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Clinical consequences of diagnostic variability in the histopathological evaluation of early rectal cancer

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ABSTRACT

Introduction: In early rectal cancer, organ sparing treatment strategies such as local excision have gained popularity. The necessity of radical surgery is based on the histopathological evaluation of the local excision specimen. This study aimed to describe diagnostic variability between pathologists, and its impact on treatment allocation in patients with locally excised early rectal cancer.
Materials and methods: Patients with locally excised pT1-2 rectal cancer were included in this prospective cohort study. Both quantitative measures and histopathological risk factors (i.e. poor differentiation, deep submucosal invasion, and lymphatic- or venous invasion) were evaluated. Interobserver variability was reported by both percentages and Fleiss' Kappa- (κ) or intra-class correlation coefficients.
Results: A total of 126 patients were included. Ninety-four percent of the original histopathological reports contained all required parameters. In 73 of the 126 (57.9%) patients, at least one discordant parameter was observed, which regarded histopathological risk factors for lymph node metastases in 36 patients (28.6%). Interobserver agreement among different variables varied between 74% and 95% or κ 0.530–0.962. The assessment of lymphovascular invasion showed discordances in 26% ($\kappa = 0.530$, 95% CI 0.375–0.684) of the cases. In fourteen (11%) patients, discordances led to a change in treatment strategy.
Conclusion: This study demonstrated that there is substantial interobserver variability between pathologists, especially in the assessment of lymphovascular invasion. Pathologists play a key role in treatment allocation after local excision of early rectal cancer, therefore interobserver variability needs to be reduced to decrease the number of patients that are over- or undertreated.

1. Introduction

Nationwide cohort studies have shown that since the implementation of screening programs, colorectal cancer is diagnosed in earlier stages of the disease [1–3]. Although radical surgery is the standard treatment of most colorectal cancers, organ sparing treatment strategies, such as endoscopic or surgical local excisions,

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have acquired a prominent position in treatment of early colorectal cancer. Moreover, local excision of suspected T1 tumours is deemed safe by multiple guidelines [4,5]. Compared with local excision, radical surgery in rectal cancer is associated with substantial morbidity [6–9]. These adverse outcomes have led to an increasing demand for organ preservation from both patients and physicians.

Currently, rectal tumours are clinically staged by endoscopic findings and imaging. Nevertheless, imaging is associated with overstaging, which has been reported for both endoscopic ultrasound and MRI [10]. For this reason, in small early rectal tumours without risk features on imaging (e.g. suspected lymph nodes or invasion of the perirectal fat), upfront local excision seems attractive. The final histopathological analysis of the specimen is essential to decide on the appropriate treatment for individual patients. If the histopathological assessment of pT1 tumours does not show risk factors for lymph node metastases and/or local recurrence, no additional treatment is recommended and patients undergo surveillance [4]. However, in patients with an increased risk of local recurrence (i.e. pT1 tumours with histopathological risk factors, or pT2 tumours), a total mesorectal excision (TME) is recommended. Therefore, a solid evaluation of histopathological risk factors after local excision is crucial to determine the best treatment allocation for patients.

Consequently, histopathological assessments should be reliable and should include the information necessary to support clinical decision-making. However, diagnostic variability between pathologists has been described in several studies [11–15]. Previous studies on interobserver variability in the histopathological assessment of colorectal cancer have predominantly focused on either one specific risk factor or the use of a particular type of (immuno)histochemical staining [11–15]. Data on overall variability and multiple risk factors or therapeutic consequences is scarce, particularly in the field of early rectal cancer [16–18].

This study aimed to describe clinically relevant diagnostic variability in the histopathological evaluation of locally excised early rectal cancer. Primary outcomes were differences in the assessment of histopathological risk factors. Second, the clinical consequences of diagnostic variability were assessed.

2. Materials and methods

2.1. Study design

Pathology data were obtained from patients included in the TESAR trial, Clinicaltrials.gov identifier: NCT02371304 [19]. The study was approved by the Institutional Review Board of the Amsterdam UMC, Vrije Universiteit Amsterdam (2019.703).

The ongoing TESAR trial enrols patients who underwent local excision for pT1-2 rectal cancer and randomises between TME and adjuvant chemoradiotherapy. Prior to randomization, a central pathology review is performed. The current study included local excisions performed between November 2015 and October 2019. Local excision techniques consisted of Transanal Endoscopic Microsurgery, Transanal Minimally Invasive Surgery, Endoscopic Mucosal Resection, Endoscopic Submucosal Dissection, Endoscopic Full Thickness Resection, Endoscopic Intermuscular Dissection and snare polypectomy.

Eligibility for the current study was based on the original histopathological reports and required stage I rectal adenocarcinomas with an intermediate risk of recurrence. Intermediate risk was defined as: 1) pT1 tumours smaller than 3 cm with at least one of the following histopathological risk factors: poor differentiation, lymphovascular invasion, and/or deep submucosal invasion (Kikuchi level sm3/Haggitt level 4); 2) pT1 tumours between 3 and 5 cm with or without additional risk factors; or 3) pT2 tumours smaller than 3 cm, well-to-moderately differentiated, without lymphovascular invasion. Central pathology review could also be requested by participating centres (n = 21). These cases were included as well. Exclusion criteria were: suspected metastatic disease on imaging; lymph node involvement on MRI of the pelvis; recurrent or simultaneous colorectal cancer; concomitant malignancies (i.e. at least 5 years disease-free); previous radiotherapy of the pelvis; and patients unfit to undergo surgery (i.e. WHO performance status >2). To assess concurrent distant metastasis and involvement of locoregional lymph nodes (i.e. < 10 mm, independent of morphologic features) CT- and MRI scans were performed in all patients. Currently, the Dutch guideline and therefore the Dutch standardized synoptic reports do not distinguish lymphatic invasion from venous invasion, consequently, the overarching term lymphovascular invasion was used to describe both entities.

2.2. Central histopathological review

All histopathological slides (i.e. both haematoxylin and eosin (H&E) and available immunohistochemistry) and paraffin tissue blocks were requested for central pathology review. Central reviews were performed by an experienced gastrointestinal pathologist, who is also part of the pathology panel of the Dutch colorectal cancer screening program (NvG). All available slides were evaluated. Both the pathologist performing the original assessment and the pathologist performing the review had access to immunohistochemistry. Differentiation grade was assessed by the World Health Organization criteria, in which the worst component of the tumour was scored. This assessment did not involve the invasive front. Venous invasion was determined as intramural or submucosal venous invasion and was evaluated based on histological features such as orphan arteries or protruding tongues. In cases of doubt, venous invasion was confirmed using a Elastica van Gieson staining to confirm the presence of an elastic lamina. Lymphatic invasion was identified in H&E stains showing single cells or groups of tumour cells present within lymphatic vessels, usually covered with endothelial cells. In cases where lymphatic invasion was not reported originally, but suspicion for lymphatic invasion was raised at central review, an additional double staining for pan-cytokeratin/D2-40 was performed for confirmation. Immunohistochemistry was only used during review in case of doubt or to provide proof of the presence of lymphovascular invasion to the referring centres. If original slides were unavailable (n = 1), H&E slides were obtained from the provided paraffin blocks. The review reports were documented separately from the original reports, and were returned to the original pathology laboratories.

Patient characteristics, as well as histopathological characteristics were collected from both the original and central review reports. Histopathological reports were deemed complete when reports included: tumour stage (T-stage), histological tumour type, differentiation grade, lymphovascular invasion, and basal and mucosal resection margin distances. Additionally, in pT1 tumours submucosal invasion depth by Kikuchi level (in sessile lesions) or Haggitt classification (in polypoid lesions) was required. In accordance with the Dutch guideline, submucosal invasion depth in mm had to be reported if submucosal invasion depth could not be determined categorically. Tumour budding was a non-obligatory parameter in the standardized histopathology reports, and was therefore not incorporated in the study. Standardized histopathology reports were used in the majority of original reports. Primary outcome was to describe the diagnostic variability in histopathological parameters between the original pathology reports and the central review reports. The secondary outcome was to describe whether discordances could lead to changes in treatment strategy.

2.3. Statistical analysis

Demographic and histopathological data and variability between original and central review reports were evaluated through descriptive statistics. Categorical data were presented as frequencies and percentages. Continuous variables were differentiated into variables with a normal distribution and variables with a non-normal distribution by assessing histograms, Q-Q plots and Shapiro-Wilk tests. Normally distributed variables were reported as mean with standard deviation and non-normally distributed data by median and interquartile range. Categorical data were analysed using Fisher's exact tests. Differences in the number of changes and completeness over reports over time were evaluated by the linear-by-linear test for trend. Interobserver agreement was calculated in percentages and by the Fleiss' kappa coefficient (κ), which compares the observed agreement with agreement due to chance. A κ of <0 reflects poor, 0–0.20 slight, 0.21–0.4 fair, 0.41–0.6 moderate, 0.61–0.8 substantial and above 0.81 almost perfect agreement [20]. The intra-class coefficient was reported to describe agreement in continuous variables. Statistical analyses were performed using SPSS, version 26 (IBM Corp., Armonk, NY, USA).

3. Results

Data from 126 patients of the prospective cohort study were collected from 22 pathology laboratories in the Netherlands. The mean age of patients was 65.9 (±8.01) years old, and 58.7% (n = 74) of the patients was male. Supplementary Material Table 1 depicts the utilized local excision techniques. The original histopathological evaluation resulted in 80 (63.5%) pT1 tumours, 44 (34.9%) pT2 tumours, and in two patients T-stage could not be evaluated (Table 1). Of the original reports, 118 (93.7%) were considered complete, and all parameters were described in the central review reports. In 73 of the 126 (57.9%) patients at least one discrepancy was observed between the original and central review report. Excluding quantitative measures (i.e. tumour size and resection margin distances), the percentage of discrepancies was 42.1% (53 of 126). Hospital volume was not associated with the presence of discrepancies (Fisher's exact, $p = 0.244$). Fig. 1 shows the number of discordant parameters per patient and Fig. 2 the number of discordant parameters per year. In 16 (12.7%) patients three or more discrepancies were present. No statistically significant association between participating centres and the presence of these discrepancies was observed (Fisher's exact, $p = 0.383$). Over time, no trend was observed in the number of discordances (Linear-by-linear, $p = 0.290$) or the completeness of reports (Linear-by-linear, $p = 0.737$).

3.1. Interobserver variability

Table 1 provides an overview of the histopathological characteristics of both the original and central review reports. The most significant discrepancies were detected in the assessment of lymphovascular invasion (Fig. 3). Lymphovascular invasion was assessed differently in 33 of the 126 (26.2%) patients. Of these patients lymphovascular invasion was diagnosed during central review in eighteen (14.3%) patients and could not be diagnosed in two (1.6%) patients. In thirteen (10.3%) patients lymphovascular invasion was either suspected or not evaluable in the original report, but could be determined or ruled out in the central review report (Fig. 3). To confirm these discrepancies additional immunohistochemistry was performed in 26 patients. During the central review lymphatic invasion was distinguished from venous invasion: 29 cases showed lymphatic invasion, 31 venous invasion, and ten cases showed both (Table 1). Overall, the percentages of agreement varied from 73.8% in the assessment of lymphovascular invasion to 95.2% in tumour stage and differentiation grade (Table 1). After adjustment of agreement for chance, Fleiss' kappa and intra-class coefficients ranged from κ 0.530 to κ 0.962 (Table 1). An almost perfect agreement was observed for tumour diameter ($\kappa = 0.937$, 95% CI 0.905–0.958), tumour stage ($\kappa = 0.899$, 95% CI 0.729–1.00), Kikuchi level ($\kappa = 0.827$, 95% CI 0.726–0.927), basal margin ($\kappa = 0.962$, 95% CI 0.945–0.974), mucosal margin ($\kappa = 0.950$, 95% CI 0.925–0.967) and the assessment of the residual tumour classification (R-classification) ($\kappa = 0.877$, 95% CI 0.736–1.00). Substantial agreement was detected for differentiation grade ($\kappa = 0.607$, 95% CI 0.472–0.741). Moderate agreement was observed for lymphovascular invasion ($\kappa = 0.530$, 95% CI 0.375–0.684).

3.2. Clinically relevant discordances

Discrepancies in the evaluation of at least one histopathological risk factor (i.e. deep submucosal invasion, poor differentiation, lymphovascular invasion) were detected in 36 (28.6%) patients, and regarded lymphovascular invasion in 33 (26.2%) patients. Clinically relevant discrepancies that led to an alteration in treatment (i.e. different T-stage, R-classification and low- vs. high-risk pT1 tumours) were observed in 14 (11.1%) patients. Clinically relevant discrepancies in R-classification, were observed in eight patients (Table 2). The evaluation of T-stage showed inconsistencies in four patients (Table 2). In one patient both T-stage and R-classification was assessed differently. High-risk pT1 tumours were revised to low-risk pT1 tumours in three patients. In these patients completion surgery was avoided. In addition, in six patients with pT2 tumours without histopathological risk factors a lymphovascular invasion was diagnosed during the review, and in one patient both poor differentiation and lymphovascular invasion were not diagnosed during central review.

4. Discussion

This study identified substantial and clinically relevant interobserver variability in the assessment of histopathological parameters in early rectal cancer, including histopathological risk factors that potentially impact treatment strategies. In particular, the histopathological risk factor lymphovascular invasion showed a relatively high diagnostic variability of 26.2% ($\kappa = 0.530$, 95% CI 0.375–0.684). Moreover, in 11% of the patients, discordances were observed that led to a change in treatment strategy.

Over 90% of the histopathological reports were complete. Other studies that investigated histopathological reports of colorectal cancer specimens, showed a lower level of completeness (41–67%) [21,22]. There are several possibilities for the observed differences. First, specialized multidisciplinary team meetings with dedicated gastrointestinal pathologists have resulted in an improvement of pathology reports [23,24]. Second, Messenger et al. reported an essential increase in the number of complete histopathological reports after the implementation of a synoptic format, such a format has been used throughout the course of this study [23]. Comparable outcomes have been reported after the implementation of a standardized report in colorectal surgical resections, which included vascular invasion, tumour budding and the number of lymph nodes harvested [25]. Given the obligatory discussion of patients in multidisciplinary team meetings, and the frequent utilization of synoptic reporting in the Netherlands, the observed level of complete reports may have differed from other studies.

The observed rate of discrepancies in lymphovascular invasion (26.2% $\kappa = 0.530$, 95% CI 0.375–0.684) in this study is high. In the evaluation of malignant colorectal polyps by Davenport et al. agreement on lymphovascular invasion was worse ($\kappa = 0.33$, 95% CI

Table 1
Baseline characteristics and agreement of histopathological reports n = 126.

Characteristic	Original report n (%)	Review report n (%)	% agreement	κ-coefficient[d]
Tumor diameter (mm)[a,b]	17 (12–24)	18 (12–25)	79.8	0.937 (0.905–0.958)
Tumor stage			95.2	0.899 (0.729–1.00)
T1	80 (63.5)	79 (62.7)		
T2	44 (34.9)	47 (37.3)		
Not evaluable	2 (1.6)	0 (0)		
Kikuchi level			90.8	0.827 (0.726–0.927)
Sm1	5 (4.0)	11 (8.7)		
Sm2	10 (7.9)	11 (8.7)		
Sm3	39 (31.0)	40 (31.7)		
Not evaluable or no m. propria	8 (6.3)	8 (6.3)		
Other (Haggitt)	13 (10.3)	9 (7.1)		
Not reported	7 (5.6)	0 (0)		
T2	44 (34.9)	47 (37.3)		
Basal margin (mm)[a]	2.0 (0.9–4.0)	2.0 (0.8–4.0)	83.6	0.962 (0.945–0.974)
Mucosal margin (mm)[a]	5.0 (3.0–6.0)	5.0 (3.0–6.0)	79.8	0.950 (0.925–0.967)
R-classification			93.7	0.877 (0.736–1.00)
Rx	13 (10.3)	9 (7.1)		
R0	79 (62.7)	84 (66.7)		
R1	34 (27.0)	33 (26.2)		
≤1 mm to carcinoma	25 (73.5)	28 (84.8)		
Carcinoma in resection plane	9 (26.5)	5 (15.2)		
Differentiation grade			95.2	0.607 (0.472–0.741)
Well-to-moderate	117 (92.9)	118 (93.7)		
Moderate	0 (0)	2 (1.6)		
Poor	6 (4.8)	4 (3.2)		
Mucinous	2 (1.6)	2 (1.6)		
Not reported	1 (0.8)	0 (0)		
Lymphovascular invasion[c]			73.8	0.530 (0.375–0.684)
No	67 (53.2)	56 (44.4)		
Suspected	12 (9.5)	0 (0)		
Yes	46 (36.5)	70 (55.6)		
Venous invasion		31 (44.3)		
Lymphatic invasion		29 (41.4)		
Both		10 (14.3)		
Not reported	1 (0.8)	0 (0)		

[a] Median and interquartile range, intra-class correlation coefficient.
[b] Tumor diameter includes the diameter of the lesion as well as the size of the infiltrating carcinoma.
[c] Lymphovascular invasion includes both lymphatic and venous invasion.
[d] κ-coefficient of <0 reflects poor, 0–0.20 slight, 0.21–0.4 fair, 0.41–0.6 moderate, 0.61–0.8 substantial and above 0.81 almost perfect agreement.

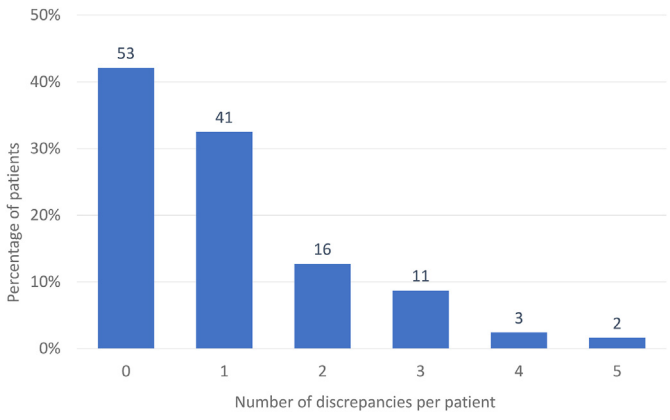

Fig. 1. Number of discordant parameters per patient.
The number of discordant parameters per patient (n = 126). X-axis: the number of discordant parameters per patient. Y-axis: the percentage of patients. The number above the bar indicates the frequency.

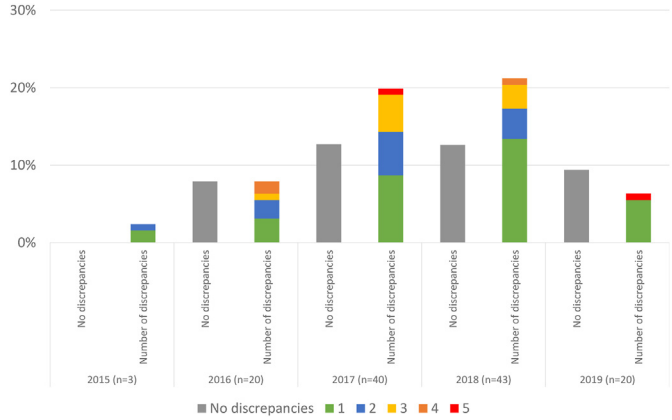

Fig. 2. Number of discordant parameters per year.
The spread of discrepancies per year. X-axis: number of discrepancies for each year. Y-axis: percentage of patients. Grey: no discrepancies, green: one discrepancy, blue: two discrepancies, yellow: three discrepancies, orange: four discrepancies, red: five discrepancies.

0.379–0.687) [26]. However, Rampioni Vinciguerra and colleagues described outcomes similar to our study (κ = 0.6, 95% CI 0.36–0.84) [17]. In this study we were unable to differentiate between lymphatic and venous invasion, since these elements were not distinguished in the frequently utilized standardized original

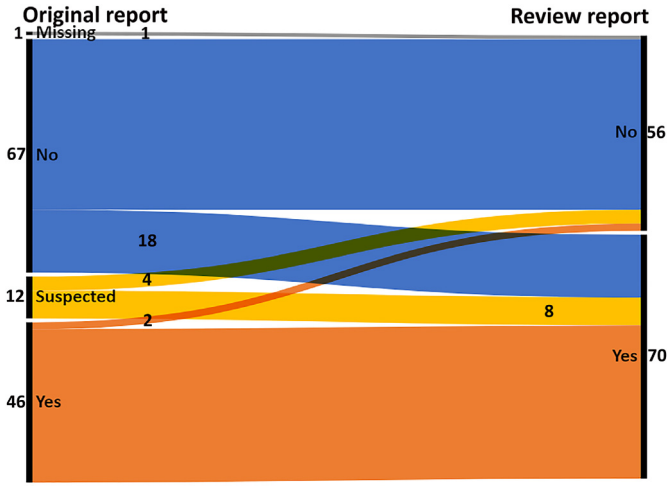

Fig. 3. Alluvial diagram of lymphovascular invasion
The original reports are presented on the left side and the central review reports on the right side. The observed discrepancies are indicated by the direction, width and numbers of the bars.

reports. Nevertheless, it has been suggested that lymphatic invasion is a stronger risk factor for lymph node metastasis than venous invasion, and for this reason it may be of clinical importance to differentiate between these factors [27,28]. Previous studies on interobserver variability in lymphovascular invasion predominantly focused on either lymphatic or venous invasion. Segregated evaluation of lymphatic and venous invasion has shown interobserver agreement with Kappa's varying between 0.22 - 0.618 and 0.18–0.617 for lymphatic and venous invasion, respectively [12,14,29–32]. To identify either lymphatic or venous invasion the use of (immuno)histochemistry has been proposed. In contrast to one's expectations, Harris et al. showed that interobserver agreement did not improve upon the addition of immunohistochemistry, but evidence is conflicting [12,14,15]. Additional immunohistochemistry techniques have shown to increase the identification rate of lymphatic and venous invasion [12,14]. Since the known association between lymphovascular invasion and lymph node metastases is founded on H&E slides, a higher detection rate of lymphovascular invasion could lead to lower predictive value of lymph node metastases. Therefore, the influence of immunohistochemistry on the identification of lymphovascular invasion and its association with the risk of lymph node metastases needs to be investigated more thoroughly in order to provide accurate positive predicting values.

Overall, there seems room for improvement in the diagnostic agreement on lymphovascular invasion in colorectal cancer and clinicians should be aware of these discrepancies. Aspects that might influence the observed discrepancies are the workload of pathologists and the possible unawareness of the clinical consequences of the assessment. These factors may contribute to diagnostic variation and might have an impact on a careful and dedicated assessment. A potential method to reduce variability and improve quality is education. For example, Kirsch et al. investigated the influence of a learning initiative, which involved detailed personal feedback, education on morphologic clues, and benchmark data, on the detection of venous invasion [29]. This study demonstrated that the learning initiative led to a significant increase in detection of vascular invasion [29]. Another possible approach to increase quality of histopathological evaluations is by discussing cases with peers or experts. Personal feedback or advice on when to perform additional immunohistochemistry might contribute to improve future evaluations, but requires an open demeanour of the consulting pathologist. In the future artificial intelligence may also help to reduce interobserver variability and improve the quality histopathological assessment. Recently, Kudo et al. published the first outcomes of a machine-learning artificial neural network that outperformed guidelines in identifying patients with lymph node metastases in T1 colorectal cancer. This network incorporated both patient- and tumour characteristics, including lymphatic- and venous invasion [33].

One of the limitations of this study was that histopathological material was re-examined by only one pathologist. Nonetheless, the study aimed to describe variability between pathologists. Therefore, a second reviewer would not have changed the number of observed discrepancies, but could have provided a better understanding of the distribution in assessments. Second, the Kappa-coefficient adjusts for agreement that is expected to occur by chance. This can lead to a paradox in variables with a high number of observations in one specific category, as can be observed in the variable differentiation grade [34,35]. In this variable the probability of agreement based on chance is relatively high, which leads to a low Kappa-coefficient. Moreover, in one case original slides were unavailable for review. In this case the resection margin distance could not be determined based on the new slides obtained from the available tissue block. In this study lymphovascular invasion that was deemed suspect in the original report and present in the review report were categorized as discordant ($n = 8$), which might be debated. If these cases would be defined as concordant, still in 19.8% ($n = 25$) of the patients lymphovascular invasion would have been assessed differently. Also, the difference in interpretation would not have influenced the percentage of 11.1% of the patients in which interobserver variation led to changes in treatment strategy. In addition, inclusion criteria for the TESAR trial consist of high-risk pT1 tumours and pT2 tumours without additional risk factors in the original report. Central reviews were performed to confirm eligibility for the TESAR trial. Therefore, one might suspect a certain bias of the pathologist. However, nine patients who were eligible based on the original assessment were excluded from the trial, whereas two patients could be included based on the review report. Since high-risk pT1 tumours were part of the inclusion criteria of this study, lymphovascular invasion was diagnosed in a relatively high percentage of patients. Only in three cases high-risk pT1 tumours were downgraded to low-risk pT1 tumours. Nevertheless, in 14.3% of the patients unreported lymphovascular invasion was diagnosed during central review. Therefore, if patients with low-risk pT1 tumours were included as well, the number of clinically relevant changes might have increased and diagnostic variability may have been even higher. Moreover, diagnostic variability as observed in this study would impact treatment strategies in this specific population. Last, we were unable to report pathological data after surgical resection or long-term follow-up data, since these are part of the ongoing TESAR trial [19].

In order to provide patients with optimal care, histopathological assessments should be reliable and interobserver variability should not lead to changes in treatment strategy. In pT1 rectal cancer the detection of histopathological risk factors defines whether a patient should undergo surveillance, radical surgery, or if the patient might be eligible for adjuvant chemoradiotherapy in a trial [19]. Therefore, pathologists play a key role in this clinical decision-making process. However, this study showed that diagnostic variability in the assessment of histopathological characteristics is substantial and potentially impacts treatment strategies. Potential approaches to decrease variability and thereby reduce over- or undertreatment of patients with early rectal cancer, may lie in education and consultation of peers.

Table 2
Discordances in histopathological reports (n = 126).

Category	Original report	Review report	Frequency (%)
Tumor diameter (incl. adenoma mm)[a]	No discrepancies		80 (63.5)
	Difference ≤ 5 mm		9 (7.1)
	Difference > 5 mm		10 (7.9)
	Not reported		27 (21.4)
Tumours stage	No discrepancies		120 (95.2)
	T1	T2	3 (2.4)
	T2	T1	1 (0.8)
	Not evaluable	Reported	2 (1.6)
Kikuchi level	No discrepancies		61 (48.4)
	Sm3	Sm2	1 (0.8)
	Haggitt 2	Haggitt3	1 (0.8)
	Haggitt	Sm	3 (2.4)
	Sm	Haggitt	1 (0.8)
	T1	T2	3 (2.4)
	T2	T1	1 (0.8)
	T2		45 (35.7)
	Not reported		10 (7.9)
Basal margin (mm)	No discrepancies		86 (68.3)
	Difference ≤0.5 mm		8 (6.3)
	Difference >0.5 mm		11 (8.7)
	Original ≤ 1 mm, in revision ≤ 1 mm specified		15 (11.9)
	Not reported/not evaluable	Specified	6 (4.8)
Mucosal margin (mm)	No discrepancies		89 (70.6)
	Difference ≤0.5 mm		1 (0.8)
	Difference >0.5 mm		12 (9.5)
	Original ≤ 1 mm, in revision ≤ 1 mm specified		2 (1.6)
	Original ≤ 1 mm, in revision > 1 mm		3 (2.4)
	Not reported	Reported	19 (15.1)
R-classification	No discrepancies		117 (92.9)
	R0	R1	2 (1.6)
	R1	R0	4 (3.2)
	Not evaluable	R0	2 (1.6)
	Not evaluable	R1	1 (0.8)
Differentiation grade	No discrepancies		119 (94.4)
	Well-to-moderate	Moderate	2 (1.6)
	Well-to-moderate	Poor	1 (0.8)
	Poor	Well-to-moderate	3 (2.4)
	Not reported		1 (0.8)
Lymphovascular invasion[b]	No discrepancies		93 (73.8)
	No	Yes	18 (14.3)
	Yes	No	2 (1.6)
	Suspected	No	4 (3.2)
	Suspected	Yes	8 (6.3)
	Not reported	No	1 (0.8)

[a] Tumor diameter includes the diameter of the lesion, not the size of the infiltrating carcinoma.
[b] Lymphovascular invasion includes both lymphatic and venous invasion.

Declaration of competing interest

This study was funded by the Dutch Cancer Society (2015-7715). Otherwise, the authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.02.008.

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