STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Long-term outcomes after endoscopic removal of malignant colorectal polyps: results from a 10-year cohort
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	Background: Deciding over optimal post-polypectomy management strategy of malignant colorectal polyps is challenging, evidence about surveillance-only strategy is limited. Aims: To evaluate long-term outcomes after endoscopic removal of malignant colorectal polyps. Methods: A single-center retrospective cohort study was conducted to evaluate outcomes after endoscopic removal of malignant colorectal polyps between 2010 and 2020. Residual disease rate and nodal metastases after secondary surgery; and local and distant recurrence rate for those with at least 1-year follow-up were investigated. Event rates for categorical and means for continuous variables with 95% confidence intervals were calculated; Fisher's exact test and Mann-Whitney test were performed. Potential risk factors of adverse outcomes were determined with univariate and multivariate logistic regression models. Results: 135 lesions (mean size: 22.1 mm, main location: 42% rectal) of 129 patients (mean age: 67.7 years; 56% male) were enrolled. Proportion of pedunculated and non-pedunculated lesions was similar, with en bloc resection in 82% and 47%, respectively. Tumor differentiation, distance from resection margins, depth of submucosal invasion, lympho-vascular invasion and budding was adequately reported in 89.6%, 45.2%, 58.5%, 31.9%, and 25.2%, respectively. Residual tumor was found in 10, and nodal metastasis in 4 out of 41 patients who underwent secondary surgical resection. Univariate analysis identified piece meal resection as risk factor for residual malignancy (OR 1.74, p=0.042). At least 1-year follow-up was available for 117 lesions of 111 patients (mean follow-up period: 5.59 years). 54%, 30%, 30%, 11%, and 16% of patients presented at 1-year, 3-year, 5-year, 7-year, and 9-10-year surveillance examinations. Adverse outcomes occurred in 9.0% (local recurrence and dissemination in 4 and 9 patients, respectively), with no difference between patients undergoing secondary surgery and surveillance-only. Conclusions: Reporting of histologic features, and adherence to surveillance colonoscopy needs improvement. Long-term adverse outcome rates might be higher than previously reported, irrespective of whether secondary surgery was performed or not.
Introduction				

Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6	see manuscript text on pages 5 and 6
Objectives	3	State specific objectives, including any prespecified hypotheses	6	Therefore, we aimed to evaluate long-term outcomes of endoscopic removal of malignant colorectal polyps by assessing residual malignancy and lymph node involvement rate after secondary surgery (first endpoint; Figure 1), and local and distant recurrence rate throughout the follow-up period both in case of secondary surgery and surveillance-only strategy, together and separately as well (second endpoint; Figure 2).
Methods				
Study design	4	Present key elements of study design early in the paper	6	This retrospective cohort study investigated outcomes after endoscopic resection of malignant colorectal polyps resected between 1st January 2010 and 31st December 2020 in the tertiary endoscopic center of University of Szeged.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7	***Study design and ethical considerations*** This retrospective cohort study investigated outcomes after endoscopic resection of malignant colorectal polyps resected between 1st January 2010 and 31st December 2020 in the tertiary endoscopic center of University of Szeged. This study was carried out in accordance with the Helsinki Declaration and was approved by the Regional and Institutional Human Medical Biological Research Ethics Committee of University of Szeged (clinical trial registration number: 4137/2018). ***Inclusion and exclusion criteria*** Lesions were enrolled if the following inclusion criteria applied: a) no invasive malignancy was suspected with pre-polypectomy examinations (histology, virtual chromoendoscopy, rectal endosonography, if performed), b) lesions appeared to be suitable for endoscopic resection based on their macroscopic appearance and adequate lifting sign, c) invasive adenocarcinoma was revealed by post-polypectomy histology, and d) depth of invasion was limited to the submucosa (T1). Lesions were excluded if polypectomy was not completed due to suspicion of an invasive tumor. Long-term outcomes were only assessed for lesions in case of which at least one-year follow-up data were available. Patients with IBD-associated neoplasia, as well as those with a clinically suspected or verified polyposis syndrome, or hereditary non-polyposis colorectal cancer based on the Amsterdam II criteria, were excluded from the analysis. During the study period, tumor testing for microsatellite instability was not routinely available for early-stage colorectal cancer.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods	6, 8	***Inclusion and exclusion criteria*** Lesions were enrolled if the following inclusion criteria applied: a) no invasive malignancy was suspected with pre-polypectomy examinations (histology, virtual

		of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants		chromoendoscopy, rectal endosonography, if performed), b) lesions appeared to be suitable for endoscopic resection based on their macroscopic appearance and adequate lifting sign, c) invasive adenocarcinoma was revealed by post-polypectomy histology, and d) depth of invasion was limited to the submucosa (T1). Lesions were excluded if polypectomy was not completed due to suspicion of an invasive tumor. Long-term outcomes were only assessed for lesions in case of which at least one-year follow-up data were available. Patients with IBD-associated neoplasia, as well as those with a clinically suspected or verified polyposis syndrome, or hereditary non-polyposis colorectal cancer based on the Amsterdam II criteria, were excluded from the analysis. During the study period, tumor testing for microsatellite instability was not routinely available for early-stage colorectal cancer. Follow-up period was defined as the time interval between the polypectomy date and the last registered date of a patient visit recorded at the electronic medical record system.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8	***Investigated parameters*** Demographic data of patients, polyp characteristics (size, location and morphology [pedunculated vs non-pedunculated, Paris classification]), method of endoscopic resection, completeness of resection based on endoscopic assessment, and rate of adverse events were collected from the electronic medical record system. Post-polypectomy histologic reports were reviewed for the following features considered to be related to high risk of adverse outcomes: determinability and involvement of resection margins (tumor cells in the cautery line, distance from resection margin reaching 1 mm or not), absolute depth of submucosal invasion (SMI; superficial SMI < 1mm, deep SMI ≥ 1 mm), tumor differentiation (low grade [well or moderately differentiated] vs high grade [poorly differentiated]), tumor budding (Bd1: 1-4 buds, Bd2: 5-9 buds, Bd3: ≥ 10 buds at the invasion front), and lympho-vascular invasion (possibly assessing lymphatic and vascular invasion separately). Reporting of Haggitt and Kikuchi classification was also assessed, but due to their limited determinability due to the common lack of muscular propria in polypectomy specimens, these were not included in quantitative analyses. Tumor markers (CEA and CA 19-9) at the time of

				endoscopic polyp removal were also assessed as potential predictors of adverse outcomes. ***Outcome measures*** Patients were divided into two groups according to the post-polypectomy management strategy applied (secondary surgery for completion vs surveillance-only). The decision between the two strategies was made on tumor board discussions considering post-polypectomy histologic results, age, co-morbidities, and preferences of patients. Rate of residual malignancy and lymph node involvement was investigated in patients undergoing secondary surgery. Local and distant recurrence during the follow-up period were investigated as adverse outcome measures in case of both secondary surgery and surveillance-only strategies. Adverse outcome rates were compared between the two strategies to assess the potential risk deriving from not having completion surgery after endoscopic resection of malignant polyps.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8	***Investigated parameters*** Demographic data of patients, polyp characteristics (size, location and morphology [pedunculated vs non-pedunculated, Paris classification]), method of endoscopic resection, completeness of resection based on endoscopic assessment, and rate of adverse events were collected from the electronic medical record system. Post-polypectomy histologic reports were reviewed for the following features considered to be related to high risk of adverse outcomes: determinability and involvement of resection margins (tumor cells in the cautery line, distance from resection margin reaching 1 mm or not), absolute depth of submucosal invasion (SMI; superficial SMI < 1mm, deep SMI ≥ 1 mm), tumor differentiation (low grade [well or moderately differentiated] vs high grade [poorly differentiated]), tumor budding (Bd1: 1-4 buds, Bd2: 5-9 buds, Bd3: ≥ 10 buds at the invasion front), and lympho-vascular invasion (possibly assessing lymphatic and vascular invasion separately). Reporting of Haggitt and Kikuchi classification was also assessed, but due to their limited determinability due to the common lack of muscular propria in polypectomy specimens, these were not included in quantitative analyses. Tumor markers (CEA and CA 19-9) at the time of endoscopic polyp removal were also assessed as potential predictors of adverse outcomes. Length of colonoscopic surveillance (i.e., last registered colonoscopy date) was also assessed. Clinical data of patients with distant metastases were reviewed searching for other, more advanced malignancy as a potential primary focus of dissemination.
Bias	9	Describe any efforts to address potential sources of bias	8	Clinical data of patients with distant metastases were reviewed searching for other, more advanced malignancy as a potential primary focus of dissemination.

Study size	10	Explain how the study size was arrived at	6, 7	Lesions were enrolled if the following inclusion criteria applied: a) no invasive malignancy was suspected with pre-polypectomy examinations (histology, virtual chromoendoscopy, rectal endosonography, if performed), b) lesions appeared to be suitable for endoscopic resection based on their macroscopic appearance and adequate lifting sign, c) invasive adenocarcinoma was revealed by post-polypectomy histology, and d) depth of invasion was limited to the submucosa (T1). Lesions were excluded if polypectomy was not completed due to suspicion of an invasive tumor. Long-term outcomes were only assessed for lesions in case of which at least one-year follow-up data were available. Patients with IBD-associated neoplasia, as well as those with a clinically suspected or verified polyposis syndrome, or hereditary non-polyposis colorectal cancer based on the Amsterdam II criteria, were excluded from the analysis. During the study period, tumor testing for microsatellite instability was not routinely available for early-stage colorectal cancer.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8	Patients were divided into two groups according to the post-polypectomy management strategy applied (secondary surgery for completion vs surveillance-only). The decision between the two strategies was made on tumor board discussions considering post-polypectomy histologic results, age, co-morbidities, and preferences of patients. Rate of residual malignancy and lymph node involvement was investigated in patients undergoing secondary surgery. Local and distant recurrence during the follow-up period were investigated as adverse outcome measures in case of both secondary surgery and surveillance-only strategies. Adverse outcome rates were compared between the two strategies to assess the potential risk deriving from not having completion surgery after endoscopic resection of malignant polyps.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8	Categorical variables were reported as event rates and relative frequencies, and continuous variables as the means with 95% confidence intervals (CI). Fisher's exact test was used to analyze categorical data, whereas Mann-Whitney test was used in case of continuous data. Potential risk factors of adverse outcomes were determined with univariate and multivariate logistic regression models. Statistical tests were performed using R statistical software version 3.1.2 (R Foundation, Vienna, Austria) and jamovi software version 2.3.24[18,19]; values of $p<0.05$ were considered significant.
		(*b*) Describe any methods used to examine subgroups and interactions	8	Fisher's exact test was used to analyze categorical data, whereas Mann-Whitney test was used in case of continuous data.
		(*c*) Explain how missing data were		

		addressed		
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8	Follow-up period was defined as the time interval between the polypectomy date and the last registered date of a patient visit recorded at the electronic medical record system. Cause of death (if available) was registered for patients who died during the follow-up period.
		(*e*) Describe any sensitivity analyses		not applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	135 endoscopically resected malignant colorectal polyps of 129 patients (age: 67.7 years [95% CI: 66.0–69.4 years]; 56% male) were enrolled during the 10-year study period.
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram	31	Table 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 9	135 endoscopically resected malignant colorectal polyps of 129 patients (age: 67.7 years [95% CI: 66.0–69.4 years]; 56% male) were enrolled during the 10-year study period. Proportion of pedunculated and non-pedunculated lesions was similar (48% vs. 45%), but while en bloc resection could be achieved in 82% of pedunculated polyps, it was feasible in only 47% of non-pedunculated lesions. Polyp characteristics are summarized in Table 1. Endoscopic polypectomy was performed with snare polypectomy and endoscopic mucosal resection (EMR) in most of the cases, endoscopic submucosal dissection (ESD), and endoscopic full-thickness resection (EFTR) was not routinely available in our institution during the study period.
		(b) Indicate number of participants with missing data for each variable of interest	9, 10, 11	Tumor marker values (CEA or CA 19-9) were available for 37 out of the total 129 patients at the time of endoscopic polyp removal.

				Although endoscopic removal was considered complete based on endoscopic assessment in 87% of the cases, histology revealed complete resection in only 56%. Completeness of resection could not be determined in 26 cases (19%) due to thermal injury of resection margins, tissue fragmentation, or lack of adequate specimen orientation after piece meal resection. Throughout the entire study period, high-risk histologic features were adequately reported as follows: tumor differentiation in 89.6%, tumor distance from resection margins in 45.2%, absolute depth of submucosal invasion in 58.5%, Haggitt/Kikuchi classification in 31.9%, lympho-vascular invasion in 31.9%, and tumor budding in 25.2%. Reporting of all features (except Haggitt/Kikuchi classification) was adequate in only 26 cases (19%), only one feature was reported in 36 cases (27%), and none in 3 cases (2%). As described above, 45 lesions of 41 patients underwent secondary surgery, and surveillance-only strategy was chosen for the other 90 lesions of 88 patients. However, only 117 lesions of 111 patients with at least one-year follow-up data available were taken into consideration when assessing long-term outcomes in order the outcomes to be adequate. Mean follow-up period for this subgroup was 5.59 years [95% CI: 5.02–6.16 years]: 40 lesions of 36 patients underwent secondary surgery for completion, and surveillance-only strategy was chosen for 77 lesions of 75 patients. During the follow-up period, participation rates at surveillance colonoscopy showed a gradually decreasing tendency: while 54% of patients presented at the 1-year surveillance colonoscopy, participation rates for 3-year, 5-year, 7-year, and 9-10-year examinations were 30%, 30%, 11%, and 16%, respectively. For each time point, participation rate was determined as the number of patients who underwent surveillance colonoscopy compared to the number of patients for whom follow-up information was available and who were alive. Remarkably, patients undergoing secondary surgery were more likely to participate at surveillance colonoscopies than those with surveillance-only strategy after polypectomy (Figure 3).
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11	Mean follow-up period for this subgroup was 5.59 years [95% CI: 5.02–6.16 years]: 40 lesions of 36 patients underwent secondary surgery for completion, and surveillance-only strategy was chosen for 77 lesions of 75 patients.
Outcome data	15*	*Cohort study*—Report numbers of	11	During the follow-up period, distant metastasis without any other, more advanced malignancy

		outcome events or summary measures over time		as a potential primary focus was detected in 9 patients (8.1%) in the entire study population. Local recurrence was also detected in 3 of these patients; and was also reported in one further patient without distant metastasis (local recurrence rate: 3.6%). Mean occurrence of local recurrence was 3.98 years (range: 1.84–7.53 years). Total rate of adverse outcomes (dissemination or local recurrence) in the entire study population was 9.0%. Cancer-related death was reported in 2 patients; therefore, tumor progression related mortality rate was 1.8%. There was no significant difference in adverse outcome rates between the two patient groups (i.e. patients undergone secondary surgery vs surveillance-only). (Table 4)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11	Rate of residual malignancy and lymph node involvement in patients undergoing secondary surgery (first endpoint) Secondary surgery was performed for 45 lesions (33.3%) of 41 patients (31.8%) 90 days (95% CI: 22.4–158.9 days) after the polypectomy on average. 53% of these lesions were located in the rectum, and 47% in the colon. At least one high risk feature was present in 82.2% (including not assessable resection margins as high-risk features as well), and this even rises to 91.1% if – as according to the most recent NCCN guideline[14, 15] – piece meal resection is also considered to be a high-risk feature. On the other hand, only 48% of lesions (37/77 cases) with at least one high-risk feature (considering not assessable margins as high-risk as well) underwent secondary surgery for completion. Surgery-related adverse events occurred in 5 cases (12.2%): post-operative confusion in one case, reoperation was necessary in 3 cases because of mechanical occlusion due to adhesions, wound dehiscence, and entero-cutaneous fistula, and one patient died of aspiration-induced bronchopneumonia as a consequence of paralytic bowel obstruction. Therefore, surgical mortality was 2.4% in our cohort. Histologic examination of surgically resected specimens revealed residual malignancy in case of 15 lesions of 10 patients (24.4%), and lymph node involvement in 4 patients (9.8%) – 3 of them (6.7%) had residual malignancy as well. All patients with residual malignancy (in whom

endoscopic resection margins were assessable) had tumor cells in the cautery line (R1) after endoscopic resection. In univariate logistic regression analysis, piece meal resection was found to be a risk factor for residual malignancy (OR 1.74, p=0.042), but the multivariate model did not confirm this (Table 2 and Table 3).

Follow-up

As described above, 45 lesions of 41 patients underwent secondary surgery, and surveillance-only strategy was chosen for the other 90 lesions of 88 patients. However, only 117 lesions of 111 patients with at least one-year follow-up data available were taken into consideration when assessing long-term outcomes in order the outcomes to be adequate. Mean follow-up period for this subgroup was 5.59 years [95% CI: 5.02–6.16 years]: 40 lesions of 36 patients underwent secondary surgery for completion, and surveillance-only strategy was chosen for 77 lesions of 75 patients.

During the follow-up period, participation rates at surveillance colonoscopy showed a gradually decreasing tendency: while 54% of patients presented at the 1-year surveillance colonoscopy, participation rates for 3-year, 5-year, 7-year, and 9-10-year examinations were 30%, 30%, 11%, and 16%, respectively. For each time point, participation rate was determined as the number of patients who underwent surveillance colonoscopy compared to the number of patients for whom follow-up information was available and who were alive. Remarkably, patients undergoing secondary surgery were more likely to participate at surveillance colonoscopies than those with surveillance-only strategy after polypectomy (Figure 3).

Long-term adverse outcomes (second endpoint)

During the follow-up period, distant metastasis without any other, more advanced malignancy as a potential primary focus was detected in 9 patients (8.1%) in the entire study population. Local recurrence was also detected in 3 of these patients; and was also reported in one further patient without distant metastasis (local recurrence rate: 3.6%). Mean occurrence of local recurrence was 3.98 years (range: 1.84–7.53 years). Total rate of adverse outcomes (dissemination or local recurrence) in the entire study population was 9.0%. Cancer-related death was reported in 2 patients; therefore, tumor progression related mortality rate was 1.8%. There was no significant difference in adverse outcome rates between the two patient groups (i.e. patients undergone secondary surgery vs surveillance-only). (Table 4)

Non-pedunculated polyp morphology was determined as a risk factor distant metastases with

				logistic regression (OR 2.51, p=0.020), although it was not confirmed by multivariate analysis (Table 5 and Table 6). None of the patients with elevated initial tumor marker values presented with adverse outcomes.
		(*b*) Report category boundaries when continuous variables were categorized		see manuscript text
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		see manuscript text
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9, 10, 12	Based on the available data, at least one high-risk histologic feature was present in 60 cases (44%). In terms of resection margins, considering only R1 cases (tumor cells can be detected at the cautery line) high risk as proposed by recent studies[11], this rate changes to 39% (53 cases). If, however, not assessable resection margins, and piece meal resection are considered high-risk features as well, 77 cases (57%), and 88 cases (65%), respectively fall into this category. Overall, 64% of patients were managed according to the NCCN recommendation (resection surgery or surveillance only). However, of the patients for whom surgical resection was recommended, only 53% underwent resection surgery. No significant difference was observed in adverse event rates between groups. (Table 7)
Discussion				
Key results	18	Summarise key results with reference to study objectives	12, 13, 14, 15	To the best of our knowledge, the results from this single-center, retrospective cohort study are the first data from the Central-European region about long-term outcomes of endoscopic removal of malignant colorectal polyps. The relatively longer follow-up period in our study compared to that reported in the majority of previous studies[20-25] and inclusion of only those with at least 1-year follow-up allowed for adequate assessment of adverse outcomes. This is also reflected in the availability of information in our study: opposed to the Haggitt/Kikuchi classification reported in only 33.8%, absolute depth of submucosal invasion as proposed by Ueno et al[28] was reported in 56.6%. Adverse outcome rate was somewhat higher than the one reported in the literature.

				Based on these results, follow-up time of our study can be considered appropriate to assess adverse outcomes. However, it should be highlighted that local recurrence was detected more than 7 years after the polypectomy in one of our cases, even with adequate participation in surveillance colonoscopies.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16	The greatest limitation of our study is its retrospective nature, both in terms of data on endoscopic polypectomies, and surveillance colonoscopies, as well as histologic data. Many high-risk histologic features were identified during the study period, and histologic guidelines for their reporting were also published in this period. This may account for incomplete histologic data in the initial study period. Virtual chromoendoscopy which may assist the recognition of deep submucosal invasion was not available in our institute at the early study period. Tumor testing for microsatellite instability was not routinely available for early-stage colorectal cancer during the study period, therefore the potential differences in adverse outcomes of sporadic and hereditary malignant colorectal polyps could not be assessed. Single center nature of the study reflects only local practice and might be contributable to the relatively smaller sample size compared to multicentric studies; on the other hand, it guarantees uniform management strategies.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16	see manuscript text
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-16	see manuscript text
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2	Supported by the ÚNKP-22-4-SZTE-296, ÚNKP-23-3-SZTE-268, and ÚNKP-23-5-SZTE-719 New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund. The project has also received funding from the EU's Horizon 2020 research and innovation program under grant agreement No. 739593.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.