Low value of second-look endoscopy for detecting residual colorectal cancer after endoscopic removal

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Background and Aims: Endoscopic resection is often feasible for submucosal invasive colorectal cancers (T1 CRCs) and usually judged as complete. If histology casts doubt on the radicality of resection margins, adjuvant surgical resection is advised, although residual intramural cancer is found in only 5% to 15% of patients. We assessed the sensitivity of biopsy specimens from the resection area for residual intramural cancer as a potential tool to estimate the preoperative risk of residual intramural cancer in patients without risk factors for lymph node metastasis (LNM).

Methods: In this multicenter prospective cohort study, patients with complete endoscopic resection of T1 CRC, scheduled for adjuvant resection due to pathologically unclear resection margins, but absent risk factors for LNM, were asked to consent to second-look endoscopy with biopsies. The results were compared with the pathology results of the surgical resection specimen (criterion standard).

Results: One hundred three patients were included. In total, 85% of resected lesions were unexpectedly malignant, and 45% were removed using a piecemeal resection technique. Sixty-four adjuvant surgical resections and 39 local full-thickness resections were performed. Residual intramural cancer was found in 7 patients (6.8%). Two of these patients had cancer in second-look biopsy specimens, resulting in a sensitivity of 28% (95% confidence interval, <58%). The preoperative risk of residual intramural cancer in the case of negative biopsy specimens was not significantly reduced ($P = .61$).

Conclusions: The sensitivity of second-look endoscopy with biopsies for residual intramural cancer after endoscopic resection of CRC is low. Therefore, it should not be used in the decision whether or not to perform adjuvant resection. (Clinical trial registration number: NCT02328664.) (Gastrointest Endosc 2020;92:166-72.)

(footnotes appear on last page of article)

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INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality in the Netherlands.[1] Due to the implementation of a nationwide screening program, an increasing proportion of submucosal invasive CRCs (T1 CRCs) is being detected with improved opportunities for endoscopic resection.[2] However, the histologic resection

specimen may show risk factors for lymph node metastasis (LNM): poor differentiation, lymphovascular invasion, >1 mm submucosal invasion, and intermediate or high-grade tumor budding.[3-6] In the case of poor differentiation or lymphovascular invasion, the Dutch guidelines on the treatment of CRC recommend adjuvant surgical segmental resection.[7] In addition, adjuvant surgical resection is recommended in the case of uncertain resection margins due to the risk for local residual cancer. Uncertain resection margins are defined as a tumor-free margin ≤1 mm (R0 ≤1 mm), an indeterminate margin due to fragmentation and piecemeal resection (Rx), or a positive margin for malignancy (R1). However, in the case of an endoscopic resection judged as complete by the endoscopist but with uncertain resection margins at histology, only 5% to 15%[8-10] of adjuvant surgical resections show residual cancer, while putting the patient at risk of operative morbidity and mortality.[9,11] This low yield of adjuvant surgical segmental resection raises the question how to predict which patients should undergo surgery. In this context, we studied whether a second-look endoscopy showing an unremarkable resection area with biopsy specimens without malignancy is indicative for the absence of residual intramural cancer. The aim of our study was to assess the sensitivity and preoperative risk reduction for residual intramural cancer of suspicious and nonsuspicious second-look endoscopy with biopsy specimens in patients with uncertain resection margins but absent risk factors for LNM.

METHODS

Patients and study design

This multicenter prospective study was conducted between June 2016 and January 2019. Patients with an endoscopically (macroscopically) completely removed T1 CRC but in whom pathology showed indeterminate or irradical resection margins (R0 ≤1 mm, Rx, or R1) but no risk factors for LNM, were included. For this reason, patients should have been scheduled for adjuvant resection. Patients were asked to consent to preoperative second-look endoscopy with biopsies from the resection area.

It did not matter whether malignancy was suspected or diagnosed before endoscopic removal or was found unexpectedly in a polyp removed without special precautions. We did not study the relationship between previous biopsies or removal attempts and the success rate of endoscopic resection.

Although patients with R0 ≤1 mm, Rx, or R1 may constitute groups with different risks for residual intramural cancer, from a clinical point of view and based on endoscopic and pathologic results, it is impossible to allocate these patients beforehand. Therefore, we took the clinical dilemma of an endoscopically judged complete resection but uncertain pathologic radicality as the starting point for the study.

Risk factors for LNM were defined as follows: poor or signet cell differentiation; lymphovascular invasion; >1 mm submucosal invasion and intermediate-grade (5-9 buds) or high-grade (≥10 buds) tumor budding.[3-6]

In general, the study was intended to reveal a real-world situation in colorectal centers with endoscopists and pathologists certified and audited by the national screening program on CRC prevention, which is currently the highest-quality standard in the Netherlands and includes yearly audits of colonoscopy quality issues and second readings of pathology specimens within each center. No external pathology referral was required, and the appropriateness of the endoscopic equipment as well as the decision on the use of advanced imaging techniques was left to the endoscopist.

If LNM risk factors were indeterminate or not reported, eg, in the case of budding, which is not routinely examined in the Netherlands, inclusion was allowed.

Although adjuvant surgical segmental resection was preferred, adjuvant resection of the endoscopic resection area with full-thickness resection techniques, such as endoscopic full-thickness resection, transanal endoscopic microsurgery, or local surgical wedge excision, was allowed. This is accepted in the Netherlands when resection margin uncertainty is the only reason for adjuvant treatment.[12-14] The choice of resection was decided by the local oncology committee.

The study was approved by the central committee on research involving human subjects (reference number NL45161.078.451) and the medical ethical committee of the Erasmus Medical Center, Rotterdam, the Netherlands (reference number METC 2015-206). Patients provided written informed consent to participate in the study. The study protocol was registered with clinicaltrials.gov (NCT02328664). All coauthors had access to the study data and reviewed and approved the final manuscript.

Second-look endoscopy

Suspicious macroscopic endoscopic features at second-look endoscopy were defined as a lesion suspected to harbor carcinoma. Advanced imaging was not required. A clean scar with normal mucosa, a benign-appearing post-polypectomy ulcer, or adenomatous remnants were considered nonsuspicious. Random biopsies (maximum of 10) were taken from the endoscopic resection area. For small scars, it was a requirement that the scar area was macroscopically denuded by the biopsies. Any (sub) mucosal irregularities in or around the polypectomy area were sampled separately.

Because of concerns by some participants that taking biopsies from an insufficiently healed polypectomy wound could cause perforation, the protocol advised waiting for 14 days before doing a second-look endoscopy. However,

not every participant shared this concern, and if biopsies were undertaken earlier, this was accepted. Biopsy specimens were collected in formalin, processed, and reported according to current standards.[15,16]

From a clinical point of view, suspicious histologic features were defined as high-grade dysplasia or (suspicion of) cancer because these cells are pathologically equal. Benign adenomatous tissue and/or ulceration was classified as nonsuspicious.

Adjuvant resection

Adjuvant resection was performed according to best clinical insights for the patients, as determined by the local multidisciplinary oncology board. We did not collect data on why a decision was made between full surgical oncologic resection or mural resection only, because this was not the purpose of our study. Pathology was processed according to the standard of care with special attention to the identification of the endoscopic resection site using TNM classification (7th edition).[17] Cases with intramural residual cancer were reviewed to assess the localization of the residue.

Data collection and aims

Data were collected prospectively using the open-source online platform OpenClinica (Free Software Foundation). Primarily, we aimed to determine (1) the sensitivity of second-look endoscopy with biopsies for residual intramural cancer; and (2) the reduction in the preoperative risk of residual intramural cancer in the case of nonsuspicious endoscopic and histologic findings. A secondary aim was to determine the number and severity of adverse events (defined according to good clinical practice and the Dutch Society of Gastroenterology) after biopsies from the polypectomy area and 90-day mortality after surgery.

Sample size calculation

It was decided beforehand that for an oncologic test, second-look endoscopy should have a sensitivity of $\geq$95% to be clinically useful. Based on a noninferiority design, with a noninferiority margin of 90%, an alpha value of 0.05, and a beta value of 0.20, binomial calculations showed that 194 patients with residual cancer in the bowel wall were needed to achieve such power. Assuming a residual cancer incidence of 20% and a dropout rate of 10%, and based on a positive outcome, 1091 patients were needed to achieve this alpha. However, in the case of a negative outcome, such numbers would not be necessary.

Interim analysis after every 100 inclusions was planned to validate these assumptions. To be sure not to jeopardize the results in the case of premature termination, a strict upper confidence interval of 99.9% of the calculated sensitivity below the margin of noninferiority (90%) was stated to terminate the study prematurely.

Statistical analysis

Confidence intervals for sensitivity were conservatively calculated using binomial statistics in Microsoft Excel for Mac Version 16.15 (Microsoft, Redmond, Wash, USA). Baseline characteristics were analyzed using standard descriptive statistics and the chi-squared test or Fisher exact test when applicable. From these, absolute risk reductions with 95% confidence intervals and chi-squared statistics were derived. In case of a zero count, 0.5 was added to each cell count to avoid division by zero (Haldane-Anscombe correction). These analyses were performed using IBM SPSS statistics version 25.

RESULTS

Patient characteristics

A total of 247 patients were prospectively registered in 25 hospitals. In total, 103 patients were eligible for inclusion (Fig. 1). The median age was 66.5 years (interquartile range, 63-71 years); 36% were female. The baseline characteristics of these patients are presented in Table 1. Most of the malignancies were located in the rectosigmoid area (86%). In 17 cases (18%), the malignant nature of the lesion had been recognized on beforehand. Twenty-five lesions were pedunculated (23%). Forty-six lesions were removed by piecemeal EMR (45%). Lymphovascular invasion, differentiation grade, and depth of invasion could not be assessed due to fragmentation in 9%, 0%, and 37% of cases, respectively, or was not reported in 0%, 7%, and 4% of cases. Tumor budding was not reported in 90% of our cases.

Adjuvant resections

Median time from the removal of the malignant polyp to the adjuvant resection was 45 days (range, 4-154 days). Types of resections are presented in Table 1. Surgical adjuvant resection was performed in 64 patients (62%). After surgery, 3 patients had a temporary ileostomy or colostomy (4.5%). One patient had a conversion from a laparoscopic to an open approach. The 90-day mortality rate after surgery was 1.5%. Adverse events occurred in 11 patients (16.6%), specifically; anastomotic leakage with relaparotomy leading to mortality in 1 patient, bleeding that required endoscopic intervention in 4 patients, prolonged ileus in 1 patient, infection (gastroenteritis, pneumonia) in 3 patients, and a cardiovascular adverse event in 1 patient. Thirty-nine patients (38%) underwent adjuvant full-thickness resection only. No adverse events were reported in this group.

Histology of the surgical specimen

The pathologist could localize the endoscopic resection area in the surgical specimen in 55 of 64 cases (86%). Four patients in the surgery group (6.0%) and 3

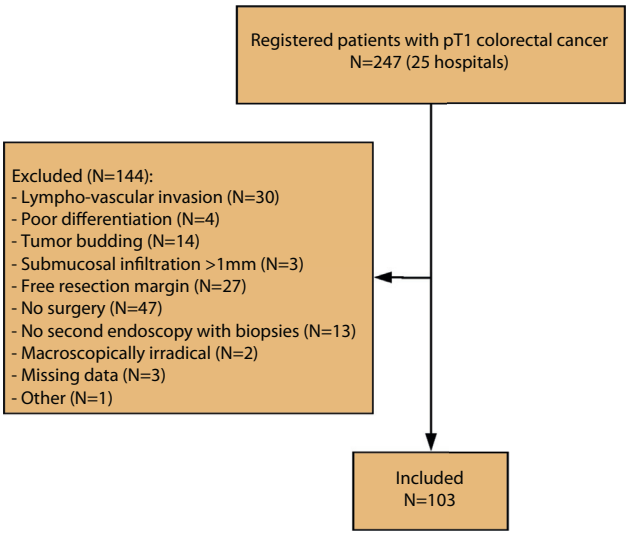

Figure 1. Flowchart and criteria for exclusion.

patients in the full-thickness resection group (7.7%) had residual intramural cancer. Overall, residual intramural cancer was found in 6.8% of patients. None of the 16 patients with R0 ≤1 mm resection margins had residual intramural cancer. Three of the residual intramural cancers were found after Rx resections, 4 after R1 resections. All residual intramural cancers were found in nonpedunculated lesions. Although not within the scope of this study, 7 cases with lymph node metastases were detected (5 cases without residual intramural cancer) despite the absence of risk factors for LNM in the pathology reports. None of these patients had suspicious second-look endoscopy or biopsy specimens. The findings are summarized in Figure 2.

The intramural residue was found just below the surface in 2 cases (found on biopsy specimens), below a band of fibrous tissue at the border of the muscularis propria (1 case) and deeply or even through the muscularis propria (4 cases). None of the latter were found with biopsies.

Second-look endoscopy, sensitivity, and risk reduction

Second-look endoscopy was performed after a median of 22 days (range, 7-63 days). A median of 4 biopsies were taken from the site (range, 1-10). No adverse events were reported after second-look endoscopy. Suspicious histology was found in 4 patients, of which 3 were also deemed endoscopically suspicious for residual cancer. Eight patients had benign adenomatous remnants.

None of the patients with 1 (n = 1) or 2 (n = 7) biopsy specimens had residual intramural cancer. There was no statistically significant relationship between the number of biopsy specimens and the probability of finding intramural residual cancer (P = .335). Second-look endoscopy with biopsies detected 2 of the 7 cases of residual intramural cancer. Among the 99 cases without residual intramural cancer, 2 had suspicious findings on biopsy specimens. This implied a specificity of 98% and a sensitivity of 28% (binomial one-sided upper 99.9% confidence limit, 86%), with a negative predictive value of 95% (95% confidence interval, 88%-98%). As the strict upper confidence limit of sensitivity was below the 90% limit of noninferiority, the study was prematurely terminated. A nonsuspicious scar at second-look endoscopy, including nonsuspicious histology, reduced the absolute preoperative risk of residual intramural cancer from 7 of 103 (6.8%) to 5 of 99 (5.1%), which is not statistically significant (P = .61).

TABLE 1. Characteristics of the patients

	Value
Total number of patients included	103
Female gender, n (%)	37 (35.9)
Age (years), median (range)	66.5 (47-88)
ASA score, n (%)	
1-2	90 (87.4)
3-4	6 (5.8)
Missing	7 (6.8)
Location of malignant lesion, n (%)	
Proximal colon	11 (10.7)
Distal colon	56 (54.3)
Rectum	36 (35.0)
Polyp morphology, n (%)	
Pedunculated	25 (23.3)
Nonpedunculated	75 (73.8)
Missing	3 (2.9)
Size (mm), median (range)	20 (6-80)
Resection technique, n (%)	
En bloc	57 (55.3)
Piecemeal EMR	46 (44.7)
Resection margin, n (%)	
Small R0 (≤1 mm free margin)	16 (15.5)
Rx (indeterminate margin)	41 (39.8)
R1 (margin not free)	46 (44.7)
Adjuvant resection type, n (%)	
Surgical resection	64 (62.1)
Low anterior resection	16
Sigmoid resection	34
Left hemicolectomy	5
Right hemicolectomy	9
Full-thickness resection, n (%)	39 (37.9)
Transanal endoscopic microsurgery	30
Endoscopic full-thickness resection	8
Laparoscopic wedge resection	1

ASA, American Society of Anesthesiologists.

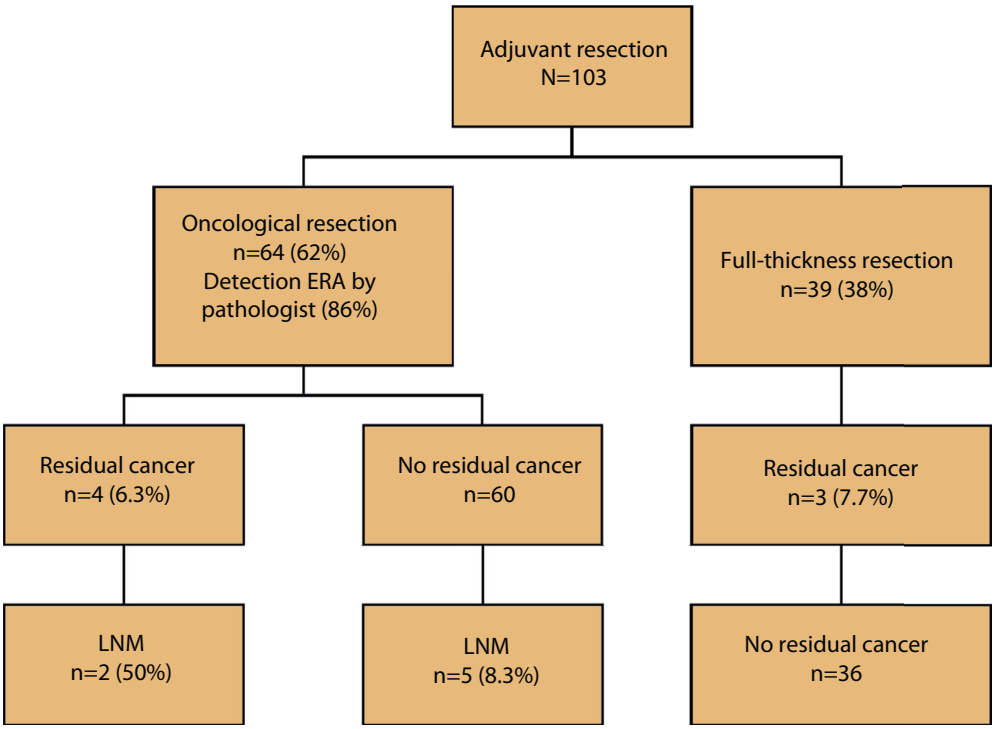

Figure 2. Results of adjuvant resection. *ERA*, Endoscopic resection area; *LNM*, lymph node metastasis.

DISCUSSION

To our knowledge, this is the first prospective study to investigate whether a second-look endoscopy with biopsies of the polypectomy site after an endoscopically judged complete resection of a T1 CRC with uncertain resection margins at histology could predict the need for adjuvant surgical resection. Unfortunately, sensitivity was only 28% with an upper 95% confidence limit of 58% and an upper 99.9% confident limit of 85%, making it implausible that sensitivity would ever cross the 90% noninferiority margin, which was prestated for an oncologic test to be of value. This resulted in premature termination of the project.

Accordingly, these data discourage the use of second-look endoscopy with biopsies to determine the need for adjuvant surgical resection. Negative biopsy specimens do not rule out residual intramural cancer, and surgical resection should be contemplated, because this is currently the standard in these circumstances.[7]

Our data revealed the risk for residual intramural cancer after an endoscopically judged complete resection with R1, Rx, or R0 ≤1 mm resection margins at histology was 6.8%. Benizri et al,[9] Shin et al,[18] and Backes et al[19] all showed 4.3% to 6.1% residual cancer in patients with an uncertain resection margin. An older meta-analysis by Hassan et al[10] showed a residual cancer rate of 14.1%. It was remarkable that none of the patients with a tumor-free margin ≤1 mm had residual malignancy in the bowel wall (16 cases). This is in accordance with Ueno et al[20] and adds to the evidence that radical margins ≤1 mm have a low risk of residual cancer. All residual intramural cancers were found in patients with a nonpedunculated lesion, which is in agreement with the findings of Kessels et al.[21]

It could be argued that it is unclear to what extent our study group consisted of patients with a superficial (sm1) T1 CRC with indeterminate resection margins due to piecemeal EMR; or patients with a deeply invasive carcinoma with indeterminate resection margins due to scope fragmentation. However, this leaves the fact that pathology cannot identify those cases separately, and the clinician is left with the dilemma of whether or not to operate. In addition, all of these resections were judged complete endoscopically, and it was our hypotheses that biopsy specimens would identify those cases with deep invasion, because these have an increased risk of residual intramural cancer.

Our results confirm the known dilemma of an 88% rate of negative findings at adjuvant surgery, a mortality rate of 1.5%, an ileostomy or colostomy rate of 4.5%, and a serious adverse event rate of 16.6%, in line with a recent study by Vermeer et al,[22] which showed no statistically significant differences between patients with pT1 and pT2-3 disease for adverse event rate and mortality. Furthermore, our results confirm the poor endoscopic recognition of T1 CRC. In a recent study of T1 CRCs found in the national screening program, a comparable

endoscopic identification rate of malignant polyps of only 19% was seen.

Although not the primary focus of this study, a remarkable finding was that, despite the absence of risk factors for LNM in the pathology reports, 7 cases with lymph node metastases were detected, of which 5 had no residual intramural cancer. This emphasizes the problem of referral criteria and the urgent need for improvement.

Several potential limitations should be discussed. First, one might argue that we did not use preconceived training and criteria to assess the polypectomy site and hence subtle remnants could have been missed. Indeed, it has been demonstrated that the use of a preconceived protocol using high-definition endoscopes with narrow-band imaging reveals more adenomatous remnants in the post-EMR surveillance situation.[23] However, biopsy remains the criterion standard on which these studies rely.

Second, due to the allowance of full-thickness resection techniques, no firm conclusions about LNM risk were possible, and we did not include LNM in our definition of residual cancer. This makes sense, because a second-look endoscopy could only be a decisive tool in cases without risk factors for LNM. In the presence of risk factors, adjuvant surgery is advised independently of intramural residual cancer status. Notwithstanding this, in our operated cases, LNM was present in 8% of patients despite the absence of LNM risk factors. It could be that the bare fact of an irradical resection should be conceived as a new risk factor for LNM, but this definitely requires further investigation. Although second-look endoscopy was performed up to 63 days after resection, we feel that this could not introduce bias because residual intramural cancer is unlikely to disappear over time. Finally, there were 8 cases with a very small scar and hence only 1 (n = 1) or 2 biopsy specimens (n = 7). One might argue that this number is perhaps too small to find residual intramural cancer. Although this might be true, none of these cases were found to have residual intramural cancer, so the results of our study would not have been different if more biopsies had been taken in these cases. Our study suggests that residual intramural cancer is generally located deep in the wall, explaining why it is invisible and not found in superficial biopsy specimens.

In summary, this study demonstrates that a second-look endoscopy with biopsies of the polypectomy area is not a reliable tool in the decision-making process when considering whether to refrain from adjuvant surgery in the case of local irradicality only.

ACKNOWLEDGMENTS

This research was supported by grants from the Boks Scholten foundation, Deventer, and the Hans Diels foundation, Gorssel, the Netherlands.

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Abbreviations: CRC, colorectal cancer; LNM, lymph node metastasis.

DISCLOSURE: *All authors disclosed no financial relationships.*

0016-5107/$36.00
https://doi.org/10.1016/j.gie.2020.01.056

Received November 26, 2019. Accepted January 22, 2020.

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