

# Full-thickness scar resection after R1/Rx excised T1 colorectal cancers as an alternative to completion surgery

Gijsbers, K.M.; Lacle, M.M.; Elias, S.G.; Backes, Y.; Bosman, J.H.; Berkel, A.M. van; ...; Dutch T1 CRC Working Grp

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Kim M. Gijsbers, MD<sup>1,2</sup>, Miangela M. Laclé, MD, PhD, FRCPath<sup>3</sup>, Sjoerd G. Elias, MD, PhD<sup>4</sup>, Yara Backes, MD, PhD<sup>1</sup>, Joukje H. Bosman, MD<sup>5</sup>, Annemarie M. van Berkel, MD, PhD<sup>6</sup>, Femke Boersma, MD<sup>7</sup>, Jurjen J. Boonstra, MD, PhD<sup>8</sup>, Philip R. Bos, MD<sup>9</sup>, Patty A.T. Dekker, MD<sup>10</sup>, Paul D. Didden, MD, PhD<sup>1</sup>, Joost M.J. Geesing, MD<sup>11</sup>, John N. Groen, MD<sup>12</sup>, Krijn J.C. Haasnoot, MD<sup>1</sup>, Koen Kessels, MD, PhD<sup>13</sup>, Anja U.G. van Lent, MD, PhD<sup>14</sup>, Lisa van der Schee, MD<sup>1</sup>, Ruud W.M. Schrauwen, MD<sup>15</sup>, Ramon-Michel Schreuder, MD<sup>16</sup>, Matthijs P. Schwartz, MD, PhD<sup>17</sup>, Tom J. Seerden, MD, PhD<sup>18</sup>, Marcel B.W.M. Spanier, MD, PhD<sup>19</sup>, Jochim S. Terhaar Sive Droste, MD, PhD<sup>20</sup>, Jurriaan B. Tuynman, MD, PhD<sup>21</sup>, Wouter H. de Vos tot Nederveen Cappel, MD, PhD<sup>22</sup>, Erik H.L. van Westreenen, MD, PhD<sup>23</sup>, Frank H.J. Wolfhagen, MD, PhD<sup>24</sup>, Frank P. Vleggaar, MD, PhD<sup>1</sup>, Frank ter Borg, MD, PhD<sup>2,\*</sup> and Leon M.G. Moons, MD, PhD<sup>1,\*</sup>, on behalf of the Dutch T1 CRC Working Group

- INTRODUCTION: Local full-thickness resections of the scar (FTRS) after local excision of a T1 colorectal cancer (CRC) with uncertain resection margins is proposed as an alternative strategy to completion surgery (CS), provided that no local intramural residual cancer (LIRC) is found. However, a comparison on long-term oncological outcome between both strategies is missing.
- METHODS: A large cohort of patients with consecutive T1 CRC between 2000 and 2017 was used. Patients were selected if they underwent a macroscopically complete local excision of a T1 CRC but positive or unassessable (R1/Rx) resection margins at histology and without lymphovascular invasion or poor differentiation. Patients treated with CS or FTRS were compared on the presence of CRC recurrence, a 5-year overall survival, disease-free survival, and metastasis-free survival.
- RESULTS: Of 3,697 patients with a T1 CRC, 434 met the inclusion criteria (mean age 66 years, 61% men). Three hundred thirty-four patients underwent CS, and 100 patients underwent FTRS. The median follow-up period was 64 months. CRC recurrence was seen in 7 patients who underwent CS (2.2%, 95% Cl 0.9%–4.6%) and in 8 patients who underwent FTRS (9.0%, 95% Cl 3.9%–17.7%). Disease-free survival was lower in FTRS strategy (96.8% vs 89.9%, *P* = 0.019), but 5 of the 8 FTRS recurrences could be treated with salvage surgery. The metastasis-free survival (CS 96.8% vs FTRS 92.1%, *P* = 0.10) and overall survival (CS 95.6% vs FTRS 94.4%, *P* = 0.55) did not differ significantly between both strategies.
- DISCUSSION: FTRS after local excision of a T1 CRC with R1/Rx resection margins as a sole risk factor, followed by surveillance and salvage surgery in case of CRC recurrence, could be a valid alternative strategy to CS.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C409, http://links.lww.com/AJG/C410, http://links.lww.com/AJG/C411, http://links.lww.com/AJG/C412, http://links.lww.com/AJG/C413

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<sup>1</sup>Department of Gastroenterology, University Medical Center Utrecht, Utrecht, the Netherlands; <sup>2</sup>Department of Gastroenterology, Deventer Hospital, Deventer, the Netherlands; <sup>3</sup>Department of Pathology, University Medical Center Utrecht, Utrecht, the Netherlands; <sup>4</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; <sup>5</sup>Department of Gastroenterology, Gorene Hart Hospital, Gouda, the Netherlands; <sup>6</sup>Department of Gastroenterology, Noordwest Hospital, Alkmaar, the Netherlands; <sup>7</sup>Department of Gastroenterology, Gelre Hospitals, Apeldoorn, the Netherlands; <sup>8</sup>Department of Gastroenterology, Leiden University Medical Center, Leiden, the Netherlands; <sup>9</sup>Department of Gastroenterology, Diakonessenhuis, Utrecht, the Netherlands; <sup>10</sup>Department of Gastroenterology, Diakonessenhuis, Utrecht, the Netherlands; <sup>11</sup>Department of Gastroenterology, Sit Jansdal, Harderwijk, the Netherlands; <sup>13</sup>Department of Gastroenterology, St. Antonius Hospital, Nieuwegein, the Netherlands; <sup>14</sup>Department of Gastroenterology, Center Hospital, Uden, the Netherlands; <sup>16</sup>Department of Gastroenterology, Catharina Hospital, Eindhoven, the Netherlands; <sup>17</sup>Department of Gastroenterology, Reander Medical Center, Amersfoort, the Netherlands; <sup>20</sup>Department of Gastroenterology, Jepartment of Gastroenterology, Reinter of Surgery, Rijnstate Hospital, Arnhem, the Netherlands; <sup>20</sup>Department of Gastroenterology, Jepartment of Gastroenterology, Reinterology, Rijnstate Hospital, Arnhem, the Netherlands; <sup>20</sup>Department of Gastroenterology, Jepartment of Gastroenterology, Jepartment of Gastroenterology, Reinterology, Reinterology, Reinterology, Reinterology, Reinterology, Sizaterdam, the Netherlands; <sup>20</sup>Department of Gastroenterology, Reinterology, Sizaterdam University Medical Centers, Location VUmc, Amsterdam, the Netherlands; <sup>22</sup>Department of Gastroenterology, Isa

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COLON

# INTRODUCTION

Over the past years, unassessable (Rx) or positive (R1) resection margins after local excision of a T1 colorectal cancer (CRC) were considered an indication for completion surgery (CS) due to the high risk of local recurrence and unclear risk of lymph node metastasis (LNM) (1-3). Recently, a strategy of local fullthickness resection of the local excision scar (FTRS) with endoscopic full-thickness resection, transanal minimally invasive surgery, or combined endoscopic-laparoscopic surgery (4-9) was promoted as an alternative treatment strategy for patients with R1/Rx resection margins after local excision of a T1 CRC, in absence of other histological risk factors of LNM (10,11). If the locally resected scar tissue showed no local intramural residual cancer (LIRC), the local excision was considered complete and therefore managed as a low-risk T1 CRC (4,6,7). However, these studies have limited or no follow-up data at all, and the oncological safety of leaving locoregional lymph nodes in situ has not yet been evaluated. A higher risk of LNM in endoscopically excised T1 CRC with positive resection margins has been shown compared with T1 CRC with a free resection margin (11,12). Furthermore, in a recent prospective study on T1 CRC with R1/ Rx resection margins without other histological risk factors of LNM, an unexpected high rate of LNM (8.3%) was detected during CS in cases without LIRC (13). Moreover, a study on transanal endoscopic microsurgery (TEM) without LIRC after endoscopic excision reported 9.4% recurrences in patients with R1/Rx resection margins (9). To refrain from CS and intensive follow-up after FTRS, it is essential that the oncological outcome of both strategies is known. Therefore, the aim of this study was to evaluate oncological outcomes for FTRS and CS after local excision of a T1 CRC with R1/Rx resection margins.

# **METHODS**

# Study design and population

A multicenter retrospective cohort study was performed. All consecutive patients diagnosed with T1 CRC between January 1, 2000, and December 31, 2017, in 20 Dutch hospitals were selected from the Netherlands Cancer Registry. Electronic medical records were reviewed, and only patients with a T1 CRC confirmed by the local pathologist were included. T1 CRC was defined as a tumor growing through the muscularis mucosae into, but not beyond, the submucosa. Exclusion criteria were patients with synchronous CRC, non-CRC-related death within 1 year, hereditary predisposition for CRC, inflammatory bowel disease, nonadenocarcinoma, missing pathology or endoscopy reports, and patients who underwent neoadjuvant radiotherapy. Demographic and clinical data were collected at the participating hospitals (Supplementary Material, http://links.lww.com/AJG/ C409). This study was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht (reference number 15-487/C) on August 18, 2015, and conducted in accordance with the Helsinki Declaration. The study conforms to the Strengthening the Reporting of OBservational Studies in Epidemiology (STROBE) guideline for cohort studies (14).

For this aim, patients within this cohort were selected based on the following eligibility criteria: (i) a macroscopically complete local excision, defined as absent residual neoplasia as judged by the endoscopist regardless of resection technique (en-bloc or piecemeal resection); (ii) Rx or R1 resection margins; (iii) absence of LVI and poor differentiation; and (iv) adjuvant therapy consisting of CS including lymphadenectomy or FTRS. Absence of high-grade tumor budding and deep submucosal invasion were not used as inclusion criteria because these were not included as high-risk features in the Dutch guideline and therefore poorly reported (1). FTRS was defined as any full-thickness endoscopic or surgical treatment without lymphadenectomy. Patients were categorized into 2 treatment strategies: (i) CS and (ii) FTRS with follow-up and salvage surgery in case of CRC recurrence.

#### Outcomes

The main outcomes were an adverse oncological event during follow-up in patients without LIRC at CS or FTRS and a 5-year overall survival (OS), disease-free survival (DFS), and metastasisfree survival (MFS). An adverse oncological event was defined as a composite of imaging-confirmed or histology-confirmed cancer recurrence during follow-up, which could be local within the scar, LNM, or distant metastasis (including LNM outside the original field of CS). A new primary CRC elsewhere in the colon or rectum was defined as metachronous cancer, not as recurrence. DFS was defined as having no CRC recurrence or CRC treatment-related death. MFS was defined as having no CRC recurrence outside the area intended to be removed with CS or CRC treatment-related death. We evaluated both DFS and MFS to discriminate for the value of salvage surgery. The finding of LNM at CS was not considered as an adverse oncological event but as unexpected LNM found in the surgical specimen. Details on statistical analysis are displayed in the Supplemental Digital Content (http://links.lww. com/AJG/C409).

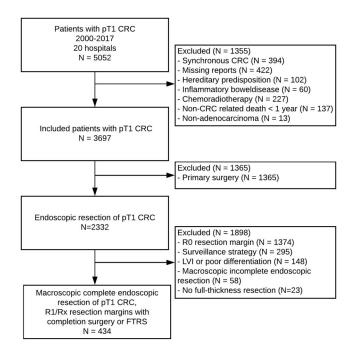
# Histologic reassessment

To evaluate the impact of second reading and the effect of tumor budding, which was not included in the original pathology report, a subset of patients within each strategy were histologically reassessed. From patients with LNM at CS, approximately 75% were randomly selected for histological reassessment by an expert gastrointestinal pathologist (M.L.). For every LNM case, 4 control cases without LNM were reassessed. Besides, approximately 50% of patients who underwent FTRS were randomly selected for histological reassessment. The hematoxylin-eosin staining slides of the original T1 CRC specimens were collected and reviewed and randomly mixed with those of cases from another study to ensure blinding of the pathologist. Definitions are displayed in the Supplemental Digital Content (http://links.lww.com/AJG/C409).

# RESULTS

# **Patient characteristics**

A study flowchart of the included patients is presented in Figure 1. A total of 434 patients treated with local excision of a T1 CRC with R1/Rx resection margins who went on for either CS or FTRS were selected. The median age of the cohort was 66 years (interquartile range 61–71 years), and 60.8% was men. CS was conducted in 334 patients and FTRS in 100 patients. An overview of the baseline characteristics of patients is listed in Table 1. Both groups were comparable based on patient characteristics (age, sex, and ASA score). In the CS group, more T1 CRC were located in the colon, and in the FTRS group, most T1 CRC were located in the rectum (P < 0.001). Details on follow-up after treatment are discussed in the Supplemental Digital Content (http://links.lww.com/AJG/C409) and Table, Supplemental Digital Content 1 (http://links.lww.com/AJG/C410).



**Figure 1.** Study flowchart. pT1, pathologic-confirmed T1; CRC, colorectal cancer; FTRS, full-thickness resection of the local excision scar; N, number; R0, free resection margin; R1, resection margin that is not free of cancer; Rx, unassessable resection margin.

**Complications after treatment.** Severe complications were seen in 37 patients who underwent CS (11.1%, 95% CI 7.8%–15.3%), of which 4 patients died (1.2%, 95% CI 0.3%–3.1%). Eighteen of these patients needed reoperation because of the surgical complications (5.4%, 95% CI 3.2%–8.5%). Severe complications were seen in 4 patients who underwent FTRS (4.0%, 95% CI 1.1%–10.2%, P = 0.034); bleeding requiring intervention occurred, and no patients died as a consequence of the treatment. More information regarding types of complications is presented in Table, Supplemental Digital Content 2 (http://links.lww.com/ AJG/C411).

LIRC and LNM. LIRC was diagnosed in 18 patients who underwent CS (18/334, 5.4%, 95% CI 3.2%-8.5%) and in 11 patients who underwent FTSR (11/100, 11.0%, 95% CI 5.5%–19.7%) (P = 0.049) (Figure 2). LIRC was recognized during FTSR in 4 of the 11 (36.4%) patients and R0 resected in 10 of the 11 (90.9%) patients. Two patients with LIRC in the FTSR group underwent an additional oncological surgery without LNM. In the groups showing LIRC, LNM and/or recurrence were seen in 27.8% (CS) and 27.3% (FTRS) of patients (P = 0.98), respectively. In patients who underwent FTSR, adverse oncological events were seen in 1 of the 4 patients (25.0%) with recognized LIRC and in 2 of the 7 patients (28.6%) with unrecognized LIRC (P = 1.00). In the CS group without LIRC, LNM were seen in 27 cases (8.5%, 95% CI 5.6%-12.4%). LNM at baseline and/or recurrence after CS together were observed in 34 patients (34/316, 10.8%, 95% CI 7.5%-15.0%). Adverse oncological events during follow-up. For the comparison of both treatment strategies, only the cases without LIRC were analyzed (Figure 2). In the CS group, recurrences were detected in 7 patients (7/316, 2.2%, 95% CI 0.9%-4.6%). All 7 patients experienced distant metastasis, and 2 of them also experienced a local recurrence at the anastomosis. Recurrences were detected after a median time of 27 months; 4 patients could be treated with

curative intent (57.1%). In the FTRS group without LIRC, recurrences were detected in 8 patients (8/89, 9.0%, 95% CI 3.9%–17.7%). Local recurrences were seen in 4 patients (after combined endoscopic-laparoscopic surgery), of whom 1 also presented with LNM and 2 with distant metastasis. The other 5 patients experienced distant metastasis, of whom 1 also experienced LNM. Recurrences were detected after a median time of 33 months; 5 patients could be treated with curative intent (62.5%). Three of the local recurrences were detected during endoscopy, whereas the preceding follow-up endoscopy showed no abnormalities. One recurrence was detected in a patient without imaging during follow-up, and the other 7 recurrences were detected in patients with CT imaging of the abdomen. Details of patients with a recurrence in the FTRS group are summarized in Table, Supplemental Digital Content 3 (http://links.lww.com/AJG/C412).

#### OS, DFS, and MFS

In the total cohort, for patients who underwent CS and FTRS, the 5-year OS (317/334; 94.9% vs 95/100; 95.0%), DFS (320/334; 95.8% vs 90/100; 90.0%), and MFS (320/334; 95.8% vs 93/100; 93.0%) were not significantly different (P = 0.79, P = 0.067 and P = 0.40 respectively). Considering the patients without LIRC, the 5-year OS rate was not significantly different between patients treated by CS (302/316; 95.6%) and patients treated by FTRS (84/ 89; 94.4%) (P = 0.83). The 5-year DFS was different between both groups (CS 306/316; 96.8%, FTRS 80/89; 89.9%, *P* = 0.019), but the MFS was not (CS 306/316; 96.8%, FTRS 82/89; 92.1%, P =0.10) (Figure 3). In the CS group, 100% of patients underwent oncologic segmental surgery against 4.5% in the FTRS group. The influence of baseline characteristics on DFS and MFS were tested (Table, Supplemental Digital Content 4, http://links.lww.com/ AJG/C413). Overall, the hazard ratios for DFS and MFS between CS and FTRS did not change substantially after adjustment for individual baseline factors, although the difference in DFS lost statistical significance after correction for tumor location (colon vs rectum) or polyp size.

#### Histological reassessment

Results of the histological reassessment are summarized in Table 2. Ninety percentage of all cases with LNM in the CS group without LIRC were assessed as having at least 1 histological risk factor (LVI, poor differentiation, or Bd2/3 tumor budding). High-grade tumor budding, which was not assessed in the initial pathology report, was seen in 55.6% of the cases. Of the control group without LNM, 38.8% was assessed as having high risk, and high-grade tumor budding was seen in 18.8% of cases. In all patients who underwent FTRS strategy without LIRC, 51.1% was assessed as having at least 1 histological risk factor. The number of unidentified risk factors was equal between both treatment strategies (49.0% in the CS group).

#### DISCUSSION

To the best of our knowledge, this is the first study comparing the oncological outcome of FTRS for R1/Rx resected T1 CRC without LVI and poor differentiation with conventional CS. We found a higher rate of LNM (8.5%) than expected in these patients, confirming the observation made in the SCAPURA trial (13). The 5-year DFS was lower in the FTRS group (89.9% vs 96.8%), but because 63% of recurrences in this group could be treated with curative intent, the 5-year OS and MFS were similar between both

#### Table 1. Baseline characteristics

	Total cohort ( $N = 434$ )	CS (N = 334)	FTSR (N = 100)	<b><i>P</i> value</b> 0.13
Age, y, median (IQR)	66 (61–71)	65 (61–70)	67 (61–71)	
Male sex, n (%)	264 (60.8)	198 (59.3)	66 (66.0)	0.23
ASA classification, n (%)				0.68
I–II	386 (89.1)	298 (89.5)	88 (88.0)	
III–IV	47 (10.9)	35 (10.5)	12 (12.0)	
Missing	1	1	0	
CCI, median (IQR)	2 (1–3)	2 (1–3)	3 (2–4)	< 0.001
Unknown	1	1	0	
Institution, n (%)				0.32
Academic	22 (5.1)	15 (4.5)	7 (7.0)	
Nonacademic	412 (94.9)	319 (95.5)	93 (93.0)	
Tumor location, N (%)				< 0.001
Rectum	105 (24.2)	41 (12.3)	64 (64.0)	
Colon	329 (75.8)	293 (87.7)	36 (36.0)	
Polyp size, mm, median (IQR)	20 (13–30)	20 (13–30)	20 (15–30)	0.24
Unknown (n)	17	15	2	
Morphology, N (%)				0.037
Pedunculated	159 (37.1)	131 (39.8)	28 (28.3)	
Nonpedunculated	269 (62.9)	198 (60.2)	71 (71.7)	
Missing	6	5	1	
Resection technique, N (%)				0.65
Piecemeal	208 (48.0)	158 (47.4)	50 (50.0)	
En-bloc	225 (52.0)	175 (52.6)	50 (50.0)	
Missing	1	1	0	
Resection margins, N (%)				0.13
R1	224 (51.6)	179 (53.6)	45 (45.0)	
Rx	210 (48.4)	155 (46.4)	55 (55.0)	
FU, mo, median (IQR)	36 (17–59)	37 (17–59)	33 (16–51)	0.34

ASA, American Society of Anaesthesiologists; CCI, Charlson Comorbidity Index; CS, completion surgery; FTSR, full-thickness scar resection; FU, follow-up; IQR, interquartile range; LN, lymph nodes; mm, millimeter; N, number; R1, resection margin that is not free of cancer; Rx, unassessable resection margin.

treatment strategies (94.4% vs 95.6% and 92.1% vs 96.8%, respectively).

In our study, a high percentage (63%) of patients with recurrence after FTRS could have salvage surgery with curative intent, which is in line with the findings of a recent meta-analysis showing a similar 60% of curative treatments once the recurrence was detected in a group of 1,023 high-risk T1 CRC patients refusing CS (15). CRC is known to recur after CS as well. The current post-CS recurrences we detected (2.2%) is lower than the reported post-surgical recurrences of 3% (16–22). This is most likely due to the selection bias toward a subgroup with a lower risk of recurrences because of the absence of LVI and poor differentiation. Moreover, the surgical mortality of 1.2% in our study is in line with the recently reported mean 1.7% mortality risk for surgery on T1 CRC (23). The risk of mortality and persisting morbidity after CS together with the proportion of recurrence, which cannot be prevented by CS, should be weighed against the risk of recurrence after FTRS corrected with the proportion of salvage surgery with curative intent once the recurrence is being detected.

The currently detected recurrence rate of 9.0% of patients in the FTRS group is comparable with the 10.8% detected LNM and recurrences in the CS group. Sixty percentage of recurrences during follow-up is being detected within 3 years, increasing up to 98% at 6 years (15). It cannot be excluded that recurrences are undetected at this moment. However, this might only have a minimal impact on MFS and OS, when 63% can be cured by salvage surgery. Altogether, it seems necessary that FTRS should be combined with a surveillance protocol aiming to detect the recurrence as early as possible to increase the chance of curative salvage surgery.

Our study shows that cases with LIRC (of whom 11.0% underwent FTRS) show higher risks of an adverse oncological event (27.3%) and are likely to benefit from CS. The problem is that

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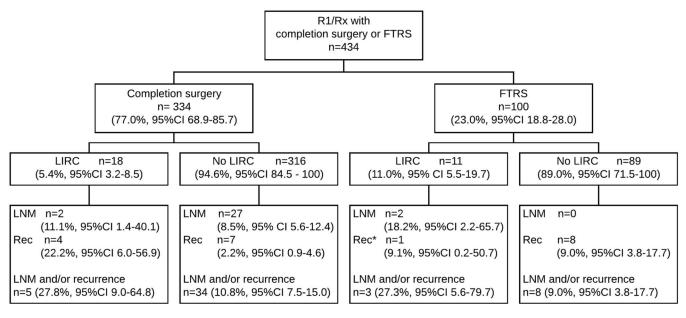


Figure 2. Percentage of LIRC, LNM, and recurrence after macroscopic radical endoscopic resection of T1 CRC with R1/Rx resection margins. \*Not all patients with LIRC at FTRS underwent completion surgery. FTRS, full-thickness resection of the local excision scar; LIRC, local intramural residual cancer; LNM, lymph node metastasis; n, number; R1, resection margin not free of cancer; Rx, unnassessable resection margin.

LIRC is hard to detect during endoscopy with biopsies of the postendoscopic resection scar alone (13). However, the risk of adverse oncological events is equal in patients with recognized and unrecognized LIRC. If LIRC is diagnosed by the physician before FTRS, which was in 36.4% of LIRC cases in our study, CS should be considered instead of performing FTRS. For patients without visible LIRC, we think that FTRS is an important step in additional local staging instead of immediate surveillance after local excision with R1/Rx resection margins. It should be noted that the number of cases is small and firm conclusions cannot be made. Besides, cases with LIRC, which are actually T2 or T3 tumors, can be detected this way (4,24,25). However, this is not a limitation of our study because we focused on patients without LIRC, and those with T2 and T3 tumors were excluded from our retrospective cohort.

Although this is the largest cohort of FTRS with long-term follow-up published yet comparing results with a similar cohort treated by CS, some limitations of this study should be emphasized. First, the histological evaluation of T1 CRC remains challenging and interobserver variability between pathologists is a known problem (26), especially with R1/Rx resection margins, due to missing or unrecognizable invasive fronts, which makes risk factors such as tumor budding or LVI difficult to rule out. Our

results underline this challenge. In our study, histological reassessment of the original H&E slides to explore the impact of unidentified histological risk features showed 90% of cases with LNM in the CS group without LIRC as having 1 or more histological risk factor(s) (poor differentiation, LVI, or high-grade tumor budding). This brings into question whether all cases should have been reassessed by expert pathologists instead of an independent sample. Because the proportion of not originally reported high-risk features was equally divided between both the CS and FTRS group (49% vs 51%), we believe that the impact of unidentified features on oncological outcomes was limited. It is also questionable whether a histological second opinion should be mandatory before performing FTRS. The detection of risk factors has been shown to vary between different expert panels (27), and performing second opinion on all pathology slides also showed that 35% of patients without LNM were assessed as having high risk as well, which would result in unnecessary CS within these cases. Besides, a second opinion would not reflect daily practice, making it difficult to extrapolate these results to daily practice. However, cases treated by CS could have been evaluated less thoroughly for other risk factors because an R1/Rx finding was considered an indication for CS on its own. Therefore, awareness among pathologists that FTRS with surveillance is an alternative

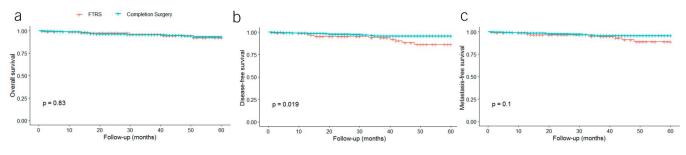


Figure 3. Overall, disease-free, and metastasis-free survival.

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	CS, sample (n = 100)	FTRS, sample (n = 47)	P value	CS, without LIRC, $LNM+ (n = 20)$	CS, without LIRC, $LNM- (n = 80)$	FTSR, without LIRC, recurrence + $(n = 6)$	FTSR, without LIRC, recurrence- (n = 41)
T2	3	0	< 0.001	2	1	0	0
<t1< td=""><td>10</td><td>0</td><td></td><td>0</td><td>10</td><td>0</td><td>0</td></t1<>	10	0		0	10	0	0
LVI, N (%)			0.040				
Positive	21	15		8 (44.5)	13 (18.8)	2 (33.3)	13 (31.7)
Negative	57	21		6 (33.3)	51 (73.9)	2 (33.3)	19 (46.3)
Unassessable	9	11		4 (22.2)	5 (7.3)	2 (33.3)	9 (22.0)
Differentiation grade			0.71				
Good/moderate	66	37		9 (50.0)	57 (82.6)	5 (83.3)	32 (78.0)
Poor	21	10		9 (50.0)	12 (17.4)	1 (16.7)	9 (222.0)
Tumor budding			0.010				
Bd1	52	22		6 (33.3)	46 (66.7)	4 (66.7)	18 (43.9)
Bd2/3	23	8		10 (55.6)	13 (18.8)	1 (16.7)	7 (17.1)
Unassessable	12	17		2 (11.1)	10 (14.5)	1 (16.7)	16 (339.0)
High risk	49	24	0.01	18 (90.0)	31 (38.8)	4 (66.7)	20 (48.8)
Low risk	45	13		1 (5.0)	44 (55.0)	2 (33.3)	11 (26.8)
Unknown risk	6	10		1 (5.0)	5 (7.2)	0	10 (24.4)

#### Table 2. Histological reassessment

CS, completion surgery; FTRS, full-thickness resection of the local excision scar; LIRC, local intramural residual cancer; LNM, lymph node metastasis.

to CS in case of absence of other histological risk factors than resection margin is important. We have seen that 55.6% of the patients with LNM and 18.8% of the patients without LNM experienced high-grade tumor budding. This suggests that adding tumor budding to the risk model could aid in predicting patients exhibiting higher risks for LNM.

A second limitation is the observed difference in proportion of LIRC between the CS and FTRS group (5.4% vs11%). Although a second opinion could be performed on the original endoscopic excised specimen, a second opinion on the scar in CS specimens was impossible because complete embedding of the scar is not part of routine practice. The histological evaluation of the local excision scar in the specimen of CS might have been performed less thoroughly than evaluation of the scar in the specimen of FTRS because histological findings show less consequences for treatment in CS. This may have caused that patients with undetected microscopic LIRC have been included in the no-LIRC CS group. Because these cases show a worse prognosis than no-LIRC cases, this may have resulted in a higher number of LNM positive cases in the CS group. However, we believe that this impact may be just small because the current number of detected recurrences in the FTRS group with a median follow-up of 3 years follows the expected line of recurrence with an expected recurrence of approximately 8%-10% at 5 years.

A third limitation is a potential confounding by indication, which may have influenced the decision to perform FTRS instead of CS. The actual reason to choose for a specific treatment strategy was not mentioned in the electronic medical records but also is likely related to availability of FTRS techniques in the individual centers and an increasing popularity of this approach in the Netherlands. From all known risk factors for LIRC and recurrence, the FTRS group showed a higher percentage of rectal lesions and nonpedunculated morphology, both known to be associated with a higher risk of LIRC and cancer recurrence (28). This makes the FTRS group rather at a higher risk of recurrence than the CS group. But it should be acknowledged that the number of events is too small to correct for baseline characteristics in a multivariable model. As mentioned earlier, there was no difference in the number of missed histological features between both groups, but a difference in unmeasured parameters cannot be excluded.

A fourth limitation is the heterogeneous follow-up. Surveillance after FTRS was not performed according to a standard protocol and was heterogeneous between patients. Approximately 50% of the FTRS group was followed up as a low-risk group, and only 52% underwent imaging during follow-up, which was also with abdominal ultrasound, known to be inadequate for detecting LNM. It is likely that patients who underwent FTRS were in a less intensive surveillance program than that should be considered optimal based on our current findings. This may have caused that recurrences were detected relatively late, with a negative impact on the proportion of curative salvage surgeries. It cannot be excluded that some of the recurrences are still undetected and will appear during follow-up. However, OS is comparable, and the current number of detected cases corresponds to the detection of recurrences at 5 years of follow-up (15).

In conclusion, patients with a local excision of a T1 CRC with R1/Rx resection margins without other histological risk factors have an 8%–9% risk for LNM. In cases where LIRC is detected, a much higher risk of LNM and recurrence is detected, although the numbers of patients are small. Finding LIRC at baseline may be indicative of a poorer tumor biology, associated with advanced stage of disease. In such cases, a stronger plea for a CS should be adopted in the discussion with the patient. However, in patients

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without LIRC, a strategy with FTRS combined with surveillance with salvage surgery in case of CRC recurrence, results in a similar 5-year MFS and OS when compared with CS and a 95% reduction in surgical interventions.

#### CONFLICTS OF INTEREST

Guarantor of the article: Leon M.G. Moons, MD, PhD.

**Specific author contributions:** Study concept and design: K.M.G., L.M.G.M., F.t.B.; acquisition of data: all authors; statistical analysis and interpretation of data: K.M.G., M.M.L., S.G.E., L.M.G.M., F.t.B.; drafting of the manuscript: K.M.G.; critical revision of the manuscript for important intellectual content: all authors; histologic review: M.M.L.; study supervision: K.M.G., L.M.G.M., F.t.B. **Financial support:** This work was supported by a grant from the Dutch Digestive Diseases Foundation (reference MG/2015-040) and the Boks Scholten Foundation.

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# **Study Highlights**

# WHAT IS KNOWN

Local full-thickness resection of the scar after local excision of a T1 CRC with an unassessable or positive resection margins is increasingly performed, but evidence on oncological outcome is lacking.

#### WHAT IS NEW HERE

Full-thickness resections of the scar with salvage surgery did not differ in metastasis-free and overall survival from completion surgery and could be a valid alternative treatment strategy for T1 CRC with an unassessable or positive resection margins as a sole risk factor.

#### REFERENCES

- Tumours. DWGfG. Dutch Colorectal Cancer Guideline 2014. http:// www.oncoline.nl/colorectaalcarcinoom.
- Hassan C, Wysocki PT, Fuccio L, et al. Endoscopic surveillance after surgical or endoscopic resection for colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Digestive Oncology (ESDO) guideline. Endoscopy 2019;51:C1.
- Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 2020;25:1–42.
- 4. Zwager LW, Bastiaansen BAJ, Bronzwaer MES, et al. Endoscopic fullthickness resection (eFTR) of colorectal lesions: Results from the Dutch colorectal eFTR registry. Endoscopy 2020;52:1014–23.
- Leicher LW, de Vos Tot Nederveen Cappel WH, van Westreenen HL. Limited endoscopic-assisted wedge resection for excision of colon polyps. Dis Colon Rectum 2017;60:299–302.
- 6. de Jong GM, Hugen N. Minimally invasive transanal surgery is safe after incomplete polypectomy of low risk T1 rectal cancer: A systematic review. Colorectal Dis 2019;21:1112–9.
- Kuellmer A, Mueller J, Caca K, et al. Endoscopic full-thickness resection for early colorectal cancer. Gastrointest Endosc 2019;89:1180–9 e1.

- Backes Y, Kappelle WFW, Berk L, et al. Colorectal endoscopic fullthickness resection using a novel, flat-base over-the-scope clip: A prospective study. Endoscopy 2017;49:1092–7.
- Jones HJS, Al-Najami I, Baatrup G, et al. Local excision after polypectomy for rectal polyp cancer: When is it worthwhile? Colorectal Dis 2021;23(4): 868–74.
- 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;45:827–34.
- Di Gregorio C, Bonetti LR, de Gaetani C, et al. Clinical outcome of lowand high-risk malignant colorectal polyps: Results of a population-based study and meta-analysis of the available literature. Intern Emerg Med 2014;9:151–60.
- Lee SJ, Kim A, Kim YK, et al. The significance of tumor budding in T1 colorectal carcinoma: The most reliable predictor of lymph node metastasis especially in endoscopically resected T1 colorectal carcinoma. Hum Pathol 2018;78:8–17.
- Gijsbers KM, Post Z, Schrauwen RWM, et al. Low value of second-look endoscopy for detecting residual colorectal cancer after endoscopic removal. Gastrointest Endosc 2020;92(1):166–72.
- 14. PLOS Medicine Editors. Observational studies: Getting clear about transparency. PLoS Med 2014;11:e1001771.
- Dang H, Dekkers N, le Cessie S, et al. Risk and time pattern of recurrences after local endoscopic resection of T1 colorectal cancer: A meta-analysis. Clin Gastroenterol Hepatol [Epub ahead of print December 1, 2020.] doi: 10.1016/j.cgh.2020.11.032.
- Belderbos TD, van Erning FN, de Hingh IH, et al. Long-term recurrencefree survival after standard endoscopic resection versus surgical resection of submucosal invasive colorectal cancer: A population-based study. Clin Gastroenterol Hepatol 2017;15:403–11 e1.
- 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.
- Nam MJ, Han KS, Kim BC, et al. Long-term outcomes of locally or radically resected T1 colorectal cancer. Colorectal Dis 2016;18:852–60.
- 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.
- Tamaru Y, Oka S, Tanaka S, et al. Long-term outcomes after treatment for T1 colorectal carcinoma: A multicenter retrospective cohort study of Hiroshima GI Endoscopy Research Group. J Gastroenterol 2017;52: 1169–79.
- Nishida T, Egashira Y, Akutagawa H, et al. Predictors of lymph node metastasis in T1 colorectal carcinoma: An immunophenotypic analysis of 265 patients. Dis Colon Rectum 2014;57:905–15.
- Kobayashi H, Higuchi T, Uetake H, et al. Resection with en bloc removal of regional lymph node after endoscopic resection for T1 colorectal cancer. Ann Surg Oncol 2012;19:4161–7.
- Vermeer NCA, Backes Y, Snijders HS, et al. National cohort study on postoperative risks after surgery for submucosal invasive colorectal cancer. BJS Open 2019;3:210–7.
- Arolfo S, Allaix ME, Migliore M, et al. Transanal endoscopic microsurgery after endoscopic resection of malignant rectal polyps: A useful technique for indication to radical treatment. Surg Endosc 2014;28:1136–40.
- Serra-Aracil X, Pallisera-Lloveras A, Mora-Lopez L, et al. Transanal endoscopic surgery is effective and safe after endoscopic polypectomy of potentially malignant rectal polyps with questionable margins. Colorectal Dis 2018;20:789–96.
- 26. Rampioni Vinciguerra GL, Antonelli G, Citron F, et al. Pathologist second opinion significantly alters clinical management of pT1 endoscopically resected colorectal cancer. Virchows Arch 2019;475:665–8.
- 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;30:104–12.
- Kudo SE, Ichimasa K, Villard B, et al. Artificial intelligence system to determine risk of T1 colorectal cancer metastasis to lymph node. Gastroenterology 2021;160:1075–84 e2.

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