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Diagnostic variability in the histopathological assessment of advanced colorectal adenomas and early colorectal cancer in a screening population

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Aim: The aim of this study was to evaluate interobserver variability between individual pathologists and a panel of pathologists in the histopathological assessment of advanced colorectal neoplasms in the Dutch bowel cancer screening population.

Methods and results: Histological slides of adenomas with high-grade dysplasia and early colorectal carcinomas (CRC) from 20 different laboratories were reviewed by the pathology panel of the Dutch bowel screening programme. Interobserver variability was reported by descriptive statistics. In addition, potential clinical consequences of discrepancies were evaluated. A total of 104 cases of adenomas with high-grade dysplasia and 83 early CRCs were reviewed. Discrepancies were observed in 41 of 104 (39.4%) adenoma cases, which potentially had clinical consequences in 16 (15.4%) cases. For CRC, discrepancies were shown in 44 of 83 cases (53.0%) and would have potentially led to alternative treatment strategies in 25 (30.1%) cases. Most frequently, discrepancies were observed in the assessment of lymphovascular invasion (23 of 73 cases, 31.5%).

Conclusion: This study showed that considerable interobserver variability is present in the histopathological assessment of advanced colorectal neoplasia, which may impact upon treatment choices. Additional stains and education, as well as intercollegial consultation, might decrease this variability.

Keywords: adenocarcinoma, adenoma, clinical pathology, colorectal neoplasms, observer variation

Introduction

Nationwide bowel cancer screening programmes have been implemented to reduce colorectal cancer (CRC)-related mortality by early detection of advanced colorectal neoplasms. Not only are CRCs detected at earlier stages: the removal of precursor lesions will ultimately prevent CRC development, resulting in a decreased incidence.[1]

The increased incidence of advanced colorectal adenomas and early CRC as a consequence of screening, together with advancements in endoscopic excision

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techniques, have resulted in a focus upon local endoscopic treatment. Subsequent surveillance and additional treatment choices are based upon the histopathological characteristics of the specimen. Therefore, outcomes of histopathological evaluations are crucial in clinical decision-making. However, many cases show diagnostic difficulties.[2]

In addition, significant interobserver variability has been previously reported.[3–8] Few studies explored the potential clinical consequences associated with this variability.[9] To increase the quality of histopathological evaluation and decrease both over- and undertreatment of patients, the Dutch bowel cancer screening programme introduced a pathology panel. This panel is available for consultation by pathologists involved in the screening programme, and provides a second opinion in the histopathological evaluation. The goal of the present study was to evaluate interobserver variability between pathologists and the pathology panel in the histopathological assessment of advanced colorectal adenomas and early CRC in the Dutch bowel cancer screening population.

Methods

STUDY DESIGN

Histopathology laboratories involved in the Dutch bowel cancer screening programme were invited to participate in the study, which aimed to mirror histopathological evaluations of advanced colorectal neoplasms of laboratories in daily practice and to identify areas of improvement. As part of an annual audit, the outcomes of the re-evaluation of individual cases were discussed with the laboratories. All participating centres and individual pathologists were required to meet the quality standards of the national screening programme, including annual audits of the laboratories and prior education of the individual pathologists by two mandatory e-learning modules.[10,11] Each case was signed out by a pathologist who is part of the bowel cancer screening programme. Double reading was not considered standard of care during this study. The most recent consecutive cases of the previous year were required from each centre: five adenomas with high-grade dysplasia and five endoscopically removed pT1 CRCs. Selected cases were specimens within the screening programme that were originally evaluated between 2018 and 2020. Data were retrieved from the initial histopathological reports. The mandatory synoptic reporting for adenomas included: type of resection, localisation, lesion diameter, type of adenoma, grade of dysplasia and the resection margin. For CRC the following characteristics were reported: the type of resection, localisation, tumour diameter, depth of invasion, Kikuchi or Haggitt level, differentiation grade, lymphovascular invasion (i.e. both lymphatic and venous invasion) and resection margin.

PANEL REVIEW

The selected cases were presented to the pathology panel for re-evaluation. Slides assessed during the initial histopathological evaluation were sent to the Radboud University Medical Centre, scanned by a 3Dhistech Pannoramic 1000 scanner with a $\times 20$ objective and $\times 1.6$ camera adapter magnification, and presented digitally to the panel using Pathomation viewer (version 1.2.1.886). The panel is comprised of five experienced pathologists (I.D.N., N.C.T.v.G., G.v.L., I.F-S., R.S.v.d.P.) specialised in the field of gastrointestinal pathology, with a specific interest in colorectal neoplasms. Three panellists were asked to perform a review of the available haematoxylin and eosin (H&E) slides and, if present, (immuno)histochemistry (IHC) slides. In addition, all original clinical information was available during review. All items reported in the original reports were reviewed. Tumour budding was not included in the evaluations, as it was not part of the synoptic reporting system in the Netherlands during 2018 and 2019. To address potential discrepancies, outcomes of individual reviews were discussed during panel meetings (with at least three panellists present), aiming to reach consensus.

Primary outcome was to evaluate discrepancies in the assessment of advanced colorectal neoplasms in a screening population between daily practice and a pathology panel. Secondary outcomes were potential clinical consequences of discrepancies, defined as a potential alteration in either recommended treatment (i.e. need for re-excision or radical oncological surgery) or necessity or interval of surveillance colonoscopy.[12–14]

STATISTICAL ANALYSES

Histological characteristics and discrepancies were assessed using descriptive statistics. Categorical data were presented by frequencies and percentages. Continuous variables were segregated into normally and non-normally distributed data, based on Q–Q plots and Shapiro–Wilk tests and reported accordingly. Associations between categorical variables were

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investigated by Fisher's exact tests. Statistical analyses were carried out using SPSS version 26 (IBM, Amonk, NY, USA).

Results

Twenty histopathology laboratories participated in the study, which led to a total of 104 adenomas and 101 CRC cases available for review. Of these laboratories three were university hospitals, 14 were large teaching hospitals and three were smaller teaching hospitals. After the exclusion of CRC cases in which only biopsies were available for re-evaluation ($n = 18$), a total of 83 CRC cases were included. Reviews were performed between February 2020 and November 2020. After discussion in panel meetings the outcome of the panel was not unanimous in three (2.9%) adenoma cases and three (3.6%) cases of CRC. In these cases, the majority vote was used for analyses. For the adenoma cases there was discussion on type ($n = 2$) and grade of dysplasia ($n = 1$). For early CRC the discussion centred around the presence of lymphatic invasion ($n = 1$) and the necessity of additional work-up ($n = 2$).

ADENOMAS WITH HIGH-GRADE DYSPLASIA

The included adenomas consisted of 71 (68.3%) polypectomies, 32 (30.8%) fragmented resections and one (1.0%) biopsy. The majority of lesions were located distally; 75% (78 of 104) of the lesions were located in the sigmoid or rectum. Adenoma size varied from 0.3 to 3.0 cm, with a median size of 1.3 cm.

In total, 41 of the 104 (39.4%) cases showed discrepancies (Supporting information, Figure S1). In 16 of the 104 (15.4%) cases, diagnosis of the panel was not consistent with high-grade dysplasia: 11 cases were rated as low-grade dysplasia and five as either adenocarcinoma or suspected adenocarcinoma (Figure 1A). In three of the five cases wherein the panel diagnosed adenocarcinoma or suspected adenocarcinoma, deeper levels and IHC were already obtained during the original assessment. In nine cases the panel advised to cut deeper levels to exclude invasive growth ($n = 8$) or to confirm possible high-grade dysplasia ($n = 1$). Overall, deeper levels were obtained during the original evaluation in 32 cases (30.8%). IHC was originally performed in nine of the 104 (8.9%) patients, and aimed to visualise the muscularis mucosae (desmin, $n = 8$); and/or tumour cells (cytokeratin $n = 2$); and/or lymphatic invasion (D2-40, $n = 2$); and/or venous invasion (CD31 or CD34, $n = 3$). No statistically significant differences in the usage of IHC or deeper levels were observed between laboratories or between university versus non-university hospitals.

The panel diagnosed a different adenoma subtype in 25 cases (Figure 1B). None of the laboratories diagnosed a traditional serrated adenoma, but the panel identified 10 cases. Discrepancies were not equally distributed among laboratories: in four laboratories no discrepancies were observed, whereas in 11 laboratories two or more cases were differentially scored (Figure 1C). In Figure 2A–C examples of discrepant cases are shown. The resection margin was reported adequately in almost all cases, re-evaluation resulted in three discrepancies; in two cases margins changed from 'not involved' to 'not evaluable' and one case from 'not evaluable' to 'not involved' (Supporting information, Figure S1).

EARLY CRC

Of the total of 83 reviewed CRC cases, 51 (61.4%) included polypectomies and 32 (38.6%) fragmented resections. Similar to the adenoma group, the CRCs were predominantly located in the sigmoid and rectum (65 of 83, 78.3%). Tumour size varied from 0.8 to 3.5 cm (median 1.4 cm).

Forty-four of the 83 (53.0%) cases showed at least one discrepancy, which involved histopathological risk factors for lymph node involvement (i.e. lymphovascular invasion and differentiation grade) in 28 (33.7%) cases (Supporting information, Figure S2). The panel reclassified one adenocarcinoma as a case of mucinous adenocarcinoma and one case as micropapillary adenocarcinoma. The most important discrepancies were two cases in which the panel could not confirm the presence of invasive growth and classified these cases as high-grade dysplasia with pseudoinvasion (Figure 3A). The panel based the review on the original H&E and IHC slides. Panellists could not definitively confirm invasion in six cases; these were classified as suspicious of adenocarcinoma. In the original work-up of two of these six cases, additional levels were cut and IHC was performed, which illustrated the careful work-up and difficult decision process in these two cases. However, in the other cases the panel suggested that deeper levels and/or IHC should have been obtained to confirm invasion. Overall, in 37 of 83 (44.6%) cases deeper levels were used by the laboratories. In

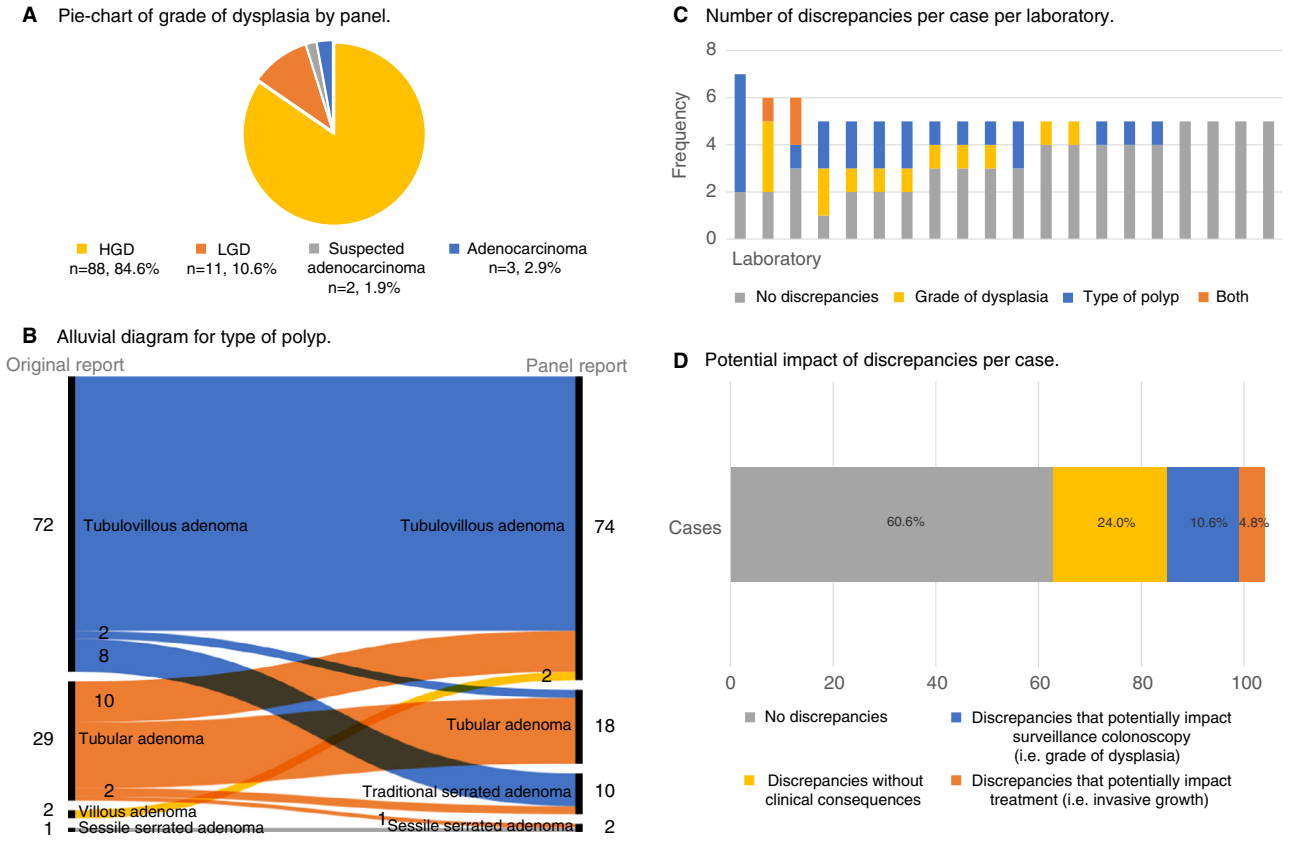

Figure 1. The assessment of advanced adenoma cases with high-grade dysplasia. **A,** Pie-chart of grade of dysplasia reported by the pathology panel. Categorised as HGD (yellow), LGD (orange), suspected adenocarcinoma (grey) and adenocarcinoma (blue). **B,** Alluvial diagram representing the assessment of polyp subtype. The original report is depicted on the left side and the re-evaluation of the pathology panel on the right side. The numbers, width and direction of the bars indicate the observed discrepancies. **C,** Discrepancies per laboratory, categorised as no discrepancies (grey) grade of dysplasia (yellow), type of polyp (blue) and both (orange). On the *x*-axis each bar indicates one laboratory in a random order. Three laboratories presented more than five adenomas to the panel. **D,** The potential impact of the observed discrepancies on clinical practice; *x*-axis: number of cases; categorised as no discrepancies (grey), discrepancies without clinical consequences (yellow), discrepancies that potentially impact surveillance colonoscopy (blue) and discrepancies that potentially impact treatment (orange). HGD, high-grade dysplasia; LGD, low-grade dysplasia.

32 (38.6%) of the 83 cases IHC was originally performed and mainly focused upon the possibility of lymphovascular invasion ($n = 23$). Evaluation of lymphatic invasion (i.e. D2-40 or podoplanin) and venous invasion [i.e. CD31, CD34, C (ERG) or Elastica von Gieson] was available in 20 and 17 cases, respectively. In 21 cases other stains were used (i.e. desmin, cytokeratin, smooth muscle actin or CAM 5.2). The utilisation of IHC varied from 0 to 100% of the cases between the laboratories (Fisher's exact test, P-value = 0.001). University hospitals performed IHC in 13.3% of the cases, compared to 44.1% of the cases in non-university hospitals (Fisher's exact test, P-value = 0.039). These were no differences in the use of deeper levels. The evaluation of lymphovascular invasion showed the highest rate of interobserver variability between original examination and the panel assessment. Discrepancies were present in 23 of 73 (31.5%) evaluable cases (Figure 3B). In six patients lymphovascular invasion was diagnosed by the panel based solely on the original H&E slides. In eight patients there was suspicion of lymphovascular invasion based on the H&E slides, but additional staining was deemed necessary to confirm this suspicion. Another area of potential conflict was submucosal invasion depth. In three cases the Kikuchi level was replaced by Haggitt level, based on the combination of the available clinical information and histological evaluation. Invasion depth was increased in four cases (three cases from Haggitt levels 2 to 3 and one case from Kikuchi level 1 to 2). In four cases the invasion depth

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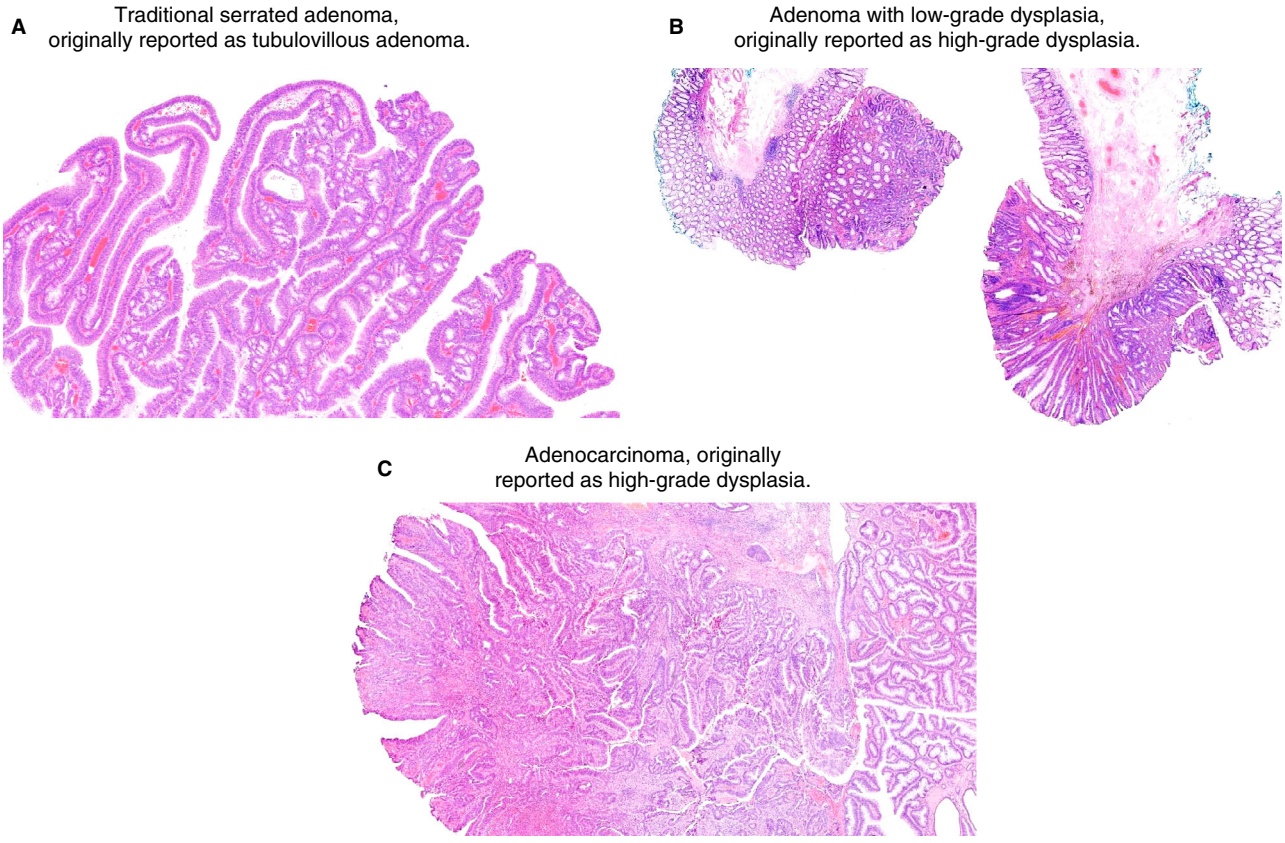

Figure 2. Examples of discrepant cases in the histopathological assessment of advanced adenomas. **A,** haematoxylin and eosin (H&E) slide of traditional serrated adenoma, originally reported as tubulovillous adenoma. **B,** H&E slide of adenoma with low-grade dysplasia, originally reported as high-grade dysplasia. **C,** H&E slide of adenocarcinoma, originally reported as high-grade dysplasia.

was deemed not evaluable by the panel. In three cases it was not evaluable by the original pathologist, while the panel was able to determine invasion depth. Resection margins were reported correctly in the vast majority of the cases; in 14 (16.9%) cases re-evaluation led to discrepancies. Of these cases, not-involved resection margins were revised into involved resection margins twice; in one case the original report diagnosed an involved resection margin, but the panel determined it not to be involved (Supporting information, Figure S2). In four cases, the panellists could not definitively determine the resection margins, whereas in seven cases previously undefined resection margins could be defined by the panel.

Figure 3C,D provides an overview of the discrepancies per laboratory, and of individual parameters. Discrepancies were not evenly distributed among laboratories. In one laboratory no discrepancies were observed, whereas in two laboratories all cases showed at least one discrepancy. Examples of discrepant cases are shown in Figure 4A,B.

POTENTIAL CLINICAL CONSEQUENCES

Based on the outcomes of the panel, several discrepancies would have resulted in an adjustment of recommended treatment or surveillance colonoscopy interval (Figure 1D, Supporting information, Figure S1). For adenomas the outcome of the panel would have had treatment consequences in five (7.7%) cases. In these cases, adenomas with high-grade dysplasia were revised and modified into either adenocarcinomas or suspected adenocarcinomas. Moreover, in 11 (10.6%) adenoma cases grade of dysplasia was assessed differently, which might have changed the necessity of a surveillance colonoscopy.[12]

For CRC, 25 of 83 (30.1%) cases showed discrepancies that would potentially have affected decision-making (Supporting information, Figure S2). In total, 31 discrepancies with potential clinical consequences were observed. In two patients, outcomes of the panel showed high-grade dysplasia with pseudoinvasion instead of adenocarcinoma (Figure 3A). Clinically

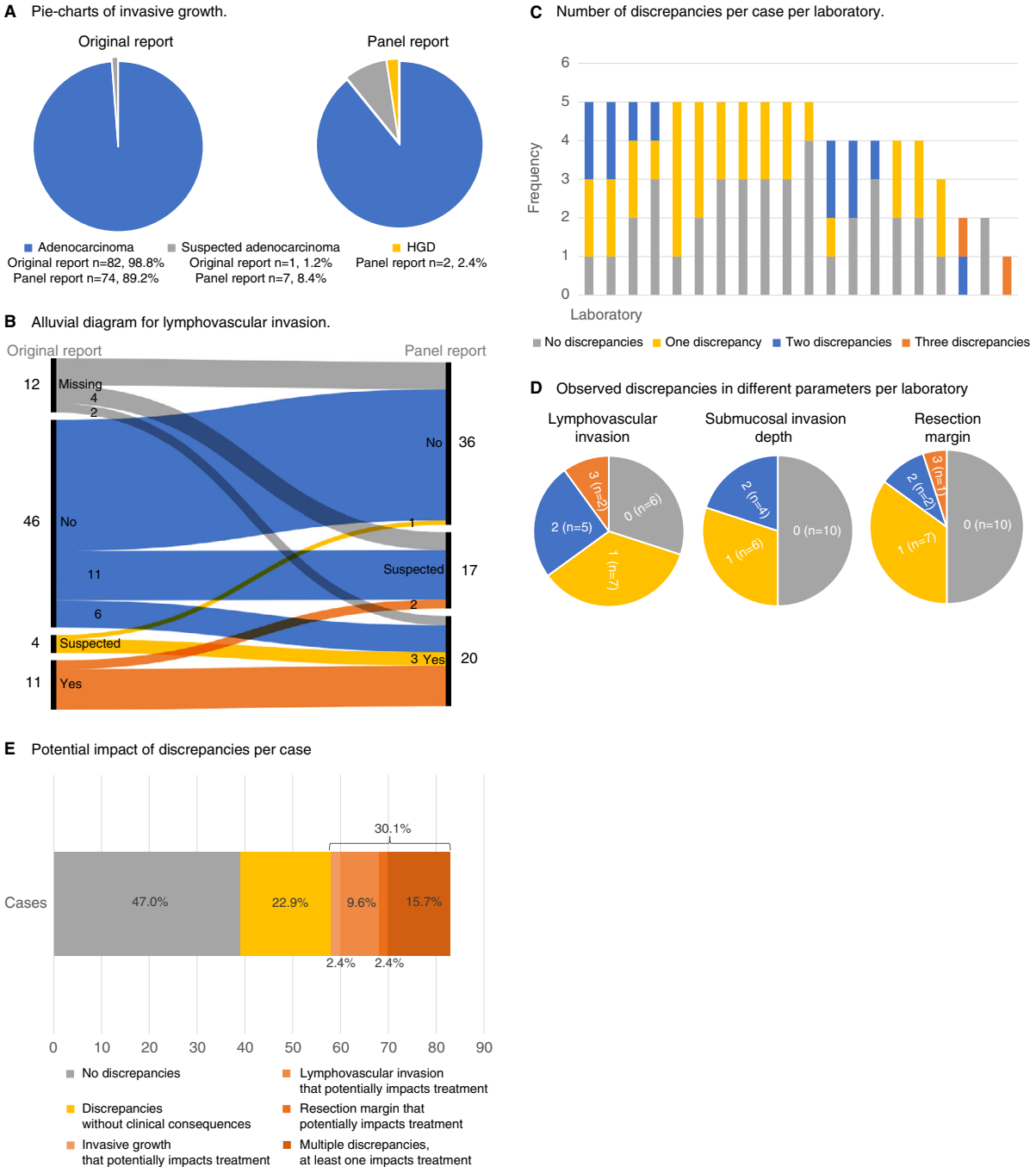

Figure 3. The histopathological assessment of early colorectal cancer (CRC). **A,** Pie-charts of invasive growth for the original report and the re-evaluation by the pathology panel, categorised as adenocarcinoma (blue), suspected adenocarcinoma (grey) and high-grade dysplasia (yellow). **B,** Alluvial diagram representing the assessment of lymphovascular invasion. The original report is depicted on the left side and the re-evaluation by the pathology panel on the right side. The numbers, width and direction of the bars indicate the observed discrepancies. **C,** Discrepancies per laboratory, categorised as no discrepancies (grey), one discrepancy (yellow), two discrepancies (blue) and three discrepancies (orange). On the *x*-axis each bar indicates one laboratory in a random order. Nine laboratories presented biopsies to the panel, which were excluded from the analyses. **D,** The number of discrepancies per parameter for each laboratory, categorised as no discrepancies (grey), one discrepancy (yellow), two discrepancies (blue) and three discrepancies (orange). The *n* represents the number of laboratories for which these discrepancies were observed. **E,** The potential impact of the observed discrepancies on clinical practice; *x*-axis: number of cases, categorised as no discrepancies (grey), discrepancies without clinical consequences (yellow) and discrepancies with clinical consequences (orange). HGD, high-grade dysplasia. [Colour figure can be viewed at wileyonlinelibrary.com]

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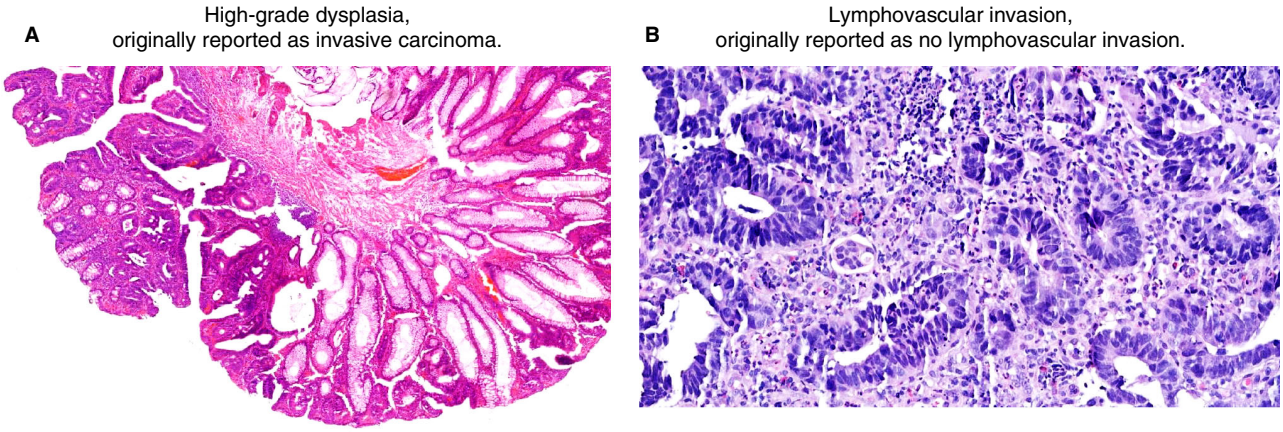

Figure 4. Examples of discrepant cases in the histopathological assessment of early colorectal cancer. **A,** haematoxylin and eosin (H&E) slide of adenoma with high-grade dysplasia, originally reported as invasive carcinoma. **B,** H&E slide of lymphovascular invasion, originally reported as no lymphovascular invasion. [Colour figure can be viewed at wileyonlinelibrary.com]

relevant discrepancies in resection margins were observed in eight cases. In 19 cases discrepancies would have potentially impacted the necessity of an oncological resection (Figure 3E, Supporting information, Figure S2). If poorly differentiated tumours and tumours with lymphovascular invasion were considered as high-risk pT1 tumours, 17 of 61 (27.9%) evaluable cases would classify as high-risk pT1 rather than low-risk pT1 and two (3.3%) as low-risk pT1 rather than high-risk pT1. As a consequence, additional surgery would either be recommended or could have been avoided. The recommendation of the panel to perform additional IHC or to cut deeper levels was associated with clinically relevant discrepancies in adenocarcinomas (Fisher's exact test, *P*-value = 0.036).

Discussion

This nationwide study identified considerable interobserver variability in the histopathological assessment of both advanced colorectal adenomas and early CRC. Discrepancies were present in both cases of advanced adenomas and endoscopically removed pT1 CRC. Most frequently, differences between the original report and the panel were observed in the assessment of lymphovascular invasion (23 of 73 evaluable cases, 31.5%). In almost one-third of early CRC cases (25 of 83 cases, 30.1%), discrepancies would have potentially led to an alternative treatment strategy.

Previous studies reported interobserver variability in the evaluation of both advanced colorectal adenomas and early CRC.[3–9,15–20] As has been observed in this study, interobserver variability has been described for the type of lesion and grading of dysplasia in colorectal adenomas. First, when daily practice is compared to a dedicated review panel, discrepancies may be observed. However, interobserver variability varies and might also be related to selection criteria or the classification system used to describe lesions.[4,5,16] For example, a two-tier instead of a three-tier system may influence outcomes.[4,5] The interobserver variability for lymphovascular invasion is well known in the literature.[7,8,21,22] Another risk factor that has often shown poor agreement in these studies is grade of differentiation.[7,8] This could not be confirmed in our series, with only one discrepant case. The contrast may be explained by the frequent use of Kappa coefficients to describe interobserver variability. When there is a relatively small group, e.g. as for poorly differentiated CRC, the coefficient corrects for agreement due to chance but might lead to a paradoxical significance.[23]

Despite the reasonable number of available studies on interobserver variability, few studies explored potential clinical consequences of variability.[9] Recently, Rampioni Vinciguerra *et al.* described that a pathologist's second opinion altered the risk classification, and thereby clinical management, in approximately 10% of the evaluated early CRCs.[9] The results of the current study add to this, and show an even higher percentage of discrepancies (30.1%) that may impact clinical decision-making. Several explanations for this difference can be given, including methodology, patient selection, possibilities of additional stains, deeper levels and method of initial reporting.[9]

Given the number of cases in which clinically relevant discrepancies were observed, there seems to be room for improvement in the standardisation of histopathological evaluations of advanced colorectal neoplasms. A proposed method to achieve a more synchronised judgement is through education and awareness initiatives. Previous studies among Dutch laboratories indicated that successful completion of an e-learning improves interobserver variability in the assessment of sessile serrated lesions and grading of dysplasia.[18,24] In addition, as has been suggested by Turner *et al.*, assessments may be standardised through consultation.[6] Internal consultation, or consultation of a panel or an expert, might improve the quality of histopathological assessments. In this study, considerations and recommendations of the panel were reported to the participating laboratories for each individual case. For example, the panel advised to cut deeper levels in nine cases of adenomas and five cases of CRC, aiming to potentially clarify uncertainties in invasive growth or resection margins. Moreover, the panel recommended IHC in two cases of adenomas and 19 cases of CRC. In cases with suspicion of lymphovascular invasion on H&E slides, immunohistochemistry, such as D2-40 or histochemical stains, such as Elastica von Gieson staining, can help to confirm the presence of either lymphatic or venous invasion. Nevertheless, interobserver variability has also been reported for special stains.[21,25] The observed association between the advice of the panel to perform additional immunohistochemistry or cut deeper levels and the clinically relevant discrepancies in CRC cases emphasises the need for thorough and dedicated evaluation of histopathological risk factors. Although we are unable to draw these conclusions based on the current study we believe that the consultation and discussion of cases with peers, as has been suggested by other studies, may enhance the quality of future evaluations.[6,9]

In spite of the detected interobserver variability in the histopathological assessment of advanced colorectal neoplasia, it should be noted that the current quality of the laboratories and pathologists is high. The annual quality assessment and audit set a high-quality standard for the laboratories participating in the bowel screening programme.[10] Laboratories are obligated to participate in both internal and external quality assurance and external quality control, all in order to improve and provide continuity in reproducibility and accuracy of diagnoses. Notwithstanding the efforts to provide these high-quality standards, in daily practice interobserver variability cannot be avoided completely. Although histopathological assessments are often referred to as the gold standard and other clinicians frequently demand a definitive statement, in difficult cases there is a grey area in which there is room for differences in interpretation and discussion between pathologists.

One of the advantages of the current study is that cases were re-evaluated based on original reports of real patients. In other studies interobserver variation is often investigated by comparing two or more re-evaluations by experts, whereas this study reflects daily practice within the national bowel cancer screening programme. One of the limitations of this study was the number of cases that had to be excluded in early CRC ($n = 18$). In these cases only biopsies were available for re-evaluation, which led to a decreased number of evaluable cases per laboratory. For this reason, the analyses on outcomes of individual laboratories or pathologists were limited. Another limitation was that the cases were selected by the participating laboratories, which potentially could have led to some selection bias and subsequently different percentages of discrepancies and clinically relevant discrepancies. Nevertheless, the centres were asked to select the final five representative cases of the preceding year and we were still able to observe a considerable number of discrepancies. Because each laboratory only submitted a small number cases this study was unable to draw any valid conclusions on the variation in usage of additional stains and IHC. Moreover, there are different IHC preferences which, in itself, may have contributed to interobserver variability. However, as we were investigating variation in daily practice we chose not to apply standardised IHC during the re-evaluations.

In addition, because re-evaluation by the panel was performed during a retrospective audit it was not possible to determine whether clinically relevant discrepancies based on European guidelines would actually have led to alterations in treatment or surveillance colonoscopy intervals. Lastly, this study included the overall outcomes of the panel and not the individual assessment of pathologists in the panel. Therefore, differences within the panel may have been underreported. However, in only three cases of adenomas and three cases of carcinomas, the outcome of the panel was not unanimous after discussion during panel meetings.

Overall, this study showed that discrepancies in histopathological evaluation between pathologists occur frequently and potentially impact treatment or surveillance strategies. Pathologists and other clinicians should be aware of these discrepancies, and methods to synchronise and improve the quality of

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histopathological evaluations, such as the consultation of peers in difficult cases, should be investigated more thoroughly.

Conflicts of interest

None.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow-chart of discrepancies and potential clinical consequences in cases of advanced adenomas with high-grade dysplasia.

Figure S2. Flow-chart of discrepancies and potential clinical consequences in colorectal cancer cases.