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Colonoscopy Intervals and Colorectal Cancer Incidence after Adenoma Removal

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ABSTRACT

BACKGROUND

More evidence is needed to inform recommendations for intervals of colonoscopy surveillance after polyp removal.

METHODS

In this ongoing noninferiority trial conducted in eight European countries, we randomly assigned patients with high-risk adenomas (defined as ≥1 adenoma with a diameter of ≥10 mm, high-grade dysplasia, or villous growth or 3 to 10 adenomas of any kind) to undergo a first colonoscopy at 5 years after polyp removal or at 3 years; surveillance at 3 years is currently recommended in guidelines. The 3-year group also underwent colonoscopy at 5 years. The primary end point is the cumulative incidence of colorectal cancer at 10 years, with a prespecified noninferiority margin of 0.7 percentage points for the upper boundary of the confidence interval for the difference between the two groups. Here, we report the results of an interim analysis conducted after 5.5 years of follow-up. Inverse probability weighting was used to account for missing data owing to nonparticipation in surveillance colonoscopy at 5 years. In this analysis, the incidence of colorectal cancer is reported with a one-sided 99.12% confidence interval; for the final analysis at 10 years, the plan is to calculate a 95.33% confidence interval to maintain an overall type I error of 5%.

RESULTS

A total of 10,799 patients underwent randomization: 5398 patients were assigned to the 5-year group and 5401 to the 3-year group. The 5-year cumulative incidence of colorectal cancer was 0.77% with less-frequent surveillance and 0.82% with more-frequent surveillance (difference, −0.05 percentage points); the upper boundary of the 99.12% confidence interval was 0.68, which met the criterion for noninferiority. The distribution of cancer stage at diagnosis did not appear to differ substantially between the two groups. A total of 5 patients died of colorectal cancer: 3 patients (0.06%) in the 5-year group and 2 (0.04%) in the 3-year group.

CONCLUSIONS

In this interim analysis of a 10-year noninferiority trial, beginning surveillance colonoscopy at 5 years after polyp removal was noninferior to beginning at 3 years with respect to the cumulative incidence of colorectal cancer at 5 years among patients with high-risk adenomas. (Funded by the Research Council of Norway and others; EPoS II ClinicalTrials.gov number, NCT02319928.)

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Colorectal cancer is a major disease worldwide, with diagnoses in more than 1.9 million patients and more than 900,000 deaths each year.[1] Most Western countries have introduced population screening programs for the prevention of colorectal cancer. As a consequence of screening, the number of persons who receive a diagnosis of premalignant colorectal polyps (adenomas and serrated lesions) is rapidly increasing.

After removal of polyps at colonoscopy, some patients are considered to be at high risk for new polyps or cancer.[2-4] For patients with high-risk adenomas (defined as ≥1 adenoma with a diameter of ≥10 mm, high-grade dysplasia, or a villous growth pattern or 3 to 10 adenomas of any kind), current guidelines in the United States as well as international guidelines recommend frequent colonoscopies for surveillance, with the first surveillance colonoscopy at 3 years after polyp removal.[5-7] However, the recommended intervals for surveillance are based on data from observational studies and two small, randomized trials with imprecise estimates,[8,9] and the guidelines emphasize the need for long-term, high-quality, randomized trials.[5-7]

Surveillance is now one of the main indications for colonoscopy in many countries. Surveillance colonoscopies represent a major burden for patients and health care systems.[10] Colonoscopy is an expensive and invasive procedure that carries a risk of adverse events and complications. Longer surveillance intervals should therefore improve cost-effectiveness and reduce the burden on patients. However, whether longer intervals are noninferior to the currently recommended intervals for the prevention of future colorectal cancer is uncertain.

Here, we report the results of an interim analysis of the European Polyp Surveillance (EPoS) II trial, which was developed to evaluate whether less-frequent surveillance (with a first surveillance colonoscopy at 5 years after polyp removal) is noninferior to more-frequent surveillance (with a first surveillance colonoscopy at 3 years, as currently recommended) for the incidence of colorectal cancer among patients with high-risk adenomas. The results of a parallel, single-group study involving patients who had serrated lesions removed at colonoscopy are reported separately in this issue of the *Journal*.[11]

Methods

Trial Design and Patients

We conducted this randomized, noninferiority trial at 49 endoscopy centers in eight European countries (Austria, Denmark, the Netherlands, Norway, Poland, Portugal, Spain, and Sweden). The EPoS project consists of two two-group, randomized, controlled trials (EPoS I and II) and one single-group study (EPoS III). Details of the trial design have been published previously.[10] In the EPoS I trial, patients with low-risk adenomas were assigned to undergo surveillance colonoscopy at 10 years after the removal of adenomas or at both 5 and 10 years. In the present trial (EPoS II), patients with high-risk adenomas, with or without one or more serrated polyps, were assigned to undergo surveillance colonoscopy at 5 and 10 years after removal or at 3, 5, and 10 years.[7,10] In the EPoS III study, patients with one or more serrated polyps and no high-risk adenomas were assigned to undergo surveillance colonoscopy at 5 and 10 years.[7,11] The primary analyses of the EPoS trials are planned to take place once the 10-year follow-up is complete.

Patients eligible for the EPoS trials were men and women 40 to 74 years of age who underwent colonoscopy with complete removal of polyps. Colonoscopies had to be performed with completed cecal intubation and adequate colonic cleansing, with a score on the Boston bowel preparation scale of at least 2 in all colonic segments; scores for each segment range from 0 to 3, with higher scores indicating better visualization.[12] After providing written informed consent, patients were assigned to EPoS I, II, or III depending on the type of polyps removed. Exclusion criteria for the present trial were the presence of a genetic cancer syndrome (e.g., the Lynch syndrome, familial adenomatous polyposis, or serrated polyposis) or inflammatory bowel disease; a history of surgical colorectal resection or colorectal cancer or a previous diagnosis of adenomas; the presence of serrated polyps that were at least 10 mm in diameter, or at least 5 mm in diameter if they were located proximal to the splenic flexure; the removal of more than 10 adenomas at colonoscopy; nonretrieval or no histopathological analysis of any polyp more than 9 mm in diameter, with undetermined risk classification; the presence of New York Heart Association class III

or IV disease; ongoing chemotherapy or radiotherapy for malignant disease; or an indication for long-lasting medical attention and nursing services.

The patients enrolled in the present trial were randomly assigned in a 1:1 ratio to undergo a first surveillance colonoscopy at 5 years after the removal of adenomas or at 3 years; surveillance at 3 years is currently recommended in guidelines.[5-7] For valid comparison of outcome distributions and to avoid lead-time bias in the assessment of the cumulative incidence of colorectal cancer at 5 years, the patients in the 3-year group also underwent colonoscopy at 5 years. Randomization was carried out with the use of dedicated software and stratified according to trial site, patient sex, and patient age (40 to 55 years, 56 to 65 years, or 66 to 74 years).

The EPoS project was designed by the investigators, overseen by an independent data and safety monitoring board, and funded by research grants in the participating countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The funders had no influence on the design or conduct of the trial and were not involved in data collection or analysis or in the writing of the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available (along with the statistical analysis plan for the 5-year interim analysis) at NEJM.org. The trial protocol was approved by ethics committees at the participating sites or in the participating countries.

INTERVENTIONS

Surveillance colonoscopy is the only protocol-defined intervention used in the EPoS trials. All colonoscopies at enrollment and all surveillance colonoscopies were performed at the participating trial centers by dedicated endoscopists who participated in quality-assurance programs for colonoscopy, as recommended in current quality guidelines from the European Society of Gastrointestinal Endoscopy and United European Gastroenterology.[13]

Each site contacted patients and scheduled surveillance colonoscopies as assigned at the protocol-defined intervals. As specified in the protocol, colonoscopies performed within 6 months before or after the assigned date for surveillance were considered to be in compliance, and this window was extended to 9 months during the coronavirus disease 2019 pandemic. Surveillance colonoscopies performed outside the assigned window and colonoscopies performed on the basis of clinical signs or symptoms were recorded as unscheduled colonoscopies in the trial database.

At surveillance colonoscopies, all detected polyps were removed and sent for histopathological assessment. Clinical data on the patients and histopathological data on the polyps that were removed were registered in the trial database. Histopathological findings were reported according to World Health Organization guidelines for classification and grading.[14] Classification and registration of polyps were carried out according to European guidelines.[15]

TRIAL END POINTS

The primary end point in all the EPoS trials is the cumulative incidence of colorectal cancer at 10 years. Prespecified secondary end points for the present trial include death from colorectal cancer, advanced and nonadvanced adenomas and serrated polyps at 5 years of follow-up, and colonoscopy-related adverse events (bleeding that led to transfusion, bowel perforation, hospitalization, or death) within 30 days after surveillance or unscheduled colonoscopy. Colorectal cancer was defined as adenocarcinoma of the colon or the rectum. Neuroendocrine or squamous-cell carcinomas are not counted as end-point events.

Trial personnel at each site queried the electronic health records of enrolled patients each year and at the end of the follow-up period for the interim analysis and recorded all the findings from scheduled surveillance colonoscopies and unscheduled colonoscopies in the trial database, as well as all new diagnoses of colorectal cancer, deaths from colorectal cancer, and deaths from any cause during follow-up. In cases of newly diagnosed colorectal cancer, the stage of cancer at diagnosis was also recorded; early-stage cancer was defined as stage I or II and late-stage cancer as stage III or IV. The data retrieved from the electronic health records are the same as the data in the national registries of the participating countries and have a high level of completeness[16]; data for analyses were retrieved directly from hospital patient records to avoid delays associated with the transfer of data to the central registries.

Because the trial was performed in countries with single-payer national health systems and unique patient identification numbers, few patients were lost to follow-up.

STATISTICAL ANALYSIS

The trial was designed to test the noninferiority of longer surveillance intervals (with surveillance beginning at 5 years) to the currently recommended shorter intervals (with surveillance beginning at 3 years). Assuming an absolute risk of colorectal cancer of 2% after 10 years and a loss to follow-up of 10%, we calculated that a sample of 6852 patients in each group (for a total of 13,704 patients) would provide the trial with 90% power to determine noninferiority, with a prespecified noninferiority margin of 0.7 percentage points for the upper boundary of the confidence interval for the difference in the incidence of colorectal cancer. On the basis of evidence from observational studies that became available after the beginning of the trial, the expected 10-year incidence of colorectal cancer was adjusted to 1.4% in 2019.[4,17-19] After consultation with the data and safety monitoring board, we updated the target sample to 4826 patients in each group, for a total of 9652 patients.

We calculated the absolute incidence at 5.5 years after enrollment (5 years plus the 6-month window permitted in the protocol) for newly diagnosed colorectal cancer and death from colorectal cancer, as well as the differences in risk between the two trial groups. For the interim analysis, follow-up ended with the diagnosis of colorectal cancer, at the 5-year surveillance colonoscopy, or at 5.5 years, whichever occurred first. Because death was a competing event, we estimated the incidence of colorectal cancer and the incidence of death as a cause-specific cumulative incidence (risk without the elimination of the competing events).[20]

We did not perform a sample-size calculation for the 5-year interim analysis. To control for type I error between the interim analysis and the planned final analysis, we applied an O'Brien–Fleming spending function (with the use of the R package gsDesign) and calculated a one-sided 99.12% confidence interval for the difference in risk for the primary end point with the use of bootstrapping. The plan for the 10-year final analysis is to calculate a 95.33% confidence interval to maintain an overall type I error of 5%. We did not establish a stopping rule for the trial at the interim analysis, because there would be no consequences from stopping the trial for any of the patients.

We calculated the percentage of patients with any identified adenomas, advanced adenomas, or serrated polyps, along with the difference between the two trial groups, with corresponding 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiple testing and should not be used to infer treatment effects. We applied no inferential statistics for death from colorectal cancer because of the low number of events. We descriptively compared disease stage (early or late) at diagnosis in the two trial groups by dividing the number of diagnoses of a given stage in each group by the number of patients enrolled in the group.

The primary analysis used inverse probability weighting to account for missing data, given that a substantial minority of the patients did not complete the 5-year surveillance colonoscopy. Logistic-regression modeling and patient characteristics (trial-group assignment, age, sex, indication for colonoscopy at enrollment, body-mass index, and country) were used to estimate the probability of each eligible patient undergoing the 5-year surveillance colonoscopy. In this context, eligible patients were those who had not died or received a diagnosis of colorectal cancer before 5 years. For analysis purposes, a stabilized weight proportional to the inverse of the estimated probability was assigned to each of the eligible patients. Patients who had previously received a diagnosis of colorectal cancer or had died were assigned a weight of 1. Analyses of the incidence of colorectal cancer and of the adenoma findings were then performed with the use of these weights among the patients who had undergone surveillance colonoscopy or had an end-point event, under the assumption that data for the patients who had not undergone surveillance colonoscopy were missing at random, conditional on measured covariates. Censoring was applied for patients who had undergone the 5-year surveillance colonoscopy but had not received a diagnosis of colorectal cancer or died. The cumulative incidence of colorectal cancer is reported with a one-sided 99.12% confidence interval, and the results for the secondary end points are reported as

weighted proportions of patients with corresponding 95% confidence intervals. All the confidence intervals were calculated with bootstrapping. A detailed description of the applied inverse probability weighting method is provided in the Supplementary Appendix.

In analyses that incorporated inverse probability weighting, patients with missing data for any of the characteristics that were used to estimate probability were excluded (primary analysis population). For unadjusted analyses that were prespecified in the statistical analysis plan, all the patients who had been enrolled in the trial were included (intention-to-treat population). In the unadjusted analyses with the full intention-to-treat population, data were censored at 5.5 years or at the date of withdrawal from the trial, whichever occurred first, if the patient had not received a diagnosis of colorectal cancer or died and had not undergone the 5-year surveillance colonoscopy. Surviving patients who had not received a diagnosis of colorectal cancer and had not undergone the 5-year surveillance colonoscopy were considered not to have colorectal cancer.

Continuous variables are reported as means, standard deviations, medians, interquartile ranges, and ranges (minimum and maximum), unless otherwise stated. Categorical variables are summarized as counts and percentages. Analyses were performed with R software, version 4.5.1 (R Core Team, Vienna, Austria), and the analysis of the primary end point was performed with the R software survival package with a multistate approach and incorporation of weights.

RESULTS

PATIENTS

The EPoS trials were open for enrollment between April 2015 and March 2020. A total of 10,799 patients were enrolled in the present trial; 5398 were assigned to the 5-year group and 5401 to the 3-year group (Fig. 1). In the primary analysis with inverse probability weighting, 9 patients in the 5-year group and 4 patients in the 3-year group were excluded because data on age at enrollment were missing.

Table 1 summarizes the characteristics of the patients at enrollment. Spain was the country with the highest number of patients enrolled, followed by Norway, Denmark, Poland, and the Netherlands. The main indication for the colonoscopy at enrollment was colorectal cancer screening (primary colonoscopy screening or colonoscopy after a positive fecal immunochemical test), followed by clinical symptoms. Characteristics of the polyps removed at the enrollment colonoscopy are summarized in Table S1 in the Supplementary Appendix. The most common histologic type of adenoma was tubular, and most polyps were located in the distal colon. Table S2 shows the representativeness of the patients in the trial as compared with patients with high-risk adenomas in general.

COLONOSCOPIES DURING FOLLOW-UP

The total burden of colonoscopy, measured as the number of colonoscopies performed between enrollment and the end of follow-up, was 4434 in the 5-year group and 8614 in the 3-year group; 4180 (48.5%) fewer colonoscopies were performed in the 5-year group than in the 3-year group. In the 5-year group, participation in 5-year surveillance was 70.4%. In the 3-year group, 79.6% of the patients participated in 3-year surveillance and 64.6% participated in 5-year surveillance (Fig. 1). In total, 366 patients (6.8%) in the 5-year group and 482 (8.9%) in the 3-year group had a colonoscopy outside the protocol-defined surveillance intervals (unscheduled colonoscopy). A comparison of the characteristics at enrollment between the patients who did undergo 5-year colonoscopy and those who did not is shown in Table S3. The risk of adverse events within 30 days after surveillance or unscheduled colonoscopy was low, with no evidence of a substantial between-group difference (Table 2).

INCIDENCE OF COLORECTAL CANCER AND DEATH

In the primary analysis with inverse probability weighting, the cumulative incidence of colorectal cancer at 5.5 years of follow-up was 0.77% in the 5-year group and 0.82% in the 3-year group (Fig. 2 and Table 2). The difference in risk was −0.05 percentage points, and the upper boundary of the 99.12% confidence interval was 0.68, which met the criterion for noninferiority (Table 2). In the unadjusted analysis in the intention-to-treat population, in which data were censored for patients who had no diagnosis of colorectal cancer and did not undergo the 5-year colonoscopy, the risk of colorectal cancer was 0.48% in

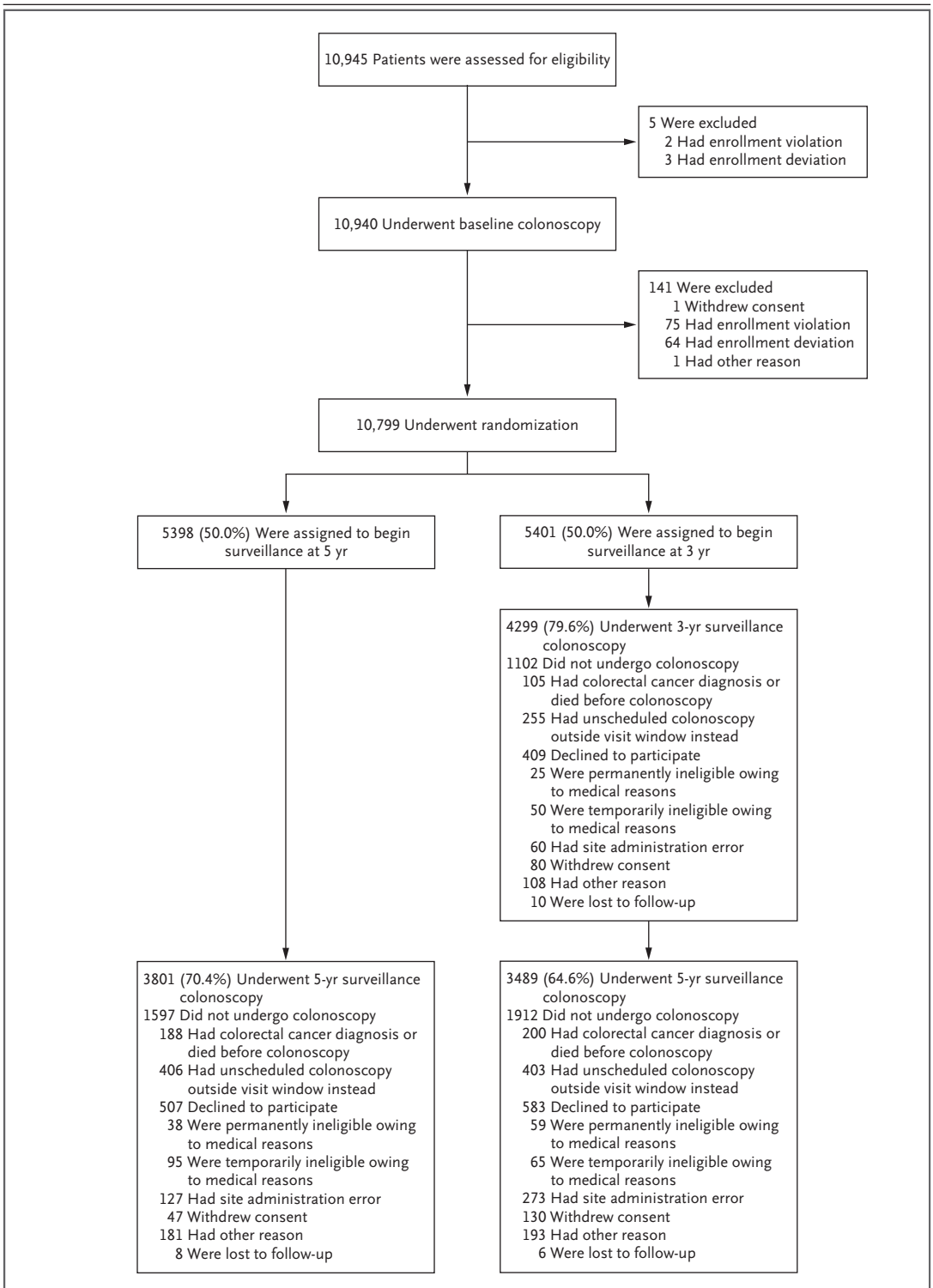


Figure 1. Screening, Randomization, and Follow-up.

Table 1. Characteristics of the Patients at Enrollment.*

Characteristic	Surveillance at 5 Yr (N=5398)	Surveillance at 3 and 5 Yr (N=5401)
Age — yr†	62.2±6.7	62.2±6.8
Sex — no. (%)		
Female	1885 (34.9)	1873 (34.7)
Male	3513 (65.1)	3528 (65.3)
BMI category — no./total no. (%)‡		
Underweight or normal weight: <25.0	1437/5094 (28.2)	1376/5082 (27.1)
Overweight: 25.0–29.9	2380/5094 (46.7)	2395/5082 (47.1)
Obese: ≥30	1277/5094 (25.1)	1311/5082 (25.8)
Missing	304/5398 (5.6)	319/5401 (5.9)
Country — no. (%)		
Spain	2830 (52.4)	2839 (52.6)
Norway	989 (18.3)	985 (18.2)
Denmark	524 (9.7)	523 (9.7)
Poland	503 (9.3)	503 (9.3)
The Netherlands	481 (8.9)	476 (8.8)
Sweden	58 (1.1)	58 (1.1)
Portugal	8 (0.1)	10 (0.2)
Austria	5 (0.1)	7 (0.1)
Indication for colonoscopy at enrollment — no./total no. (%)		
Primary screening	689/5389 (12.8)	688/5390 (12.8)
Positive FIT	3513/5389 (65.2)	3520/5390 (65.3)
Symptoms	1092/5389 (20.3)	1093/5390 (20.3)
Other	95/5389 (1.8)	89/5390 (1.7)
Missing	9/5398 (0.2)	11/5401 (0.2)
Had adverse event within 30 days after enrollment colonoscopy — no. (%)	71 (1.3)	60 (1.1)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. FIT denotes fecal immunochemical test.
† Data on age were missing for 9 patients in the 5-year group and for 4 patients in the 3-year group.
‡ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

the 5-year group and 0.48% in the 3-year group at 5.5 years of follow-up (Table S4). The difference in risk was 0 percentage points, and the upper bound of the 99.12% confidence interval was 0.38. Table S5 shows how colorectal cancer was detected in each group. In the 5-year group, 9 of 25 patients with a diagnosis of colorectal cancer had cancer that was detected at unscheduled colonoscopies, as did 5 of 23 in the 3-year group. Sensitivity analyses in the intention-to-treat population with the use of censoring at 5 years showed results similar to those of the primary analysis (Table S6). The incidence of early-stage colorectal cancer or of late-stage colorectal cancer did not appear to differ substantially between the groups (Fig. 3). The risk of death from colorectal cancer was low in both groups: 3 patients (0.06%) in the 5-year group died, as did 2 (0.04%) in the 3-year

Table 2. End Points.*

End Point	Overall (N = 10,786)	Surveillance at 5 Yr (N = 5389)	Surveillance at 3 and 5 Yr (N = 5397)	Difference in Risk (99.12% or 95% CI)†
				percentage points
Diagnosis of colorectal cancer‡				
No. of patients	48	25	23	
Cumulative incidence with IPW — %	0.79	0.77	0.82	–0.05 (0.68)
Death from colorectal cancer — no. of patients/total no. (%)§	5/10,799 (0.05)	3/5398 (0.06)	2/5401 (0.04)	
Death from any cause — no. of patients/total no. (%)§	366/10,799 (3.55)	183/5398 (3.60)	183/5401 (3.50)	
Identification of advanced adenoma				
No. of patients	934	421	513	
Cumulative incidence with IPW — %	12.74	11.07	14.55	–3.48 (–4.98 to –1.96)
Identification of adenoma				
No. of patients	5055	2133	2922	
Cumulative incidence with IPW — %	63.44	54.82	71.77	–16.95 (–19.02 to –14.86)
Identification of serrated polyps				
No. of patients	2563	987	1576	
Cumulative incidence with IPW — %	33.69	25.95	41.63	–15.68 (–17.89 to –13.41)
Colonoscopy-related adverse event¶				
No. of patients	42	24	18	
Cumulative incidence with IPW — %	0.57	0.63	0.52	0.11 (–0.24 to 0.47)

* Data shown are from analyses with inverse probability weighting (IPW), unless otherwise specified; 13 patients (9 in the 5-year group and 4 in the 3-year group) who had undergone randomization were excluded from the analyses with IPW because data on age at enrollment were missing. Results of prespecified intention-to-treat analyses are provided in the Supplementary Appendix.

† The difference in risk was calculated as the cumulative incidence in the 5-year group minus the cumulative incidence in the 3-year group; if the difference is greater than 0, the risk was higher with less-frequent surveillance. The confidence interval (CI) for the difference in risk for colorectal cancer is reported as the upper boundary of a one-sided 99.12% confidence interval; other confidence intervals shown are two-sided 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity.

‡ Shown are numbers of patients who received a diagnosis of colorectal cancer within 5.5 years after enrollment. Neuroendocrine tumors and squamous-cell carcinomas were not counted as end-point events. Risks were calculated as the cumulative incidence of colorectal cancer, and death was included in the analysis as a competing risk.

§ Data are shown for the intention-to-treat population, which included all the patients who had undergone randomization. Percentages indicate the cumulative incidence estimated with adjustment for follow-up time and may not correspond to direct proportions.

¶ Numbers reflect colonoscopy-related adverse events (bleeding that led to transfusion, bowel perforation, hospitalization, or death) that occurred within 30 days after any surveillance or unscheduled colonoscopy.

group; all-cause mortality was similar in the two group (3.60% and 3.50%, respectively) (Table 2).

ADVANCED ADENOMAS, ADENOMAS, AND SERRATED POLYPS

In the analysis with inverse probability weighting, the weighted percentage of patients with any advanced adenoma was 11.07% in the 5-year group and 14.55% in the 3-year group (difference, –3.48 percentage points; 95% confidence interval [CI], –4.98 to –1.96) (Table 2). In the unadjusted intention-to-treat analysis with censoring, the percentage was 10.66% in the 5-year group and 10.82% in the 3-year group (difference, –0.16 percentage points; 95% CI, –1.49 to 1.17). The percentage of patients with an adenoma of any kind was lower in the 5-year group (54.82% vs. 71.77%), as was the percentage with serrated polyps (25.95% vs. 41.63%) (Table 2).

DISCUSSION

In this 5-year interim analysis of our 10-year trial, the incidence of colorectal cancer at 5 years was

low, and beginning surveillance at 5 years after the removal of high-risk adenomas was noninferior to beginning surveillance at 3 years. We used a stringent criterion for this interim analysis in order to preserve most of the alpha error for the 10-year analysis. The upper boundary of the confidence interval was just below the noninferiority margin, narrowly meeting the criterion for noninferiority. The preplanned, unadjusted intention-to-treat analysis confirmed the results of the primary analysis with inverse probability weighting.

Possibly because of improvement in the quality of colonoscopy, the risk of colorectal cancer after the removal of advanced adenomas or multiple adenomas has been lower in more-recent studies than in older observational studies.[17-19] Therefore, we revised the sample-size calculation after the beginning of the trial (see the protocol). Our findings indicate a low absolute risk of colorectal cancer for patients who had high-risk adenomas removed. More than 99% of the patients in this trial did not receive a diagnosis of colorectal cancer within 5 years after polyp removal. This finding may trigger a discussion of the categorization of these patients as being at high risk for colorectal cancer.[5-7] In a 2019 clinical practice guideline for colorectal cancer screening, the panel considered an absolute colorectal cancer risk of 3% over 15 years to be the lowest threshold for a clinically relevant risk that warrants action.[21]

The main basis for the current recommendation of first surveillance after 3 years for patients with high-risk adenomas is data from older studies with small sample sizes.[8,9] The results of our trial may encourage updates to the recommendations for surveillance intervals. Although previous studies were mainly observational and did not apply eligibility criteria in accordance with current recommendations, our trial was randomized, and the inclusion criteria required that all the patients undergo a complete colonoscopy at enrollment with adequate colonic cleansing and complete removal of all identified polyps, in accordance with current recommendations.[22] Therefore, our estimates may be more relevant to clinical practice than those from previous studies.

An important finding in this trial was that the two groups did not appear to differ substantially with respect to the stage of colorectal cancer at diagnosis. Adenomas of any kind were found more commonly with more-frequent surveillance, with a between-group difference of 3.5 percentage points in the incidence of advanced adenomas. The larger number of adenomas identified after two colonoscopies than after one colonoscopy is probably the result of some adenomas being missed in a single colonoscopy, with repetition leading to greater detection.[23,24] Whether the higher level of detection is beneficial for patients remains to be seen. Two considerations suggest that it may not be beneficial. First, the between-

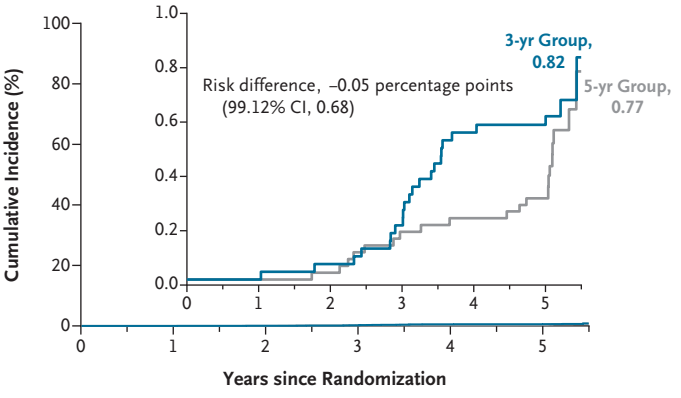


Figure 2. Cumulative Incidence of Colorectal Cancer in the Two Trial Groups.

Inverse probability weighting was used for the analysis. The upper boundary of the one-sided 99.12% confidence interval is shown. The inset shows the same data on an expanded y axis. CI denotes confidence interval.

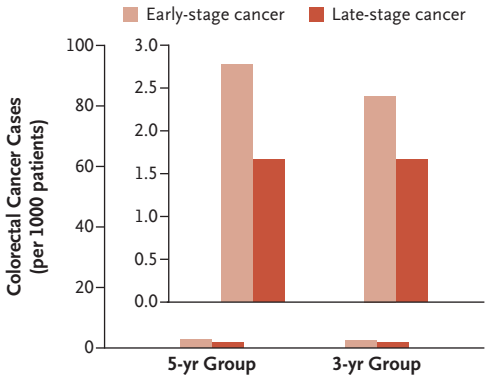


Figure 3. Incidence of Colorectal Cancer Classified as Early Stage or Late Stage at Diagnosis.

Shown are numbers of cases of early-stage cancer and of late-stage cancer per 1000 patients according to trial group. Two cases of colorectal cancer with unknown stage at diagnosis (one in each group) are excluded. The inset shows the same data on an expanded y axis.

group difference in the percentage of patients with advanced adenomas identified was small, and even advanced adenomas grow slowly. Clinically significant lesions that are missed until the 10-year follow-up are still likely to be identified before malignant transformation. Our findings with regard to the stage of colorectal cancer at diagnosis after 5 years of follow-up suggest that detection at 10 years may be early enough to prevent advanced-stage cancer. Second, evidence from an observational study suggests that a higher level of adenoma detection, calculated as the number of colonoscopies in which an adenoma is identified divided by the total number of colonoscopies performed, may not contribute meaningfully to greater protection from colorectal cancer once the level of detection exceeds 25 to 30%.[25] With adenomas identified in more than 50% of the patients in each group in this trial, the observed level of detection may be sufficient to protect patients from the development of colorectal cancer. The 10-year analysis may provide further insight.

The strengths of our trial are the randomized design, the participation of many countries, the large sample size, the use of the incidence of colorectal cancer as the primary end point, and the use of high-quality colonoscopy at enrollment. The comparison of our findings with those of a contemporary single-group study involving patients with serrated lesions may help in the evaluation of risks across patient groups and the discussion of tailored interventions.[11] Limitations of this trial include the percentage of the patients who underwent the planned surveillance colonoscopy at 5 years (only 70% in the 5-year group and 65% in the 3-year group). We assume that some of the patients who did not participate in 5-year surveillance may have yet-undiagnosed colorectal cancer, and therefore, our primary analysis used inverse probability weighting to account for missing colonoscopy data. Finally, no sample-size calculation was performed for this 5-year interim analysis, and thus, we used a very conservative 99.12% confidence interval.

In this randomized trial comparing surveillance that begins at 5 years after the removal of high-risk adenomas with surveillance that begins at 3 years, the incidence of colorectal cancer at 5 years was low and did not appear to be higher in the 5-year group than in the 3-year group. This interim analysis of a 10-year trial showed noninferiority of 5-year surveillance to 3-year surveillance among patients with high-risk adenomas.

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