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Kessels, K.; Backes, Y.; Elias, S.G.; Blink, A. van den; Offerhaus, G.J.A.; Bergeijk, J.D. van; ... ; Dutch T1 Colorectal Canc Working

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Koen Kessels,[*,‡,a] Yara Backes,[*,a] Sjoerd G. Elias,[§] Aneya van den Blink,[*,‖] G. Johan A. Offerhaus,[¶] Jeroen D. van Bergeijk,[#] John N. Groen,[**] Tom C. J. Seerden,[‡‡] Matthijs P. Schwartz,[§§] Wouter H. de Vos tot Nederveen Cappel,[‖‖] Bernhard W. M. Spanier,[¶¶] Joost M. J. Geesing,[##] Marjon Kerkhof,[***] Peter D. Siersema,[*,‡‡‡] Paul Didden,[*] Jurjen J. Boonstra,[§§§] Lorenza Alvarez Herrero,[‡] Frank H. J. Wolfhagen,[‖‖‖] Frank ter Borg,[¶¶¶] Anja U. van Lent,[###] Jochim S. Terhaar sive Droste,[****] Wouter L. Hazen,[‡‡‡‡] Ruud W. M. Schrauwen,[§§§§] Frank P. Vleggaar,[*] Miangela M. Laclé,[¶] Leon M. G. Moons,[*] on behalf of the Dutch T1 Colorectal Cancer Working Group

*Department of Gastroenterology and Hepatology, §Julius Center for Health Sciences and Primary Care, ¶Department of Pathology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; ‡Department of Gastroenterology and Hepatology, Sint Antonius Hospital, Nieuwegein, The Netherlands; ‖Department of Critical Care Medicine, Vrije Universiteit University Medical Center Amsterdam, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; #Department of Gastroenterology and Hepatology, Gelderse Vallei Hospital, Ede, The Netherlands; **Department of Gastroenterology and Hepatology, Sint Jansdal Hospital, Harderwijk, The Netherlands; ‡‡Department of Gastroenterology and Hepatology, Amphia Hospital, Breda, The Netherlands; §§Department of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, The Netherlands; ‖‖Department of Gastroenterology and Hepatology, Isala Hospital, Zwolle, The Netherlands; ¶¶Department of Gastroenterology and Hepatology, Rijnstate Hospital, Arnhem, The Netherlands; ##Department of Gastroenterology and Hepatology, Diakonessenhuis Hospital, Utrecht, The Netherlands; ***Department of Gastroenterology and Hepatology, Groene Hart Hospital, Gouda, The Netherlands; ‡‡‡Department of Gastroenterology and Hepatology, Radboud University Medical Center, Radboud University, Nijmegen, The Netherlands; §§§Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden University, Leiden, The Netherlands; ‖‖‖Department of Gastroenterology and Hepatology, Albert Schweitzer Hospital, Dordrecht, The Netherlands; ¶¶¶Department of Gastroenterology and Hepatology, Deventer Hospital, Deventer, The Netherlands; ###Department of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, The Netherlands; ****Department of Gastroenterology and Hepatology, Jeroen Bosch Hospital, Den Bosch, The Netherlands; ‡‡‡‡Department of Gastroenterology and Hepatology, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands; §§§§Department of Gastroenterology and Hepatology, Bernhoven Hospital, Uden, The Netherlands

BACKGROUND & AIMS: **Risk stratification for adverse events, such as metastasis to lymph nodes, is based only on histologic features of tumors. We aimed to compare adverse outcomes of pedunculated vs nonpedunculated T1 colorectal cancers (CRC).**

METHODS: **We performed a retrospective study of 1656 patients diagnosed with T1CRC from 2000 through 2014 at 14 hospitals in The Netherlands. The median follow-up time of patients was 42.5 months (interquartile range, 18.5–77.5 mo). We evaluated the association between tumor morphology and the primary composite end point, adverse outcome, adjusted for clinical variables, histologic variables, resection margins, and treatment approach. Adverse outcome was defined as metastasis to lymph nodes, distant metastases, local recurrence, or residual tissue. Secondary end points were tumor metastasis, recurrence, and incomplete resection.**

RESULTS: **Adverse outcome occurred in 67 of 723 patients (9.3%) with pedunculated T1CRCs vs 155 of 933 patients (16.6%) with nonpedunculated T1CRCs. Pedunculated morphology was independently associated with decreased risk of adverse outcome (adjusted odds ratio [OR], 0.59; 95% CI, 0.42–0.83; $P = .003$). Metastasis, incomplete resection, and recurrence were observed in 5.8%, 4.6%, and 3.9% of pedunculated T1CRCs vs 10.6%, 8.0%, and 6.6% of nonpedunculated T1CRCs, respectively. Pedunculated morphology was independently associated with a reduced**

[a]Authors share co-first authorship.

Abbreviations used in this paper: CRC, colorectal cancer; HR, hazard ratio; IQR, interquartile range; LN, lymph node; LNM, lymph node metastasis; OR, odds ratio; T1CRC, T1 colorectal cancer.

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risk of metastasis (adjusted OR, 0.62; 95% CI, 0.41–0.94; $P = .03$), incomplete resection (adjusted OR, 0.57; 95% CI, 0.36–0.91; $P = .02$), and recurrence (adjusted hazard ratio, 0.52; 95% CI, 0.32–0.85; $P = .009$). Metastasis, incomplete resection, and recurrence did not differ significantly between low-risk pedunculated vs nonpedunculated T1CRCs (0.8% vs 2.9%, $P = .38$; 1.5% vs 0%, $P = .99$; 1.5% vs 0%; $P = .99$). However, incomplete resection and recurrence were significantly lower for high-risk pedunculated vs nonpedunculated T1CRCs (6.5% vs 12.5%; $P = .007$; 4.4% vs 8.6%; $P = .03$).

CONCLUSIONS: **In a retrospective study of patients with T1CRC, we found pedunculated morphology to be associated independently with a decreased risk of adverse outcome in a T1CRC population at high risk of adverse outcome. Incorporating morphologic features of tumors in risk assessment could help predict outcomes of patients with T1CRC and help identify the best candidates for surgery.**

Keywords: Colonoscopy; Endoscopic Mucosal Resection; Colon Cancer; Prognostic Factor.

See related editorial on page 1035.

The frequency of early colorectal cancer (CRC) has been increasing since the introduction of national screening programs. In 2015, 48% of detected CRCs in the Dutch screening program were stage I CRCs, in line with other Western countries.[1–3] T1 colorectal cancer (T1CRC) without metastasis is the earliest form of stage I CRC and is defined as tumor growing through the muscularis mucosae into the submucosa without invading the muscularis propria.[4] Lymph node metastasis (LNM) risk of T1CRC is 8% to 14%.[5–12] Therefore, most patients with T1CRC can be cured with an endoscopic resection. However, current risk models have insufficient ability to predict which patients with an endoscopically resected T1CRC should have additional surgery.[13]

Complete endoscopic resection of pedunculated T1CRCs is more feasible compared with nonpedunculated T1CRCs. In addition, pedunculated T1CRCs may have a lower metastasis risk compared with nonpedunculated T1CRCs.[9,14–16] In the present study, we evaluated the association between morphology (pedunculated vs nonpedunculated) and adverse outcome.

Methods

Study Design

We performed a multicenter retrospective cohort study. Patients with T1CRC, defined as tumor growing through the muscularis mucosae into, but not beyond, the submucosa,[17] diagnosed between January 1, 2000, and December 31, 2014, in 14 Dutch hospitals (2 academic and 12 nonacademic), were selected from The Netherlands Cancer Registry. Electronic medical records were reviewed. Patients with synchronous CRC, non–CRC-related death within 1 year, hereditary predisposition for CRC, inflammatory bowel disease, carcinoid, missing pathology or endoscopy reports, and who underwent neoadjuvant radiotherapy were excluded. In addition, patients without reported morphology in the endoscopy report were excluded.

Determinant

The determinant of interest was morphology, stratified as pedunculated vs nonpedunculated. Because closing the snare followed by dehydration and formalin fixation procedures can alter morphology, morphology was based on the endoscopist's judgement. T1CRC was considered pedunculated in case of presence of a stalk or Paris Classification 0–Ip was reported. Nonpedunculated T1CRC included flat or sessile tumors.[18–20]

End Points

The primary composite end point was adverse outcome, defined as any of the following: LNM, distant metastasis, local recurrence, or residual tissue. We used a composite end point rather than only LNM because the surgical referral rate is known to be higher for patients with nonpedunculated T1CRCs. Restricting our analysis to patients treated with surgery (ie, patients with known N status) therefore would introduce selection bias. The end point could be reached by both endoscopically and surgically treated patients, allowing an equal comparison of pedunculated and nonpedunculated T1CRCs. LNM was defined as tumor-positive lymph nodes (LNs) in the surgical specimen. Distant metastasis was defined as metastasis to extracolonic organs confirmed with imaging or histology. Local recurrence was defined as carcinoma in biopsy tissue from the anastomosis after surgery or from the polypectomy scar after endoscopic resection. Residual tissue was defined as carcinoma in the surgical specimen after endoscopic resection, irrespective of whether endoscopic resection was macroscopically complete or not.

Secondary end points included metastasis, recurrence, and incomplete resection separately. We defined metastasis as LNM for patients who underwent surgery or distant metastasis regardless of treatment. Recurrence was defined

as local recurrence or distant metastasis regardless of treatment. Incomplete resection was defined as residual tissue in the colectomy specimen after secondary surgery or local recurrence regardless of treatment.

Confounders

Clinical confounders included age, sex, tumor localization (right colon vs left colon vs rectum), and tumor size.[9,13,21–24] The right colon was defined as the colon proximal to and including the splenic flexure and the left colon as the colon distal to the splenic flexure excluding the rectum. Histologic confounders included lymphovascular invasion (absent vs present), differentiation grade (good or moderate vs poor), and resection margins (negative [R0] vs not assessable [Rx] vs positive [R1]). R0 resection was defined as a cancer-free resection margin irrespective of distance in millimeters. In patients treated with primary endoscopy and secondary surgery, endoscopic resection margins were used and in patients treated with primary surgery, surgical resection margins were used. Although invasion depth is an acknowledged risk factor for stratification of T1CRCs into low- or high-risk groups, invasion depth was not included as a confounder because the classification for submucosal invasion depth is inherently different between pedunculated and nonpedunculated T1CRCs.[23,25,26] Treatment approach and LN yield were considered confounders because surgery decreases recurrence risk in high-risk T1CRC and a high LN yield has been associated with a decreased risk for recurrence.[21,22] Patients were categorized into 3 subgroups: endoscopic resection, surgical resection with fewer than 10 LNs retrieved, and surgical resection with 10 or more LNs retrieved. Transanal endoscopic microsurgery was considered an endoscopic treatment because no lymphadenectomy was performed.

Statistical Analysis

Baseline characteristics were compared between pedunculated and nonpedunculated T1CRCs using standard descriptive statistics. In addition, the risk for adverse outcome, metastasis, recurrence, and incomplete resection between low-risk pedunculated and nonpedunculated T1CRC, and high-risk pedunculated and nonpedunculated T1CRC, was compared using descriptive statistics. T1CRCs were classified as high risk if 1 or more of the following criteria were present: (1) poor differentiation, (2) deep submucosal invasion (>1000 μm or sm2–3 for nonpedunculated; Haggitt 4 for pedunculated), (3) lymphovascular invasion, or (4) Rx/R1 resection margins, in line with current guidelines.[23,25,26] If all of these criteria were absent, T1CRCs were classified as low risk. If 1 of the criteria was unknown and no other high-risk factors were present, risk status was classified as unknown.

What You Need To Know

Background

Current histologic prediction models have insufficient discriminative ability to identify patients who benefit from surgical treatment after endoscopic resection. Although it has been suggested that pedunculated T1 colorectal cancers (T1CRCs) have a lower risk for metastasis and incomplete resection as compared with nonpedunculated T1CRCs, a direct comparison has not yet been performed and current risk stratification for surgery is based on histology only.

Findings

Pedunculated morphology was associated independently with a decreased risk for an adverse outcome (ie, lower risk for lymph node metastasis, distant metastasis, local recurrence, or residual tissue). The absolute risk for adverse outcomes in patients with pedunculated T1CRC was nearly half that of patients with nonpedunculated T1CRCs (9.3% vs 16.6%, respectively). In patients with low-risk T1CRC, defined as the absence of the following criteria: poor differentiation, deep submucosal invasion, lymphovascular invasion, and Rx/R1 resection margins, the rates of metastasis, incomplete resection, and recurrence rates did not differ significantly between pedunculated vs nonpedunculated morphology. However, incomplete resection and recurrence rates were significantly lower for high-risk pedunculated vs nonpedunculated T1CRCs.

Implications for patient care

Morphology has a promising potential to refine risk stratification in patients with T1CRC and therefore should be incorporated in future risk stratification. This study underlines that the ratio of included pedunculated and nonpedunculated T1CRCs should be taken into account when extrapolating the risk for adverse outcomes as reported in the current literature to individual patients in clinical practice, and necessitates adequate reporting of morphology type in future T1CRC studies.

We evaluated whether morphology was associated with adverse outcome using univariable and multivariable logistic regression analyses and adjusted for confounders in a 4-step approach. First, we adjusted for clinical factors. Second, we additionally adjusted for histologic factors (lymphovascular invasion and differentiation grade). In a third step, we additionally adjusted for resection margins. We chose this approach because histologic factors were missing in a considerable number of patients. Fourth, we additionally adjusted for treatment approach. The association between morphology and the secondary end points metastasis and incomplete

resection was evaluated in the same manner. The association between morphology and recurrence was evaluated with univariable and multivariable Cox regression analyses, expressed in hazard ratios (HRs) with 95% CI. We adjusted for the same confounders as the primary end point and additionally adjusted for LNM because this is a well-established risk factor for recurrence.[4,27] The follow-up period started at the date of diagnosis and ended at the date of detection of recurrence, death, or last follow-up evaluation. We found no violation of the proportionality of the hazard assumption by examining the scaled Schoenfeld residuals.

Several confounding variables had missing values. Multivariate imputation by chained equations (10 imputation data sets, 25 iterations, healthy convergence) was performed before data analysis (package mice in R).[28] Rubin's rules were used to pool results across imputation data sets.[29]

Statistical analysis was performed using IBM SPSS Statistics version 24 (SPSS, Inc, Chicago, IL) and R version 3.2.2 (RStudio, Inc, Boston, MA).

Results

Study Population

We identified 2346 patients diagnosed with T1CRC between 2000 and 2014 in participating hospitals. Of these, 1656 patients with a median follow-up time of 42.5 months (interquartile range [IQR], 18.5–77.5 mo) were eligible for analysis (Figure 1). The cohort consisted of 723 pedunculated T1CRCs (43.7%) followed up for a median of 45.6 months (IQR, 20.6–80.3 mo), and 933 (56.3%) nonpedunculated T1CRCs followed up for a median of 40.9 months (IQR, 17.2–73.6 mo).

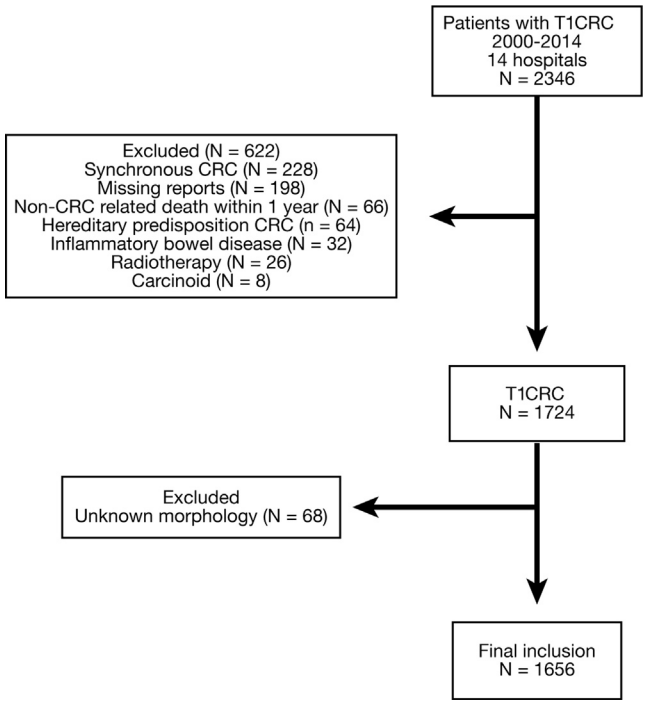

Figure 1. Study flow chart. T1CRC, T1 colorectal cancer.

Baseline characteristics of patients with pedunculated vs nonpedunculated T1CRCs are presented in Table 1. Compared with patients with nonpedunculated T1CRCs, patients with pedunculated T1CRCs were younger (69 vs 71 y; $P < .001$) and more often treated with primary endoscopy (52.8% vs 27.4%; $P < .001$). Moreover, pedunculated T1CRCs more often were located in the left colon (80.5% vs 44.4%; $P < .001$) and were smaller (20 vs 23 mm; $P < .001$). LN yield more often was low (<10 retrieved LNs) in patients with pedunculated T1CRCs (71.9% vs 54.7%; $P < .001$). The presence of lymphovascular invasion and poor differentiation did not differ significantly, however, R0 resection was achieved less often in patients with pedunculated T1CRCs (69.8% vs 75.3%; $P = .04$). If patients underwent an endoscopic resection of T1CRC, R0 resection was achieved in 63.7% of pedunculated vs 46.9% of nonpedunculated T1CRCs.

Adverse Outcome

Adverse outcomes were observed in 13.4% (222 of 1656; 95% CI, 11.8–15.2) of patients. This concerned 93 patients with LNM, 39 with distant metastasis, 33 with local recurrences, 18 with local and distant metastasis, and 58 with residual tumor in the surgical specimen when additional surgery was performed, with 17 patients having 2 or 3 adverse oncologic events. The median time to recurrence was 23.1 months (IQR, 10.1–43.2 mo) and did not differ significantly between patients with pedunculated and nonpedunculated T1CRCs (median, 19.2 mo; IQR, 10.7–43.7 mo; median, 24.8 mo; IQR, 9.8–43.2 mo; respectively; $P = .77$).

Adverse outcomes were observed in 9.3% (67 of 723; 95% CI, 7.4–11.6) of patients with pedunculated vs 16.6% (155 of 933; 95% CI, 14.4–19.1) of patients with nonpedunculated T1CRCs. Adverse outcomes did not differ significantly between low-risk pedunculated vs low-risk nonpedunculated T1CRCs (2.3% vs 2.9%; $P = .99$), however, adverse outcomes were significantly lower for high-risk pedunculated vs nonpedunculated T1CRCs (14.0% vs 21.2%; $P = .01$) (Table 2).

In univariable analysis, pedunculated morphology was associated with a decreased risk for adverse outcome (unadjusted odds ratio [OR], 0.51; 95% CI, 0.38–0.70; $P < .001$). After adjusting for clinical variables, histologic variables, resection margins, and treatment approach, the pedunculated morphology remained independently associated with a decreased risk for adverse outcome (adjusted OR, 0.59; 95% CI, 0.42–0.83; $P = .003$).

Metastasis, Incomplete Resection, and Recurrence

Metastasis was observed in 8.5% (141 of 1656; 95% CI, 7.2–10.0) of patients: 93 with LNM and 57 with

Table 1. Baseline Characteristics of Pedunculated Vs Nonpedunculated T1CRCs

	Pedunculated (N = 723)	Nonpedunculated (N = 933)	*P* value
Age, *y*, mean (SD)	69 (63–76)	71 (64–78)	<.001
Unknown	0	2	
Male sex, N (%)	410 (56.7)	516 (55.3)	.57
Tumor localization, N (%)			
Right colon	23 (3.2)	244 (26.2)	<.001
Left colon	581 (80.5)	415 (44.5)	
Rectum	118 (16.3)	273 (29.3)	
Unknown	1	1	
Treatment approach, N (%)			
Primary endoscopy	382 (52.8)	256 (27.4)	<.001
Secondary surgery	220 (30.4)	190 (20.4)	
Primary surgery	121 (16.7)	487 (52.2)	
Number of retrieved lymph nodes, N (%)[a]			
<10 lymph nodes	240 (71.9)	367 (54.7)	<.001
≥10 lymph nodes	94 (28.1)	304 (45.3)	
Unknown	7	6	
Tumor size, *mm*, median (IQR)	20 (15–30)	23 (15–39)	<.001
Unknown	59	67	
Lymphovascular invasion, N (%)			
Present	58 (17.5)	63 (14.9)	.33
Absent	274 (82.5)	361 (85.1)	
Unknown	391	509	
Differentiation grade, N (%)			
Good/moderate	477 (94.5)	715 (95.5)	.42
Poor	28 (5.5)	34 (4.5)	
Unknown	218	184	
Invasion depth in nonpedunculated T1CRCs, N (%)			
Superficial (SM1 or <1000 μm)	-	132 (31.4)	-
Deep (SM2/3 or ≥1000 μm)	-	289 (68.6)	
Unknown	-	512	
Invasion depth in pedunculated T1CRCs, N (%)		-	-
Superficial (Haggitt 1–3)	411 (86.3)	-	
Deep (Haggitt 4)	65 (13.7)	-	
Unknown	247		
Resection margins, N (%)[b]			.04
R0	492 (69.8)	682 (75.3)	
Rx	85 (12.1)	95 (10.5)	
R1	128 (18.2)	129 (14.2)	
Unknown	18	27	

IQR, interquartile range; T1CRC, T1 colorectal cancer.
[a]Presented for patients who underwent surgery.
[b]In patients treated with primary endoscopy: endoscopic resection margins; in patients treated with secondary surgery: endoscopic resection margins; in patients treated with primary surgery: surgical resection margins.

distant metastasis. Incomplete resections were observed in 6.5% (108 of 1656; 95% CI, 5.4–7.9) of patients: 50 with local recurrence, 57 with residual tissue when a secondary surgery was performed, and 1 with both local recurrence and residual tissue. Recurrences were observed in 5.4% (90 of 1656; 95% CI, 4.4–6.7) of patients: 39 with distant metastasis, 33 with local recurrences, and 18 with local and distant metastasis. Details on metastasis, incomplete resection, and recurrence stratified per treatment approach are shown in Supplementary Table 1.

Metastasis, incomplete resection, and recurrence were observed in 5.8% (42 of 723; 95% CI, 4.3–7.8), 4.6% (33 of 723; 95% CI, 3.2–6.4), and 3.9% (28 of 723; 95% CI, 2.6–5.6) of patients with pedunculated vs 10.6% (99 of 933; 95% CI, 8.7–12.8), 8.0% (75 of 933; 95% CI, 6.4–10.0), and 6.6% (62 of 933; 95% CI, 5.2–8.5) of patients with nonpedunculated T1CRCs, respectively. Metastasis, incomplete resection, and recurrence did not differ significantly between low-risk pedunculated vs nonpedunculated T1CRCs (0.8% vs 2.9%, $P = .38$; 1.5% vs 0%, $P = .99$; and 1.5% vs 0%, $P = .99$; respectively). However, incomplete resection and recurrence rates were significantly lower for high-risk pedunculated vs nonpedunculated T1CRCs (6.5% vs 12.5%, $P = .007$; 4.4% vs 8.6%, $P = .03$; respectively) (Table 2).

In univariable analysis, pedunculated morphology was associated with a decreased risk for metastasis (unadjusted OR, 0.52; 95% CI, 0.36–0.76; $P < .001$), decreased risk for incomplete resection (unadjusted OR, 0.55; 95% CI, 0.36–0.83; $P = .005$), and decreased risk for recurrence (unadjusted HR, 0.54; 95% CI, 0.35–0.85;

Table 2. Risk for Adverse Outcome, Metastasis, Incomplete Resection, and Recurrence in Pedunculated Vs Nonpedunculated T1CRCs Stratified for Risk Status

	Pedunculated		Nonpedunculated		
	Patients, n	Events, n (%)	Patients, n	Events, n (%)	*P* value
Low risk	130		35		
Adverse outcome		3 (2.3)		1 (2.9)	.99
Metastasis		1 (0.8)		1 (2.9)	.38
Incomplete resection		2 (1.5)		0 (0)	.99
Recurrence		2 (1.5)		0 (0)	.99
High risk	293		513		
Adverse outcome		41 (14.0)		109 (21.2)	.01
Metastasis		24 (8.2)		61 (11.9)	.10
Incomplete resection		19 (6.5)		64 (12.5)	.007
Recurrence		13 (4.4)		44 (8.6)	.03
Unknown risk group	300		385		
Adverse outcome		23 (7.7)		45 (11.7)	.08
Metastasis		17 (5.7)		37 (9.6)	.06
Incomplete resection		12 (4.0)		11 (2.9)	.41
Recurrence		13 (4.3)		18 (4.7)	.83

NOTE. T1CRCs were classified as high-risk T1CRCs if 1 or more of the following criteria were present: (1) poor differentiation, (2) deep submucosal invasion (>1000 μm or sm2–3 for nonpedunculated T1CRCs, Haggitt 4 for pedunculated T1CRC), (3) lymphovascular invasion, (4) Rx/R1 resection margins. When all these factors were absent, it was considered a low-risk T1CRC. The unknown risk group concerns T1CRCs in which 1 of these histologic features was unknown and no high-risk factors were present.
T1CRC, T1 colorectal cancer.

$P = .007$). After adjusting for clinical variables, histologic variables, resection margins, and treatment approach, the pedunculated morphology remained independently associated with a decreased risk for metastasis (adjusted OR, 0.62; 95% CI, 0.41–0.94; $P = .03$) and incomplete resection (adjusted OR, 0.57; 95% CI, 0.36–0.91; $P = .02$) (Table 3). Moreover, after adjusting for the same variables plus LNM, the pedunculated morphology remained independently associated with a decreased risk for recurrence (adjusted HR, 0.52; 95% CI, 0.32–0.85; $P = .009$) (Table 3).

Discussion

This study presents a large-scale comparison of adverse outcomes between T1CRCs with different morphology. We observed an almost 2-fold lower adverse outcome rate in patients with pedunculated compared with nonpedunculated T1CRCs (9.3% vs 16.6%), and pedunculated T1CRCs had a favorable outcome even after adjusting for clinicopathologic confounders. We observed no significant differences in adverse outcomes between low-risk pedunculated and nonpedunculated T1CRCs. Our study thereby does not support that traditionally defined low-risk sessile T1CRCs must undergo surgery because of an intrinsically aggressive behavior.

The favorable outcome in patients with pedunculated T1CRCs implies that the reported risk of adverse outcomes in T1CRC cohorts is influenced by the ratio of included pedunculated and nonpedunculated T1CRCs. We should take this into account when extrapolating the risk for adverse outcomes as reported in the current literature to individual patients in clinical practice. Moreover, this necessitates adequate reporting of morphology type together with stratified adverse outcome rates in future T1CRC studies. In addition, the combined positive predictive value of current histologic markers is as low as 10% to 15%, which means that 85% to 90% of patients undergo major surgery without any clinical benefit.[13] Our results suggest that morphology may refine risk stratification, helping to expand the proportion of T1CRC patients treated with endoscopic resection.

Although patient numbers were low in the low-risk nonpedunculated T1CRC group, our study suggests that risk for adverse outcomes is similar in pedunculated and nonpedunculated low-risk T1CRCs. A low percentage of low-risk nonpedunculated T1CRCs is in line with previous studies.[9,30] Several factors have contributed to this. First, if only 1 of the high-risk factors was absent, patients could not be classified as low risk. Adverse outcome rates in the unknown group are between the rates found in the low- and high-risk groups, suggesting that the actual number of patients with low-risk T1CRC was higher. Second, achieving a R0 resection is more difficult in nonpedunculated compared with pedunculated T1CRCs.[31] Finally, current risk stratification is limited. Our study group recently developed a new model to better predict the need for adjuvant surgery in patients with pedunculated T1CRCs.[32] With this model, a higher number of pedunculated T1CRCs could be classified as low risk compared with conventional models (68% vs 35%). This may be a first step toward a T1CRC risk assessment taking morphology into account.

Table 3. Risk for Adverse Outcome, Metastasis, Incomplete Resection, and Recurrence in 723 Pedunculated T1CRCs Vs 933 Nonpedunculated T1CRCs

	P, n (%)	NP, n (%)		OR (95% CI)	*P* value
Adverse outcome,[a]	67 (9.3)	155 (16.6)	Unadjusted	0.51 (0.38–0.70)	<.001
222 events in 1656 T1CRCs (13.4%)			Adjusted for clinical factors[b]	0.53 (0.38–0.73)	<.001
			Adjusted for clinical and histologic high-risk factors[c]	0.49 (0.35–0.69)	<.001
			Adjusted for clinical and histologic high-risk factors and margins[d]	0.49 (0.35–0.69)	<.001
			Adjusted for clinical and histologic high-risk factors, margins, and treatment[e]	0.59 (0.42–0.83)	.003
Metastasis,[f]	42 (5.8)	99 (10.6)	Unadjusted	0.52 (0.36–0.76)	<.001
141 events in 1656 T1CRCs (8.5%)			Adjusted for clinical factors[b]	0.52 (0.35–0.78)	.002
			Adjusted for clinical and histologic high-risk factors[c]	0.48 (0.32–0.72)	<.001
			Adjusted for clinical and histologic high-risk factors and margins[d]	0.48 (0.32–0.72)	<.001
			Adjusted for clinical and histologic high-risk factors, margins, and treatment[e]	0.62 (0.41–0.94)	.03
Incomplete resection,[g]	33 (4.6)	75 (8.0)	Unadjusted	0.55 (0.36–0.83)	.005
108 events in 1656 T1CRCs (6.5%)			Adjusted for clinical factors[b]	0.56 (0.36–0.87)	.01
			Adjusted for clinical and histologic high-risk factors[c]	0.55 (0.35–0.86)	.009
			Adjusted for clinical and histologic high-risk factors and margins[d]	0.54 (0.34–0.85)	.008
			Adjusted for clinical and histologic high-risk factors, margins, and treatment[e]	0.57 (0.36–0.91)	.02
				HR (95% CI)	
Recurrence,[h]	28 (3.9)	62 (6.6)	Unadjusted	0.54 (0.35–0.85)	.007
90 events in 1656 T1CRCs (5.4%)			Adjusted for clinical factors[b]	0.60 (0.37–0.96)	.03
			Adjusted for clinical and histologic high-risk factors[c]	0.57 (0.36–0.92)	.02
			Adjusted for clinical and histologic high-risk factors and margins[d]	0.58 (0.36–0.92)	.02
			Adjusted for clinical and histologic high-risk factors, margins, and LNM[i]	0.61 (0.38–0.99)	.05
			Adjusted for clinical and histologic high-risk factors, margins, LNM, and treatment[j]	0.52 (0.32–0.85)	.009

P, pedunculated T1CRC; NP, nonpedunculated T1CRC; T1CRC, T1 colorectal cancer.
[a]Defined as lymph node metastasis, distant metastasis, local recurrence, residual tissue in the colectomy specimen when secondary surgery was performed, or a combination of these outcomes.
[b]Adjusted for clinical factors: age (continuous), sex (male vs female), location (left colon vs right colon vs rectum), and tumor size (continuous).
[c]Adjusted for clinical factors and histologic factors: lymphovascular invasion (absent vs present) and differentiation grade (good/moderate vs poor).
[d]Adjusted for clinical factors, histologic factors, and resection margins (R0 vs Rx vs R1).
[e]Adjusted for clinical and histologic factors, resection margins, and treatment group (endoscopy vs surgery with <10 retrieved LNs vs surgery with ≥10 retrieved LNs).
[f]Defined as lymph node metastasis or distant metastasis.
[g]Defined as local recurrence after endoscopic or surgical treatment, or residual tissue in the colectomy specimen when a secondary surgery was performed.
[h]Defined as distant metastasis, local recurrence, or both (after endoscopic or surgical treatment).
[i]Adjusted for clinical and histologic factors, resection margins, and the presence of LNM.
[j]Adjusted for clinical and histologic factors, resection margins, the presence of LNM, and treatment group (endoscopy vs surgery with <10 retrieved LNs vs surgery with ≥10 retrieved LNs).

Few previous studies have compared adverse outcomes between pedunculated and nonpedunculated T1CRCs. A systematic review published in 2005 regarding histologic risk factors and unfavorable outcomes of patients with T1CRCs found a significant difference in recurrence and metastasis in pedunculated vs nonpedunculated T1CRCs of 0.4% (1 of 238) vs 6.2% (4 of 64) and 0.8% (5 of 595) vs 3.6% (13 of 357), respectively. No difference in LNM rate was observed (9.7% [12 of 124] vs 10.5% [17 of 162]).[9] This study, however, reviewed several small nonconsecutive cohorts. In addition, no adjustment for confounders was performed and treatment approach was not taken into account. A more recent population-based study including 411 patients with T1CRC diagnosed between 1982 and 2011, reported a 5-year cumulative recurrence rate of 5.2% for pedunculated and 6.3% for nonpedunculated T1CRCs ($P = .66$).[33] However, this comparison was based on only 15 recurrences vs 90 recurrences in our study. In addition, inclusion bias may have occurred because only endoscopic benign-appearing T1CRCs were included. A study of the Scottish Surgical Research Group on 485 patients with T1CRCs, which were identified through the screening program between 2000 and 2012, found no significant difference in adverse outcomes between pedunculated and nonpedunculated T1CRCs after adjustment for confounders.[34] However, this study only included patients who underwent endoscopic resection (followed by segmental resection or not), which may have led to exclusion of nonpedunculated high-risk T1CRCs unfit for endoscopic resection in particular, leading to an underestimation of adverse outcomes in the nonpedunculated T1CRC group.

This study had some limitations. Adequate histologic diagnosis of pedunculated T1CRC is challenging.[35,36] A recent histologic review of a subgroup of 128 pedunculated T1CRCs from our cohort by pathologists with special expertise in gastrointestinal pathology showed that approximately 10% of cases were overstaged (ie, T1CRC diagnosis was revised as pseudo-invasion or high-grade dysplasia).[37] This may underestimate the adverse outcomes of pedunculated T1CRCs in our cohort. However, our previous study did not evaluate the percentage of missed T1CRCs diagnosed histologically as premalignant lesions. In addition, pseudo-invasion and biopsy-related displaced epithelium simulating malignancy also have been described in nonpedunculated T1CRCs, which might balance the potential underestimation in pedunculated T1CRCs.[38] Finally, differentiating T1CRC from its precursor lesions is an up-to-date challenge and our cohort reflects daily clinical practice.[36] Because of the retrospective design, another limitation of this study was that some variables had a large number of missing data. As a result, we had to classify a relatively large number of T1CRCs as having an unknown risk status (41%). To minimize bias introduced by missing data in the regression analysis, we performed multiple imputations. Furthermore, we performed the regression analysis in a stepwise approach, in which we first adjusted for clinical variables with a low missing rate followed by adjustment for histologic variables with a higher missing rate.

In conclusion, pedunculated morphology was associated independently with a decreased risk for adverse outcomes and the absolute risk for adverse outcomes in patients with pedunculated T1CRCs was nearly half that of patients with nonpedunculated T1CRCs. In patients with low-risk T1CRCs, rates of metastasis, incomplete resection, and recurrence rates did not differ significantly between pedunculated vs nonpedunculated morphology. However, incomplete resection and recurrence rates were significantly lower for high-risk pedunculated vs nonpedunculated T1CRCs. Our results suggest that morphology has a promising potential to refine risk stratification in patients with T1CRCs and encourage incorporation of morphology in risk stratification. Furthermore, our study underlines that the ratio of included pedunculated and nonpedunculated T1CRCs should be taken into account when extrapolating the risk for adverse outcomes as reported in the current literature to individual patients in clinical practice and necessitates adequate reporting of morphology in future T1CRC studies.

Ethics

This study was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht (reference number 15-487/C) and was performed in accordance with the Helsinki Declaration. The study conforms to the STrengthening the Reporting of OBservational studies in Epidemiology guideline.[39]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.08.041.

References

1. Toes-Zoutendijk E, Kooyker AI, Elferink MA, et al. Stage distribution of screen-detected colorectal cancers in the Netherlands. Gut 2018;67:1745–1746.
2. Amri R, Bordeianou LG, Sylla P, et al. Impact of screening colonoscopy on outcomes in colon cancer surgery. JAMA Surg 2013;148:747–754.
3. Logan RF, Patnick J, Nickerson C, et al. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. Gut 2012;61:1439–1446.
4. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–1474.
5. Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology 2004;127:385–394.

6. Nascimbeni R, Burgart LJ, Nivatvongs S, et al. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum 2002;45:200–206.
7. Kitajima K, Fujimori T, Fujii S, et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol 2004;39:534–543.
8. Ricciardi R, Madoff RD, Rothenberger DA, et al. Population-based analyses of lymph node metastases in colorectal cancer. Clin Gastroenterol Hepatol 2006;4:1522–1527.
9. Hassan C, Zullo A, Risio M, et al. Histologic risk factors and clinical outcome in colorectal malignant polyp: a pooled-data analysis. Dis Colon Rectum 2005;48:1588–1596.
10. Okabe S, Shia J, Nash G, et al. Lymph node metastasis in T1 adenocarcinoma of the colon and rectum. J Gastrointest Surg 2004;8:1032–1039; discussion 1039–1040.
11. Tominaga K, Nakanishi Y, Nimura S, et al. Predictive histopathologic factors for lymph node metastasis in patients with nonpedunculated submucosal invasive colorectal carcinoma. Dis Colon Rectum 2005;48:92–100.
12. Egashira Y, Yoshida T, Hirata I, et al. Analysis of pathological risk factors for lymph node metastasis of submucosal invasive colon cancer. Mod Pathol 2004;17:503–511.
13. Bosch SL, Teerenstra S, de Wilt JH, et al. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 2013;45:827–834.
14. Cranley JP, Petras RE, Carey WD, et al. When is endoscopic polypectomy adequate therapy for colonic polyps containing invasive carcinoma? Gastroenterology 1986;91:419–427.
15. Matsuda T, Fukuzawa M, Uraoka T, et al. Risk of lymph node metastasis in patients with pedunculated type early invasive colorectal cancer: a retrospective multicenter study. Cancer Sci 2011;102:1693–1697.
16. Yoshii S, Nojima M, Nosho K, et al. Factors associated with risk for colorectal cancer recurrence after endoscopic resection of T1 tumors. Clin Gastroenterol Hepatol 2014;12:292–302.e3.
17. Sobin LH, Gospodarowics MK, Wittekind C. TNM classification of malignant tumours. UICC International Union Against Cancer, 2009.
18. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58:S3–S43.
19. Kudo S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy 1993;25:455–461.
20. Rutter MD, Chattree A, Barbour JA, et al. British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland guidelines for the management of large non-pedunculated colorectal polyps. Gut 2015;64:1847–1873.
21. Ikematsu H, Yoda Y, Matsuda T, et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology 2013;144:551–559; quiz e14.
22. Backes Y, Elias SG, Bhoelan BS, et al. The prognostic value of lymph node yield in the earliest stage of colorectal cancer: a multicenter cohort study. BMC Med 2017;15:129.
23. Watanabe T, Muro K, Ajioka Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol 2018;23:1–34.
24. Williams JG, Pullan RD, Hill J, et al. Management of the malignant colorectal polyp: ACPGBI position statement. Colorectal Dis 2013;15(Suppl 2):1–38.
25. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi64–vi72.
26. ASGE Standards of Practice Committee, Fisher DA, Shergill AK, et al. Role of endoscopy in the staging and management of colorectal cancer. Gastrointest Endosc 2013;78:8–12.
27. Gunderson LL, Jessup JM, Sargent DJ, et al. Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol 2010;28:264–271.
28. van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. J Stat Software 2011;45:1–67.
29. Marshall A, Altman DG, Holder RL, et al. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol 2009;9:57.
30. Suh JH, Han KS, Kim BC, et al. Predictors for lymph node metastasis in T1 colorectal cancer. Endoscopy 2012;44:590–595.
31. Backes Y, de Vos Tot Nederveen Cappel WH, van Bergeijk J, et al. Risk for incomplete resection after macroscopic radical endoscopic resection of T1 colorectal cancer: a multicenter cohort study. Am J Gastroenterol 2017;112:785–796.
32. Backes Y, Elias SG, Groen JN, et al. Histologic factors associated with need for surgery in patients with pedunculated T1 colorectal carcinomas. Gastroenterology 2018;154:1647–1659.
33. Lopez A, Bouvier AM, Jooste V, et al. Outcomes following polypectomy for malignant colorectal polyps are similar to those following surgery in the general population. Gut 2019;68:111–117.
34. Richards CH, Ventham NT, Mansouri D, et al. An evidence-based treatment algorithm for colorectal polyp cancers: results from the Scottish Screen-detected Polyp Cancer Study (SSPoCS). Gut 2018;67:299–306.
35. Loughrey MB, Shepherd NA. The pathology of bowel cancer screening. Histopathology 2015;66:66–77.
36. Shepherd NA, Griggs RK. Bowel cancer screening-generated diagnostic conundrum of the century: pseudoinvasion in sigmoid colonic polyps. Mod Pathol 2015;28(Suppl 1):S88–S94.
37. Backes Y, Moons LM, Novelli MR, et al. Diagnosis of T1 colorectal cancer in pedunculated polyps in daily clinical practice: a multicenter study. Mod Pathol 2017;30:104–112.
38. Panarelli NC, Somarathna T, Samowitz WS, et al. Diagnostic challenges caused by endoscopic biopsy of colonic polyps: a systematic evaluation of epithelial misplacement with review of problematic polyps from the Bowel Cancer Screening Program, United Kingdom. Am J Surg Pathol 2016;40:1075–1083.
39. PLoS Medicine Editors. Observational studies: getting clear about transparency. PLoS Med 2014;11:e1001711.

Reprint requests
Address requests for reprints to: Leon M. G. Moons, MD, PhD, Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Heidelberglaan 100, PO Box 85500, 3508 GA Utrecht, The Netherlands. e-mail: l.m.g.moons@umcutrecht.nl.

Conflicts of interest
The authors disclose no conflicts.

Supplementary Table 1. Adverse Outcomes in Pedunculated and Nonpedunculated T1CRCs Stratified Between Primary Endoscopy, Secondary Surgery, and Primary Surgery

	Overall (N = 1656)		Pedunculated (N = 723)		Nonpedunculated (N = 933)	
	Total, n	Events, n (%)	Total, n	Events, n (%)	Total, n	Events, n (%)
Primary endoscopy						
Recurrence	638		382		256	
Local		21		7		14
Distant		10		5		5
Local + distant		11		6		5
Total		42 (6.6)		18 (4.7)		24 (9.4)
Secondary surgery						
Recurrence	410		220		190	
Local		5		2		3
Distant		8		3		5
Local + distant		3		0		3
LNM		34		19		15
Residual disease		58		18		40
Total		97 (23.7)		39 (17.7)		58 (30.5)
Primary surgery						
Recurrence	608		121		487	
Local		7		0		7
Distant		21		5		16
Local + distant		4		0		4
LNM		59		6		53
Total		83 (13.7)		10 (8.3)		73 (15.0)
Overall	1656	222 (13.4)	723	67 (9.3)	933	155 (16.6)

LNM, lymph node metastasis; T1CRC, T1 colorectal cancer.