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Background and Aims: In contrast to the adverse event (AE) risk of endoscopic resection (ER) of adenomas, the intra- and postprocedural AE risks of ER of T1 colorectal cancer (CRC) are scarcely reported in the literature. It is unclear whether ER of early CRCs, which grow into the submucosal layer and sometimes show incomplete lifting, is associated with an increased AE risk. We aimed to identify the AE rate after ER of T1 CRCs and to identify the risk factors associated with these AEs.

Methods: Medical records of patients with T1 CRCs diagnosed between 2000 and 2014 in 15 hospitals in the Netherlands were reviewed. Patients who underwent primary ER were selected. The primary outcome was the occurrence of endoscopy-related AEs. The secondary outcome was the identification of risk factors. Multivariate logistic regression was performed.

Results: Endoscopic AEs occurred in 59 of 1069 (5.5%) patients, among which 37.3% were classified as mild, 59.3% as moderate, and 3.4% as severe. AEs were postprocedural bleeding (n = 40, 3.7%), perforation (n = 13, 1.2%), and postpolypectomy electrocoagulation syndrome (n = 6, 0.6%). No fatal AEs were observed. Independent predictors for AEs were age >70 years (odds ratio, 2.11; 95% confidence interval, 1.12-3.96) and tumor size >20 mm (odds ratio, 2.22; 95% confidence interval, 1.05-4.69).

Conclusions: In this large multicenter retrospective cohort study, AE rates of ER of T1 CRC (5.5%) are comparable with reported AE rates for adenomas. Larger tumor size and age >70 years are independent predictors for AEs. This study suggests that endoscopic treatment of T1 CRCs is not associated with an increased periprocedural AE risk. (Gastrointest Endosc 2020;91:142-52.)

(footnotes appear on last page of article)

INTRODUCTION

The incidence of submucosal invasive colorectal cancer (T1 CRC) is increasing worldwide.[1] The most important reason for this increase is the implementation of population-based screening programs in several countries.[2] In the Netherlands, up to 48% of screen-detected CRCs are early stage CRCs, which is in line with other western countries.[3,4] T1 CRC is defined as a tumor with invasion through the muscularis mucosa and not beyond the submucosa.[5] A subset of T1 CRCs, ie, those with a low risk for lymph node metastasis, can be treated endoscopically.[6] Endoscopic resection (ER) of these low-risk T1 CRCs is associated with low incomplete resection and recurrence rates.[7,8] Even if histologic high-risk factors appear to be present and adjuvant surgery is required, ER does not negatively affect the oncologic outcome.[7] Moreover, ER is associated with lower costs and lower mortality rates compared with surgical resection for CRCs.[9,10]

Multiple studies have reported the adverse event (AE) rate after ER of premalignant lesions.[11-14] Reported risk factors for AEs in premalignant lesions are as follows: age >70 years, comorbidity, larger lesion size, the use of anticoagulant drugs, morphology, accessibility, and location of the lesion.[11,12,15-18] Prophylactic clip placement is reported as

a protecting factor for AEs.[19] Little is known about intraprocedural and postprocedural AE risks with ER of T1 CRC. A recent study reported cancer as a risk factor for postprocedural bleeding after endoscopic submucosal dissection (ESD).[20] In contrast, the risk for postprocedural bleeding did not differ between ER of adenomas and carcinomas in another study.[21] Although an increasing body of evidence shows that ER of T1 CRC is oncologically safe, the periprocedural AE risk associated with ER of T1 CRC is currently unknown. One might hypothesize that ER of these early CRCs is associated with an increased AE risk, because these tumors grow into the submucosal layer and sometimes show incomplete lifting. Therefore, we aimed to identify the AE rate after primary ER of T1 CRCs in a large retrospective multicenter cohort study. The secondary aims of our study were to identify the risk factors associated with these endoscopic AEs and to identify the risk factors associated with R1 or Rx resection.

METHODS

Patients and study design

This is a multicenter retrospective cohort study conducted in a subcohort of the T1 CRC registration cohort initiated by the Dutch T1 CRC working group. Patients diagnosed with T1 CRC between January 1, 2000, and December 1, 2014, in 13 nonacademic and 2 academic hospitals were selected from the Netherlands Comprehensive Cancer Registry (IKNL database). The medical records of all patients were reviewed. Patients were included in the cohort if T1 CRC diagnosis was confirmed by the local pathologist. Exclusion criteria were inflammatory bowel disease and hereditary predisposition for CRC, nonadenocarcinoma, neoadjuvant (chemo)radiotherapy, synchronous advanced-stage CRC, or CRC diagnosis in the previous 5 years before detection of T1 CRC, missing endoscopy or pathology reports, or death within 1 year after treatment that was not CRC related (patients were included if death within 1 year after treatment was CRC related or procedure related). Patients were included in the present analysis if they were treated with primary ER of T1 CRC, with or without adjuvant surgery. Patients were excluded if the primary treatment was surgery or transanal minimally invasive surgery (TAMIS). We considered TAMIS as a surgical procedure because this was performed by surgeons in the included hospitals and not by endoscopists. This study was approved by the Medical Ethical Review Committee of the University Medical Centre Utrecht (reference number 15-487/C) on August 18, 2015, in accordance with the ethical principles of the Declaration of Helsinki.

Data collection

Medical charts were reviewed to collect patient information. Endoscopy reports were used to collect information about the resection technique (en bloc or piecemeal) and ER method (EMR, ESD, conventional snare resection). Tumor characteristics included morphology, location, and lesion size. Kudo and Paris classifications were not reported in most of the endoscopy reports and could therefore not be assessed. Pedunculated morphology was defined as the presence of a stalk or Paris 0-Ip, and nonpedunculated morphology was defined as a flat or sessile tumor.[22,23] Location was classified as the proximal colon if the tumor was present in the cecum, colon ascendens, or colon transversum. If the tumor was present in the splenic flexure, colon descendens, sigmoid, or rectum, it was classified as in the distal colon. Deep invasion was defined as invasion depth $\geq$1000 μm (SM2-3) for nonpedunculated T1 CRCs and Haggit 4 classification for pedunculated T1 CRCs.[24,25] Superficial invasion (<1000 μm) was defined as SM1 for nonpedunculated T1 CRCs and Haggit 1 to 3 for pedunculated T1 CRCs.[24,25]

Endpoint

The primary endpoint was the occurrence of endoscopy-related AEs within 30 days after the endoscopic procedure. When adjuvant surgery was required within these 30 days, AEs were counted until the date of surgery. AEs after adjuvant surgery were considered surgical-related AEs. Severity of AEs was graded according to the registration of the American Society for Gastrointestinal Endoscopy.[26] We only considered 30-day AEs that resulted in prolonged hospitalization, clinical evaluation after hospital discharge, or an additional intervention, such as antibiotic therapy, blood transfusion, repeat colonoscopy, or surgery. An intraprocedural bleeding that could be managed during the procedure (eg, adrenaline injection, hemoclip placement) and did not require an additional postprocedural intervention (eg, blood transfusion, repeat colonoscopy) or prolonged hospitalization of more than 1 day, was not classified as an AE. Postpolypectomy electrocoagulation syndrome (PPES) was defined as fever, abdominal pain, peritoneal signs, or leukocytosis without a proven perforation of the bowel wall.[27] If multiple polyps with different histology were resected and the patient had a postprocedural AE, it was not always clear whether the adenoma or carcinoma caused the AE when repeat colonoscopy was not performed. In this case, we assumed that the resected T1 CRC resulted in an AE to avoid an underestimation of the number of AEs.

Secondary endpoints were the identification of independent risk factors for endoscopic AEs and the identification of risk factors for an R1 or Rx resection, which can also be regarded as an AE. As not all necessary information was available in the Dutch T1 CRC cohort, we collected additional information from the patient medical records. This information included treatment of AEs, intraprocedural hemoclip placement for prophylaxis, and use of anticoagulant therapy. Unfortunately, details on anticoagulant therapy were often missing in the medical records. Although type of anticoagulant therapy was usually

reported, it was not reported whether anticoagulant therapy was continued or correctly stopped before the procedure. This specific information is crucial to determine whether anticoagulant therapy is a risk factor for postprocedural bleeding, because guidelines recommend discontinuing anticoagulant therapy before ER.[28] Because this information is important for the postprocedural bleeding risk, we chose to not include this information in our analysis. The additional information (treatment of AEs, hemoclip placement, and use of anticoagulant therapy) was collected for all patients who developed an AE and a random selection of controls in a 1:3 ratio. This subcohort was used for the AE risk-factor analysis.

The determinant of interest was the number of AEs after ER of T1 CRC. Possible predictors of interest (based on previous literature) were age, American Society of Anesthesiologists (ASA) classification, tumor characteristics (morphology, size, and location), invasion depth, and prophylactic clip placement.[11,12,15-18,21]

Positive resection margins were defined as an R1 resection, and cancer-free resection margins irrespective of distance in millimeters was defined as an R0 resection. When the pathologist was unable to determine the resection margins, it was defined as an Rx resection. We defined R1 and Rx resection as a high-risk factor for recurrence as shown in a previous study about this cohort.[7] The determinant of interest was the number of T1 CRCs with an R1 or Rx resection. Possible predictors of interest were age, ASA classification, tumor characteristics (morphology, size, and location), resection technique, and resection method.[7]

Statistical analysis

Baseline characteristics were reported for the entire cohort using standard descriptive statistics. Categorical data are presented as frequencies and percentages. Continuous data are presented as means (standard deviation [SD]) and medians (interquartile range [IQR]) for normally distributed and skewed data, respectively.

The subcohort was used for the analysis of possible predictors of AEs. Univariate and multivariate analysis was performed using logistic regression analysis, adjusted for the predictors of interest (ie, age, ASA classification, tumor characteristics, invasion depth, and prophylactic clip placement).

Subanalysis was performed to compare the AE rate between pedunculated and nonpedunculated T1 CRC. For the analysis of possible predictors for R1 or Rx resection, univariate and multivariate analyses were performed. The total cohort was used for these 2 analyses.

Age and polyp size were included in the univariate and multivariate analyses as categorical variables. We categorized age into $\leq$70 years and >70 years and tumor size into size $\leq$20 mm and >20 mm. These cut-off values were predefined and based on cut-off values used in other studies.[11,29] We repeated the analysis with age and size as continuous variables to explore whether that influenced the results.

Information about AEs was available for all patients. However, several confounding variables had missing values (Table 1). Missing data were missing completely at random (MCAR) according to the MCAR Test by Little et al ($P <$ .01).[30] Multiple imputation was used before data analysis because exclusion of patients with missing values could decrease the power of the study due to the smaller sample size.[31,32] Multiple imputation by chained equations was performed (20 imputation datasets, 25 iterations, healthy convergence). Results were pooled across imputed datasets using Rubin's rules.[33] For completeness, sensitivity analyses of patients who had all variables present (without imputation for missing data) were performed (Supplementary Tables 1 and 2, available online at www.giejournal.org). A 2-sided P value <.05 was considered significant for all analyses. Analyses were carried out using IBM SPSS version 24.

RESULTS

Patient characteristics

A total of 2599 patients with T1 CRC are included in the Dutch T1 CRC cohort. In total, 720 patients did not meet the inclusion criteria and were excluded from this study (Fig. 1). After exclusion of another 810 patients treated with primary surgery or TAMIS, 1069 patients treated with primary ER for T1 CRC were eligible for analysis in our study (Fig. 1).

The median age of the total cohort was 69 years (IQR, 63-76 years), and 57.0% were male. In total, 430 of 1069 patients (40.2%) received adjuvant surgery, and 21 of 1069 patients (2.0%) received adjuvant chemotherapy after ER of T1 CRC. The median follow-up time between ER of T1 CRC and the end of follow-up (defined as the last follow-up visit or date of death) was 39.0 months (IQR, 18.0-75.6 months). Baseline characteristics of the total cohort are presented in Table 1.

Tumor characteristics

Most tumors were located in the distal colon (92.8%) and were resected by snare resection (66.1%) or EMR (31.0%). The median tumor size in our cohort was 20 mm (IQR, 12-25 mm). In total, 648 of 1069 patients (62.4%) had pedunculated T1 CRC, and 390 of 1069 patients (37.6%) had nonpedunculated T1 CRC (Table 1); morphology was missing in 31 patients.

Adverse events

Among the 1069 included patients, 59 patients (5.5%; 95% confidence interval [CI], 4.2-7.1) developed an endoscopic AE. In 45 of 59 patients (76.3%), we were confident that T1 CRC resection caused the AE. In 4 of 59 patients (6.8%), multiple polyps were resected during the initial

TABLE 1. Baseline characteristics

	Total cohort (N = 1069): nonadjusted data	Missing (%)*	Total cohort (N = 1069): adjusted data†
Age (years), median (IQR)	69 (63-76)	0	69 (63-76)
Age >70 years, n (%)	451 (42.2)	0	451 (42.2)
Male gender, n (%)	609 (57.0%)	0	609 (57.0)
ASA score, n (%)			
ASA I-II	841 (80.8)		866 (81.0)
ASA III-IV	200 (19.2)		203 (19.0)
Missing	28	2.6	
Location T1 CRC, n (%)			
Distal	986 (92.5)		989 (92.8)
Proximal	80 (7.5)		80 (7.2)
Missing	3	0.3	
Polyp size (mm)			
Mean (SD)	20.3 (11.6)		20.4 (11.5)
Median (IQR)	20 (12-25)		20 (12-25)
Missing	92	8.6	
Polyp size, >20 mm, n (%)	509 (52.1)		555 (51.9)
Missing	92	8.6	
Morphology, n (%)			
Pedunculated	648 (62.4)		665 (62.2)
Nonpedunculated	390 (37.6)		404 (37.8)
Missing	31	2.9	
Resection technique, n (%)			
Piecemeal	288 (27.5)		296 (27.7)
En bloc	759 (72.5)		773 (72.3)
Missing	22	2.1	
Resection method, n (%)			
EMR	326 (31.5)		331 (31.0)
Snare	704 (68.0)		707 (66.1)
ESD	5 (0.5)		31 (2.9)
Missing	34	3.2	
Differentiation grade, n (%)			
Good/moderate	684 (94.2)		857 (80.2)
Poor	42 (5.8)		212 (19.8)
Missing	343	32.1	
Invasion depth, n (%)‡			
Superficial	449 (81.2)		760 (71.1)
Deep	104 (18.8)		309 (28.9)
Missing	516	45.4	
Lymphovascular invasion, n (%)			
Present	88 (17.1)		257 (24.0)
Absent	428 (82.9)		812 (76.0)
Missing	553	51.7	

(*continued on the next page*)

TABLE 1. Continued

	Total cohort (N = 1069): nonadjusted data	Missing (%)*	Total cohort (N = 1069): adjusted data†
Resection margins, n (%)			
R0	558 (52.2)		574 (53.7)
R1	274 (25.6)		285 (26.7)
Rx	200 (18.7)		210 (19.6)
Missing	37	3.5	
Additional treatment after ER, n (%)			
Adjuvant surgery	430 (40.2)		430 (40.2)
Adjuvant chemotherapy	21 (2.0)		21 (2.0)
Wait and see	618 (57.8)	0	618 (57.8)

IQR, Interquartile range; *ASA*, American Society of Anesthesiologists; *CRC*, colorectal cancer; *SD*, standard deviation; *ESD*, endoscopic submucosal resection; *ER*, endoscopic resection.
*Percentage of patients with missing data in the total cohort.
†Adjusted data after multiple imputation.
‡Superficial invasion, SM1 or Haggit 1-3; deep invasion, SM2-3 or Haggit 4.

colonoscopy, and repeat colonoscopy was performed after the AE (postprocedural bleeding). Although T1 CRC was the largest resected polyp during the initial colonoscopy, a focus of postprocedural bleeding was not found during the repeat colonoscopy. In 10 of 59 patients (16.9%), repeat colonoscopy was not performed after an AE, and we were therefore not confident that T1 CRC caused the AE. The most common AE was postprocedural bleeding (n = 40, 3.7% median time between ER and bleeding was 0 days [range, 0-30 days; IQR, 0-6 days]), followed by perforation (n = 13, 1.2%), and PPES (n = 6, 0.6%). In 16 patients, an intraprocedural AE occurred but was not considered an AE because these patients were only admitted to the hospital for overnight observation without additional interventions. An overview of the treatment and severity grade of the AEs are outlined in Table 2. In total, 37.3% (22 of 59) of the AEs were classified as mild, 59.3% (35 of 59) as moderate, and 3.4% (2 of 59) as severe. No fatal AEs were observed.

The overall AE rate did not differ between pedunculated (36 of 648; 5.6%) and nonpedunculated T1 CRC (21 of 390; 5.4%) (P = .907). The AE rate for pedunculated and nonpedunculated T1 CRC stratified for different resection techniques is shown in Table 3. Most AEs occurred in pedunculated T1 CRCs resected by EMR (6.5%; 95% CI, 3.2-11.6).

Postprocedural bleeding

Postprocedural bleeding was treated with repeat colonoscopy and hemoclip placement in 16 of 40 (40%) patients. Thirteen patients (33%) were readmitted to the hospital for observation without additional interventions. Repeat colonoscopy without additional interventions occurred in 9 of 40 patients (23%) because no active bleeding source was found during the colonoscopy. Surgery was performed in 2 of 40 patients (5%). One patient was admitted for postprocedural bleeding directly after ER; during this hospital admission, the patient developed a perforation and sigmoid resection was performed. The second patient was treated for bleeding with adrenaline injections and hemoclip placement directly after ER during the initial colonoscopy. Due to persistent bleeding, a sigmoid resection was performed in an urgent setting. Thirteen cases (32.5%) of postprocedural bleeding were classified as mild and 27 (67.5%) as moderate.

Perforation

Perforation occurred in 13 patients (13 of 1069; 1.2%). T1 CRC morphology was nonpedunculated in 8 of 13 patients (61.5%) and pedunculated in 5 of 13 patients (38.5%). Perforation occurred more often in patients with nonpedunculated T1 CRC (8 of 404; 2%) compared with pedunculated T1 CRC (5 of 665; 0.8%) (P = .018).

In 5 of 13 patients, the perforation occurred the day after ER. Surgery was performed in 4 of 5 patients, and repeat colonoscopy was performed in 1 of 5 patients with hemoclip placement followed by hospital admission of 7 days with antibiotic therapy. Perforation occurred the same day as the ER in 8 of 13 patients. Surgery was performed in 4 of 8 patients, of which 1 patient developed peritoneal metastases. In 1 of 8 patients, perforation occurred during the initial endoscopy directly after ER and was immediately closed with hemoclip placement followed by hospital admission of 7 days. In 3 of 8 patients, conservative management with antibiotic therapy sufficed. Three cases of perforation (23%) were classified as mild, 8 (62%) as moderate, and 2 (15%) as severe.

Postpolypectomy electrocoagulation syndrome

Postpolypectomy electrocoagulation syndrome occurred in 6 patients (0.6%), 2 of whom (33%) were

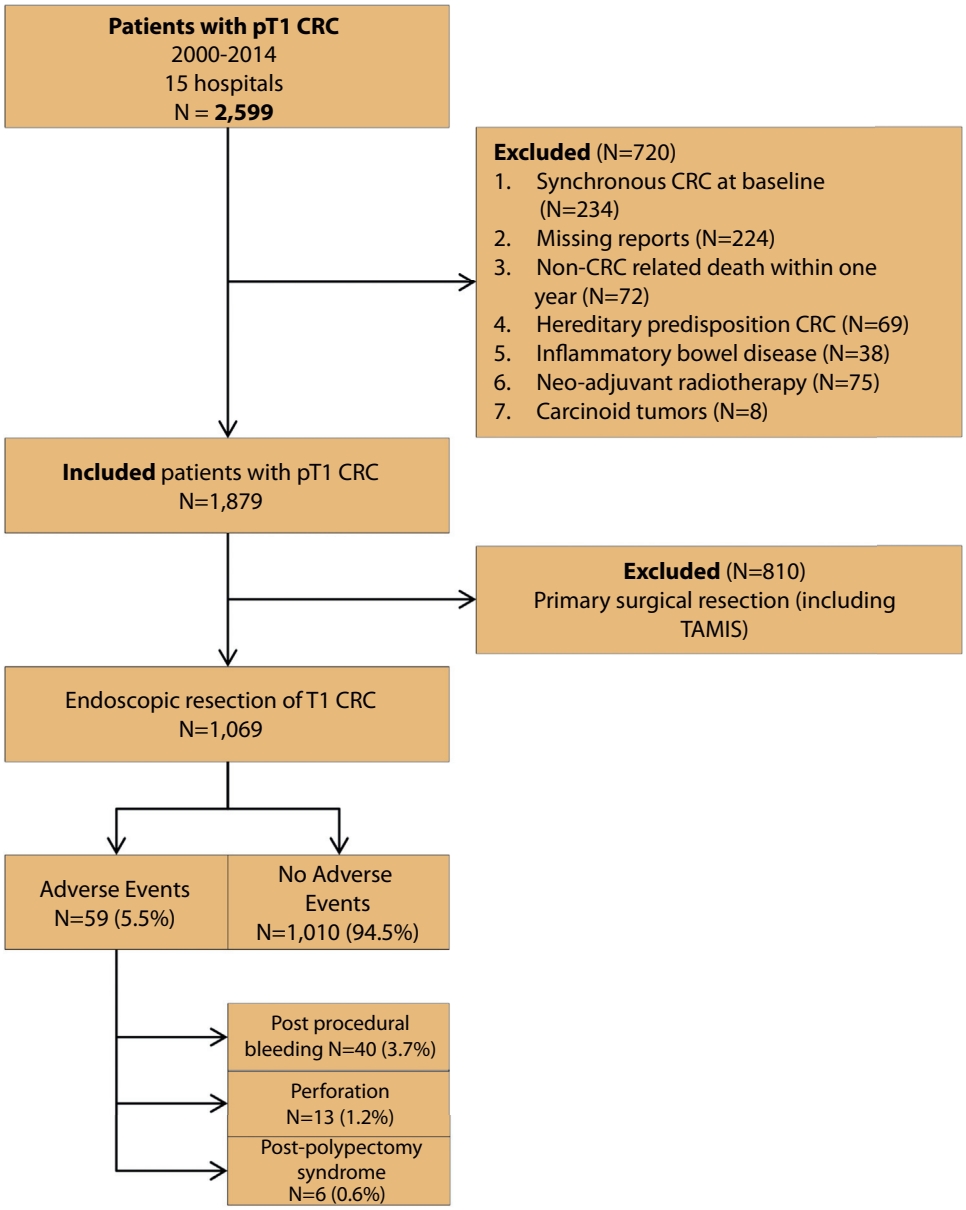

Figure 1. Flowchart of study. *CRC*, Colorectal cancer; *TAMIS*, transanal minimally invasive surgery.

readmitted to the hospital without additional interventions, and 4 (66%) patients were treated with antibiotic therapy. All cases were classified as mild AEs.

Among the 72 patients who were excluded because of death within 1 year after treatment that was not CRC related, 42 patients were treated with primary endoscopic treatment. An AE (delayed bleeding) developed in 3 of 42 patients (1 mild AE, 1 moderate AE, and 1 severe AE).

Risk factors for adverse events

Risk factor analyses were first evaluated without imputation for missing data (Supplementary Tables 1 and 2). After imputation for missing data, risk factors associated with endoscopic AEs were evaluated again (Table 4). A total of 59 patients who developed an AE were compared with 230 random control patients from the T1 CRC cohort without an AE (subcohort). Univariate analysis showed that patients who developed an AE were more often older than 70 years (62.7% vs 45.2%, $P = .018$) and tumor size was larger than 20 mm (71.2% vs 54.8%, $P = .043$).

After adjusting for potential confounders (ASA classification, morphology, invasion depth, and prophylactic hemoclip placement), tumor size >20 mm (odds ratio [OR], 2.22; 95% CI,1.15-4.69) and age >70 years (OR, 2.11; 95% CI, 1.12-3.96) remained associated with an increased risk for developing AEs after ER of T1 CRC. Analysis with continuous variables did not alter the outcomes.

TABLE 2. Severity classification and treatment of endoscopic adverse events

Adverse event	Treatment	Severity grade[26]			
		Mild	Moderate	Severe	Fatal
Postprocedural bleeding	Hospital admission ≤3 nights (without intervention)	13			
Postprocedural bleeding	Repeat colonoscopy (no intervention)		9		
Postprocedural bleeding	Repeat colonoscopy with hemoclip placement		16		
Postprocedural bleeding	Surgery		2		
Perforation	Re-endoscopy with antibiotic therapy and hospital admission of 7 nights		1		
Perforation	Re-endoscopy with hemoclip placement	1			
Perforation	Antibiotic therapy with hospital admission of 12 nights			1	
Perforation	Antibiotic therapy with hospital admission ≤3 nights	2			
Perforation	Surgery		7		
Perforation	Surgery with respiratory insufficiency + admission ICU >1 night			1	
PPES	Hospital admission ≤ 3 nights (no intervention)	2			
PPES	Antibiotic therapy	4			
Total		22	35	2	0

ICU, Intensive care unit; *PPES*, postpolypectomy electrocoagulation syndrome.

TABLE 3. Adverse event rate for pedunculated and nonpedunculated T1 CRCs stratified for different resection techniques (n = 1010; morphology in combination with resection technique missing in 59 patients)

	Number of patients	% adverse events	95% CI
Pedunculated T1 CRC			
Snare resection	478	5.2	3.4-7.6
EMR	154	6.5	3.2-11.6
Nonpedunculated T1 CRC			
Snare resection	216	5.1	2.6-8.9
EMR	157	6.4	3.1-11.4
ESD	5	0.0	–

CRC, Colorectal cancer; *CI*, confidence interval; *ESD*, endoscopic submucosal dissection.

Risk factors for postprocedural bleeding

Risk factors associated with postprocedural bleeding were analyzed separately because the group of patients with postprocedural bleeding consisted of 40 patients. These 40 patients were compared with 249 patients (random controls from the total T1 CRC cohort) (Table 5). Univariate analysis showed that patients who developed postprocedural bleeding were more often older than 70 years (67.5% vs 45.8%, $P = .013$).

After adjusting for ASA classification, morphology, invasion depth, polyp size, and prophylactic hemoclip placement, only age >70 years (OR, 2.62; 95% CI, 1.24-5.54) was associated with an increased risk for postprocedural bleeding (Table 5). Analysis with continuous variables did not alter the outcomes. We performed a subanalysis of nonpedunculated T1 CRCs >20 mm, because ESD is mostly performed in this particular group. Postprocedural bleeding did not occur more often in nonpedunculated T1 CRCs >20 mm compared with all other T1 CRCs (0.7% vs 3.0%, $P = .588$).

Separate analysis of perforation and PPES was not performed because the numbers were too small for logistic regression analysis.

Risk factors for R1 or Rx resection

Risk factors associated with R1 or Rx resection were analyzed. In total, 574 of 1069 patients (53.7%) had an R0 resection and 495 of 1069 patients (46.3%) had an R1 or Rx resection. Univariate analysis showed that patients who had an R1 or Rx T1 CRC resection were more often treated with piecemeal resection (43.2% vs 14.3%, $P < .01$), had nonpedunculated morphology (50.7% vs 26.7%, $P < .01$), and were located in the proximal colon (9.7% vs 5.6%, $P = .02$), compared with patients who had R0 T1 CRC resection. After adjusting for potential confounders (age, ASA classification, localization, polyp size, morphology, resection technique,

TABLE 4. Risk analysis of adverse events (adverse events, n = 59 versus controls, n = 230; subcohort)

Predictor	Adverse event		Multivariate analysis	
	No	Yes	OR (95% CI)	*P* value
Age, n (%)				
≤70 years	126 (54.8)	22 (37.3)	Reference	–
>70 years	104 (45.2)	37 (62.7)	2.111 (1.124-3.964)	.020
ASA score, n (%)				
I-II	180 (78.3)	44 (74.6)	Reference	–
III-IV	50 (21.7)	15 (25.4)	0.944 (0.457-1.949)	.876
Localization, n (%)				
Distal	212 (92.2)	50 (84.7)	Reference	–
Proximal	18 (7.8)	9 (15.3)	2.265 (0.865-5.933)	.096
Polyp size, n (%)				
≤20 mm	104 (45.2)	17 (28.8)	Reference	–
>20 mm	126 (54.8)	42 (71.2)	2.224 (1.054-4.694)	.036
Morphology, n (%)				
Nonpedunculated	84 (36.5)	22 (37.3)	Reference	–
Pedunculated	146 (63.5)	37 (62.7)	1.048 (0.492-2.236)	.902
Invasion depth, n (%)*				
Superficial	160 (69.6)	42 (71.2)	Reference	–
Deep	70 (30.4)	17 (28.8)	0.806 (0.350-1.857)	.612
Prophylactic hemoclip placement, n (%)				
No	195 (84.8)	51 (86.4)	Reference	–
Yes	35 (15.2)	8 (13.6)	0.836 (0.350-1.995)	.687

OR, Odds ratio; *CI*, confidence interval; *ASA*, American Society of Anesthesiologists.
*Superficial invasion, SM1 or Haggit 1-3; deep invasion, SM2-3 or Haggit 4.

and resection method), nonpedunculated morphology (OR, 2.352; 95% CI, 1.744-3.171, $P < .01$) and piecemeal resection technique (OR, 4.569; 95% CI, 3.254-6.415, $P < .01$) were independent predictors for R1 or Rx resection (Supplementary Table 3, available online at www.giejournal.org).

DISCUSSION

This large-scale, multicenter cohort study on AEs after ER of T1 CRC shows an overall AE rate of 5.5%. Our multicenter collaboration of 15 hospitals enabled us to evaluate a high number of T1 CRCs and therefore closely reflects daily practice. The most common AEs were postprocedural bleeding (3.7%), followed by perforation (1.2%) and PPES (0.6%). Most AEs were classified as mild to moderate (97%), and no fatal AEs occurred. Peritoneal metastases were observed in 1 patient in whom perforation occurred. Tumor size >20 mm and age >70 years were associated with an increased risk of AEs after ER of T1 CRC. Age >70 years was particularly associated with an increased risk of postprocedural bleeding after ER of T1 CRC. Remarkably, an association with a proximal T1 CRC location and postprocedural bleeding was not found in our data. Nonpedunculated morphology and piecemeal resection were associated with an R1 or Rx resection.

We hypothesized that ER of early CRCs is associated with an increased AE risk because these tumors grow into the submucosal layer and sometimes show incomplete lifting. However, we did not find this association. A possible explanation could be that more than 60% of T1 CRCs in our cohort had pedunculated morphology and did not show deep submucosal invasion (Haggit 4). Therefore, these lesions could be removed by snare resection or EMR instead of ESD. No significant differences in AE rates were found between pedunculated and nonpedunculated T1 CRCs (5.4% vs 5.7%), not even after stratification for resection technique.

There are limited data on AE risks after ER of T1 CRC. A recent study has described carcinoma as an independent risk factor for postprocedural bleeding (OR, 3.4; 95% CI, 1.08-10.71.[20] The postprocedural bleeding rate for ER of CRC was 7.9%, which is higher than in our study. However, all procedures were performed by ESD.[20] In contrast, in our study only 3% of patients were treated

TABLE 5. Risk analysis of postprocedural bleeding (postprocedural bleeding, n = 40 vs controls, n = 249; subcohort)

	Postprocedural bleeding		Multivariate analysis	
Predictor	**No**	**Yes**	**OR (95% CI)**	***P* value**
Age, n (%)				
≤70 years	135 (54.2)	13 (32.5)	Reference	–
>70 years	114 (45.8)	27 (67.5)	2.616 (1.236-5.537)	.012
ASA score, n (%)				
I-II	195 (78.3)	29 (72.5)	Reference	–
III-IV	54 (21.7)	11 (27.5)	1.057 (0.467-2.394)	.895
Localization, n (%)				
Distal	225 (90.4)	37 (92.5)	Reference	–
Proximal	24 (9.6)	3 (7.5)	0.817 (0.211-3.172)	.771
Polyp size, n (%)				
≤20 mm	108 (43.4)	13 (32.5)	Reference	–
>20 mm	141 (56.6)	27 (67.5)	1.657 (0.703-3.902)	.247
Morphology, n (%)				
Nonpedunculated	94 (37.8)	12 (30.0)	Reference	
Pedunculated	155 (62.2)	28 (70.0)	1.029 (0.430-2.462)	.948
Invasion depth, n (%)*				
Superficial	170 (68.3)	32 (80)	Reference	
Deep	79 (31.7)	8 (20)	0.469 (0.169-1.306)	.147
Prophylactic hemoclip placement, n (%)				
No	36 (14.5)	7 (17.5)	Reference	–
Yes	213 (85.5)	33 (82.5)	1.102 (0.433-2.804)	.839

OR, Odds ratio; *CI*, confidence interval; *ASA*, American Society of Anesthesiologists.
*Superficial invasion, SM1 or Haggit 1-3; deep invasion, SM2-3 or Haggit 4.

with ESD. ESD is mostly performed in large (>20 mm), nonpedunculated T1 CRCs. The bleeding risk in this particular group of our cohort was not higher than the bleeding risk of the total cohort. Moreover, this study was performed in an expert center with larger lesions, which does not reflect daily practice.[20] Another smaller, single-center study reported a postprocedural bleeding rate of 4.4% after ER of T1 CRC and 3.8% after ER of adenoma.[21] Our findings are roughly in line with this study, but with a sample size of more than 1000 patients in 15 different hospitals, the generalizability of our study is much greater.

The AE risk of ER of adenomas has been studied extensively. Reported incidence rates of postprocedural bleeding in larger adenomas (>20 mm) vary between 4.7% and 10.9%.[11,12,14] Risk factors for postprocedural bleeding are larger adenoma size (>20 mm), localization in the proximal colon, age >70 years, and aspirin use.[11,12] The postprocedural bleeding rates in our T1 CRC cohort are lower than bleeding rates after ER of adenomas reported in the literature. A possible explanation could be that we excluded all patients with intraprocedural bleeding who were treated immediately without prolonged hospitalization (>1 day) or additional interventions. The perforation rate in our cohort (1.2%) is comparable with the perforation rate after EMR of adenomas (>20 mm), which ranges from 0.5% to 2.2%.[11,13,34] Perforation occurred more often in patients with nonpedunculated T1 CRC, which is also reported in the literature for adenomas.[17] However, the consequences of a perforation after ER of T1 CRC might be more severe than after ER of adenomas, as metachronous peritoneal metastases might be a factor after perforation. We observed 1 case in which a perforation had occurred and metachronous peritoneal metastases were found. However, we also observed peritoneal metastases in 6 patients without perforation. Based on our study with just 1 single case, it is impossible to determine whether this peritoneal metastasis was a consequence of the perforation or rather co-existed. Postpolypectomy electrocoagulation syndrome is a less-common AE with an incidence of 1%, which is compatible with our findings.[13] Risk factors for PPES are polyp size >20 mm, nonpolypoid morphology, and hypertension.[35,36] Due to the low number of patients with PPES in our cohort, we could not define specific risk factors for PPES.

Larger tumor size and age >70 years were associated with AEs. This corresponds with risk factors for AEs after ER of adenomas.[11,12,15-18,29,35,36] Larger lesion size will result in a larger mucosal defect after ER and creates the potential for deeper injury into the (sub)mucosa.[12]

However, there are studies that did not find an association between lesion size and AEs.[15,18] Although some studies reported age as an independent risk factor for AEs,[11,12,15] other studies did not.[34,37] As we also found age >70 years to be an independent risk factor for AEs, we advocate to be more aware of AEs in elderly patients, particularly in patients older than 70 years of age. Tumor localization in the proximal colon as a risk factor for postprocedural bleeding is often reported.[11,12,16,17] However, we did not find this association in our cohort. Presumably, this is due to the low number of patients with proximally located T1 CRC in our cohort.

Apart from the periprocedural AEs as discussed in our study, long-term oncologic safety is even more important to guarantee the safety of ER of T1 CRC. Oncologic safety after ER of T1 CRC of our cohort has been reported previously by Backes et al.[7] This study showed that a "wait-and-see" policy with limited follow-up is justified in patients with low-risk T1 CRC.[7] Another study about our T1 CRC cohort reported that ER of high-risk T1 CRCs before surgical resection has no adverse effect (risk of lymph node metastasis or recurrence) on long-term outcomes.[38] Together with the results of our study, we can conclude that ER of T1 CRCs can safely be attempted. However, some potential limitations about this study need to be discussed. First, this is a retrospective cohort study, which potentially limits the generalizability of our results. AEs could be underreported, and detailed information in the pathology report such as invasion depth, cautery effect due to snare resection or EMR, or incomplete collection of resected pieces, was not always reported correctly. This information is important because it can hamper the ability of pathologists to determine the nature of the resected polyp with certainty.

There was limited information on anticoagulant therapy in the medical files, whereas the use of anticoagulant therapy is a well-known risk factor for postprocedural bleeding.[37] In addition, several other confounding variables had missing data, which could decrease the power of our analysis. Hence, we decided to impute for missing data. Second, we only included T1 CRCs diagnosed until 2014. Only a few ESDs and EMRs were included in our study, whereas these resection techniques are mostly used to date. This could have an impact on the interpretation of these results in today's daily clinical practice. Third, due to the retrospective design of our study, we did not know whether the endoscopist suspected an early cancer before ER. For this reason, we did not know how the decision was made to use a specific resection technique. Also, the individual skill level of the endoscopists was not known, which could have an influence on the AE rate. Finally, there could be a possible selection bias because we were not always confident whether the resected T1 CRC caused the AE.

In conclusion, the AE rate and risk factors of ER of T1 CRCs are comparable with those for ER of adenomas. Our study shows that ER of T1 CRCs can safely be attempted. More caution is warranted for ER of T1 CRC in patients older than 70 years and large T1 CRCs (>20 mm).

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Abbreviations: AE, adverse event; ASA, American Society of Anesthesiologists; CI, confidence interval; CRC, colorectal cancer; ER, endoscopic resection; ESD, endoscopic submucosal dissection; IQR, interquartile range; OR, odds ratio; PPES, post-polypectomy electrocoagulation syndrome; TAMIS, transanal minimally invasive surgery.

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SUPPLEMENTARY TABLE 1. Risk factor analysis of adverse events without imputation for missing data (adverse events, n = 28 versus controls, n= 470; total cohort)

	Multivariate analysis	
Predictor	**OR (95% CI)**	***P* value**
Age, n (%)		
≤70 years	Reference	–
>70 years	1.383 (0.623-3.067)	.425
ASA score, n (%)		
I-II	Reference	–
III-IV	2.434 (1.049-5.648)	.038
Localization, n (%)		
Distal	Reference	–
Proximal	2.414 (0.550-10.599)	.243
Polyp size, n (%)		
≤20 mm	Reference	–
>20 mm	2.041 (0.870-4.790)	.101
Morphology, n (%)		
Nonpedunculated	Reference	–
Pedunculated	1.069 (0.345-3.309)	.908
Invasion depth, n (%)*		
Superficial	Reference	–
Deep	0.723 (0.234-2.234)	.574

571patients from the total cohort were excluded from this analysis because of missing data.
OR, Odds ratio; *CI*, confidence interval; *ASA*, American Society of Anesthesiologists.
*Superficial invasion, SM1 or Haggit 1-3; deep invasion, SM2-3 or Haggit 4.

SUPPLEMENTARY TABLE 2. Risk factor analysis of postprocedural bleeding (postprocedural bleeding, n = 21 vs controls, n = 477; subcohort)

	Multivariate analysis	
Predictor	**OR (95% CI)**	***P* value**
Age, n (%)		
≤70 years	Reference	–
>70 years	2.105 (0.833-5.321)	.116
ASA score, n (%)		
I-II	Reference	–
III-IV	1.969 (0.742-5.223)	.173
Localization, n (%)		
Distal	Reference	–
Proximal	2.396 (0.390-14.722)	.346
Polyp size, n (%)		
≤20 mm	Reference	–
>20 mm	1.725 (0.674-4.416)	.256
Morphology, n (%)		
Nonpedunculated	Reference	–
Pedunculated	1.038 (0.265-4.068)	.958
Invasion depth, n (%)*		
Superficial	Reference	–
Deep	0.158 (0.019-1.313)	.088

571 patients from the total cohort were excluded from this analysis because of missing data.
OR, Odds ratio; *CI*, confidence interval; *ASA*, American Society of Anesthesiologists.
*Superficial invasion, SM1 or Haggit 1-3; deep invasion, SM2-3 or Haggit 4.

SUPPLEMENTARY TABLE 3. Risk factor analysis for R0 versus R1/Rx resection

	Resection		Univariate analysis	Multivariate analysis	
Predictor	**R0 (n = 574)**	**R1/Rx (n = 495)**	***P* value**	**OR (95% CI)**	***P* value**
Age, n (%)					
≤70 years	330 (57.5)	288 (58.2)	.826	Reference	
>70 years	244 (42.5)	207 (41.8)		0.911 (0.695-1.195)	.502
ASA score, n (%)					
I-II	471 (82.1)	395 (79.8)	.367	Reference	
III-IV	103 (17.9)	100 (20.2)		1.049 (0.743-1.482)	.786
Localization, n (%)					
Distal	542 (94.4)	447 (90.3)	.020	Reference	
Proximal	32 (5.6)	48 (9.7)		0.918 (0.521-1.615)	.765
Polyp size, n (%)					
≤20 mm	276 (48.1)	239 (48.3)	.962	Reference	
>20 mm	298 (51.9)	256 (51.7)		1.300 (0.970-1.743)	.079
Morphology, n (%)					
Nonpedunculated	153 (26.7)	251 (50.7)	<.01	2.352 (1.744-3.171)	<.01
Pedunculated	421 (73.3)	244 (49.3)		Reference	
Resection technique, n (%)					
Piecemeal	82 (14.3)	214 (43.2)	<.01	4.569 (3.254-6.415)	<.01
En bloc	492 (85.7)	281 (56.8)		Reference	
Resection method, n (%)					
EMR	161 (28.0)	174 (35.2)	.082	Reference	
Snare	401 (69.9)	310 (62.6)		1.191 (0.874-1.623)	.268
ESD	12 (2.1)	11 (2.2)		0.666 (0.198-2.244)	.509

OR, Odds ratio; *CI*, confidence interval; *ASA*, American Society of Anesthesiologists; *ESD*, endoscopic submucosal dissection.