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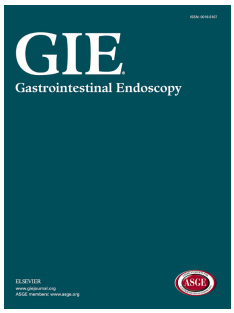

Low value of second-look endoscopy in detecting residual colorectal cancer after endoscopic removal.

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Abstract

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 (RIC) is found in only 5% to 15% of patients. We assessed sensitivity of biopsies from the resection area for RIC as a potential tool to estimate the preoperative risk of RIC in patients without risk factors for lymph node metastasis (LNM).

Methods
In this multicenter prospective cohort study, patients with complete endoscopic resection of a T1-CRC, scheduled for adjuvant resection due to pathologically unclear resection margins, but absent risk factors for LNM, were asked to consent for second-look endoscopy with biopsies. The results were compared with 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% removed using a piecemeal resection technique. Sixty-four adjuvant surgical resections and 39 local full-thickness resections were performed. RIC was found in 7 patients (6.8%). Two of these patients had cancer in second-look biopsies, resulting in a sensitivity of 28% (95% CI, <58%). The preoperative risk of residual intramural cancer in case of negative biopsy specimens was not significantly reduced (p = 0.61).

Conclusions
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.
https://clinicaltrials.gov/show/NCT02328664

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 CRC (T1-CRC) is detected with improving opportunities for endoscopic resection [2]. However, the histological resection specimen may show risk factors for lymph node metastasis (LNM): poor differentiation, lympho-vascular invasion, >1 mm submucosal invasion and intermediate or high-grade tumor budding [3-6]. In case of poor differentiation or lymphovascular invasion, the Dutch guideline on the treatment of CRC recommends adjuvant surgical segmental resection [7]. In addition, adjuvant surgical resection is recommended in 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 indeterminable margin due to fragmentation and piecemeal resection (Rx) or a positive margin for malignancy (R1). However, in case of an endoscopic resection which is 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 biopsies without malignancy is indicative for the absence of residual intramural cancer. The aim of our study was to assess sensitivity and preoperative risk reduction for residual intramural cancer of respectively suspicious and nonsuspicious second-look endoscopy with biopsies 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 were included with an endoscopically (macroscopically) completely removed T1-CRC but in whom pathology showed indeterminable or irradical resection margins (R0 ≤ 1 mm, Rx or R1) but no risk factors for LNM. For this reason, patients should have been scheduled for adjuvant resection. Patients should 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. Besides, 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 on beforehand. Therefore, we took the clinical dilemma of an endoscopically judged complete resection but uncertain pathological radicality as starting point for the study.
Risk factors for LNM were defined as follows: poor or signet cell differentiation; lympho-vascular invasion; >1 mm submucosal invasion and intermediate (5-9 buds); or high (≥10 buds) grade 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 colorectal cancer prevention, which is currently the highest quality standard in the Netherlands and includes yearly audits of colonoscopy quality issues and second reading of pathology specimens within each center. No external pathology referral was required, and the appropriateness of endoscopic equipment as well as the use of advanced imaging techniques was left at the decision of the endoscopist.
If LNM risk factors were indeterminable or not reported—for instance 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 (eFTR), transanal endoscopic microsurgery (TEM) 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 made by decision of the local oncological 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 their written informed consent to participate in the study. The study protocol was registered with the clinicaltrials.gov number 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 postpolypectomy ulcer or adenomatous remnants were considered nonsuspicious. The endoscopic resection area was randomly biopsied with a maximum of 10. For small scars, it was demanded that the scar area was macroscopically denuded by biopsies. Any (sub)mucosal irregularities in or around the polypectomy area were biopsied separately.

Due to concerns by some participants that taking biopsies of an insufficiently healed polypectomy wound could cause perforation, the protocol advised to wait for 14 days before doing a second-look endoscopy. However, not every participant shared this concern, and if biopsies were taken 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 histological 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 non-suspicious.

Adjuvant resection

Adjuvant resection was performed according to best clinical insights for the patients, as determined in the local multidisciplinary oncological board. We did not collect data on why a decision was made between full surgical oncological resection or mural resection only, as this was not the purpose of our study.

Pathology was processed according to standard of care with special attention to the identification of the endoscopic resection site using TNM (7^{th} edition) [17].

Cases with intramural residual cancer were reviewed to assess the localization of the residue.

Data collection and aims

Data were prospectively collected using the open source online platform OpenClinica [18]. 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 case of nonsuspicious endoscopic and histological findings. Secondary, we aimed to determine the number and severity of adverse events (defined according to GCP and the Dutch Society of Gastroenterology) of biopsies from the polypectomy area and 90-day mortality after surgery.

Sample size calculation

It was prestated that for an oncological test, second-look endoscopy should have a sensitivity of ≥95% to be clinically useful. Based on a noninferiority design, with a noninferiority margin of 90%, an alpha of 0.05, and a beta of 0.20, binomial calculations resulted in 194 patients with residual cancer in the bowel wall needed to achieve such power. Assuming a residual cancer incidence of 20% and a dropout rate of 10%. Based on a positive outcome, 1091 patients were needed to achieve this alpha. However, in case of 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 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. Baseline characteristics were analyzed using standard descriptive statistics and chi-square test or Fisher exact when applicable. From these, absolute risk reductions with 95% confidence intervals and chi-square 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 (Figure 1). Median age was 66.5 years (IQR 63 – 71 years); 36% was female. Baseline characteristics of these patients are presented in Table 1. The majority of malignancies were located in the rectosigmoid (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%). Lympho-vascular 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, three 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 out of 64 cases (86%). Four patients in the surgery group had residual intramural

cancer (6.0%) and 3 patients in the full-thickness resection group (7.7%). Overall, residual intramural cancer was found in 6.8% of patients. None of the 16 patients with a R0 ≤1mm resection margins had residual intramural cancer. Three of the residual intramural cancers were found after Rx resections, four 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 absence of risk factors for LNM in the pathology reports. None of these patients had suspicious second-look endoscopy or biopsies. Findings are summarized in Figure 2.
The intramural residue was found just below the surface in 2 cases (found on biopsies), 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 was 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. Besides, 8 patients had benign adenomatous remnants.
None of the patients with 1 (n=1) or 2 (n=7) biopsies had residual intramural cancer. There was no statistically significant relationship between number of biopsies and the probability of finding intramural residual cancer (p = 0.335). 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 in biopsies. 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% CI, 88% - 98%). As the strict chosen 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 7/103 (6.8%) to 5/99 (5.1%), which is not statistically significant (p = 0.61).

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% non-inferiority margin which was pre-stated for an oncological 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 biopsies do not rule out residual intramural cancer and surgical resection should be contemplated, as 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 R 0 ≤1mm resection margins at histology was 6.8%. Benizri et al [9], Shin et al [19], and Backes et al [20] 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 ≤1 mm tumor free margin had residual malignancy in the bowel wall (16 cases). This is in accordance with Ueno et al [21] and adds to the evidence that radical margins ≤1 mm have a low risk of residual cancer. Besides, all residual intramural cancers were found in patients with a non-pedunculated lesion, which is in correspondence with the findings of Kessels et al [22].
It could be argued that it is unclear to what extend our study group consisted of patients with a superficial (sm1) T1-CRC with indeterminable resection margins due to pEMR; or patients with a deeply invasive carcinoma having indeterminable 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 whether or not to operate. In addition, all these resections were endoscopically judged complete, and it was our hypotheses that biopsies would identify those cases with deep invasion, as these have an increased risk of residual intramural cancer.

Our results confirm the known dilemma of a 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%, which is in line with a recent study by Vermeer et al [23], 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 among 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 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, with 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 [24]. However, biopsies remain 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, as a second-look endoscopy could only be a decisive tool in cases without risk factors for LNM. In presence of risk factors, adjuvant surgery is advised independently of intramural residual cancer status. This does not withstand that in our operated cases, LNM were present in 8% of patients despite 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 is definitely subject to further investigation. Although, second-look endoscopy was performed up to 63 days after resection we feel that this could not introduce bias as 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 biopsies (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 deeply in the wall, explaining why it is invisible and not found in superficial biopsies.

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 to refrain from adjuvant surgery in case of local irradicality only.

Figures and tables

Figure 1: Flowchart and reason for exclusion.

Figure 2: Results of adjuvant resection. ERA = Endoscopic resection area, LNM = lymph node metastasis

	n	% / range
Total number of patients included	103	
Female gender	37	(35.9%)
Age in years	66.5	(47 - 88)
ASA score		
- ASA 1-2	90	(87.4%)
- ASA 3-4	6	5.8%)
- Missing	7	(6.8%)
Location malignant lesion		
- Proximal colon	11	(10.7%)
- Distal colon	56	(54.3%)
- Rectum	36	(35.0%)
Polyp morphology		
- Pedunculated	25	(23.3%)
- Nonpedunculated	75	(73.8%)
- Missing	3	(2.9%)
Size in mm, median (range)	20	(6 - 80)
Resection technique, n (%)		
- En-bloc	57	(55.3%)
- Piecemeal EMR	46	(44.7%)
Resection margin:		
- Small R0 (≤1 mm free margin)	16	(15.5%)
- Rx (undeterminable margin)	41	(39.8%)
- R1 (margin not free)	46	(44.7%)

Adjuvant resection type		
Surgical resection	64	(62.1%)
- Low anterior resection	16	
- Sigmoid resection	34	
- Left hemicolectomy	5	
- Right hemicolectomy	9	
Full thickness resection	39	(37.9%)
- Transanal endoscopic microsurgery	30	
- Endoscopic full-thickness resection	8	
- Laparoscopic wedge resection	1	

Table 1: characteristics of included patients.

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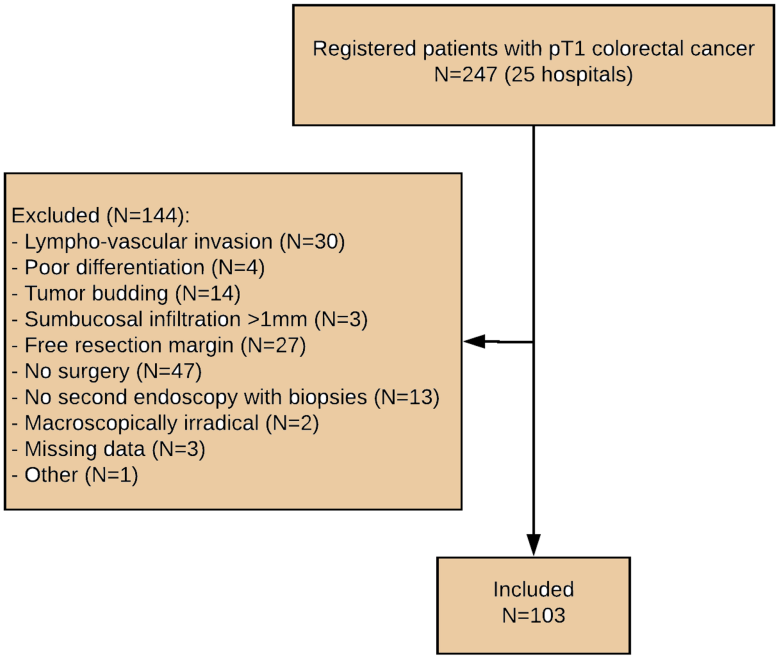

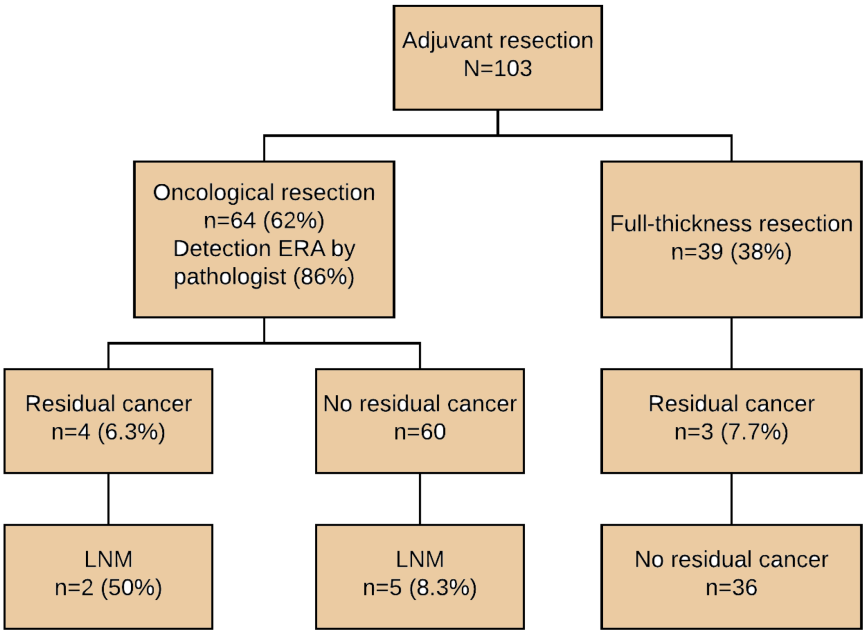

Abbreviations

ASA = American Society of Anesthesiologists
eFTR = endoscopic full-thickness resection
EMR = endoscopic mucosal resection
ERA = endoscopic resection area
GCP = good clinical practice
LNM = lymph node metastasis
METC = medical ethical committee
R0≤1mm = a ≤ 1 mm free resection margin
R1 = a resection margin which is not tumor-free
Rx = an indeterminable resection margin
RIC = residual intramural cancer
T1 CRC = submucosal invasive colorectal cancer
TEM = transanal endoscopic microsurgery