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ELECTRONIC ENDOSCOPY

Risk and Time Pattern of Recurrences After Local Endoscopic Resection of T1 Colorectal Cancer: A Meta-analysis

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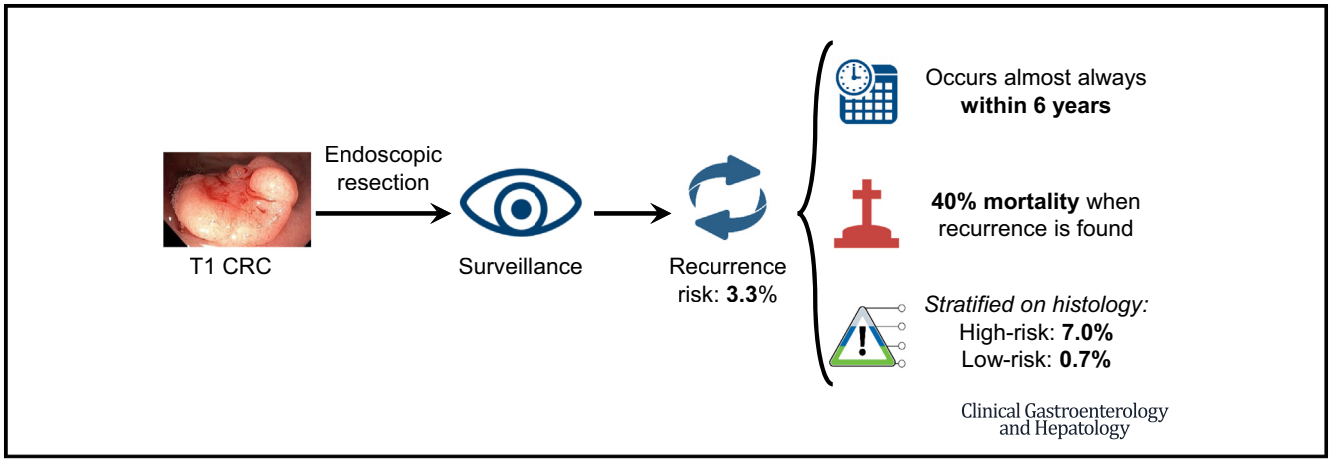

BACKGROUND & AIMS: Growing numbers of patients with T1 CRC are being treated with local endoscopic resection only and as a result, the need for optimization of surveillance strategies for these patients also increases. We aimed to estimate the cumulative incidence and time pattern of CRC recurrences for endoscopically treated patients with T1 CRC.

METHODS: Using a systematic literature search in PubMed, EMBASE, Web of Science and Cochrane Library (from inception till 15 May 2020), we identified and extracted data from studies describing the cumulative incidence of local or distant CRC recurrence for patients with T1 CRC treated with local endoscopic resection only. Pooled estimates were calculated using mixed-effect logistic regression models.

RESULTS: Seventy-one studies with 5167 unique, endoscopically treated patients with T1 CRC were included. The pooled cumulative incidence of any CRC recurrence was 3.3% (209 events; 95% CI, 2.6%-4.3%; $I^2 = 54.9\%$), with local and distant recurrences being found at comparable rates (pooled incidences 1.9% and 1.6%, respectively). CRC-related mortality was observed in 42 out of 2519 patients (35 studies; pooled incidence 1.7%, 95% CI, 1.2%-2.2%; $I^2 = 0\%$), and the CRC-related mortality rate among patients with recurrence was 40.8% (42/103 patients). The vast majority of recurrences (95.6%) occurred within 72 months of follow-up. Pooled incidences of any CRC recurrence were 7.0% for high-risk T1 CRCs (28 studies; 95% CI, 4.9%-9.9%; $I^2 = 48.1\%$) and 0.7% (36 studies; 95% CI, 0.4%-1.2%; $I^2 = 0\%$) for low-risk T1 CRCs.

CONCLUSIONS: Our meta-analysis provides quantitative outcome measures which are relevant to guidelines on surveillance after local endoscopic resection of T1 CRC.

Keywords: T1 Colorectal Carcinoma; Therapeutic Endoscopy; Follow-Up; Recurrence.

Abbreviations used in this paper: CI, confidence interval; JSCCR, Japanese Society for Cancer of the Colon and Rectum; T1 CRC, early invasive colorectal cancer.

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With the introduction of population-based screening programs, a growing number of early invasive colorectal cancers (T1 CRCs) are detected and treated with local endoscopic resection.[1] The decision to proceed to additional surgery or surveillance mainly depends on the estimated oncologic benefit of surgery, the operative risk, and patient preferences. When using current risk stratification models (which are based on histologic high-risk features, such as positive resection margins, deep submucosal invasion, grade 3 differentiation, lymphovascular invasion, and high-grade tumor budding[2]), >80% of high-risk patients referred for surgical resection turn out not to have lymph node metastasis.[3] Besides, colorectal surgery involves a significant risk of morbidity and mortality for older patients,[4] who comprise a considerable proportion of the main target group of screening programs.[5] As a result, there has been an increasing tendency toward wait-and-see strategies after local endoscopic resection of T1 CRC.[1]

To determine the optimal frequency and method of surveillance, it is important to know how often, and at which moments in follow-up local or distant CRC recurrences exactly occur. However, for endoscopically treated patients with T1 CRC, the definite answers to these questions have not yet been provided. As a result, surveillance for these patients is quite heterogeneous in clinical practice,[6] with possible negative consequences, such as decreased efficacy of surveillance or increased health care costs because of underuse or overuse of follow-up modalities, respectively.

The aim of this meta-analysis was to estimate the cumulative incidence and time pattern of local or distant CRC recurrences after local endoscopic resection of T1 CRC.

What You Need to Know

Background

To determine the optimal frequency and method of surveillance after local endoscopic resection of early-invasive colorectal cancer (T1 CRC), it is important to know how often and at which moments in follow-up disease recurrences exactly occur.

Findings

Of the 5167 pooled endoscopically treated T1 CRC patients, 209 experienced CRC recurrence (pooled cumulative incidence: 3.3%), with the vast majority of recurrences occurring within 72 months of follow-up. When CRC recurrence is found, 40.8% of patients die from the disease.

Implications For patient care

Our study provides quantitative outcome measures which give guidance for determining appropriate surveillance strategies after local endoscopic resection of T1 CRC.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[7] Details on the search strategy, extracted data, definitions, and risk of bias assessment are found in the Supplementary Methods.

Selection Criteria

Inclusion criteria were: (1) histologically confirmed patients with T1 CRC treated with endoscopic tumor resection alone, (2) proportion of CRC recurrences reported for endoscopically treated patients with T1 CRC, and (3) original peer-reviewed articles. T1 CRCs were defined as tumors with histologic tumor invasion through the muscularis mucosa and into, but not beyond, the submucosa. Endoscopic resection was defined as local endoscopic tumor excision via the intestinal lumen without lymph node dissection. Exclusion criteria were: (1) surgically treated patients with T1 CRC (this also involves local surgical resection techniques, such as transanal minimally invasive surgery, transanal endoscopic microsurgery, and surgical resections for endoscopic treatment-related adverse events, such as perforations), (2) down-staged T1 CRC after neoadjuvant radiotherapy, (3) patients receiving adjuvant chemotherapy or radiotherapy, (4) hereditary predisposition for CRC, (5) inflammatory bowel disease, (6) case reports or studies with <5 patients with T1 CRC treated with endoscopic tumor resection alone, (7) studies without original patient data, such as reviews or meta-analyses, (8) conference articles, and (9) animal studies. No language restrictions were used. In case of cohort overlap between studies, the cohort with the largest number of patients with T1 CRC or covering the largest period was selected.

Data Acquisition

Data-extraction and risk of bias assessment were independently performed by 4 authors (HD, ND, PPO, LF). In case of disagreement without consensus after discussion, a fifth assessor (JJB) was decisive. Relevant study-level parameters and patient-level data of cases of recurrence were extracted. The risk of bias was assessed using a modified Newcastle-Ottawa Scale.[8] To ensure the quality of the extracted data and the risk of bias assessment, an additional random data check was performed by the decisive assessor.

Study Outcomes

The primary outcome was the cumulative incidence and time pattern of CRC recurrence (local, distant, or

both) during follow-up. Local recurrence was defined as intraluminal CRC at the site of the previous resection, and distant recurrence as lymph node metastasis or distant metastasis. Sufficient data on nonmalignant recurrences (eg, adenomas, serrated polyps) and metachronous lesions detected during follow-up were rarely reported and therefore could not be analyzed. Secondary outcomes were the cumulative incidence and time pattern of local CRC recurrence only, any local CRC recurrence, any distant CRC recurrence, and CRC-specific mortality.

Statistical Analyses

All analyses were performed in R version 3.6.2[9] using the package *metaphor*.[10] Cumulative incidences of all study outcomes were modelled on the logit scale using mixed-effects logistic regression, a method that provides more reliable pooled estimates when events are relatively rare.[11] Results were then converted back to proportions and presented as point estimates and 95% confidence intervals (CI). Risk of publication bias was examined using a funnel plot with the study size on the y-axis.[12]

Statistical heterogeneity was quantified using the I^2 statistic and tau-squared (τ^2). To explore possible sources of heterogeneity, we performed univariable metaregression and subgroup analyses with predefined potential predictors: study characteristics (eg, publication year, study design), individual items from the risk of bias assessment, follow-up characteristics (eg, follow-up duration and intensity), and clinical characteristics (eg, location, resection technique, histology). Multivariable metaregression could not be performed because of insufficient data. Only subgroups with $\geq$5 patients with T1 CRC and for which the exact number of events could be determined, were included in subgroup analyses.

Results

Study Characteristics

Of the 4444 articles identified by our literature search, 71 studies reporting unique patient cohorts were included in our meta-analysis (Figure 1).[13-83] These studies included a total of 5167 endoscopically treated patients with T1 CRC with data on the cumulative incidence of CRC recurrence. For 67 studies it was also possible to determine the number of patients with local or distant recurrence, or both. Thirty-five studies reported data on CRC-specific mortality for endoscopically treated patients with T1 CRC.

Detailed study information and risk of bias assessment are shown in Supplementary Table 1. The publication year of the included studies ranged between 1975 and 2020; most of the analyzed patients were reported in studies published in the last decade (Supplementary Figure 1). Twenty-nine studies were performed in Asia (2043 patients), 32 in Europe (2902 patients), 9 in North-America (208 patients), and 1 in South America (14 patients). Only 6 studies[26,35,39,45,61,81] had maximum scores for all 6 risk of bias items. Publication bias was not evident from the funnel plot (Supplementary Figure 2). It was often not possible to extract data on patient, treatment, tumor, or follow-up characteristics for the group of endoscopically treated patients with T1 CRC because most studies did not specifically aim to investigate endoscopically treated patients with T1 CRC.

Fifty-six studies reported data on the endoscopic resection techniques used: these included snare polypectomy (without submucosal lifting; 33 studies), endoscopic mucosal resection (25 studies), endoscopic submucosal dissection (17 studies), and endoscopic full-thickness resection (2 studies). In 59 studies, it was possible to determine the mean (33 studies; range, 3.8–132 months) or minimum follow-up duration (51 studies; range, 1–60 months). Twenty-seven studies reported complete data on the follow-up scheme (ie, the number of follow-up modalities used and the timing per modality). Based on these data, schemes of comparable intensity were categorized into 3 groups ("not strict," 7; "strict," 10; and "very strict," 10). None of the studies reported data on compliance to follow-up.

Pooled Estimates of All Included Studies

Overall, CRC recurrence was found in 209 out of 5167 patients. The pooled cumulative incidence of any CRC recurrence was 3.3% (95% CI, 2.6%–4.3%; $I^2 = 54.9\%$; Figure 2). Forest plots and pooled incidences of local recurrence only (1.6%; 95% CI, 1.1%–2.3%; $I^2 = 50.6\%$), any local recurrence (1.9%; 95% CI, 1.3%–2.7%; $I^2 = 65.6\%$), and any distant recurrence (1.6%; 95% CI, 1.1%–2.4%; $I^2 = 46.5\%$) are shown in Supplementary Figures 3–5. CRC-related mortality was observed in 42 out of 2519 patients (35 studies); the pooled incidence was 1.7% (95% CI, 1.2%–2.2%; $I^2 = 0\%$; Supplementary Figure 6). The rate of CRC-related death among patients with recurrence was 40.8% (42/103). Almost all CRC-related deaths could be attributed to disease progression (metastatic disease); only in 1 case (patient ID 12066 no. 8; Supplementary Table 2), the cause of death was an adverse event related to salvage surgery.

Metaregression showed that none of the study characteristics, items from the risk of bias assessment, or follow-up characteristics were able to explain the inter-study heterogeneity of the primary outcome (Supplementary Table 3). Notably, follow-up duration and follow-up intensity were not significantly associated with an increased or decreased incidence of any CRC recurrence (all $P > .5$). Comparable results were found for all secondary outcomes (data not shown).

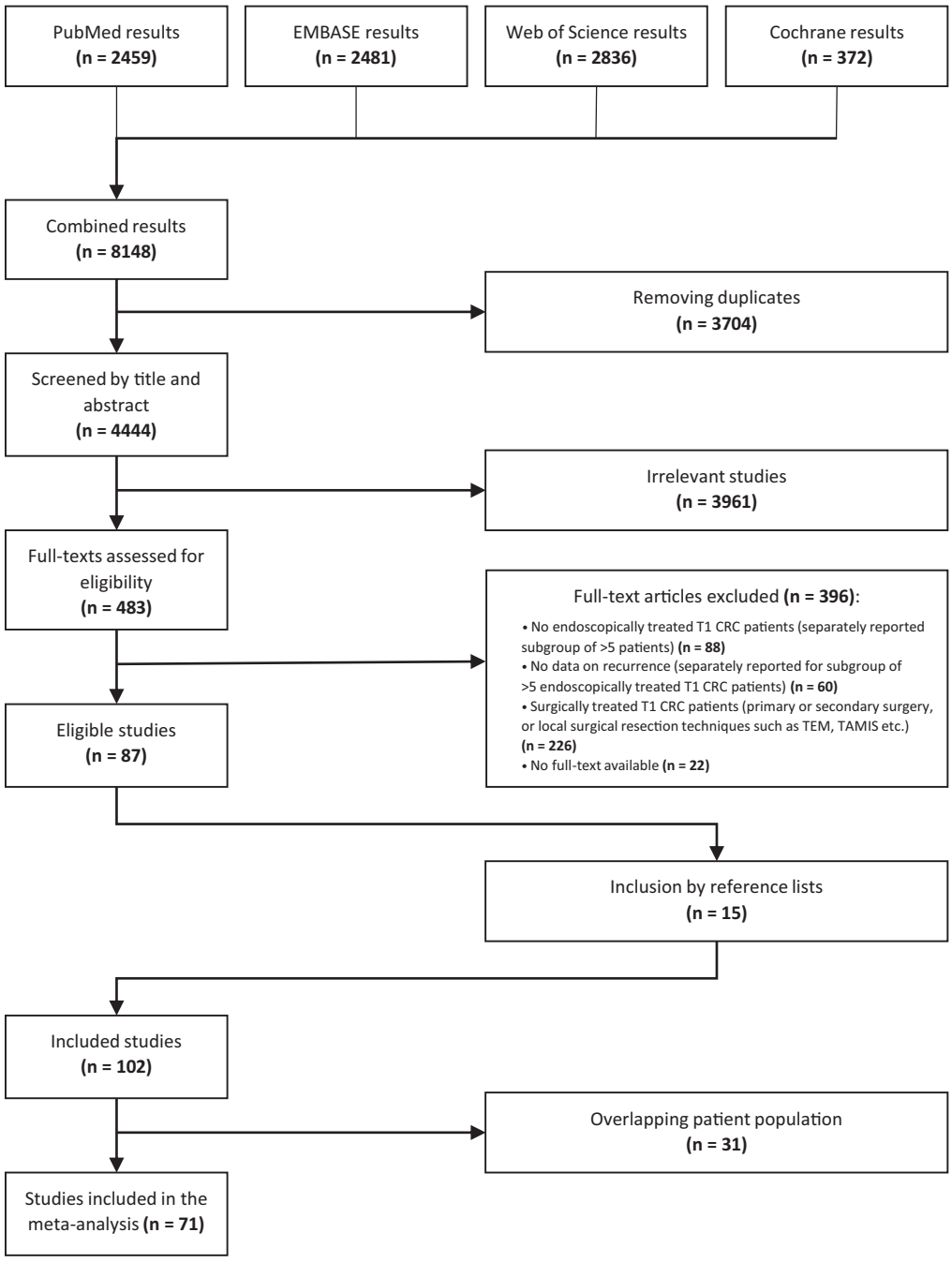


Figure 1. Flow diagram of the selection process. TAMIS, transanal minimally invasive surgery; TEM, transanal endoscopic microsurgery.

Time Pattern of Colorectal Cancer Recurrence

Patient-level data of all 209 cases of recurrence are shown in Supplementary Table 2. The type of recurrence was reported in 192 cases (87 local, 77 distant, 28 both). The follow-up modality by which the recurrence was detected was explicitly stated in only 9 cases (5 via imaging and 4 via colonoscopy). The management of recurrences was reported in 50 cases: 8 were treated with endoscopic resection alone, 33 with salvage surgery, 4 with chemotherapy or radiotherapy, 3 received palliative care, and 2 were not treated because of comorbidities or patient's refusal. Of the 42 CRC-related deaths, the time to death from endoscopic resection was only reported in 7 cases (range, 19–72 months).

The time to recurrence was reported in 114 cases. Most of recurrences (95.6%) occurred within 72 months of follow-up (Figure 3). This pattern was consistently observed for all secondary recurrence outcomes and when restricting the analyses to studies with a mean follow-up duration of $\geq$36 months, a minimum follow-up duration of $\geq$24 months, $\geq$2 follow-up modalities used, or a strict or very strict follow-up scheme (data not shown).

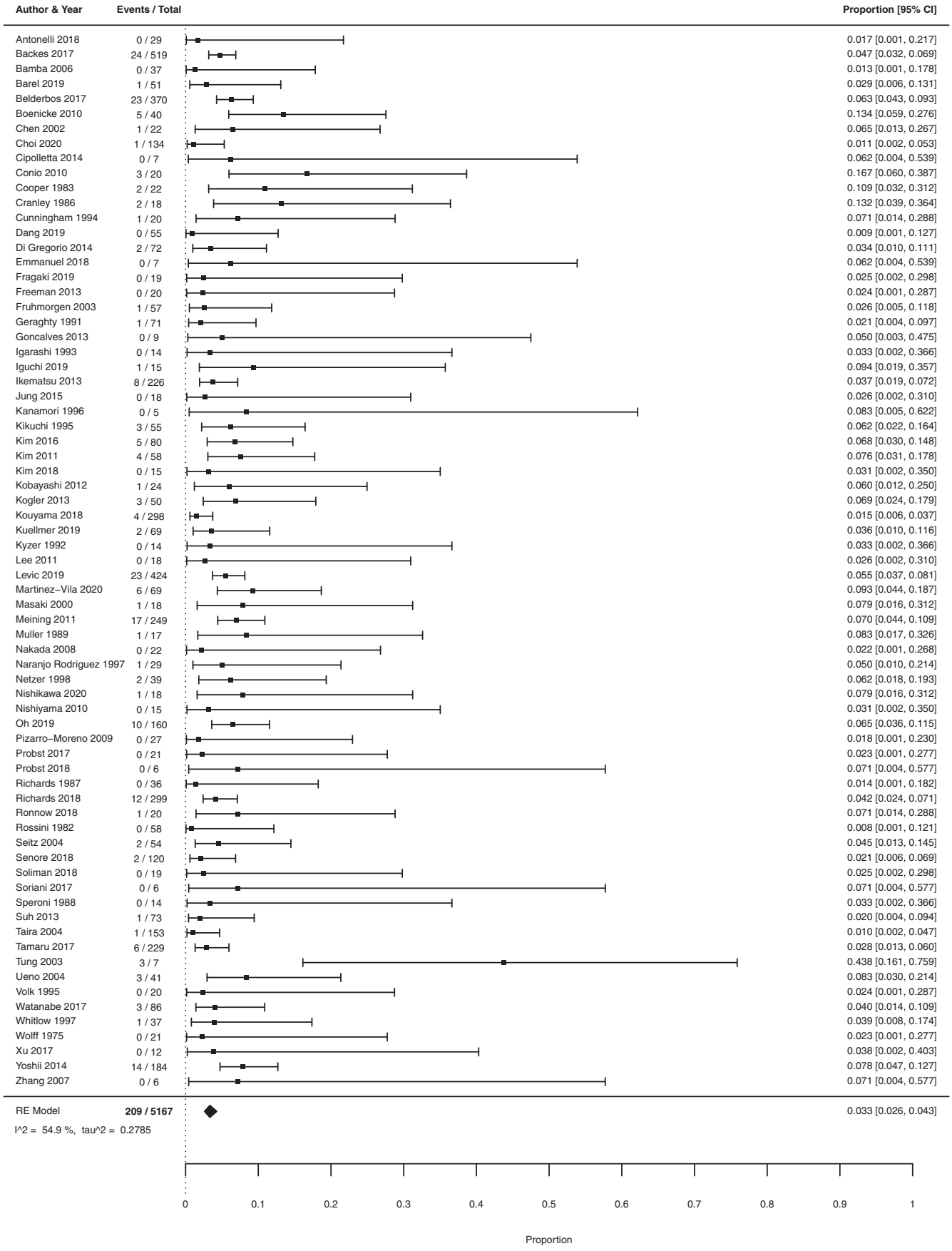


Figure 2. Forest plot with cumulative incidences of any CRC recurrence. To visualize incidence estimates of studies with 0 events, a continuity correction of +0.5 was applied. Values of the pooled estimates, I^2 and τ^2 are calculated using a model without continuity correction.

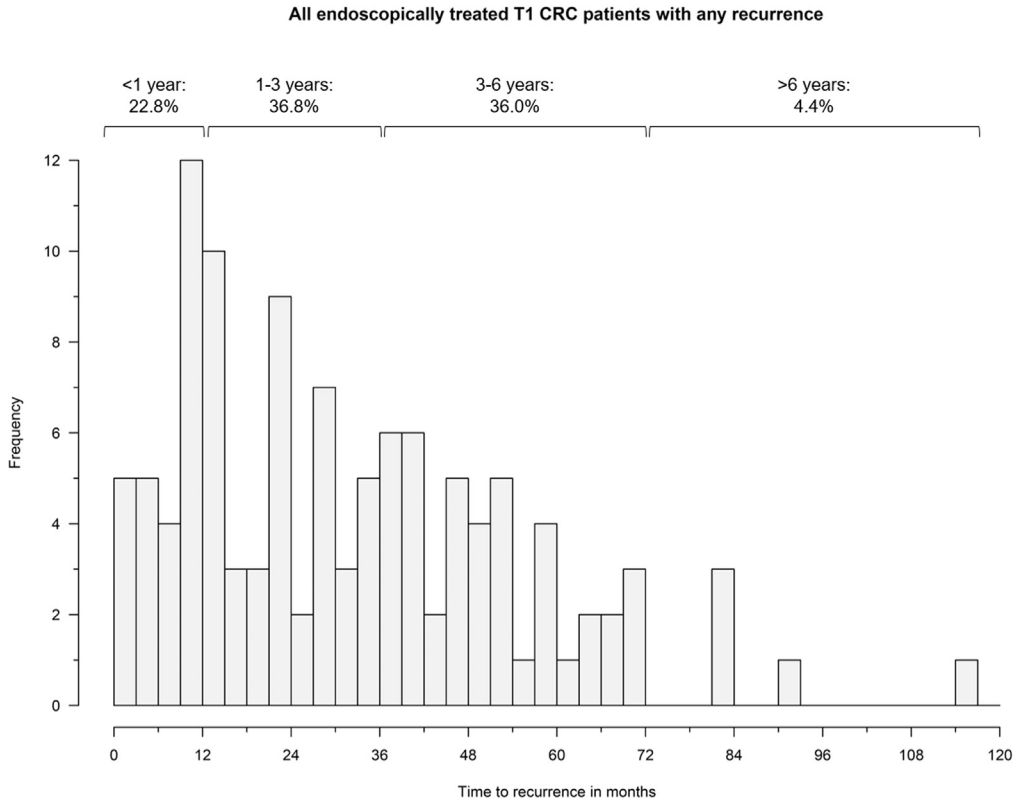


Figure 3. Time to any CRC recurrence after endoscopic resection of T1 CRC.

Subgroup Analyses

Subgroup analyses stratified on key clinical characteristics are shown in Table 1 (primary outcome), Supplementary Tables 4–7 (secondary outcomes), and Supplementary Analysis 1 (forest plots for each subgroup). For the primary outcome, there was considerable variation in the number of studies/patients per subgroup and risk differences between related subgroups. Therefore, we performed additional metaregression analyses to identify which factor influenced the risk of recurrence the most. Of all clinical characteristics, histologic risk status had the most significant association with the cumulative incidence of any CRC recurrence ($P = .012$; Supplementary Table 8). Based on this finding, we then concentrated on in-depth subgroup analyses stratified on tumor histology.

Twenty-eight studies reported subgroups of ≥5 high-risk patients with T1 CRC with sufficient data on recurrence incidence, and 36 studies did so for subgroups of ≥5 low-risk patients with T1 CRC. Definitions of high- and low-risk T1 CRCs were heterogeneous across these studies (Supplementary Figure 7): most used 4 or all 5 criteria of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 (ie, positive resection margins, deep submucosal invasion, grade 3 differentiation, lymphovascular invasion, and high-grade tumor budding[2]).

Figure 4 shows that the overall (ie, not stratified on JSCCR criteria used) pooled cumulative incidence of any CRC recurrence was 7.0% for high-risk T1 CRCs (82/1023 events; 95% CI, 4.9%–9.9%; $I^2 = 48.1\%$) and 0.7% (10/1499 events; 95% CI, 0.4%–1.2%; $I^2 = 0\%$) for low-risk T1 CRCs. Most recurrences from low-risk T1 CRCs were local only; of the 4 cases with distant recurrence, 2 (patient ID 12769 no. 1 and 15127/11514 no. 1) were initially classified as low-risk but turned out to have lymphovascular invasion on revision. Patient 12769 no. 1 was also the only CRC-related death in the low-risk group (955 patients analyzed; pooled estimate, 0.1%; 95% CI, 0.0%–0.7%; $I^2 = 0\%$). For high-risk patients, the pooled incidences of local recurrence only, any local, and any distant recurrence were 3.6% (95% CI, 2.4%–5.4%; $I^2 = 7.7\%$), 5.0% (95% CI, 3.2%–7.6%; $I^2 = 39.9\%$), and 3.5% (95% CI, 1.9%–6.1%; $I^2 = 60.0\%$), respectively. The pooled incidence of CRC-specific mortality was 4.5% (95% CI, 3.2%–6.3%; $I^2 = 0\%$), and the rate of CRC-related death among high-risk patients with recurrence was 46.5% (33/71). Of the 77 high- and low-risk cases with data on time to recurrence, most (98.7%) experienced recurrence within 72 months of follow-up.

Additional subgroup analyses stratified on individual high-risk features and number of JSCCR criteria used are detailed in the Supplementary Results.

Discussion

Growing numbers of patients with T1 CRC are being treated with local endoscopic resection only, as also

Table 1. Key Subgroup Analyses for the Outcome "Any CRC Recurrence"

	Pooled estimates of any CRC recurrence, % (95% CI; number of studies included in subgroup analyses)	
	Lower risk ——————————> Higher risk	
Patient characteristics		
Gender	Males: 1.6 (0.4–6.3; 6 studies)	Females: 4.4 (2.5–7.6; 5 studies)
Tumor characteristics		
Location	Colon: 0.8 (0.2–2.8; 11 studies)	Rectum: 5.7 (2.0–15.2; 11 studies)
Morphology	Ip: 1.0 (0.1–7.2; 9 studies)	Non-Ip: 6.1 (3.5–10.5; 13 studies)
Endoscopic resection		
En bloc vs piecemeal	En bloc: 1.0 (0.4–2.1; 11 studies)	Piecemeal: 4.8 (2.3–9.7; 5 studies)
Endoscopic resection technique used	ESD: 1.8 (0.7–4.1; 12 studies)	EMR: 4.5 (1.6–11.6; 8 studies)
	Snaring: 2.7 (1.9–3.9; 21 studies) eFTR: 2.7 (0.7–10.0; 2 studies)	
Histology		
Overall risk status (not stratified on number of JSCCR criteria used)	Low-risk T1 CRC: 0.7 (0.4–1.2; 36 studies)	High-risk T1 CRC: 7.0 (4.9–9.9; 28 studies)
Margin status	R0: 1.2 (0.4–3.5; 26 studies)	Not-R0: 11.2 (4.9–23.4; 10 studies)
Tumor budding grade	Bd1: 2.6 (1.1–6.0; 7 studies)	≥Bd2: 7.3 (2.8–17.8; 3 studies)
Lymphovascular invasion	Absent: 1.4 (0.7–3.0; 25 studies)	Present: 4.2 (0.6–24.6; 8 studies)
Differentiation grade	Grade 1-2: 2.3 (1.4–3.7; 28 studies)	Grade 3: 19.8 (7.9–41.3; 4 studies)
Invasion depth	Superficial: 1.2 (0.5–3.1; 20 studies)	Deep: 8.5 (5.7–12.5; 11 studies)

All category definitions are detailed in the Supplementary Methods.
CI, confidence interval; CRC, colorectal cancer; eFTR, endoscopic full-thickness resection; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; Ip, pedunculated; JSCCR, Japanese Society for Cancer of the Colon and Rectum; T1 CRC, early invasive colorectal cancer.

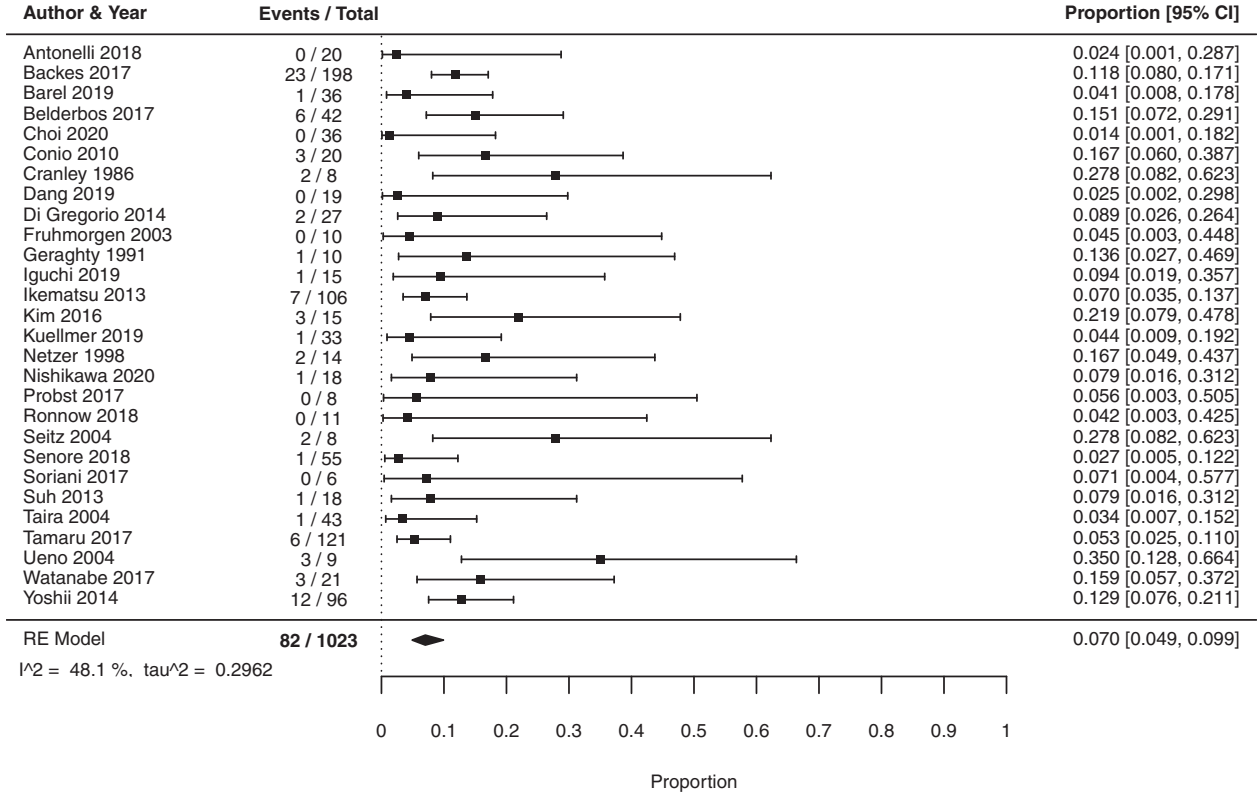
observed in our study (Supplementary Figure 1). There is therefore an increasing need for the optimization of surveillance strategies for these patients. In this meta-analysis, we aimed to provide quantitative measures of follow-up outcomes that give guidance for determining appropriate surveillance strategies after endoscopic treatment of T1 CRC. The main strength of our study is that we have comprehensively analyzed the largest pooled series of endoscopically treated patients with T1 CRC so far.

Of all 5167 endoscopically treated patients with T1 CRC analyzed, we found that 3.3% experience disease recurrence, with most of recurrences occurring within 72 months of follow-up. Univariable metaregression showed that the risk of recurrence was most significantly influenced by histologic risk status. These findings suggest that tumor histology is the most important factor to be taken into account in establishing surveillance recommendations for endoscopically treated patients with T1 CRC.

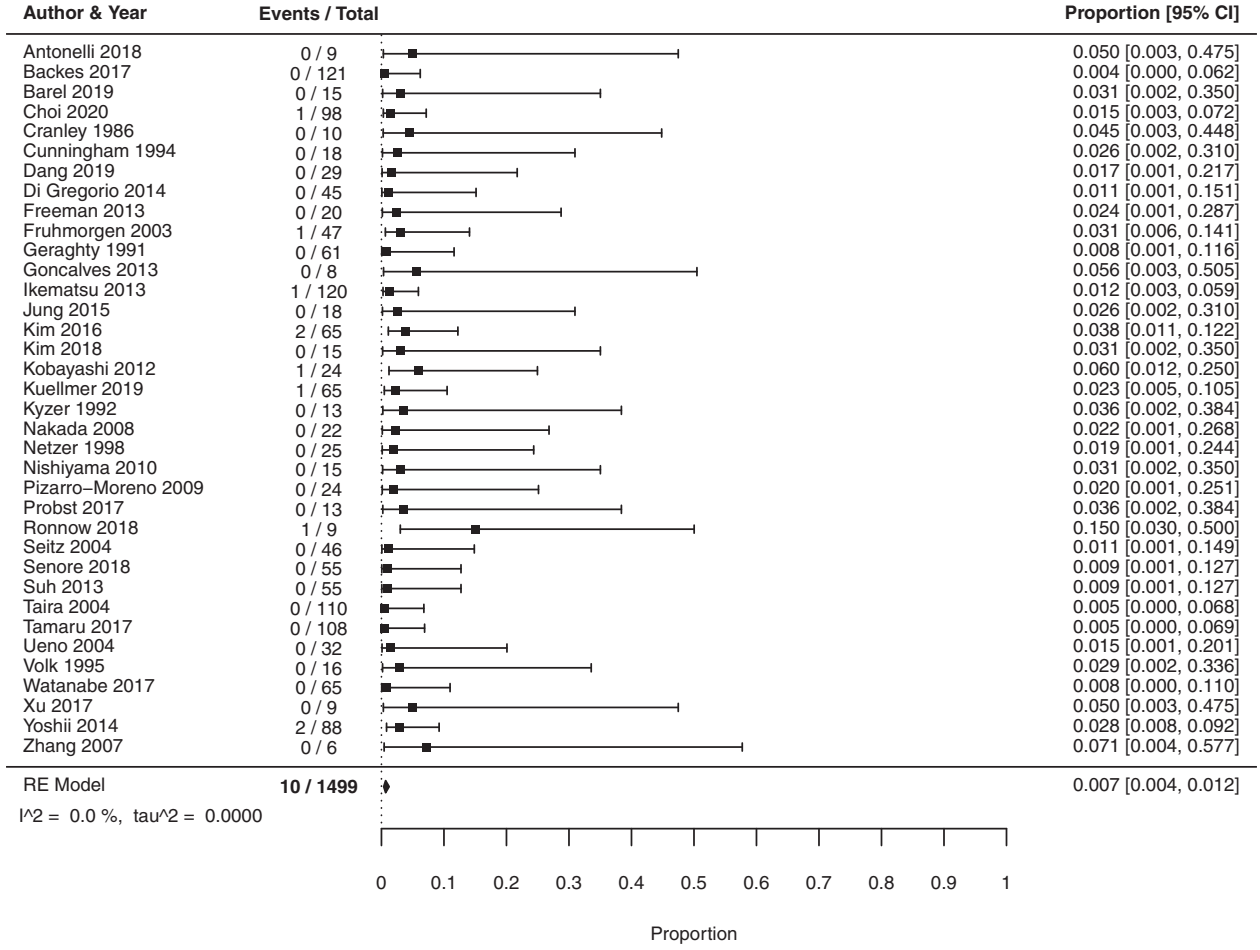
Subgroup analyses showed that CRC recurrence rarely occurs in endoscopically treated low-risk T1 CRCs (0.7%). Most of the recurrences found are local only; the risk of any distant recurrence (including lymph node metastasis) seems to be negligible. Interestingly, comparable recurrence rates of intraluminal CRC have been reported after endoscopic resection of colorectal polyps with high-grade dysplasia,[84] suggesting that existing surveillance recommendations for such lesions[85] may also be applied to low-risk T1 CRCs. However, an important prerequisite for adopting such a strategy with colonoscopic surveillance alone is that the pathologist has confirmed the low-risk status of the tumor with a high level of certainty. In 2 of the 4 patients with distant recurrence after low-risk T1 CRC, it was explicitly stated that the tumor had been misclassified on revision of the histology: both turned out to have lymphovascular invasion making them high-risk T1 CRC. These findings underline the importance of accurate histologic evaluation of the initial tumor.

For endoscopically treated high-risk T1 CRC, the recurrence rate was 7.0%, which is comparable with rates reported in surgically treated patients with T1 CRC.[86] We also observed that local and distant recurrences were found at comparable rates and that almost all recurrences occurred within 72 months after endoscopic resection. These findings suggest that monitoring of local and distant recurrences up to 6 years of follow-up should be considered for high-risk T1 CRCs. However, in contrast to low-risk patients, it seems to be much more difficult to formulate specific surveillance recommendations for high-risk patients with T1 CRC because of the heterogeneity of this subgroup. Patients with any single or different combinations of certain high-risk features could fall within the high-risk group, and the criteria for high-risk T1 CRC are not uniform throughout the world, as also observed in our study. This heterogeneity could be problematic because recent studies suggest that not all high-risk criteria are of equal importance in risk stratification. For example, T1 CRCs

A


Author & Year
Events / Total
Proportion [95% CI]
Antonelli 2018 0 / 20 0.024 [0.001, 0.287]
Backes 2017 23 / 198 0.118 [0.080, 0.171]
Barel 2019 1 / 36 0.041 [0.008, 0.178]
Belderbos 2017 6 / 42 0.151 [0.072, 0.291]
Choi 2020 0 / 36 0.014 [0.001, 0.182]
Conio 2010 3 / 20 0.167 [0.060, 0.387]
Cranley 1986 2 / 8 0.278 [0.082, 0.623]
Dang 2019 0 / 19 0.025 [0.002, 0.298]
Di Gregorio 2014 2 / 27 0.089 [0.026, 0.264]
Fruhmorgen 2003 0 / 10 0.045 [0.003, 0.448]
Geraghty 1991 1 / 10 0.136 [0.027, 0.469]
Iguchi 2019 1 / 15 0.094 [0.019, 0.357]
Ikematsu 2013 7 / 106 0.070 [0.035, 0.137]
Kim 2016 3 / 15 0.219 [0.079, 0.478]
Kuellmer 2019 1 / 33 0.044 [0.009, 0.192]
Netzer 1998 2 / 14 0.167 [0.049, 0.437]
Nishikawa 2020 1 / 18 0.079 [0.016, 0.312]
Probst 2017 0 / 8 0.056 [0.003, 0.505]
Ronnow 2018 0 / 11 0.042 [0.003, 0.425]
Seitz 2004 2 / 8 0.278 [0.082, 0.623]
Senore 2018 1 / 55 0.027 [0.005, 0.122]
Soriani 2017 0 / 6 0.071 [0.004, 0.577]
Suh 2013 1 / 18 0.079 [0.016, 0.312]
Taira 2004 1 / 43 0.034 [0.007, 0.152]
Tamaru 2017 6 / 121 0.053 [0.025, 0.110]
Ueno 2004 3 / 9 0.350 [0.128, 0.664]
Watanabe 2017 3 / 21 0.159 [0.057, 0.372]
Yoshii 2014 12 / 96 0.129 [0.076, 0.211]
RE Model 82 / 1023 0.070 [0.049, 0.099]
I^2 = 48.1 %, tau^2 = 0.2962
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
Proportion

B


Author & Year
Events / Total
Proportion [95% CI]
Antonelli 2018 0 / 9 0.050 [0.003, 0.475]
Backes 2017 0 / 121 0.004 [0.000, 0.062]
Barel 2019 0 / 15 0.031 [0.002, 0.350]
Choi 2020 1 / 98 0.015 [0.003, 0.072]
Cranley 1986 0 / 10 0.045 [0.003, 0.448]
Cunningham 1994 0 / 18 0.026 [0.002, 0.310]
Dang 2019 0 / 29 0.017 [0.001, 0.217]
Di Gregorio 2014 0 / 45 0.011 [0.001, 0.151]
Freeman 2013 0 / 20 0.024 [0.001, 0.287]
Fruhmorgen 2003 1 / 47 0.031 [0.006, 0.141]
Geraghty 1991 0 / 61 0.008 [0.001, 0.116]
Goncalves 2013 0 / 8 0.056 [0.003, 0.505]
Ikematsu 2013 1 / 120 0.012 [0.003, 0.059]
Jung 2015 0 / 18 0.026 [0.002, 0.310]
Kim 2016 2 / 65 0.038 [0.011, 0.122]
Kim 2018 0 / 15 0.031 [0.002, 0.350]
Kobayashi 2012 1 / 24 0.060 [0.012, 0.250]
Kuellmer 2019 1 / 65 0.023 [0.005, 0.105]
Kyzer 1992 0 / 13 0.036 [0.002, 0.384]
Nakada 2008 0 / 22 0.022 [0.001, 0.268]
Netzer 1998 0 / 25 0.019 [0.001, 0.244]
Nishiyama 2010 0 / 15 0.031 [0.002, 0.350]
Pizarro–Moreno 2009 0 / 24 0.020 [0.001, 0.251]
Probst 2017 0 / 13 0.036 [0.002, 0.384]
Ronnow 2018 1 / 9 0.150 [0.030, 0.500]
Seitz 2004 0 / 46 0.011 [0.001, 0.149]
Senore 2018 0 / 55 0.009 [0.001, 0.127]
Suh 2013 0 / 55 0.009 [0.001, 0.127]
Taira 2004 0 / 110 0.005 [0.000, 0.068]
Tamaru 2017 0 / 108 0.005 [0.000, 0.069]
Ueno 2004 0 / 32 0.015 [0.001, 0.201]
Volk 1995 0 / 16 0.029 [0.002, 0.336]
Watanabe 2017 0 / 65 0.008 [0.000, 0.110]
Xu 2017 0 / 9 0.050 [0.003, 0.475]
Yoshii 2014 2 / 88 0.028 [0.008, 0.092]
Zhang 2007 0 / 6 0.071 [0.004, 0.577]
RE Model 10 / 1499 0.007 [0.004, 0.012]
I^2 = 0.0 %, tau^2 = 0.0000
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
Proportion

with deep submucosal invasion only may not have an increased risk of distant disease,[87] and T1 CRCs with positive resection margins only may be mainly at risk for local recurrence.[88] Unfortunately, the data did not allow us to thoroughly investigate the contribution of each individual risk factor or different combinations of risk factors to the risk of recurrence. This makes it difficult to establish surveillance recommendations that are appropriate for all high-risk patients with T1 CRC. For now, since large prospective studies on endoscopically treated high-risk T1 CRCs are lacking, it might be useful to also consider other potentially relevant clinical characteristics, such as tumor location, morphology, and resection technique used. Although univariable meta-regression showed that these factors did not have the most significant association with the risk of recurrence, it should be kept in mind that both selection bias and a lack of statistical power could have influenced these results.

An important finding of our study, especially for high-risk patients with T1 CRC, is that around 40% of patients with recurrence eventually die from it. These data suggest that the odds of survival seem to be quite unfavorable when recurrence is found. However, it is questionable whether earlier detection of recurrence, such as by more intensive surveillance, increases CRC-specific survival or not. To illustrate, for more advanced stages (ie, >T1) of CRCs, overwhelming evidence from the last decade suggests that more intensive surveillance after surgical resection does not improve patient survival compared with less intensive strategies.[89] Accordingly, these studies have triggered a tendency toward reducing the number of unnecessary procedures and personalizing surveillance strategies for CRC patients.[90,91] It might be that the aforementioned findings from studies in advanced-stage CRCs can also be extrapolated to T1 CRCs, because the benefit of surveillance after CRC resection seems to be independent of CRC stage, with a comparable proportion of potentially curable recurrences found after the removal of tumors of different stages.[92]

Based on the findings of our meta-analysis, we propose the following surveillance recommendations and starting points for future research (Figure 5). First, surveillance strategies for endoscopically treated patients with T1 CRC should be stratified on histologic risk status. For patients with completely resected low-risk T1 CRC, we suggest performing a full colonoscopy after 1 year,[93] followed by surveillance according to guidelines on follow-up after polypectomy.[85] We strongly recommend against monitoring of distant recurrence for this group, provided that the low-risk status of the tumor has been confirmed with a high level of certainty. Patients with high-risk T1 CRC should be offered personalized surveillance through shared decision making, while also taking into account the physical status and life expectancy of the patient. Monitoring of local and distant recurrences can be considered, and if possible, surveillance should preferably be performed up to 6 years of follow-up. Intensive surveillance strategies should be considered cautiously, because robust evidence that intensive surveillance improves survival outcomes is currently lacking. In our opinion, intensive surveillance involves the follow-up schemes that have been classified as "very strict" in our study (eg, "colonoscopy at 3, 6, and 12 months, then every 6 months until year 2, then annually until year 5; carcinoembryonic antigen testing, abdominal ultrasound, and chest radiography every 6 months until year 5"[31]). To further refine surveillance recommendations for patients with endoscopically treated high-risk T1 CRC, future research should mainly focus on clarifying the risk of recurrence for tumors with single or

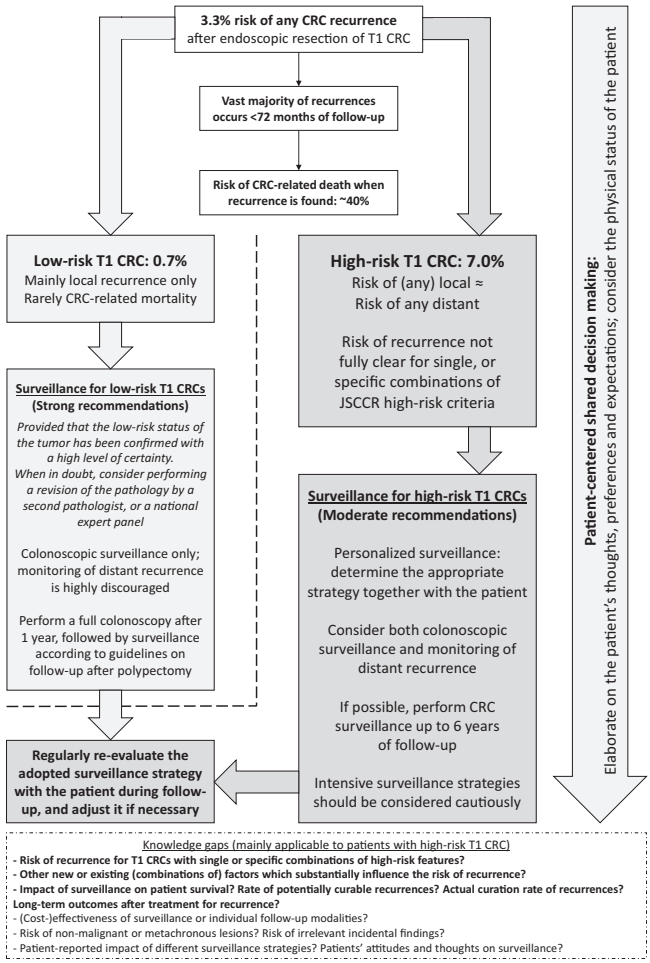


Figure 5. Overview of the main study findings, surveillance recommendations, and knowledge gaps.

Figure 4. Forest plots with cumulative incidences of any CRC recurrence for (*A*) high- and (*B*) low-risk T1 CRCs. To visualize incidence estimates of studies with 0 events, a continuity correction of +0.5 was applied. Values of the pooled estimates, I^2 and τ^2 are calculated without the continuity correction.

specific combinations of high-risk features, identifying new factors that substantially influence the risk of recurrence, and investigating how surveillance strategies of different intensities affect patient outcomes.

The most important limitation of our study relates to the quality of the source data, which determines the quality of a meta-analysis. Unfortunately, relevant data on patient, treatment, tumor, and follow-up characteristics could not always be retrieved for our patient group of interest, because most studies did not specifically aim to investigate follow-up outcomes of endoscopically treated patients with T1 CRC. As a result, several studies did not receive maximum scores on certain risk of bias items, and a considerable number of studies and patients could not be included in the different subgroup and metaregression analyses. A previous meta-analysis[94] tried to circumvent these issues by using stricter study selection criteria: they only included studies written in English with more than 12 months of follow-up, using at least 4 JSCCR criteria and with the possibility to separate the outcomes according to the histologic risk category. We chose not to adopt such a strategy because the use of too many selection criteria could result in the exclusion of important studies.[95] Instead, we chose to first select studies as sensitively as possible. This explains why many more studies and patients were included in our meta-analysis (71 vs 8 studies; 5167 vs 1221 patients). We then performed extensive predefined metaregression and subgroup analyses on this larger group. In this way, we tried to provide a comprehensive overview of this topic, while also accounting as adequately as possible for factors that could considerably influence the results.

Conclusions

Among 71 studies with a total of 5167 unique endoscopically treated patients with T1 CRC, we found that the pooled cumulative incidence of any CRC recurrence was 3.3%, with most occurring within 72 months of follow-up. The odds of survival seem to be quite unfavorable when recurrence is found, with 40.8% of patients eventually dying from it. Of all clinical characteristics analyzed, the risk of recurrence was most significantly influenced by histologic risk status (7.0% in high-risk vs 0.7% in low-risk T1 CRCs). Our meta-analysis provides quantitative measures of relevant follow-up outcomes, which can form the basis for evidence-based surveillance recommendations for endoscopically treated patients with T1 CRC.

Supplementary Material

Note: To access the supplementary material accompanying this article, please click here.

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Nik Dekkers, MD (Data curation: Equal; Investigation: Equal; Writing – review & editing: Equal);
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Conflicts of interest
These authors disclose the following: Jeanin E. van Hooft is a consultant of Boston Scientific, Cook Medical, and Medtronic; and received a research grant from Cook Medical. Jurjen J. Boonstra is a consultant of Boston Scientific. All other authors disclose no conflicts.

Supplementary Methods

Search Strategy

A systematic literature search was conducted in the electronic databases of PubMed, EMBASE, Web of Science, and Cochrane Library from inception until May 15, 2020. The search strategy included search terms for "T1 CRC," "endoscopic resection," and "recurrence." After removing duplicates, 2 authors (HD, JvdK) assessed the eligibility of studies independently from each other. Reference sections of included studies were also scanned for additional eligible studies. In case of disagreement without consensus after discussion, a third assessor (JJB) was decisive. The detailed search strategies per electronic database are shown below.

PubMed: n = 2459 hits on May 15, 2020

("Colorectal Neoplasms"[Mesh] OR (("Intestine, Large"[Mesh] OR large intestin*[tw] OR "Colon"[tw] OR "colonic"[tw] OR "colorectal"[tw] OR "Rectum"[tw] OR "rectal"[tw] OR "cecum"[tw] OR "coecum"[tw] OR "cecal"[tw] OR "coecal"[tw] OR "large bowel"[tw] OR lower gastro*[tw]) AND ("Neoplasms"[Mesh:NoExp] OR Neoplas*[tw] OR "Carcinoma"[Mesh:NoExp] OR carcinoma*[tw] OR "Adenocarcinoma"[Mesh:NoExp] OR Adenocarcinoma*[tw] OR "cancer"[tw] OR "cancers"[tw] OR "Polyps"[Mesh:NoExp] OR "Intestinal Polyps"[Mesh] OR "polyp"[tw] OR "polyps"[tw] OR "tumor"[tw] OR "tumors"[tw] OR "tumour"[tw] OR "tumours"[tw] OR malignan*[tw] OR dysplas*[tw]))) AND ("T1"[tw] OR "T 1"[tw] OR "cT1"[tw] OR "c T1"[tw] OR "pT1"[tw] OR "p T1"[tw] OR "early"[ti] OR "stage I"[tw] OR "stage 1"[tw] OR "stage1"[tw] OR submucosa*[tw] OR "Dukes A"[tw] OR "Stage A"[tw]) AND ("Colonoscopy"[Mesh] OR Colonoscop*[tw] OR sigmoidoscop*[tw] OR "Endoscopy"[Mesh:NoExp] OR Endoscop*[tw] OR rectoscop*[tw] OR "Proctoscopy"[Mesh] OR proctoscop*[tw] OR polypect*[tw] OR "Endoscopic Mucosal Resection"[Mesh] OR "ESD"[ti] OR "EMR"[ti] OR "eFTR"[ti] OR (("locally"[tw] OR "local"[tw]) AND (resect*[tw] OR dissect*[tw] OR excis*[tw]))) AND ("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh] OR Recurren*[tw] OR "Disease Progression"[Mesh:NoExp] OR progress*[tw] OR relaps*[tw] OR reoccur*[tw] OR reappear*[tw] OR return*[tw] OR "Neoplasm, Residual"[Mesh] OR residual*[tw] OR incomplete resect*[tw] OR "Reoperation"[Mesh] OR Reoperat*[tw] OR "Neoplasm Metastasis"[Mesh] OR metastas*[tw] OR "metastatic"[tw]) NOT ("Case Reports" [Publication Type] OR "case report"[ti] OR "case reports"[ti]) NOT ("Animals" [Mesh] NOT "Humans"[Mesh])

EMBASE: n = 2481 hits on May 15, 2020

(colon tumor/ or exp colon cancer/ or colon polyp/ or colorectal tumor/ OR rectum tumor/ OR exp rectum cancer/ OR rectum polyp/ OR ((exp large intestine/ OR large intestin*.ti,ab. OR "cecum".ti,ab. OR "coecum".ti,ab. OR "cecal".ti,ab. OR "coecal".ti,ab. OR "Colon".ti,ab. OR "colonic".ti,ab. OR "colorectal".ti,ab. OR "Rectum".ti,ab. OR "rectal".ti,ab. OR "large bowel".ti,ab. OR lower gastro*.ti,ab.) AND (neoplasm/ OR Neoplas*.ti,ab. OR carcinoma/ OR carcinoma*.ti,ab. OR adenocarcinoma/ OR Adenocarcinoma*.ti,ab. OR "cancer".ti,ab. OR "cancers".ti,ab. OR polyp/ OR exp intestine polyp/ OR "polyp".ti,ab. OR "polyps".ti,ab. OR "tumor".ti,ab. OR "tumors".ti,ab. OR "tumour".ti,ab. OR "tumours".ti,ab. OR malignan*.ti,ab. OR malignant neoplasm/ OR dysplasia/ or gastrointestinal dysplasia/ OR dysplas*.ti,ab.))) AND ("T1".ti,ab. OR "T 1".ti,ab. OR "cT1".ti,ab. OR "c T1".ti,ab. OR "pT1".ti,ab. OR "p T1".ti,ab. OR "early".ti. OR "stage I".ti,ab. OR "stage 1".ti,ab. OR "stage1".ti,ab. OR submucosa/ OR submucosa*.ti,ab. OR "Dukes A".ti,ab. OR "Stage A".ti,ab.) AND (intestine endoscopy/ or exp colonoscopy/ or rectoscopy/ or sigmoidoscopy/ OR Colonoscop*.ti,ab. OR sigmoidoscop*.ti,ab. OR endoscopy/ OR Endoscop*.ti,ab. OR rectoscop*.ti,ab. OR proctoscop*.ti,ab. OR polypectomy/ OR endoscopic polypectomy/ OR polypect*.ti,ab. OR endoscopic mucosal resection/ OR endoscopic submucosal dissection/ OR exp transanal endoscopic surgery/ OR "ESD".ti. OR "EMR".ti. OR "eFTR".ti. OR local excision/ OR ((local therapy/ OR "locally".ti,ab. OR "local".ti,ab.) AND (resect*.ti,ab. OR dissection/ OR dissect*.ti,ab. OR excision/ OR excis*.ti,ab.))) AND (recurrent disease/ OR tumor recurrence/ OR Recurren*.ti,ab. OR progress*.ti,ab. OR relapse/ OR relaps*.ti,ab. OR reoccur*.ti,ab. OR reappear*.ti,ab. OR return*.ti,ab. OR minimal residual disease/ OR residual*.ti,ab. OR incomplete resect*.ti,ab. OR reoperation/ OR Reoperat*.ti,ab. OR exp metastasis/ OR metastas*.ti,ab. OR "metastatic".ti,ab.) NOT (case report/ OR "case report".ti. OR "case reports".ti.) NOT (animal/ NOT human/) NOT "conference abstract".pt.

Web of Science: n = 2836 hits on May 15, 2020

TS=((large intestin* OR "Colon" OR "colonic" OR "colorectal" OR "Rectum" OR "rectal" OR "cecum" OR "coecum" OR "cecal" OR "coecal" OR "large bowel" OR lower gastro*) AND (Neoplas* OR carcinoma* OR Adenocarcinoma* OR "cancer" OR "cancers" OR "polyp" OR "polyps" OR "tumor" OR "tumors" OR "tumour" OR "tumours" OR malignan* OR dysplas*)) AND (TS=("T1" OR "T 1" OR "cT1" OR "c T1" OR "pT1" OR "p T1" OR "stage I" OR "stage 1" OR "stage1" OR submucosa* OR "Dukes A" OR "Stage A") OR TI="early") AND TS=(Colonoscop* OR sigmoidoscop* OR Endoscop* OR rectoscop* OR proctoscop* OR polypect* OR "ESD" OR "EMR" OR "eFTR" OR (("locally" OR "local") AND (resect* OR dissect* OR excis*))) AND TS=(Recurren* OR progress* OR relaps* OR reoccur* OR reappear* OR return* OR residual* OR incomplete resect* OR Reoperat* OR metastas* OR "metastatic") NOT TI=("mouse" OR "mice" OR "murine" OR "rat" OR "rats" OR "animal" OR "animals" OR "rodent" OR "rodents")

Refined by: [excluding] DOCUMENT TYPES: (MEETING ABSTRACT)

Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, ESCI.

COCHRANE: n = 372 hits on May 15, 2020

((large intestin* OR "Colon" OR "colonic" OR "colorectal" OR "Rectum" OR "rectal" OR "cecum" OR "coecum" OR "cecal" OR "coecal" OR "large bowel" OR lower gastro*) AND (Neoplas* OR carcinoma* OR Adenocarcinoma* OR "cancer" OR "cancers" OR "polyp" OR "polyps" OR "tumor" OR "tumors" OR "tumour" OR "tumours" OR malignan* OR dysplas*)) AND ("T1" OR "T 1" OR "cT1" OR "c T1" OR "pT1" OR "p T1" OR "stage I" OR "stage 1" OR "stage1" OR submucosa* OR "Dukes A" OR "Stage A" OR "early") AND (Colonoscop* OR sigmoidoscop* OR Endoscop* OR rectoscop* OR proctoscop* OR polypect* OR "ESD" OR "EMR" OR "eFTR" OR (("locally" OR "local") AND (resect* OR dissect* OR excis*))) AND (Recurren* OR progress* OR relaps* OR reoccur* OR reappear* OR return* OR residual* OR incomplete resect* OR Reoperat* OR metastas* OR "metastatic") NOT ("mouse" OR "mice" OR "murine" OR "rat" OR "rats" OR "animal" OR "animals" OR "rodent" OR "rodents")

Data Extraction

The following parameters were extracted: study characteristics (publication year, single-center or multicenter study, study design, inclusion period, geographical location), patient characteristics (number of endoscopically treated patients with T1 CRC, mean age, sex, comorbidities), treatment characteristics (en bloc or piecemeal resection; endoscopic resection technique: snare polypectomy, endoscopic mucosal resection, [hybrid] endoscopic submucosal dissection, or endoscopic full-thickness resection), tumor characteristics (location, mean tumor size, morphology), histology (high- or low-risk T1 CRC, high-risk definitions, use of immunohistochemical stainings for lymphovascular invasion, status of the resection margins, number of patients with deep submucosal invasion, grade 3 differentiation, lymphovascular invasion, and high-grade tumor budding), follow-up characteristics (mean and minimum follow-up duration, follow-up modalities used, timing per follow-up modality), and follow-up outcomes (number of local or distant recurrences, CRC-specific mortality). For cases of recurrence, we also tried to extract individual patient-level data on all aforementioned parameters and additional recurrence information (method of detection, time to recurrence, TNM stage, treatment for recurrence, and cause of death).

Data were primarily extracted from the studies included in the meta-analysis (n = 71; see flowchart in Figure 1). In a few cases, additional details on follow-up characteristics or individual recurrence cases were extracted from studies with cohort overlap, provided that they reported the same cohort (ie, same centers, same time period) and the same recurrence cases (ie, same age, gender, tumor location, recurrence type, time to recurrence). In case of any inconsistency between the included study and its overlapping counterparts, data from the included study were decisive. When only medians and (interquartile) ranges were reported for continuous variables, we estimated the mean using the approximation method described by Luo et al,[1] which provides more accurate estimations than conventional methods.

Definitions and Classifications

Studies explicitly or implicitly stating retrospective data collection (eg, reporting "we reviewed the patient records" in the methods section, "prospective studies will be needed" in the paragraph on study limitations) were classified as retrospective. Studies reporting "a retrospective analysis of prospectively collected data" were classified as prospective. When all authors were from 1 center and it was not reported how many centers the T1 CRC patients originated from, the study was classified as single-center.

Patients with T1 CRC who did not undergo follow-up were not included in the total number of analyzed patients with T1 CRC. "Endoscopic polypectomies" without explicit mention of submucosal injection for lifting were considered as conventional snare polypectomies, provided that they were reported in studies published before the introduction of endoscopic submucosal dissection or endoscopic full-thickness resection (ie, before 2001[2,3]). For 3 studies,[4-6] the total number of analyzed patients with T1 CRC also consisted of a small proportion (9/226, 5/41, and 6/55) of T1 CRCs resected by transanal endoscopic microsurgery (TEM). Although local surgical resection techniques, such as transanal endoscopic microsurgery, were 1 of the exclusion criteria, we chose not to exclude these few patients, because doing so would lead to considerable loss of other data (eg, exact numbers of high- and low-risk patients could not be exactly determined anymore after excluding the transanal endoscopic microsurgery patients).

High-risk definitions per study were classified based on which and how many high-risk criteria of the JSCCR guidelines 2019 (ie, positive resection margins, deep submucosal invasion, grade 3 differentiation, lymphovascular invasion, and high-grade tumor budding[7]) were used. Grade 3 differentiation was defined as poorly differentiated adenocarcinoma, mucinous, or signet ring cell carcinoma.[8] High-grade tumor budding was defined as $\geq$Bd2.[9] Deep submucosal invasion was defined as Haggitt level 4[10] for pedunculated T1 CRC, and an invasion depth $\geq$1000 μm or Kikuchi level $\geq$Sm2[11] for nonpedunculated T1 CRCs. Haggitt levels reported for nonpedunculated lesions (eg, "Sessile polyps are classified as Level 4 if carcinoma extends beyond the muscularis mucosa"[12]) were not taken into account. Lymphovascular invasion was defined as the presence of CRC cells within an endothelial or internal elastic lamina-confined lumen.[8] Because exact numbers of T1 CRCs with lymphatic, vascular, or venous invasion were mostly

not separately reported, lymphovascular invasion was categorized into "present" and "absent." Resection margins were classified as R0 (no dysplastic cells at the resection margins), R1 (dysplastic cells close to or at the resection margins), or Rx (margins could not be reliably assessed). Because definitions for positive (R1) resection margins were not uniform between studies and the exact numbers of R1 or Rx margins were not always separately reported, we categorized margin status into "R0" and "not-R0."

Follow-up intensity was classified by grouping follow-up schemes that used comparable follow-up modalities and intervals per modality. Schemes with a mean of $\leq$2 follow-up modalities per year (eg, "annual colonoscopy for 5 years, then every 3 years thereafter"[13]) were classified as "not strict," schemes with a mean of 2–4 modalities per year (eg, "colonoscopy at 3–6 months and then annually; annual abdominothoracic CT + CEA"[14]) as "strict," and schemes with a mean of $\geq$4 modalities per year (eg, "colonoscopy at 3, 6, and 12 months, then every 6 months until year 2, then annually until year 5; CEA + abdominal ultrasound + chest radiography every 6 months until year 5"[15]) as "very strict." When the follow-up duration was not separately reported for the analyzed patients with T1 CRC, we recorded the follow-up duration of all patients undergoing endoscopic treatment, as an alternative indication for follow-up duration to be used in sensitivity analyses.

Risk of Bias Assessment

The Newcastle-Ottawa Scale for cohort studies[16] was modified as follows. First, the items "Comparability of cohorts" and "Selection of the non-exposed cohort" were excluded because no comparative outcome measures were meta-analyzed. The item "Ascertainment of exposure" was also not evaluated, because we only included patients with histologically confirmed T1 CRC. The item "Was follow-up long enough for outcomes to occur" was changed into "Information on follow-up duration of analyzed patients with T1 CRC reported" (0, no; 1, yes), and reported follow-up durations were included in metaregression analyses as continuous variables. Because the incidence, time pattern, and type of recurrence largely depend on the intensity of follow-up (ie, number of follow-up modalities used, frequency per modality), we also added an item called "Information on follow-up intensity reported" (0, no; 1, yes; reported follow-up intensities were included as categorical variables in metaregression analyses). The influence of each individual risk of bias item on the study outcomes was evaluated in metaregression analyses. We chose not to add scores for all risk of bias items together and include these summary scores in the analyses because it has been shown that the use of such scores to identify "low- or high-quality" studies can be problematic.[17]

Supplementary Results

Subgroup Analyses Stratified on Histologic Characteristics

Because of the considerable heterogeneity in definitions of high- and low-risk T1 CRCs, we tried to investigate the influence of certain (combinations of) high-risk features on the study outcomes by performing additional subgroup analyses (Supplementary Analysis 1). First, analyses stratified on individual high-risk features showed that pooled cumulative incidences of any CRC recurrence were relatively higher when a certain high-risk feature was present. However, for patients who did not have that high-risk feature, pooled incidences were still around 1%–3%. We then further stratified the high- and low-risk subgroup analyses on the number of JSCCR criteria used. For low-risk patients, pooled cumulative incidences decreased with the increasing number of JSCCR criteria used, with the lowest incidence in subgroup analyses restricted to studies using all 5 JSCCR criteria (0.3%; 95% CI, 0.0%–0.7%; $I^2 = 65.8\%$). For high-risk patients, pooled incidences varied between the subgroups analyzed. In high-risk subgroup analyses restricted to studies using $\leq$3 JSCCR criteria, pooled incidences of any CRC recurrence were >10% (<50 patients per subgroup analysis). In high-risk subgroup analyses restricted to studies using >3 JSCCR criteria, pooled incidences of any CRC recurrence were ~6% (~500 patients per subgroup analysis).

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