency surgical intervention. According to Dutch guidelines, such patients must undergo a completing colonoscopy within 3 months after resection to detect synchronous neoplasia [8].

To date, no study has analysed the ability of 1-year post-operative surveillance colonoscopy to detect metachronous colorectal tumours or anastomotic recurrences. Since 2005 but before the implementation of routine colonoscopies as per the 2014 guidelines, we had performed the first follow-up colonoscopy 1 year after colorectal resection in the majority of our patients. The main aim of this study is to present the results of 11 years of endoscopic follow-up after surgery for CRC. In addition, based on our findings, we provide a recommendation regarding the optimal interval for first colonoscopy surveillance after curative resection.

Methods

Data and Definitions

At Amphia Hospital, patients diagnosed with CRC and treated with curative surgery were offered colonoscopy to detect recurrent disease. Patients who were diagnosed and treated between January 2005 and December 2015 were retrospectively reviewed. Our surgical team prospectively collected data on all CRC patients undergoing colorectal surgery because of a malignancy between 2005 and 2010. From 2011 onwards, trained personnel of the National Cancer Registration Centre (Integraal Kanker Centrum Nederland, IKNL) entered the data of CRC patients into the National Dutch Colorectal Audit database (DCRA). Data consisted of patient characteristics, preoperative imaging diagnostics, location of the tumour within the colon and/or rectum and whether or not a complete preoperative colonoscopy was performed. Data regarding surgery included curative surgical treatment. The results regarding postoperative colonoscopies as a part of the surveillance programme, completion colonoscopies, or other imaging techniques that were used to detect colorectal recurrence were retrospectively retrieved from medical charts. Major complications after colonoscopy requiring surgery or postponing colonoscopy were also

ascertained. Colonoscopies were deemed complete if the bottom of caecum, ileocaecal valve, or terminal ileum was visualized and reported. Anastomotic recurrence was defined as tumour growth in the previous anastomotic suture line, irrespective of synchronous metastatic or other local recurrence [18]. Local recurrence was defined as tumour growth outside or inside the colonic/rectal wall, which can extend through this wall with perforation and/or invasion of adjacent organs or structures [19]. Metachronous tumours or second primary tumours were defined as luminal tumours located elsewhere in the colon or rectum at least 6 months after curative surgery for the primary tumour. Preoperative colonoscopy had to be complete in these patients for them to classify a new luminal tumour as metachronous. During follow-up interval, most of the patients were seen by the surgeon every 3 months during the first year and every 6 months thereafter. In the Netherlands, each follow-up visit includes a physical examination, measurement of the serum carcinoembryonic antigen (CEA), ultrasound of the abdomen and chest X-ray. Chest CT, abdominopelvic CT, or positron emission tomography (PET) was performed when there was high suspicion of recurrence of disease on routine imaging studies. Recurrence of disease did not include distant metastases to other organs.

Inclusion and Exclusion Criteria

Patients were included if they had undergone surgery for their index CRC between 2005 and 2015. Patients were excluded if they had a previous history of CRC, an appendix carcinoma or pseudomyxoma peritonei (PMP). Patients were also excluded if they had undergone surgery for palliative purposes (palliative resection or debulking, palliative bypass, or palliative colostomy/ileostomy due to obstructing symptoms). Amphia Hospital is a referral centre for (colorectal) liver metastases. Patients who were referred to Amphia Hospital by another hospital because of liver metastasis were also excluded.

Ethical Approval

For ethical approval, we consulted the national institutional review board's Medical research Ethics Committees United (MEC-U). Referring to this study (reference number W17.073), confirmation was received that the Medical Research Involving Human Subject Act (WMO) does not apply; therefore, official approval of this study by the MEC-U was not required under the WMO. We also consulted the institutional review board of Amphia Hospital (AMOA), and they confirmed that no formal written waiver of ethics approval was required, because of the retrospective design of the study.

Statistical Analysis

The Kolmogorov–Smirnov test was used to determine whether the variables were normally distributed. Data are presented as the means and SD for normally distributed data and as medians and interquartile ranges (IQR) for non-normally distributed data. Differences in continuous variables between and among groups were tested using independent *t* tests and one-way ANOVA, respectively. A two-sided *P* value of less than 0.05 indicated statistical significance. All of the data analyses were performed with IBM SPSS software, version 24.

Results

Between 2005 and 2015, 2750 patients underwent surgery for CRC. In this patient group, 330 patients (12.0%) were excluded because of non-curative treatment (Table 1). The remaining 2420 patients (88.0%) were eligible for analysis (Fig. 1). A total of 1340 patients were male.

Preoperative colonoscopies were complete in 1332 patients (55.0%). In 279 (11.6%) patients, no preoperative colonoscopy had been performed. In the remaining 809 (33.4%) patients, colonoscopy was incomplete mostly due to tumour obstruction. The rectum was the most common tumour location, followed by the sigmoid and caecum. Several types of resections were performed as outlined in Table 2. Among these resections, right hemicolectomy was performed most frequently, followed by low anterior resection and (recto) sigmoidal resection. Among the 2420 patients who had undergone surgery for CRC, eight patients had hereditary nonpolyposis colorectal cancer syndrome (HNPCC), and ten patients had IBD (seven patients with ulcerative colitis and three patients with Crohn's disease).

Of the 2420 patients who had undergone curative surgery, 1644 (67.9%) had at least one colonoscopy during follow-up. A flowchart is provided in Fig. 1. The remaining 776 (32.1%) patients did not undergo surveillance colonoscopy. The median age was statistically significant lower in the colonoscopy

group (67 years (IQR 60–74) vs. 76 years (IQR 68–82), $P < 0.0001$). The main reasons for not participating in the colonoscopy surveillance programme were patient related factors, such as advanced age, co-morbidity and patient preference. Follow-up colonoscopy was not performed in patients after a total colectomy with a permanent ileostomy or in patients after trans-anal endoscopic microsurgery (TEM), who underwent endoscopic ultrasound surveillance instead of normal colonoscopy surveillance. These patients are referred to as “other” in Fig. 1.

In the first 6 months after resection, 240 patients underwent their first follow-up colonoscopy. One hundred and forty-three (59.6%) of these patients were subjected to a completing colonoscopy. During these procedures, a total of five synchronous tumours (3.5%) were detected (T1 stadium $N = 3$, T3 stadium $N = 2$). In the remaining 97 patients (40.4%), colonoscopy was performed as a part of the surveillance programme, and four tumours (4.1%) were detected, two of them were classified as T1 and the other two tumours as T2. One of these four tumours was an anastomotic recurrence, and the remaining three were primary tumours. In these first 6 months, there were nine patients (3.6%) who did not participate in the colonoscopy surveillance programme but developed anastomotic recurrence ($N = 1$), local recurrence ($N = 7$), or a second primary tumour ($N = 1$). These tumours were diagnosed with positron emission tomography–computed tomography (PET-CT) or computed tomography (CT). Most patients had their first follow-up colonoscopy between 6 and 18 months postoperatively ($n = 1016$, 61.8%). Twenty-six patients underwent completing colonoscopy, which revealed no additional synchronous tumours. So in the first 18 months in 169 completing colonoscopies, five synchronous tumours were found (3.0%). Thirty colorectal tumours were found with colonoscopy in the remaining 990 patients between the first 6 and 18 months (3.0%). Twenty-four patients were diagnosed with recurrent disease without colonoscopy (2.3%), 22 patients had local recurrence, one patient had anastomotic recurrence and one patient had a second primary tumour. The results for later time intervals regarding the first postoperative colonoscopy and their findings are given in Table 3. In total, at the first postoperative surveillance endoscopic follow-up, 50 tumours were found among 1475 patients who attended to the colonoscopy surveillance programme and 47 patients in which tumours were detected by other diagnostic imaging modalities (PET-CT, CT, or MRI) or perioperatively (during laparotomy), rather than by colonoscopy (2.9%).

Including completing colonoscopies, in 1644 patients who underwent a first follow-up colonoscopy, 55 (3.3%) colorectal tumours were found (Table 3; Fig. 1). The results for later time intervals regarding the second and third postoperative colonoscopy are given in Tables 4 and 5 in the Appendices.

Table 1 Number of excluded patients presented as N (%)

Exclusion criteria	Excluded patients, $N = 330$ (%*)
Palliative colostomy/ileostomy	125 (37.9%)
Palliative resection/debulking	57 (17.3%)
Referred liver patient	42 (12.7%)
History of colorectal cancer	41 (12.4%)
Palliative bypass	33 (10.0%)
Appendix carcinoma/PMP	17 (5.2%)
No surgical intervention	11 (3.3%)
Liver first	4 (1.2%)

*Percentage of patients who were excluded

Fig. 1 Flowchart of 2420 patients attending follow-up after surgery for colorectal cancer

Iatrogenic perforation that required acute surgery was found in three (0.14%) out of 2141 patients who underwent preoperative colonoscopy in this series. Two

Table 2 Overview of different type of resections that were performed arranged from right to left sided resections

Type of resection	Number of patients, N = 2420 (%)
Ileocaecal resection	36 (1.5%)
Right hemicolectomy	723 (29.9%)
Transversal resection	62 (2.6%)
Left hemicolectomy	167 (6.9%)
(Recto)sigmoidal resection	346 (14.3%)
Anterior resection	117 (4.8%)
Hartmann procedure	174 (7.2%)
Low anterior resection	495 (20.4%)
Abdominal perineal resection	230 (9.5%)
Subtotal colectomy	31 (1.3%)
Transanal endoscopic microsurgery	31 (1.3%)
Total colectomy with pouch	1 (0.04%)
Total colectomy with ileostomy	5 (0.2%)
Abdominal polypectomy	2 (0.1%)

patients had a right hemicolectomy and one had a transversal resection. In the 2797 postoperative colonoscopies, iatrogenic perforation occurred in four patients, which was followed by emergency surgery (0.14%). One patient underwent a sigmoid resection, one patient underwent a right hemicolectomy, and two patients had revision of their colostomy due to a perforation near the colostomy. One of these latter two patients had a complicated course after colonoscopy, with severe abdominal sepsis due to intraabdominal abscesses and underwent multiple laparotomies requiring prolonged stay at the intensive care unit. In one case, colonoscopy had to be postponed because of a significant decrease in oxygen levels to below 85% after sedation was administered.

Discussion

The aim of this study was to determine the incidence of CRC recurrence found by means of endoscopic surveillance after curative resection. We found an incidence of 3.1% between the first 6 and 18 months postoperative, which is similar to rates in some other cohorts [20–22],

Table 3 Time intervals of patients receiving their *first* surveillance colonoscopy and tumour findings after curative resection

Time interval	Number of patients	Total number of tumours found	Anastomotic recurrence	Local recurrence	2nd primary tumour	Diagnostic imaging
0–6 months	249	18	2	7	9	
Completing	143	5	–	–	5	–
Surveillance	97	4	1	–	3	–
No colonoscopy	9	9	1	7	1	2× PET 2× CT
0.5–1.5 year	1040	54	16	24	14	
Completing	26	0	0	0	0	–
Surveillance	990	30	15	2	13	–
No colonoscopy	24	24	1	22	1	12× CT 9× PET 1× periop 2× MRI
1.5–2.5 year	270	23	10	10	3	
Completing	–	–	–	–	–	–
Surveillance	259	12	8	1	3	–
No colonoscopy	11	11	2	9	–	8× CT 3× PET
2.5–3.5 year	83	5	1	2	2	
Completing	–	–	–	–	–	–
Surveillance	82	4	1	1	2	–
No colonoscopy	1	1	–	1	–	1× Periop
> 3.5 year	49	2	0	2	0	
Completing	–	–	–	–	–	–
Surveillance	47	0	–	–	–	–
No colonoscopy	2	2	–	2	–	1x PET 1x CT

although higher incidence rates between 6.3% and 41% [23–27] and much lower incidence rates between 0.6 and 1.3% [28–30] have also been reported. A comparison of our results with the current literature is challenging for several reasons. First, there is no consensus definition of metachronous and synchronous tumours. In the literature, the time interval used to distinguish between these tumours ranges from 6 months to 3 years after curative surgery. In most reports, metachronous cases are defined as a second CRC at a site other than that of the anastomosis that appeared at least 6 months after primary surgery [31]. However, there are reports that use a different time interval (12 months [30]) or do not define the time interval [20, 32]. Second, there is heterogeneity in the duration of follow-up among different reports, and there are differences among studies in the study population. Some cohorts are based on national CRC databases or patients from multicentre studies, whereas other studies only included patients operated on in a single centre, as with our cohort.

Ninety-seven patients had their first postoperative colonoscopy within 6 months, and four metachronous CRC cases were detected. Remarkably, preoperative colonoscopies in these patients were classified as complete. These tumours were labelled metachronous CRC but could alternatively be considered as synchronous because these lesions might have been undetected and therefore not removed during preoperative colonoscopy. If appropriate

endoscopic removal of premalignant lesions is performed at the time of diagnosis of the primary tumour, any lesions found during following colonoscopies are categorized as metachronous [6]. However, it is possible that some of these synchronous lesions were missed during preoperative colonoscopy, meaning this index colonoscopy should be classified as incomplete. These colonoscopies could be of questionable quality due to poor intestinal preparation. Flat adenomas or depressed lesions have a fairly high malignant potential [33, 34]. These adenomas are considered difficult to trace during diagnostic or surveillance colonoscopy, especially when the bowel is poorly prepared. Another potential explanation for the detection of metachronous CRC in these patients is that the development of CRC was accelerated and aggressive.

In this study, most of the patients received their first postoperative colonoscopy approximately 18 months after curative surgery; this is consistent with Cooper et al. [21]. However, a third of the patients had no surveillance; this might be explained by co-morbidity, age, or disease-related factors. Unfortunately, in 84 patients (10.8%), surveillance was not fulfilled for unknown reasons. Seven of these patients (8.3%) developed a second CRC with a median time interval of 30 months (range 3–60 months) after curative surgery. These tumours were all classified as local recurrence and were found with PET-CT or CT scan. The survival benefit to these patients likely would have

improved if they had continued to attend at the colonoscopy surveillance programme.

Unfortunately, because of the retrospective nature of this study, no survival analyses could be made because of the high risk of selection bias, as physicians might have discouraged surveillance colonoscopy in patients for whom the potential benefit of surveillance was low. Such patients have more co-morbidities than other patients or have progressive disease, which increases the risk of death relative to that of healthier patients who did undergo surveillance colonoscopy. Moreover, the patients who were offered colonoscopy were significantly younger than the patients in the no-colonoscopy group. However, there are studies that found a survival benefit compared to patients who did not attend to an endoscopic follow-up programme [30, 35–37]. Three published randomized controlled trials (RCTs) involving intensive follow-up found no benefit compared to a normal surveillance programme [26, 27, 38]. Three systematic reviews found a higher 5-year survival with a reduction of mortality of 9–13% in intensive follow-up group compared with the control group [39–41]. However, in these reviews, intensive follow-up involved all diagnostic modalities within the full follow-up schedule (imaging, CEA and colonoscopy) and do not consider the effects of colonoscopy alone. In one published RCT, comparison among surveillance schedules was performed, with other diagnostic modalities (CEA and imaging) held constant. This trial showed no better survival in patients who attended to an intensive follow-up schedule [42]. In this study, local recurrences were included, which do not necessarily grow intraluminally. Endoscopic surveillance alone would not be useful enough for patients with local recurrence; therefore, other imaging techniques should be part of a surveillance programme [43, 44]. In the first 18 months after curative surgery, we detected 33 tumours with imaging (PET-CT, CT and MRI) and one CRC perioperatively. This case concerns an 89-year-old male who presented with an ileus and underwent emergency surgery because of a pelvic tumour which was grown into the small intestines. After the total follow-up time, 77 tumours were found with other imaging modalities (Tables 3, 4 and 5).

In general, it is recommended to perform a preoperative diagnostic colonoscopy and a colonoscopy after curative surgery for CRC during follow-up. Unfortunately, colonoscopy entails some risk of complications, as well as patient discomfort during preparation and the procedure itself. Complications can be mild, such as a minor bleeding, which can be solved with clipping and/or local adrenaline injections, but they can also be severe, requiring emergency surgery. The incidence of iatrogenic perforation was 0.14% for both

preoperative and surveillance colonoscopies. This is near the complication norm of the Dutch guidelines (< 0.1%) [8, 45].

Early surveillance colonoscopy 1 year after curative surgery can be a cost-effective measure and thereby reduce medical costs [46, 47]. However, to evaluate the optimal frequency and interval for surveillance colonoscopy, a prospective multicentre study should be performed to evaluate the results of colonoscopy after surgery. To evaluate and determine efficient surveillance colonoscopy intervals, current colonoscopy guidelines should be evaluated by an RCT in which patients, who undergo colonoscopy early after 3 or 6 months postoperatively, are compared with those undergoing normal surveillance colonoscopy after 1, 3 and 5 years.

There are several biases in this retrospective observational cohort. Because of the retrospective design of this cohort, there was no randomization of patients. In addition, no distinction was made between colon and rectum among different age groups. Furthermore, no reliable distinction could be made between colonoscopies that were routine procedures in asymptomatic surveillance patients and those that were indicated based on developed symptoms or physical or laboratory findings. Additionally, the frequency and intervals of subsequent follow-up colonoscopy varied in our study population. Finally, it is globally accepted that most colorectal malignancies arise from adenomas and that screening or surveillance colonoscopy is recommended for the early detection of these adenomas or polyps. Such screening could lead to the detection of endoscopically curable stages of these lesions and avoid second operations. In this study, only malignant findings were analysed. Unfortunately, data regarding the numbers of detected advanced adenomas or polypectomies and their polyp characteristics including histology and size are not present in our database.

In conclusion, the results of this study indicate that it is relevant to perform colonoscopy for CRC to screen for anastomotic recurrence and metachronous tumours. We recommend a short-term surveillance colonoscopy approximately 1 year after curative surgery.

Compliance with Ethical Standards For ethical approval, we consulted the national institutional review board's Medical research Ethics Committees United (MEC-U). Referring to this study (reference number W17.073), confirmation was received that the Medical Research Involving Human Subject Act (WMO) does not apply; therefore, official approval of this study by the MEC-U was not required under the WMO. We also consulted the institutional review board of Amphia Hospital (AMOA), and they confirmed that no formal written waiver of ethics approval was required, because of the retrospective design of the study.

Conflict of Interest The authors declare that they have no conflict of interest.

Appendix

Table 4 Time intervals of patients receiving their *second* colonoscopy surveillance with tumour findings after first follow-up colonoscopy

Time interval	Number of patients	2nd recurrence of CRC	Total number of tumours found	Anastomotic recurrence	Local recurrence	2nd primary tumour	Diagnostic imaging
0–1 year	223	3	31	13	10	8	
Surveillance	206	1	14	7	–	7	–
No colonoscopy	17	2	17	6	10	1	4× periop 10× CT 3× PET
1–2 year	204	0	12	4	6	2	
Surveillance	199	–	7	3	2	2	–
No colonoscopy	5	–	5	1	4	–	1× CT 4× PET
2–3 year	193	1	8	4	0	4	
Surveillance	192	–	7	3	–	4	–
No colonoscopy	1	1	1	1	–	–	1× PET
> 3 year	233	1	5	1	2	2	
Surveillance	231	–	3	1	–	2	–
No colonoscopy	2	1	2	–	2	–	2× CT

Table 5 Time intervals of patients receiving their *third* colonoscopy with tumour findings after follow-up colonoscopy

Time interval	Number of patients	2nd recurrence of CRC	Total number of tumours found	Anastomotic recurrence	Local recurrence	2nd primary tumour	Diagnostic imaging
0–1 year	93	1	6	0	4	2	
Surveillance	89	1	2	–	–	2	
No colonoscopy	4	–	4	–	4	–	4× PET-CT
1–2 year	92	3	6	3	2	1	
Surveillance	90	2	4	3		1	
No colonoscopy	2	1	2		2		1× PET CT 1× CT
2–3 year	82	1	2	0	0	2	
Surveillance	82	1	2	–	–	2	
No colonoscopy	0	0	–	–	–	–	
> 3 year	64	0	3	1	0	2	
Surveillance	64	–	3	1	–	2	
No colonoscopy	0	–	–	–	–	–	

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