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Colonoscopic surveillance after colonoscopic polypectomy of a low-risk polyp

Incidence of invasive colorectal cancer, adenoma with high-grade dysplasia, and subsequent polyps

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Abstract

OBJECTIVE The aim of the study is to determine the incidence of CRC, adenomas with high-grade dysplasia, and subsequent polyps in patients who underwent a polypectomy of (a) low-risk polyp(s).

OUTCOMES Primary outcomes were the incidence of CRC, adenomas with high-grade dysplasia, subsequent polyps, and CRC/Adenoma in patients initially classified as 'low-risk'. Secondary outcomes were predictors for CRC/Adenoma and subsequent polyps, stratified for different follow-up time intervals (< 3 years, 3-5 years, and > 5 years).

METHODS Patients included at MST underwent index colonoscopy with polypectomy from 2014 to 2017. Patients were either classified as low-risk or high-risk. Patients were followed until surveillance colonoscopy, diagnosis of CRC, or death, ending in 2021. Cox regression analyses were performed for primary outcomes and logistic regression analyses for secondary outcomes.

RESULTS Of the 775 eligible patients, 450 were enrolled in the low-risk cohort (58.0% male; mean age, 62.8 ± 8.95 years; mean follow-up time 3.96 ± 1.87 years from index colonoscopy). For CRC, no significant risk factors were found. Increasing age (HR 1.02; 95% CI 1.00-1.03) and increased amount of polyps (HR 1.42; 95% CI 1.26-1.59) had an increased risk for subsequent polyps. For adenoma with high-grade dysplasia, both villous and tubulovillous adenoma compared to tubular adenoma (HR 11.8; 95% CI 1.22-115 and HR 7.24, 95% CI 1.44-36.5, respectively) had an increased risk and left-sided located polyps compared to right-sided (HR 0.09; 95% CI 0.01-0.78) had a lower risk. CRC/Adenoma had no significant risk factors.

CONCLUSION No risk factors were found to be associated with the development of CRC and CRC/Adenoma. Age and amount of polyps are associated with the recurrence of subsequent polyps. Adenoma growth pattern and location are predictors for adenomas with high-grade dysplasia.

Keywords: colorectal cancer, low-risk polyp, colonoscopy, adenomas

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths globally in 2020. In addition, CRC ranks third in incidence (1). To enhance prevention of the development of CRC a colonoscopy is used as a method of screening. It enables detection and removal of polyps, adenomas or early-developing cancers, reducing mortality and incidence of CRC (2–4). To properly assess the follow-up time for surveillance colonoscopy, there are existing guidelines, classifying different types and sizes of polyps with corresponding follow-up times for a surveillance colonoscopy (5).

Various guidelines have been issued by different organisations. For low-risk polyps (1-4 adenomas), the American Gastroenterological Association (AGA) recommends a five-year follow-up polyp surveillance (6). In contrast to AGA, the European Society for Gastrointestinal Endoscopy (ESGE) and the European Union Guidelines (EUG) both recommend that these patients can return to the routine screening program or a surveillance colonoscopy after ten years if routine screening is not possible (7,8). The difference in these guidelines is based on limited evidence regarding the risk of CRC after polypectomy (9).

Currently, large studies are being conducted with the aim of gathering more evidence regarding surveillance colonoscopy, the European Polyp Surveillance (EPoS) trials (10). The reason for this is that current guidelines are mainly based on expert consensus, while results from wide-scale clinical studies are lacking. Because the guidelines are hardly based on reliable data, there are concerns about both the benefit of frequent surveillance colonoscopy and its cost-effectiveness (10). The EPoS trial wants to provide the evidence, however, results are not expected until 2028 (10).

To this day, the guideline currently followed at Medisch Spectrum Twente (MST) and in the Netherlands states that after polypectomy of low-risk polyp, a surveillance colonoscopy is performed after three or five years, with the exception in case of one small (< 10 mm) left-sided adenoma (11). Since both the EU and ESGE guidelines have a twice as long follow-up interval, or even just return to routine screening (7,8,12), the present study will investigate the risk of CRC, adenomas with high-grade dysplasia, and subsequent polyps in the follow-up after a first colonoscopy.

The aim of the study is to determine the incidence of CRC, adenomas with high-grade dysplasia, and subsequent polyps who underwent a polypectomy of (a) low-risk polyp(s). By providing a clear and comprehensive overview of these outcomes, it will come one step closer to decide whether or not to adhere to the currently followed guidelines.

Methods

Study design and population

This retrospective cohort study used data of patients that underwent colonoscopy with polypectomy from 2014 to 2017 at MST, a large teaching hospital in Enschede, the Netherlands. The study protocol was approved by the hospital's ethical review board. Patients aged 18 years or older with no history of CRC or polyps that underwent colonoscopy with polypectomy and underwent at least one surveillance colonoscopy between 2014 and 2021 were eligible for this study. Patients were required to have had at least one low-risk polyp at index colonoscopy. Patients were excluded if there were missing colonoscopy data, missing pathological data, history of adenomas or CRC, incomplete colonoscopy, incomplete removal of polyps, hereditary cancer syndrome, and history of bowel resection.

Data collection

Data was collected from the electronic patient records in the Healthcare Information eXchange (HiX) used at MST. At index colonoscopy, the following data were obtained: demographic characteristics (age, gender, body mass index (BMI)), date of index colonoscopy, indication for colonoscopy, polyp type, polyp size, amount of polyps, adenoma growth pattern, dysplasia grade, and location. At the subsequent colonoscopies, obtained data were date of colonoscopy, presence of CRC, subsequent polyps, polyp type, polyp size, amount of polyps, adenoma growth pattern, dysplasia grade, and location.

Patient classification

Patients were classified based on pathological and histological characteristics at index colonoscopy according to Dutch guidelines (11). Patients were classified as 'low-risk' in the case of complete removal of 1 – 4 adenomas, all < 10 mm with low grade dysplasia, irrespective of villous components, or a serrated polyp < 10 mm without dysplasia. Patients were classified as 'high-risk' in the case of complete removal of at least 1 adenoma ≥ 10 mm or with high-grade dysplasia, or ≥ 5 adenomas, or any serrated polyp ≥ 10 mm with dysplasia.

Outcomes

In case CRC and adenoma with high-grade dysplasia had considerably low numbers in different analyses, they were merged into one dependent variable, namely CRC or adenoma with high grade dysplasia.

Primary outcomes of this study were the incidence of CRC, adenomas with high-grade dysplasia, subsequent polyps, and CRC or adenoma with high-grade dysplasia (from now on *CRC/Adenoma*) in patients initially classified as 'low-risk'.

Secondary outcomes were predictors for CRC/Adenoma and subsequent polyps stratified for different follow-up time intervals (< 3 years, 3-5 years, and > 5 years).

Statistical analysis

Clinical characteristics are reported as means with standard deviations or median with interquartile ranges (IQR) for continuous variables, as appropriate, or as numbers with corresponding percentages for categorical variables. Pearson Chi-square tests or Fisher's exact tests are used comparing study groups for categorical, unpaired variables, as appropriate. Student's t-test or the Mann-Whitney U test are used to compare study groups for continuous variables. For each patient, the time between index colonoscopy and subsequent colonoscopy

was calculated. Cox proportional hazard regression models are performed to calculate hazard ratios (HRs) for the time to event variables. Logistic regressions were used to assess odds ratios (ORs) for the different follow-up time intervals. For both Cox and logistic regression analyses, univariate significant variables with p-values < 0.10 were included in the multivariate models using forward conditional selection. Kaplan-Meier analysis was performed to show the overall survival time. A p-value of $p < 0.05$ is considered significant and 95% confidence intervals (CIs) are reported where appropriate. IBM SPSS Statistics 25 is used for analysis of all data, RStudio is used for visual enhancement.

Results

Cohort characteristic

A total of 1615 patients were assessed for enrollment. Of these 1615 patients, 134 did not undergo surveillance colonoscopy. The remaining 1481 patients were included for data collection. Of these, 706 patients did not meet various inclusion criteria (see **Figure 1**). Ultimately, there were 775 patients who met eligibility criteria and underwent an index colonoscopy between 2014 and 2017. Their mean age (± standard deviation) at index colonoscopy was 63.9 ± 7.84 years, 38.2% were female, 450 (58.1%) were assigned to the low-risk adenoma group, and 325 (41.9%) were assigned to the high-risk adenoma group. Patients were followed from index colonoscopy for a median of 3.4 years (interquartile range: 3.0–5.2 years). By the end of the study period, 8 colorectal cancers were detected in the low-risk adenoma group, and 3 in the high-risk adenoma group. Of the 450 patients in the low-risk cohort, 313 (69.6%) ended up with subsequent polyps at the end of the study period. In the high-risk cohort, this percentage was 72.6%, which represents 236 patients. In the low-risk cohort, 2.00% of the patients (9 cases) had adenomas with high-grade dysplasia present at the time of surveillance colonoscopy, this was 2.40% of the patients (8 cases) in the high-risk cohort. There were significant differences between the low-risk and high-risk cohorts in terms of age (P = .011), polyp type (P = .012), follow-up time, amount of polyps, polyp size, adenoma growth pattern, dysplasia grade, location, and indication (all P < .001) (**Table 1**). Results of the high-risk cohort can be found in the **Supplementary Material**.

Figure 1. Flowchart of eligible patients

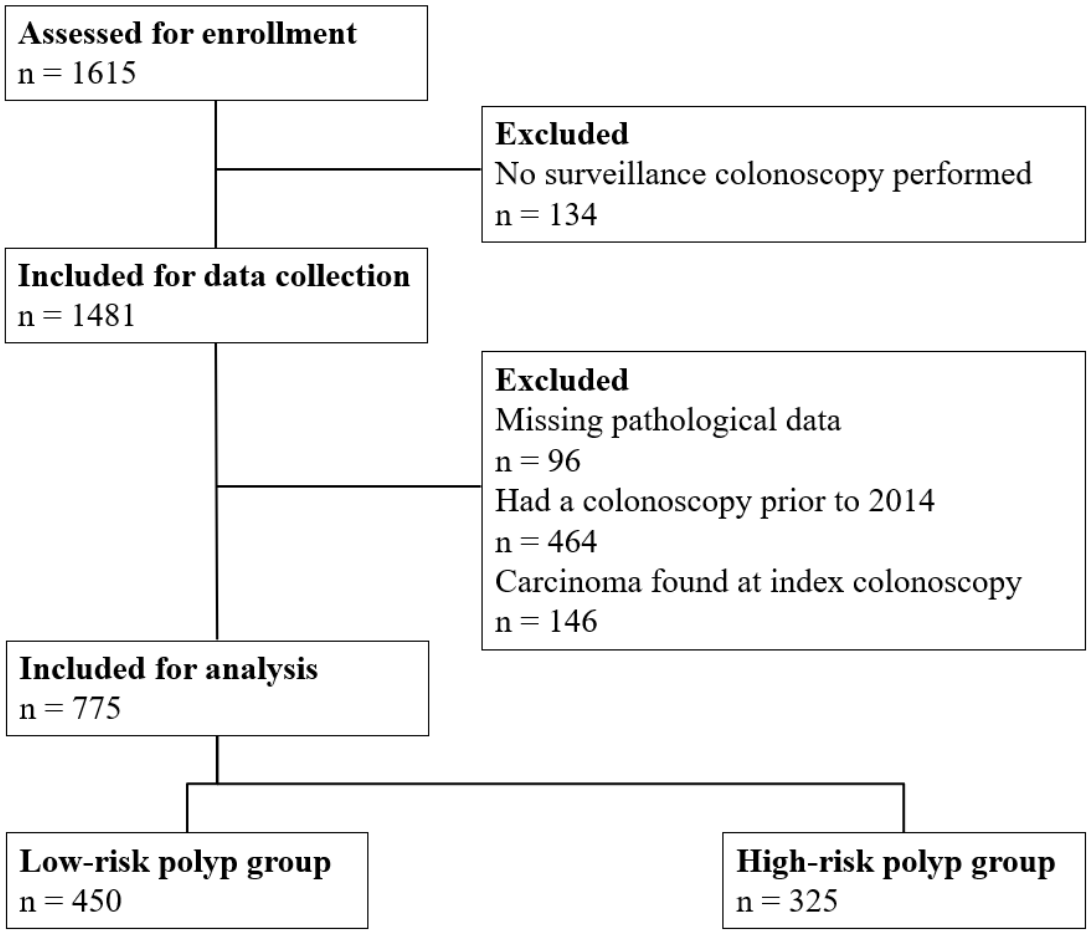


Table 1. Characteristics of study cohort at index colonoscopy. Data are presented as mean ± standard deviation or n (%) unless otherwise stated

Characteristics	Group			p-value
	Overall cohort n (%)	Low-risk n (%)	High-risk n (%)	
All patients	775 (100.0)	450 (100.0)	325 (100.0)	
Gender				.011
Male	479 (61.8)	261 (58.0)	218 (67.1)	
Female	296 (38.2)	189 (42.0)	107 (32.9)	
Age, years	63.9 ± 7.84	62.8 ± 8.95	65.5 ± 5.61	.001
Body Mass Index, kg·m^{-2}	27.9 ± 4.54	28.1 ± 4.57	27.7 ± 4.55	.306
Follow-up time, years	3.65 ± 1.74	3.96 ± 1.87	3.22 ± 1.52	.001
Amount of polyps	2.73 ± 2.45	1.92 ± 0.98	3.84 ± 3.30	.001
Polyp size	8.60 ± 6.07	5.00 ± 1.87	13.6 ± 6.36	.001
Adenoma growth pattern				.001
Tubular	482 (62.2)	314 (69.8)	168 (51.7)	
Villous	21 (2.70)	10 (2.20)	11 (3.40)	
Tubulovillous	207 (26.7)	78 (17.3)	129 (39.7)	
No adenoma	65 (8.40)	48 (10.7)	17 (5.20)	
Dysplasia grade				.001
Low-grade	658 (84.9)	403 (89.6)	255 (78.5)	
High-grade	61 (7.90)		61 (18.8)	
No dysplasia	56 (7.20)	47 (10.4)	9 (2.80)	
Location				.001
Right-sided	285 (36.8)	216 (48.0)	69 (21.2)	
Left-sided	476 (61.4)	225 (50.0)	251 (77.2)	
Unknown	*14 (1.80)*	*9 (2.00)*	*5 (1.50)*	
Polyp type				.012
Serrated	63 (8.10)	46 (10.2)	17 (5.20)	
Not serrated	710 (91.6)	402 (89.3)	308 (94.8)	
Unknown	*2 (0.30)*	*2 (0.40)*		
Indication				.001
Screening	398 (51.4)	311 (69.1)	87 (26.8)	
Complaints	377 (48.6)	139 (30.9)	238 (73.2)	
Outcome				
CRC	11 (1.40)	8 (1.80)	3 (0.90)	.374
Subsequent polyps	549 (70.8)	313 (69.6)	236 (72.6)	.379
Adenoma with high-grade dysplasia	17 (2.20)	9 (2.00)	8 (2.50)	.805

Hazard ratios for time to event outcomes

For time to CRC, no variable was significant in univariate analysis. Univariate significant hazard ratios for subsequent polyps were observed for female compared to male (HR 0.79; 95% CI 0.63-1.00), age (HR 1.02; 95% CI 1.00-1.03), amount of polyps (HR 1.43; 95% CI 1.28-1.61), polyp size (HR 1.07; 95% CI 1.01-1.14), and screening compared to complaints (HR 1.32; 95% CI 1.04-1.67). When these variables were included in multivariate analysis, only age and amount of polyps remained significant (HR 1.02; 95% CI 1.00-1.03 and HR 1.42; 95% CI 1.26-1.59, respectively). In the univariate analyses for adenoma with high-grade dysplasia, both villous adenoma compared to tubular adenoma (HR 14.4; 95% CI 1.49-140) and left-sided located polyps compared to right-sided (HR 0.11; 95% CI 0.14-0.90) were significant. Tubulovillous adenoma and no adenoma compared to tubular adenoma were included in multivariate analysis (both $P < 0.10$). In multivariate analysis, villous adenoma compared to tubular adenoma and left-sided located polyps compared to right-sided remained significant (HR 11.8; 95% CI 1.22-115 and HR 0.09; 95% CI 0.01-0.78, respectively), with the addition of tubulovillous adenoma compared to tubular adenoma (HR 7.24, 95% CI 1.44-36.5). After univariate analysis for CRC/Adenoma, only screening compared to complaints, and villous and tubulovillous adenoma compared to tubular adenoma were suitable for multivariate analysis (all $P < 0.10$), but were not found significant in the model. See **Table 2** for a complete overview of the hazard ratios.

Table 2. Hazard ratios for the primary outcomes

n		**8**			**313**			**9**			**17**	
Parameter		**uHR[a]**	**mHR[b]**		**uHR**	**mHR**		**uHR**	**mHR**		**uHR**	**mHR**
Gender												
Male		1			1			1			1	
Female		1.84			0.79*			0.70			0.95	
Age, years		1.08			1.02*	1.02*		0.99			1.03	
BMI, kg·m^{-2}		1.09			1.00			0.89			1.02	
Amount of polyps		0.86			1.43**	1.42**		1.08			0.96	
Polyp size		1.14			1.07*			1.24			1.18	
Adenoma growth pattern												
Tubular		1			1			1	1		1	
Villous		0.00			1.41			14.4*	11.8*		6.26+	
Tubulovillous		2.44			1.12			4.71^{+}	7.24*		2.66+	
No adenoma		0.00			1.06			5.16^{+}	4.72^{+}		2.16	
Dysplasia grade												
Low-grade		1			1			1			1	
No dysplasia		0.04			1.14			2.88			1.65	
Location												
Right-sided		1			1			1	1		1	
Left-sided		1.53			0.92			0.11*	0.09*		0.55	
Polyp type												
Not serrated		1			1			1			1	
Serrated		0.04			1.05			1.29			0.78	
Indication												
Complaints		1			1			1			1	
Screening		3.91^{+}			1.32*			1.32			2.44^{+}	
	Cox regression for colorectal cancer			**Cox regression for subsequent polyps**			**Cox regression for adenoma with high-grade dysplasia**			**Cox regression for CRC/Adenoma**		

[a]; uHR: univariate Hazard Ratio. [b]; mHR: multivariate Hazard Ratio. **: Significant difference at the .01 level (2-tailed); *: Significant difference at the .05 level (2-tailed); $^{+}$: Significant difference at the 0.10 level (2-tailed).

Risk factors for secondary outcomes

In CRC/Adenoma, 98 patients had a surveillance coloscopy within 3 years, 125 after 3-5 years and 227 after more than 5 years. The incidence of CRC/Adenoma in these different time intervals was 7 (7.14%), 6 (4.80%) and 3 (1.32%), respectively. No significant risk factors emerged in any of the univariate or multivariate analyses. A complete listing of ORs can be found in **Table 3**.

Table 3. Odds ratios for colorectal cancer or adenoma with high-grade dysplasia after index coloscopy

	Follow-up time interval (years)					
	< 3		**3-5**		**> 5**	
n (%)	98	(21.8)	125	(27.8)	227	(50.4)
CRC/Adenoma (% of interval)	7	(7.14)	6	(4.80)	3	(1.32)
Parameter	**OR[a]**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Gender						
Male	1		1		1	
Female	1.15	0.24-5.43	0.69	0.12-3.92	2.67	0.24-29.8
Age, years	1.00	0.91-1.09	0.99	0.90-1.08	1.28^{+}	0.97-1.70
BMI, kg·m^{-2}	1.14	0.92-1.42	0.94	0.78-1.14	1.07	0.87-1.31
Amount of polyps	0.66	0.30-1.49	0.57	0.23-1.43	1.08	0.27-4.35
Polyp size	1.12	0.77-1.63	1.11	0.72-1.69	1.09	0.58-2.06
Adenoma growth pattern						
Tubular	1		1		1	
Villous	-		4.94	0.44-55.0	-	-
Tubulovillous	3.98	0.62-25.6	0.79	0.08-7.40	3.11	0.27-35.4
No adenoma	3.53	0.46-27.2	-	-	-	-
Dysplasia grade						
Low-grade	1		1		1	
No dysplasia	2.03	0.36-11.4	-	-	-	-
Location						
Right-sided	1		1		1	
Left-sided	0.90	0.19-4.28	0.17	0.02-1.49	1.81	0.16-20.3
Polyp type						
Not serrated	1		1		1	
Serrated	0.83	0.09-7.43	-	-	-	-
Indication						
Complaints	1		1		1	
Screening	1.26	0.27-5.96	1.53	0.30-7.91	6.96	0.62-78.3

[a]; OR: Odds Ratio. **: Significant difference at the .01 level (2-tailed); *: Significant difference at the .05 level (2-tailed); $^{+}$: Significant difference at the 0.10 level (2-tailed).

Of the patients who had surveillance colonoscopy within 3 years, 78 (79.6%) had subsequent polyps. In both univariate and multivariate analysis, no significant predictors were found. A rate of 69.6% (87 patients) in the 3-5 years follow-up time interval presented with subsequent polyps at the time of surveillance colonoscopy. In univariate analysis, female compared to male (OR 0.33; 95% CI 0.15-0.72), amount of polyps (OR 1.84; 95% CI 1.21-2.80), no adenoma compared to tubular adenoma (OR 0.08; 95% CI 0.02-0.38), no dysplasia compared to low-grade dysplasia (OR 0.18; 95% CI 0.05-0.64), and serrated polyps compared to non serrated polyps (OR 0.12; 95% CI 0.03-0.45) were significant predictors. Polyp size was also included in multivariate analysis ($P < 0.10$). In multivariate analysis, 3 variables remained significant: female compared to male (mOR 0.27; 95% CI 0.11-0.65), polyp size (mOR 1.70; 95% CI 1.08-2.67), and serrated polyps compared to non serrated polyps (mOR 0.13; 95% CI 0.3-0.57). Two variables were in both univariate and multivariate analysis significant predictors for subsequent polyps in 227 patients that had surveillance colonoscopy after more than 5 years. These predictors were age (OR 1.05; 95% CI 1.02-1.08 and mOR 1.04; 95% CI 1.01-1.08) and amount of polyps (OR 1.82; 95% CI 1.21-2.74 and mOR 1.73; 95% CI 1.15-2.61) (**Table 4**).

Table 4. Odds ratios for subsequent polyps after index coloscopy

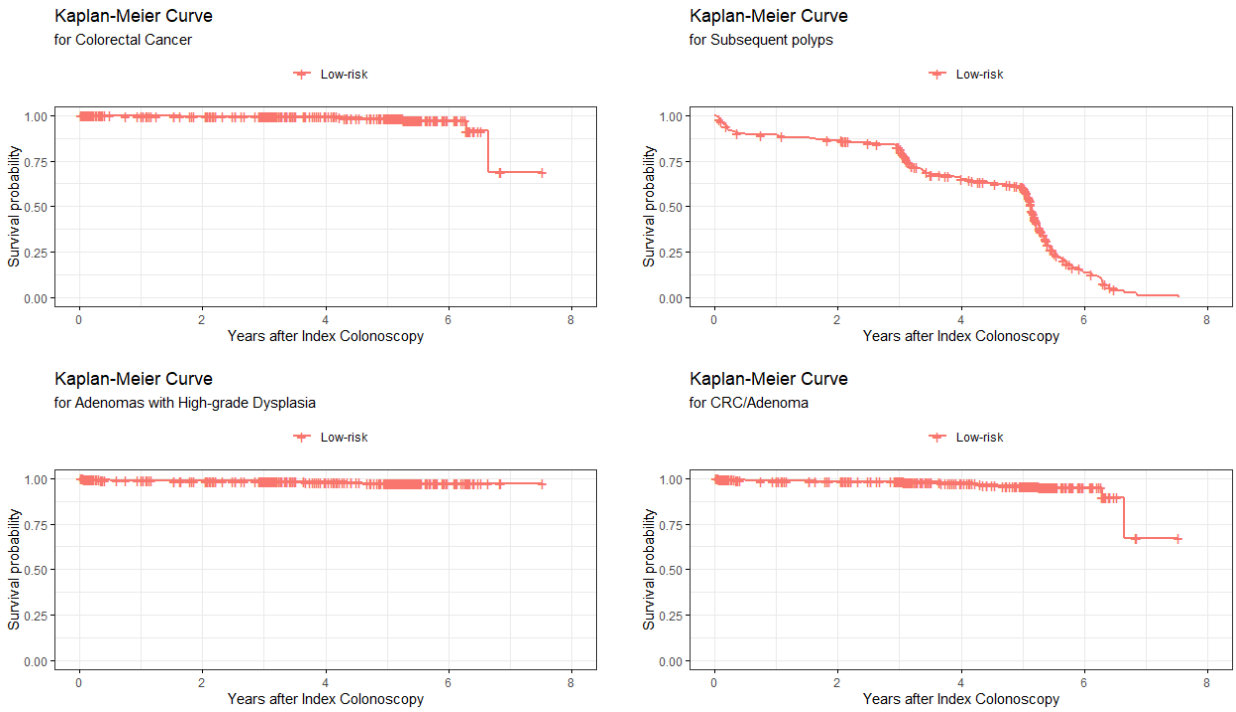
	Follow-up time interval (years)					
	< 3		**3-5**		**> 5**	
n (%)	98	(21.8)	125	(27.8)	227	(50.4)
Subsequent polyps (% of interval)	78	(79.6)	87	(69.6)	148	(65.2)
Parameter	**OR[a]**	**mOR[b]**	**OR**	**mOR**	**OR**	**mOR**
Gender						
Male	1		1	1	1	
Female	0.76		0.33**	0.27**	0.68	
Age, years	1.03		1.03		1.05**	1.04**
BMI, kg·m^{-2}	1.13		0.98		1.00	
Amount of polyps	0.88		1.84**	1.70*	1.82**	1.73**
Polyp size	0.93		1.20^{+}		1.14	
Adenoma growth pattern						
Tubular	1		1		1	
Villous	0.00		0.51		0.54	
Tubulovillous	0.51		1.13		1.71	
No adenoma	1.04		0.08**		0.67	
Dysplasia grade						
Low-grade	1		1		1	
No dysplasia	1.24		0.18**		0.50	
Location						
Right-sided	1		1		1	
Left-sided	0.60		0.73		1.62^{+}	
Polyp type						
Not serrated	1		1	1	1	
Serrated	1.86		0.12**	0.13**	0.51	
Indication						
Complaints	1		1		1	
Screening	1.16		1.83		1.42	

[a]; OR: Odds Ratio. [b]; mOR: multivariate Odds Ratio. **: Significant difference at the .01 level (2-tailed); *: Significant difference at the .05 level (2-tailed); $^{+}$: Significant difference at the 0.10 level (2-tailed).

Kaplan-Meier analysis for overall survival

In case of CRC, the proportion that had no event after 5 years was estimated at 98.3% (SE (Standard Error) = 0.80%). For subsequent polyps, after 5 years, it was estimated that a proportion of 60.9% (SE = 2.40%) had no subsequent polyps. An estimated proportion of 97.3% (SE = 0.90%) had no adenoma with high-grade dysplasia. For CRC/Adenoma, a proportion estimated at 96.0% (SE = 1.10%) had no event. Median survival is achieved only in the case of subsequent polyps, being 5.15 years (95% CI 5.11-5.19). Survival curves for the respective outcomes can be found in **figure 2**.

Figure 2. Kaplan-Meier analyses for primary outcomes



Discussion

This retrospective cohort study in the Netherlands investigated the incidence of CRC, adenomas with high-grade dysplasia, subsequent polyps, and CRC/Adenoma after polypectomy of a low-risk polyp. Increasing age (HR 1.02) and increased amount of polyps (HR 1.42) were associated with a higher risk for the recurrence of subsequent polyps. Villous and tubulovillous adenoma compared to tubular adenoma (HR 11.8 and HR 7.24, respectively) were associated with a higher risk for the development of adenomas with high-grade dysplasia, whereas left-sided located polyps compared to right-sided was associated with a lower risk (HR 0.09). No risk factors have been found for either CRC or CRC/Adenoma.

The purpose of this study was to assess the possibility and responsibility of conforming the guidelines used in MST to the ESGE and EUG guidelines. Reason for this was the discrepancy between the guidelines of ESGE and EUG (7,8) and the guidelines of AGA and the Dutch guidelines used in MST (6,11). The first mentioned organizations advise patients with low-risk polyps at index colonoscopy to have a surveillance coloscopy after 10 years, or even to return to routine screening. The AGA and the guidelines used in MST advise to have these patients return for a surveillance coloscopy as early as 5 years after index coloscopy.

Before interpreting the results of this study, there are a few relevant remarks to be made. This study strengthens the knowledge about the incidence of CRC, adenomas with high-grade dysplasia, and subsequent polyps in patients at MST. Another strength is the stratification for different follow-up time intervals, to examine whether the predictors for secondary outcomes differ between them. Nevertheless, there are also a number of limitations in this study. When collecting the data, only the characteristics of the 'most severe' polyp were noted (i.e. polyp type, adenoma growth pattern, dysplasia grade, and location). This may potentially lead to a distorted understanding, since not all characteristics of all polyps found during index colonoscopy were included. Besides demographic data such as gender, age and BMI, no other possible aspects that could affect the outcome measures were used. These include family anamnesis, socioeconomic status, alcohol consumption and the number of pack-years. For further research, it may be interesting to collect demographic and clinical data on a broader scale. A control group in which no polyps were found during index colonoscopy was not used. Therefore, no similarities and/or discrepancies could be found in the analyses. Complementary, it is not clear whether the current hazards and risks of primary and secondary outcomes are due to surveillance colonoscopy after five years, or whether they would have been the same if there had been no surveillance colonoscopy after five years. There was no patient with a follow-up period of at least 10 years in this study. This makes it difficult to say whether it is justifiable to adjust the guidelines based on these results. In order to do so, several studies would have to be conducted with a follow-up interval of at least 10 years. Another limitation is the very low incidence in both CRC and adenomas with high-grade dysplasia. In the analyses for primary outcomes, these account for 8 and 9 cases respectively, i.e. 17 cases as a combined outcome. In the analyses for secondary outcomes, these cases are even lower, namely 7, 6 and 3 cases for the different follow-up time intervals (< 3 years, 3-5 years and > 5 years, respectively). Furthermore, there is no Boston Bowel Preparation Scale noted per patient. Therefore, the assessment of the cleanliness of the colon is not included, while it does affect the quality of the colonoscopy. In addition, this was a single-centre study conducted on a relatively small population, and its confirmation on a larger, multicentre cohort is warranted to achieve generalisability.

No variable was found to be associated with the development of CRC. In other studies, increasing age, increased BMI, villous and tubulovillous adenomas, increasing polyp size and large serrated polyps were associated with CRC (13–16). These differences can be explained because in these studies the study populations are much larger with higher incidence of CRC. In addition, the mean ages are much lower, polyps ≥ 10 mm are included in the analyses, and BMI was used as a categorical variable with different cut-off values (≤ 25 $kg \cdot m^{-2}$, 25-30 $kg \cdot m^{-2}$, and ≥ 30 $kg \cdot m^{-2}$). There may also be a difference in the assessment of histopathological patient reports between medical centers, perhaps also in the determination of a tubulovillous adenoma or villous adenoma. In our study, no one with serrated polyps developed CRC. Moreover, this study is focused on patients with low-risk polyps, a criteria for which is that the polyp is < 10 mm. Thus, there would be a limited factor in the affect of large serrated polyps on CRC anyway. Increasing age and increased amount of polyps were found to be independently associated with a higher risk for the recurrence of subsequent polyps. Yamaji *et al*. (17) indeed confirmed this for age, just like Chi *et al*. (18) confirmed this for amount of polyps. Compared to tubular adenomas, villous and tubulovillous adenomas were associated with the incidence of adenomas with high-grade dysplasia, as shown by Huang *et al*. (19). Another study showed (13) that right-sided located polyps compared to left-sided polyps were more likely to develop adenomas with high-grade dysplasia, just like our study shows that left-sided polyps compared to right-sided polyps are less likely to develop adenomas with high-grade dysplasia. No significant predictors were found for CRC/Adenoma in time to event analysis, as well as in the different time intervals. This can be explained in the same manner as was done above for CRC. No predictors were found for subsequent polyps in patients who had a surveillance colonoscopy within 3 years. For the patients that had surveillance colonoscopy after 3 to 5 years, female compared to male and serrated polyps compared to non serrated polyps were independently associated with a lower risk developing subsequent polyps. An increased amount of polyps had a higher risk for the recurrence of subsequent polyps. In the group of patients that had surveillance colonoscopy after 5 years, increasing age and increasing amount of polyps were independently associated with a higher risk of developing subsequent polyps. No literature was found for all follow-up time intervals (< 3 years, 3-5 years, and > 5 years), since follow-up time is commonly used as a predictor rather than a criterion to classify patients into different groups for analyses.

To conclude, no predictors were found for the development of CRC and CRC/Adenoma. An increasing age and increasing amount of polyps are predictors for the development of subsequent polyps. Adenoma growth pattern and location are predictors for adenomas with high-grade dysplasia. Male gender, increasing polyp size and polyp type are predictors for subsequent polyps in the group of patients that had surveillance colonoscopy 3 to 5 years after index colonoscopy. Predictors for subsequent polyps in the group that had surveillance colonoscopy more than 5 years after index colonoscopy are increasing age and increased amount of polyps. Patients with low-risk polyps may not need surveillance colonoscopy within 5 years, but it is too premature to determine that on the basis of these results. Additional, larger studies are needed to assess a higher incidence of CRC and adenomas with high-grade dysplasia, as well as a longer follow-up time, to evaluate and possibly adjust the current guidelines.

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Supplementary Material

As additional material, the same analyses were done for the high-risk cohort. The results can be found in this section. The outcome measures were as follows:

In case CRC and adenoma with high-grade dysplasia had considerably low numbers in different analyses, they were merged into one dependent variable, namely CRC or adenoma with high grade dysplasia.

Primary outcomes of this study were the incidence of CRC, subsequent polyps, adenoma with high-grade dysplasia, and CRC or adenoma with high-grade dysplasia (from now on *CRC/Adenoma*) in patients classified as 'high-risk'.

Secondary outcomes were predictors for CRC/Adenoma with high-grade dysplasia and subsequent polyps stratified for different follow-up time intervals (< 3 years, 3-5 years, and > 5 years).

Hazard ratios for time to event outcomes in the high-risk cohort

In univariate analysis for CRC, two variables were suited for multivariate analysis (age, HR 1.27; 95% CI 0.98-1.64 and polyp size, HR 1.13; 95% CI 1.02-1.25). In multivariate analysis, neither remained significant. Hazard ratios were found in both univariate and multivariate analysis for subsequent polyps. In univariate analysis, amount of polyps (HR 1.09; 95% CI 1.06-1.12) and left-sided located polyps compared to right-sided (HR 0.70; CI 95% 0.52-0.94) were found significant. Amount of polyps remained the only significant in multivariate analysis (HR 1.09; 95% CI 1.06-1.12). For adenoma with high-grade dysplasia, two significant univariate variables were found, being no adenoma compared to tubular adenoma (HR 8.79; 95% CI 1.24-62.5) and serrated polyps compared to non serrated (HR 5.34; 1.08-26.6). In multivariate analysis, only serrated polyps compared to non serrated remained significant (HR 5.34; 95% CI 1.08-26.6). In the analyses for CRC/Adenoma with high-grade dysplasia, both univariate and multivariate, there were no significant variables (**Table S1**).

Table S1. Hazard ratios for the primary outcomes in the high-risk cohort

n		**3**			**236**			**8**			**11**	
Parameter		**uHR[a]**	**mHR[b]**		**uHR**	**mHR**		**uHR**	**mHR**		**uHR**	**mHR**
Gender												
Male		ref			ref			ref			ref	
Female		0.97			0.81			1.27			1.18	
Age, years		1.27^{+}			1.02			0.98			1.05	
BMI, kg·m^{-2}		0.93			0.97			0.84^{+}			0.87^{+}	
Amount of polyps		1.20			1.09**	1.09**		1.03			1.04	
Polyp size		1.13*			0.99			0.90			1.01	
Adenoma growth pattern												
Tubular		ref			ref			ref			ref	
Villous		-			0.89			-			-	
Tubulovillous		0.423			0.86			2.65			1.45	
No adenoma		-			0.89			8.79*			5.34^{+}	
Dysplasia grade												
Low-grade		ref			ref			ref			ref	
High-grade		0.04			0.90			2.54			1.86	
No dysplasia		0.03			0.90			-			-	
Location												
Right-sided		ref			ref			ref			ref	
Left-sided		26.3			0.70*			29.2			28.5	
Polyp type												
Not serrated		ref			ref			ref	ref		ref	
Serrated		0.05			0.97			5.34*	5.34*		4.63^{+}	
Indication												
Complaints		ref			ref			ref			ref	
Screening		45.4			1.13			0.63			1.13	
	Cox regression for colorectal cancer			**Cox regression for subsequent polyps**			**Cox regression for adenoma with high-grade dysplasia**			**Cox regression for CRC/Adenoma**		

[a]; uHR: univariate Hazard Ratio. [b]; mHR: multivariate Hazard Ratio. **: Significant difference at the .01 level (2-tailed); *: Significant difference at the .05 level (2-tailed); $^{+}$: Significant difference at the 0.10 level (2-tailed).

Risk factors for secondary outcomes in the high-risk cohort

In CRC/Adenoma, 94 patients had a surveillance coloscopy within 3 years, 173 after 3-5 years and 58 after more than 5 years. The incidence of CRC/Adenoma in these different time intervals was 7 (7.44%), 4 (1.16%) and 2 (3.40%). For both the less than 3 years and 3 to 5 years time intervals, no variables presented as significant in univariate analysis. In the more than 5 years time interval, only polyp size was an univariate significant variable (OR 1.21; 95% CI 1.02-1.42). No significant risk factor appeared in multivariate analysis (**Table S2**).

Table S2. Odds ratios for colorectal cancer or adenoma with high-grade dysplasia after index coloscopy in the high-risk cohort

	Follow-up time interval (years)					
	< 3		**3-5**		**> 5**	
n (%)	94	(28.9)	173	(53.2)	58	(17.8)
CRC/Adenoma (% of interval)	7	(7.44)	2	(1.16)	2	(3.40)
Parameter	**OR[a]**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Gender						
Male	1	1	1	1	1	1
Female	0.62	0.11-3.40	2.29	0.14-37.3	2.29	0.14-38.9
Age, years	0.91	0.80-1.05	1.15	0.88-1.51	-	-
BMI, kg·m^{-2}	0.85	0.66-1.09	0.88	0.62-1.26	0.91	0.66-1.27
Amount of polyps	0.98	0.82-1.18	0.51	0.15-1.76	1.01	0.55-1.85
Polyp size	0.98	0.85-1.13	0.78	0.55-1.12	1.21*	1.02-1.42
Adenoma growth pattern						
Tubular	1	1	1	1	1	1
Villous	-	-	-	-	-	-
Tubulovillous	1.27	0.24-6.67	-	-	1.58	0.09-26.8
No adenoma	2.87	0.25-33.1	-	-	-	-
Dysplasia grade						
Low-grade	1	1	1	1	1	1
High-grade	0.66	0.07-5.83	-	-	-	-
No dysplasia	-	-	-	-	-	-
Location						
Right-sided	1	1	1	1	1	1
Left-sided	-	-	-	-	-	-
Polyp type						
Not serrated	1	1	1	1	1	1
Serrated	2.73	0.27-27.3	27.5	1.53-494	-	-
Indication						
Complaints	1	1	1	1	1	1
Screening	1.19	0.22-6.50	0.28	0.02-4.52	-	-

[a]; OR: Odds Ratio. **: Significant difference at the .001 level (2-tailed); *: Significant difference at the .05 level (2-tailed); [+]: Significant difference at the 0.10 level (2-tailed).

Of the patients who had surveillance colonoscopy within 3 years, 77 patients (81.9%) had subsequent polyps. BMI and tubulovillous adenoma compared to tubular adenoma were included in multivariate analysis (both $P < 0.10$), but were not found to be risk factors for the recurrence of subsequent polyps. A rate of 71.1% (123 patients) in the 3-5 time interval presented with subsequent polyps at the time of surveillance colonoscopy. In univariate analysis, female compared to male (OR 0.43; 95% CI 0.22-0.86), amount of polyps (OR 1.33; 95% CI 1.10-1.62), polyp size (OR 0.94; 95% CI 0.89-0.99), tubulovillous adenoma compared to tubular adenoma (OR 0.50; 95% CI 0.25-0.99) were found to be significant. Left-sided located polyps compared to right-sided located polyps was included in the multivariate model ($P < 0.10$). Amount of polyps remained the only significant variable in multivariate analysis (OR 1.33; 95% CI 1.10-1.62). In the group of patients that underwent surveillance colonoscopy after more than 5 years, 62.1% had recurrent polyps (36 patients). No significant variables were found in univariate and multivariate analysis (**Table S3**).

Table S3. Odds ratios for subsequent polyps after index coloscopy in the high-risk cohort

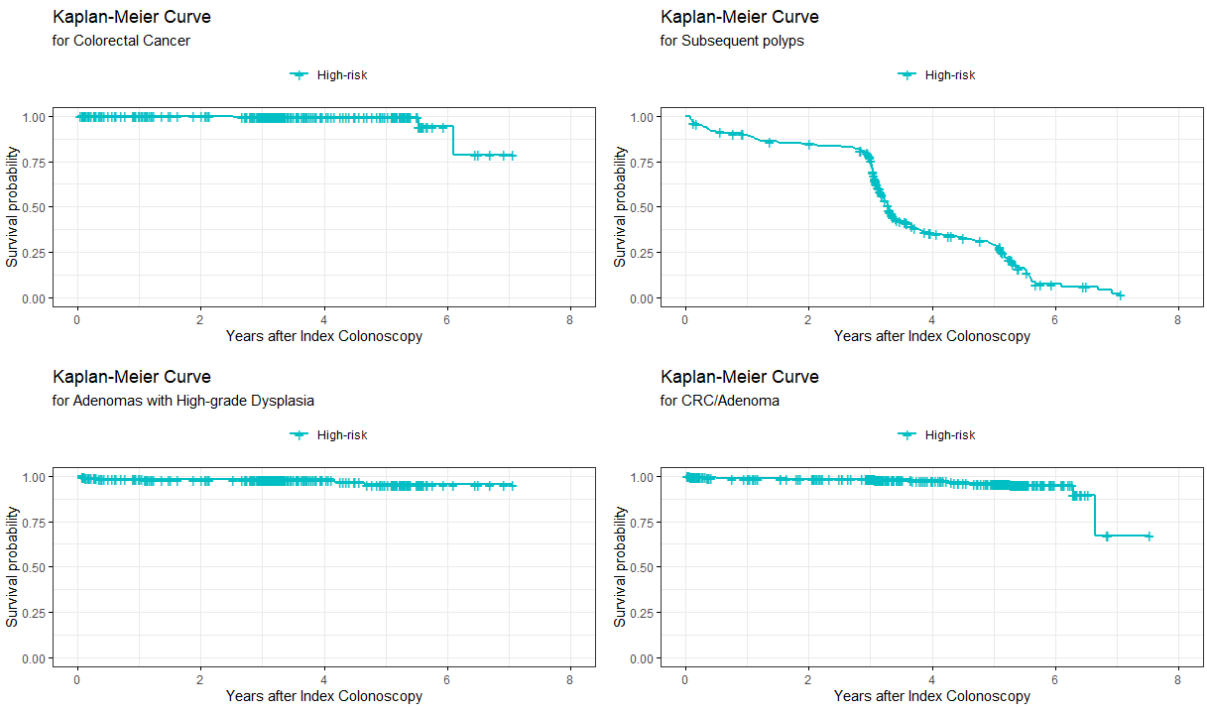
	Follow-up time interval (years)					
	< 3		**3-5**		**> 5**	
n (%)	94	(28.9)	173	(53.2)	58	(17.8)
Subsequent polyps (% of interval)	77	(81.9)	123	(71.1)	36	(62.1)
Parameter	**OR[a]**	**mOR[b]**	**OR**	**mOR**	**OR**	**mOR**
Gender						
Male	1		1		1	
Female	0.48		0.43*		0.34^{+}	
Age, years	1.04		1.00		1.04	
BMI, kg·m^{-2}	0.93		1.03		1.01	
Amount of polyps	1.20^{+}		1.33**	1.33**	1.17	
Polyp size	1.03		0.94*		0.97	
Adenoma growth pattern						
Tubular	1		1		1	
Villous	1.26		0.60		0.70	
Tubulovillous	3.56^{+}		0.50*		0.35^{+}	
No adenoma	0.62		1.80		0.12^{+}	
Dysplasia grade						
Low-grade	1		1		1	
High-grade	1.90		0.55		0.28	
No dysplasia	0.48		-		0.23	
Location						
Right-sided	1		1		1	
Left-sided	0.87		0.35^{+}		1.41	
Polyp type						
Not serrated	1		1		1	
Serrated	0.41		2.51		0.18	
Indication						
Complaints	1		1		1	
Screening	0.87		1.86		2.50	

[a]; OR: Odds Ratio. [b]; mOR: multivariate Odds Ratio. **: Significant difference at the .001 level (2-tailed); *: Significant difference at the .05 level (2-tailed); $^{+}$: Significant difference at the 0.10 level (2-tailed).

Kaplan-Meier analysis for overall survival

In case of CRC, the proportion that had no event after 5 years was estimated at 99.6% (SE = 0.40%). For subsequent polyps, after 5 years, it was estimated that a proportion of 28.8% (SE = 2.90%) had no subsequent polyp. An estimated proportion of 95.3% (SE = 2.10%) had no adenoma with high-grade dysplasia. For CRC/Adenoma, a proportion estimated at 94.9% (SE = 2.10%) had no event. Median survival is achieved only in the case of subsequent polyps, being 3.29 years (95% CI 3.20-3.37). Survival curves for the respective outcomes can be found in **figure S1**.

Figure S1. Kaplan-Meier analyses for primary outcomes



No difference was found in the overall survival between the low-risk and high-risk cohorts for CRC, adenoma with high-grade dysplasia and CRC/Adenoma (Log-rank: $P = 0.85$; $P = 0.34$ and $P = 0.46$, respectively). For subsequent polyps, there was a significant difference in overall survival between the low-risk and high-risk cohorts (Log-rank: $P < 0.001$) (**Figure S2**).

Figure S2. Kaplan-Meier analyses for primary outcomes, low-risk cohort vs. high-risk cohort