Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Predictors of colorectal neoplasia after polypectomy: based on initial and consecutive findings

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ABSTRACT

Background: Colorectal adenoma patients are kept under surveillance because of the risk of developing metachronous neoplasia. The aim is to determine predictors of neoplasia development after polypectomy.

Methods: It is an observational cohort study. 433 Patients who had ≥1 adenoma removed between 1988 and 2004 were included, with follow-up until 2010. Multivariate analysis of patient and adenoma characteristics was performed at initial colonoscopy and at consecutive positive examinations. The main outcome measured was the development of metachronous (advanced) adenomas during follow-up.

Results: Median follow-up was 85 months. Multivariate analysis identified male sex, ≥3 adenomas, high-grade dysplasia and age ≥55 years as risk factors for metachronous lesions at first surveillance. Analysis using life expectancy as a timescale showed ≥3 adenomas to be the only predictive factor. The time to second or third metachronous adenoma did not depend on the number of adenomas. Patients with ≥3 adenomas were five years older at the time of their first polypectomy compared with those with fewer adenomas, but of the same age at the first recurrence. Prevalence of high-grade dysplasia was associated with age and high-grade dysplasia in the prior adenoma independent of time interval.

Conclusions: Adenoma development after polypectomy occurs in a regular and repetitive way. Our data suggest that only the interval between the initial colonoscopy and the first follow-up colonoscopy should be based on initial findings, i.e. number of adenomas, and that subsequent colonoscopies can be planned at predetermined intervals.

KEYWORDS

Adenoma, colonoscopy, colorectal neoplasms, polypectomy, surveillance

INTRODUCTION

Colorectal cancer (CRC) is one of the most common causes of cancer mortality in Western countries.[1,2] Most colorectal cancers develop from a benign precursor lesion, the adenoma. Adenomas with so-called advanced features have the highest risk to develop into CRC. The definition of an advanced adenoma is >25% villous histology, and/or size larger than 1 cm, and/or presence of high-grade dysplasia.[3-6] Removal of adenomas has been shown to reduce the incidence and mortality of CRC.[3,7-10] Following polypectomy of adenomas, patients are generally kept under endoscopic surveillance because of an increased risk of developing metachronous neoplasia.[3,6]

Apart from the risk of complications, surveillance endoscopies are a significant burden in terms of medical resources and costs.[11-14] It is therefore important to identify predictive factors for adenoma recurrence in order to select patients for follow-up and to determine appropriate surveillance intervals. In the current guidelines, risk stratification is based on studies that focused on adenoma and patient characteristics at first colonoscopy.[4,8,15]

Since 1988, follow-up after polypectomy at our Institution has been done following the national guidelines.[16,17] This allowed us to analyse data from a long follow-up period with consecutive endoscopies. Therefore, in this study we not only focused on the results of the first polypectomy, but used the findings of all examinations during this follow-up

period. The objective of this study was to determine predictive factors for the development of adenomas and advanced neoplasia after polypectomy. Based on the results, a proposal for appropriate surveillance intervals is formulated.

MATERIALS AND METHODS

Patient selection

A database search was performed in the Dutch Pathological Anatomic National Automatic Archive (PALGA) in order to retrieve records of patients who had undergone polypectomy of at least one colorectal adenoma at our institution between 1988 and 2004. Up to July 2010, data were retrospectively collected from the medical charts. Subjects were included if they were 18 years or older and had undergone polypectomy of at least one histologically proven adenoma during a complete colonoscopy. Patients were excluded if any of the following risk factors for CRC were present: a personal medical history of CRC, Lynch syndrome or other hereditary predisposition syndrome or inflammatory bowel disease. Also patients with a liver transplantation were excluded because of their increased risk of advanced lesions.[18]

During the study period the national guidelines underwent some modifications with respect to follow-up after polypectomy of adenomatous polyps. From 1988-1997, the national guidelines advised a yearly follow-up colonoscopy after polypectomy until a 'clean' colon. And then again after three years in case of multiple or after five years in case of a single adenoma.[17] In 1997 the colonoscopy after one year was no longer deemed necessary.[4,19] In 2001, the guidelines were revised, recommending follow-up after six years in case of ≤2 adenomas, and after three years in case of ≤3 adenomas.[16]

A time interval of at least six months between examinations was used to define metachronicity of adenomas, which is consistent with similar studies.[15,20,21] For patients to be included in this study, data from at least one complete surveillance colonoscopy had to be available. As a rule all lesions had to be removed and histologically categorised. If patients had more than one lesion, they were categorised according to their most advanced lesion. Basically all polyps were sent for histology and we estimate that less than 10% were not. If no histology was obtained, polyps were not included in the analysis. Adenoma location was defined as proximal or distal, relative to the splenic flexure. Adenoma size was derived from the histopathological report. When the original histology reports were incomplete or described moderate-grade dysplasia, samples were revised by the pathologist (HH) and dysplasia was categorised as low-grade or high-grade according to current guidelines.[22]

Statistical analysis

Associations between patient and adenoma characteristics were analysed using the Chi-square test. Associations between these characteristics and life expectancy and age were tested by the Mann-Whitney U-test. Univariate and multivariate Cox regression analyses with patient and adenoma characteristics were performed using the interval between colonoscopies as a timescale to identify possible risk factors for the development of metachronous adenomas and carcinomas during follow-up. Risk factors that had a p-value <0.15 at univariate analysis were incorporated in a multivariate analysis using a stepwise backward procedure ending with p<0.05. End of follow-up was determined by the last complete colonoscopy or death. Risks were expressed using hazard ratios (HR) with their 95% confidence intervals (CI). A CI not including the value 1.0 and a p-value <0.05 indicated a significant association. Data were analysed with SPSS software version 17.0.

Due to the association between rate of adenoma recurrence with sex and age, and because of differences in sex and age among the various subgroups of patients, the analyses were repeated by log-rank test using an age-related timescale.[23,24] Risks were expressed using odds ratios (OR) with their 95% CI. In order to adjust for sex, age and birth cohort, the median life expectancy – projected on a negative x-axis – was chosen as a timescale. Median life expectancy at the first examination was derived from the sex-specific annual reports of mortality in the general Dutch population provided by the Central Bureau of Statistics (CBS).[25] These mortality data were also used to calculate the standardised mortality rate (SMR) of the patients as the ratio between observed and expected deaths. Differences in ranges of age at death were studied by means of the F-test. Left censoring of data was involved in the analysis of life expectancy. However, since the application to perform this calculation is not provided by commonly available software, the calculations were performed using Excel software (version 2007).

RESULTS

Patient and baseline adenoma characteristics

In total, 488 patients were identified. Of these, 55 were excluded because one or more previously identified risk factors for CRC were present, or because of incomplete data. The final analysis therefore included 433 patients (mean age 55, range 24-82, 41% males). Twenty-nine patients had an adenoma in their history and their follow-up for this study started when their first metachronous lesion was removed. A total of 404 patients had their first adenoma diagnosis during the study period. In total, 239 adenomas were revised by our pathologist to meet current guidelines. Our patient group had an

estimated SMR of 1.10 (95% CI 0.74-1.42, p=0.637). All causes of death during follow-up were known and were not related to colorectal cancer.

Adenoma characteristics at baseline are summarised in *table 1*. Baseline colonoscopy revealed ≥3 adenomas in 67 cases (16%). An advanced adenoma was found in 251 cases (58%).

Associations between patient and adenoma characteristics at baseline

Male sex in the 404 newly diagnosed patients was associated with having ≥3 adenomas (p=0.04). Having ≥3 adenomas was also associated with high-grade dysplasia (p=0.003), size ≥1 cm (p=0.001) and proximal location (p<0.001). High-grade dysplasia was associated with size ≥1 cm (p<0.001) and villous features (p<0.001). The median life expectancy at the time of diagnosis was lower in cases with ≥3 adenomas than in those cases with fewer adenomas (24.9 vs 30.0 years respectively, p <0.001).

Follow-up

The median follow-up period was 85 months (range 9-260). The median number of colonoscopies that had been performed during follow-up was 2 (mean 2.3, range 1-7). During follow-up, 219 out of the 433 patients (51%) developed at least one adenoma. Characteristics of these metachronous findings are depicted in *table 1*. Compared with baseline adenomas, incident adenomas were more often smaller than 1 cm, generally showed tubular growth, and more often low-grade dysplasia.

The occurrence of these metachronous findings during follow-up in the 404 newly diagnosed patients from diagnosis until observed mortality is shown in *figure 1*. During patients' lifetime, new adenomas occurred after an interval of about 6-8 years.

During follow-up, 86 patients (20%) were diagnosed with an advanced adenoma and two patients (0.7%) with CRC. In the first patient who developed CRC (male, 59 years at the time of diagnosis of first adenoma), one small tubular adenoma was found at initial colonoscopy. A colonoscopy after two years because of symptoms proved normal, whereas five years later CRC was detected at the third colonoscopy. The second patient (female, 51 years at diagnosis of first adenoma) initially had one advanced adenoma (larger than 1 cm, high-grade dysplasia with tubulovillous features, distally located). After five years she had a second colonoscopy which proved to be negative. Her third colonoscopy took place after ten years and demonstrated one small villous adenoma with low-grade dysplasia. CRC was diagnosed at the fourth colonoscopy, 15 years after the initial colonoscopy. Neither of these two tumours were tested for microsatellite instability of tumour DNA or the immunohistochemical expression of mismatch repair genes.

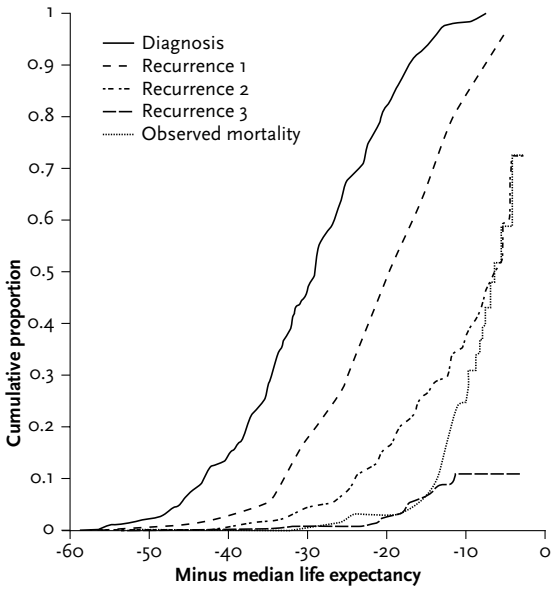
Risk factors for metachronous adenoma at first surveillance

Univariate analysis revealed male sex (p=0.001), age ≥55 years (p=0.004), ≥3 adenomas at colonoscopy (p=0.001), proximal location (p=0.01) and high-grade dysplasia (p=0.03) to be risk factors for first metachronous adenoma.

Table 1. *Adenoma characteristics: findings at baseline and follow-up colonoscopies*

	Initial colonoscopy (n = 433)	Adenoma recurrence (n = 219)
Number of adenomas		
One	284 (65.6%)	147 (67.1%)
Multiple	149 (34.4%)	72 (32.9%)
<3 adenomas	366 (84%)	186 (85%)
>3 adenomas	67 (16%)	33 (15%)
Histology		
Tubular	234 (54%)	157 (71.6%)
Tubulovillous	149 (34.4%)	49 (22.4%)
Villous	37 (8.5%)	5 (2.3%)
Serrated	7 (1.6%)	4 (1.8%)
Unknown	6 (1.4%)	2 (0.9%)
Size		
<1 cm	257 (59.4%)	193 (88.1%)
>1 cm	160 (37%)	21 (9.6%)
Unknown	16 (3.6%)	5 (2.3%)
Degree of dysplasia		
Low-grade	273 (63%)	185 (84.5%)
High-grade	156 (36%)	31(14.2%)
Unknown	4 (0.9%)	1 (0.5%)
Carcinoma		2 (0.7%)
Location		
Proximal	136 (31.4%)	113 (51.6%)
Distal	284 (65.6%)	96 (42.9%)
Unknown	13 (3%)	10 (4.6%)

Figure 1. *Diagnosis, metachronous adenomas and death during follow-up*



The occurrence of metachronous adenomas during follow-up from diagnosis till observed death on a life expectancy scale. Adenomas recurred with a median interval of about eight years.

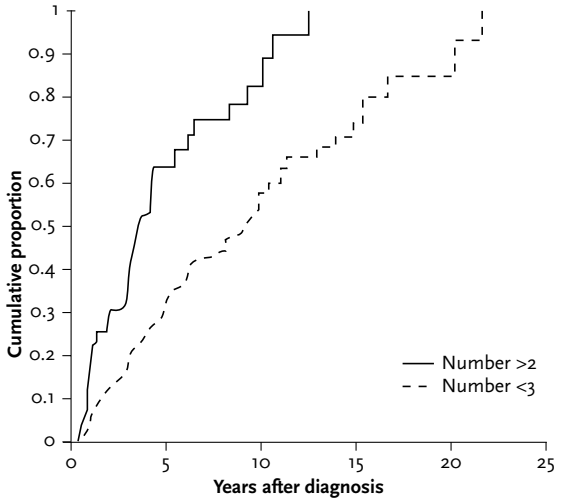
Multivariate analysis showed male sex (HR=1.59; 95% CI 1.18-2.13; p=0.003), ≥3 adenomas (HR=1.92; 95% CI 1.34-2.77; p<0.001) and age (HR=1.04, 95% CI 1.02-1.05, p<0.001) to be independent risk factors. A Kaplan-Meier plot stratified for number of lesions, unadjusted for age or sex, is shown in *figure 2*. A 30% cumulative proportion was found after 2.5 years in patients with ≥3 adenomas, and after five years in patients with 1-2 adenomas.

As sex and age were strongly associated with the number of adenomas found at colonoscopy, the analysis was repeated using life expectancy as a timescale. In a multivariate analysis, the only independent risk factor for first adenoma recurrence was having more than two adenomas (OR=1.88; 95% CI 1.35-2.63; p<0.001). The difference in age at diagnosis disappeared at first recurrence (*figure 3*) when stratified for this predicting factor. Thus, having more than two adenomas was associated with a shorter interval to the first recurrence, as shown in *figure 2*.

Risk factors for metachronous adenoma at second and third surveillance

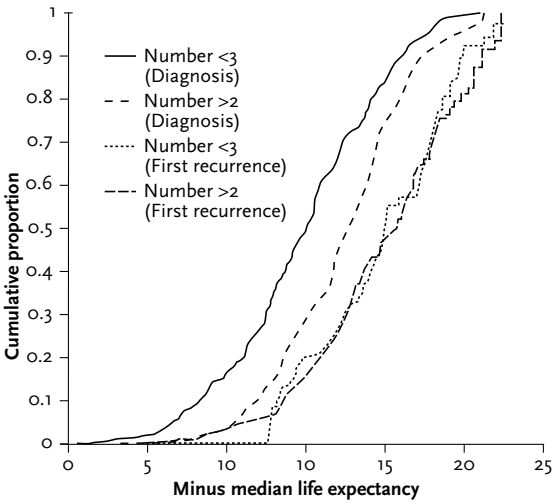
Follow-up after adenoma development of adenomas at first surveillance was available in 147 patients, 40 of whom could be studied after development of their second adenoma. When analysed by using either adenoma interval or life expectancy as a timescale, sex, age at, and characteristics of first or second recurrent disease were not found to be risk factors for the incidence of second and third metachronous adenomas. Again, cumulative proportions of 30% were reached after about five years, and 50% after about eight years.

Figure 2. *First metachronous adenoma stratified for number of adenomas at diagnosis: Kaplan-Meier curve*



Incidence of first metachronous adenoma stratified for number of adenomas at diagnosis over the years after diagnosis. Patients who had more than two adenomas will have their first recurrence earlier (p<0.001).

Figure 3. *First metachronous adenoma stratified for number of adenomas at diagnosis: life expectancy scale*



Incidence of adenoma at diagnosis and first adenoma recurrence, stratified for number of lesions at diagnosis, during lifetime till death. Age at diagnosis depends on the number of adenomas, but at first recurrence all patients have the same age.

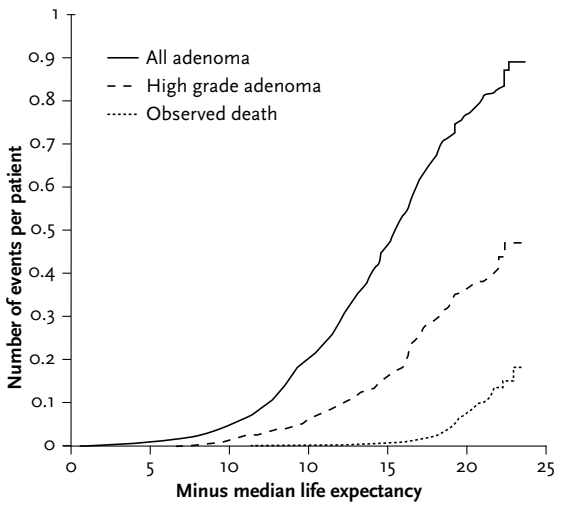
Prevalence of adenoma with high-grade dysplasia

Multivariate Cox regression analysis identified age (HR=1.05; 95% CI 1.03-1.07; p<0.001) and high-grade dysplasia in the preceding adenoma (HR=1.73; 95% CI 1.13-2.64; p=0.012) as independent risk factors for the development of adenomas with high-grade dysplasia after combining all of the time intervals between positive colonoscopies. Analysis using life expectancy as a timescale, stratified for rank number of recurrence, confirmed that high-grade dysplasia was an independent predictor of the development of recurrent high-grade dysplasia (OR=1.81; 95% CI 1.20-2.72; p=0.004). When stratifying for high- and low-grade dysplasia in all consecutive adenomas and their metachronous lesions, the prevalence of adenomas with high-grade dysplasia proved to be independent of the length of the interval between colonoscopies.

Overall natural course of colorectal adenomas

All data were used to graphically depict the course of the incidence of colorectal adenomas, both in total and of those with high-grade dysplasia (*figure 4*). A patient was estimated to experience 3.6 positive colonoscopies on average, baseline colonoscopy included. Of the 3.6 positive colonoscopies, 1.9 concerned adenomas with high-grade dysplasia.

Figure 4. *Cumulative incidence of total number of adenomas and of adenomas with high-grade dysplasia*



Overall natural course of repetitive incidence of total number of adenomas and of adenomas with high-grade dysplasia till observed death on a life expectancy scale.

DISCUSSION

Numerous studies on the risk of development of metachronous colorectal adenomas have been published so far.[4,6,15,20,26-30] However, our study is quite different from previous studies due to a median follow-up of 85 months and in a great majority of patients the follow-up intervals were determined according to the national guidelines. This follow-up is longer than in most other studies with follow-up periods ranging from 18-47 months.[15,26,27] The long follow-up allowed us to analyse not only the influence of potential risk factors on first surveillance, but also on second and third metachronous adenoma.

The advantage of using life expectancy as a timescale in the analyses is that it allows for proper adjustment for differences in sex, age and birth cohort at the start of follow-up among the patients. This enables a comparison of the incidence of events at the same phase of life, and makes graphical depiction of the natural course of the disease possible. As a result, the estimate can be made that on average an adenoma patient will be confronted with more than three positive colonoscopies during his or her lifetime, of which nearly two will show adenomas with high-grade dysplasia.

Our analysis showed that after polypectomy for adenomatous polyps, adenomas developed in more than 50% of the patients. In 20% of patients, advanced neoplasia was found during a median follow-up of seven years. This high frequency of metachronous adenomas is in accordance with findings of other studies.[6,20,31] Only two of our patients (0.7%) developed a carcinoma, which is comparable with other results.[15]

Multivariate analysis in our patient group showed male sex, three or more adenomas and high-grade dysplasia to be significant risk factors for any metachronous adenomas. Older age and high-grade dysplasia were identified as risk factors for development of high-grade dysplasia neoplasia. When these factors were analysed using life expectancy as a timescale, only the presence of three or more adenomas proved to be an independent predictor of adenoma development. No additional risk factor was found for any further new lesions. This method of analysis demonstrated that high-grade dysplasia in a preceding adenoma formed a risk for a next advanced neoplastic lesion. Other studies have also identified these risk factors.[4,6,15,20,26-30] Number, size, proximal location, tubulovillous features and age have all been identified as predictors of metachronous adenomas.[4,26-29,32] A pooled multivariate analysis and a more recent systematic literature review found older age, male sex, number, size and proximal location to be associated with metachronous (advanced) neoplasia.[15,33] In a recent Dutch study, data of 2990 patients who underwent surveillance colonoscopies in ten hospitals were analysed. They found these same risk factors, but also that adenomas with more than 75% villous histology, size >1 cm and proximal location predicted recurrence of high-risk adenoma.[34] In contrast to our study, high-grade dysplasia was not identified as a risk factor for first recurrence.

The studies mentioned above provided the basis for practical recommendations on surveillance. The Dutch study forms the basis of a scoring table in the newest Dutch guidelines just published.[34,35] But they are all mainly based on baseline characteristics and not on further findings during longer follow-up. International guidelines are summarised in *table 2a* and the recently published Dutch guidelines are added in *table 2b*.[5,16,35-38]

Our analysis on second and third adenoma development revealed no risk factors at all. The fact that three or more adenomas found at baseline colonoscopy was associated with a shorter interval to the first recurrence, but not to any further metachronous adenomas, is worth noting. Apparently, patients who present later for their first examination are at older age and more often men, and have more adenomas with a higher prevalence of high-grade dysplasia. It appears that patients with more than two adenomas have their first adenoma develop earlier (30% after 2.5 years) compared with the rest of the study group (30% after five years), and that the metachronous adenomas more often contain high-grade dysplasia. However, at the time of finding the first metachronous adenoma, the age difference has disappeared. Interestingly, from that moment on recurrence intervals are about the same regardless of any risk factors. Hence, our

Table 2a. *Overview of guidelines for surveillance after polypectomy*

Guidelines (ref)	Criteria: if..	Interval recommended
American[37,38]	<3 adenomas and tubular and LGD and <1cm	5-10 years
	3-10 adenomas or any advanced feature	3 years
European [5]	<3 and <1 cm and tubular and LGD and no family history[1]	5 years
	All other	3 years
German[5]	Tubular and <1 cm and no family history[1]	10 years
	All other	3 years
UK[5,36]	<3 adenomas and <1 cm	5 years
	3-4 adenomas or >1 cm	3 years
	All other	1 years
Dutch 2002[16]	<3 adenomas	6 years
	>2 adenomas	3 years

LGD= low-grade dysplasia; [1]no first-degree relatives with colorectal cancer.

Table 2b. *Dutch guideline for surveillance after polypectomy 2013*

Adenoma characteristics	Value	Score
Number of adenomas	0-1	0
	2-4 >5	1
		2
At least 1 adenoma >1 cm	No	0
	Yes	1
At least 1 villous adenoma (>75% villous features)	No	0
	Yes	1
At least 1 proximal adenoma	No	0
	Yes	1

Total score at index colonoscopy	Interval recommended
0	No surveillance
1-2	5 years
3-5	3 years
Total score at surveillance colonoscopy	
0	5 years
1-2	5 years
3-5	3 years

study shows that the period to second metachronous adenoma development no longer depends on the number of adenomas at subsequent investigations. When patients were stratified for high- and low-grade dysplasia, a significant relation was found between high-grade dysplasia at a preceding positive examination and high-grade dysplastic lesions during further follow-up, but again, this did not depend on the interval between colonoscopies.

A few studies have been published in which risk of metachronous adenoma was assessed by including the findings of follow-up colonoscopies.[39-41] They divided patients into groups with low- and high-risk findings. Extending surveillance intervals for low-risk groups may be considered.[39,40]

One of the limitations of our study is that no information was available on the precise conditions under which the colonoscopies were performed apart from documented caecal intubation. Factors such as withdrawal time and cleanliness of the colon, which are known to influence the detection rate of neoplastic lesions, had not been systematically recorded.[42,43] During our study, the bowel preparation protocol was not changed over time and cleanliness of the colon was overall good, as was shown in two studies in our centre.[44,45]

Another limitation is that no data were available on patients' family histories and that a small number of follow-up endoscopies were performed for diagnostic purposes. Finally, the graphs and recommendations from this study in the Dutch population may possibly not be extrapolated to other populations.

In summary, our study shows that the number of adenomas at baseline colonoscopy is the primary determinant and independent risk factor for early metachronous adenoma development. The number of adenomas was associated with high-grade dysplasia, proximal location and male sex. However, all these characteristics were significantly associated with advanced age at presentation. Therefore, our statistical analysis was properly adjusted for age, sex and birth cohort by using life expectancy as a timescale. Our long follow-up period and the subsequent results of several consecutive examinations gave us the opportunity to analyse the time elapsed between the development of adenomas. Our graphs could be used to abstract the interval time in future follow-up guidelines. When, for example, an adenoma recurrence proportion of 30% is accepted, an interval of approximately 2.5 years could be implemented when more than two adenomas were found at the first positive colonoscopy. For the second surveillance endoscopy, however, a time interval of five years would be appropriate for all patients, irrespective of the initial number of adenomas. Only the prevalence of advanced neoplasia will be higher in patients with preceding high-grade dysplasia and does not depend on the interval. To conclude, we believe our results, which are based on a long follow-up period and consecutive findings, will be useful when updating guidelines.

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