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INTER-OBSERVER VARIATION IN THE HISTOLOGICAL DIAGNOSIS OF POLYPS IN COLORECTAL CANCER SCREENING

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Abstract

Aim: To determine the inter-observer variation in the histological diagnosis of colorectal polyps.

Methods and results: 440 polyps were randomly selected from a colorectal cancer (CRC) screening program. Polyps were first evaluated by a general (324 polyps) or expert (116 polyps) pathologist, and subsequently re-evaluated by an expert pathologist. Conditional agreement was reported and inter-observer agreement was determined by using Kappa statistics. In 421/440 polyps (96%) agreement for the non-adenomatous or adenomatous nature was obtained, corresponding with a very good kappa of 0.88. Differentiating adenomas as non-advanced and advanced obtained consensus in 266/322 adenomas (83%), with a moderate kappa of 0.58. For the non-adenomatous or adenomatous nature, both general and expert pathologists, and expert pathologists among each other, showed very good agreement (kappa-values (95%CI); 0.89(0.83-0.95) and 0.86(0.73-0.98), respectively). Categorizing adenomas as non-advanced and advanced showed moderate agreement between general and expert pathologists, and between expert pathologists (kappa-values (95%CI); 0.56(0.44-0.67) and 0.64(0.43-0.85), respectively).

Conclusions: General and expert pathologists demonstrate very good inter-observer agreement for differentiating non-adenomas from adenomas, but only moderate agreement for non-advanced and advanced adenomas. The considerable variation in the interpretation of advanced histology suggests that more objective criteria are required for risk stratification in screening and surveillance guidelines.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death in the Western world [1, 2]. The detection and removal of adenomatous colorectal lesions reduces CRC incidence and mortality [3, 4]. Advanced adenomas have a greater likelihood of malignant transformation and development of metachronous adenomas than non-advanced adenomas [5]. Conversely, hyperplastic lesions carry minimal risk of adenoma occurrence [6, 7].

Histopathological diagnosis of colorectal lesions plays a crucial role in patient management and surveillance after polypectomy. Postpolypectomy surveillance guidelines stratify patients in high and low risk according to their risk of an advanced neoplasia at subsequent colonoscopy. Current guidelines recommend a surveillance colonoscopy 3 years after removal of an advanced adenoma or 3 or more non-advanced adenomas, and 5 to 10 years after removal of 1 or 2 non-advanced adenomas [8]. Histopathologic assessment of colorectal polyps is also vital in screening for CRC. Advanced adenomas are considered the surrogate marker for CRC risk and are a primary end-point of screening [9]. As many countries have implemented or are preparing nation-wide CRC screening [10, 11], accurate pathologic assessment of colorectal lesions is of paramount importance.

Concern has been raised about the reproducibility of the histological interpretation, between general and between expert gastrointestinal pathologists [12, 13]. The aim of the present study was to evaluate inter-observer variation in histological diagnosis of colorectal polyps detected in a CRC screening program. Furthermore, inter-observer variation was assessed between general and expert gastrointestinal pathologists, and between expert gastrointestinal pathologists.

Methods

Study setting

As part of a Dutch population-based randomized screening trial (CORERO I trial) we randomly selected 440 polyps. The CORERO I study has been described in detail elsewhere [14]. In brief, this randomized population-based trial compared uptake and diagnostic yield of guaiac based fecal occult blood test (g-FOBT), fecal immunochemical test (FIT) and flexible sigmoidoscopy (FS) screening for CRC. Recruitment took place between November 2006 and November 2007. In total 15,011 individuals aged 50-74 years old were 1:1:1 randomized to be invited for gFOBT, FIT or FS screening. Participants with a positive gFOBT (Hemoccult II) or FIT (OC-Hemodia Latex; ≥50 nanogram haemoglobin/ml) were referred for colonoscopy. Participants to FS screening were referred for colonoscopy when one of the following criteria was met: presence of a polyp with a diameter ≥10 mm; an adenoma with villous histology (≥25% villous) or high-grade dysplasia; three or more adenomas; ≥20 hyperplastic polyps; or invasive CRC.

Sampling procedure and organization

All polyps detected at FS or colonoscopy were removed. The inter-observer evaluation was conducted on 440 randomly selected polyps; 324 polyps were detected at colonoscopy in participants with a positive gFOBT or FIT (FOBT polyps), and 116 polyps were detected during FS (FS polyps). For initial pathological evaluation, the 324 FOBT polyps were evaluated by a general pathologist (n=23) and the 116 FS polyps were evaluated by an expert gastrointestinal pathologist (n=1). Subsequently, all 440 samples were blindly re-evaluated by an (one of two) expert gastrointestinal pathologist.

Criteria for pathologic classification

The WHO classification was adopted to classify the selected polyps as non-adenomatous or adenomatous [15]. Adenomatous lesions were further categorized according to histologic type, degree of dysplasia, and absence or presence of infiltrating carcinoma. In agreement with the National Polyp study and other studies on CRC screening, we defined a tubular adenoma as an

adenoma with less than 25% villous component. Adenomas having a 25% - 75% or more than 75% villous component, were defined as tubulo-villous and villous adenoma, respectively[16-21]. The degree of dysplasia was classified as low or high grade dysplasia. According to the revised Vienna criteria, patients with intramucosal carcinoma or carcinoma in situ were classified as having high-grade dysplasia [22]. Advanced adenomas were defined as adenomas of at least 10mm, or as adenomas with villous histology (≥25%villous) or with high-grade dysplasia. CRC was defined as invasion of malignant cells beyond the muscularis mucosa and was classified according to the TNM classification [23-25].

Statistical analysis

Descriptive statistics were used to analyze and report the data. Conditional agreement was reported using percentages. Inter-observer agreement was determined by using Cohen κ statistics, which are widely used mathematical coefficients adjusting for agreement by chance alone. A value of 0 indicates no agreement better than what would be expected by chance alone. Values of < 0.21, 0.21–0.40, 0.41–0.60, 0.61–0.80 and >0.80 correspond to poor, fair, moderate, substantial and very good inter-observer agreement, respectively. In addition, as the kappa coefficient is influenced by the prevalence and bias of ratings, the prevalence-index and bias-index was calculated. A prevalence effect exists when the proportion of agreements on the positive classification differs from that of the negative classification. If the prevalence index is high (prevalence of a positive rating is very high or very low), chance agreement is also high and kappa is reduced. A bias effect exists if each observer rates a differing proportion of cases as positive. If the disagreement is asymmetrical, bias is large and kappa is higher than when bias is low or absent [26]. The histological diagnoses were categorized as non-adenomatous or adenomatous. Adenomatous lesions were further categorized as non-advanced or advanced based on histology only. For further categorization, the degree of dysplasia was classified as low or high grade dysplasia. Adenomas were categorized as tubular adenoma or adenoma with ≥25% villous component. In addition, inter-observer agreement was calculated for polyps that were represented by diminutive (1-5mm), small (6-9mm), and large (≥10mm) polyps. The size of each

polyp was measured during the endoscopy using an open biopsy forceps with 7mm span. Furthermore, inter-observer agreement between a general and expert pathologist, and between expert pathologists was assessed. Statistical analysis was performed using the SPSS 15.0 program (SPSS Inc. Chicago, IL). A two-sided p-value of < 0.05 was considered statistically significant.

Results

Polyp characteristics

In total, 440 colorectal polyps were evaluated. The polyp characteristics as described by the initial pathologist are shown in Table 1. The initial pathologists identified 106 non-adenomas (24%) and 334 adenomas (76%). Ninety-five of the 440 polyps (22%) were classified as advanced adenomas. The FOBT polyps were, as compared to the FS polyps, significantly larger and more often of advanced histology.

Inter-observer variation

Table 2 shows the agreement among pathologists on histological diagnosis of colorectal polyps. In 421 out of 440 polyps (96%) agreement for the non-adenomatous or adenomatous nature of polyps was obtained. More specifically, pathologists agreed on 99 non-adenomas and 322 adenomas, corresponding with a very good kappa-value of 0.88 (95% CI; 0.83 - 0.94) (prevalence-index 0.51, bias-index 0.01). Categorizing the 322 adenomatous lesions as non-advanced and advanced obtained consensus in 266 adenomas (83%). There was consensus for 198 non-advanced adenomas and 68 advanced adenomas. Inter-observer agreement for classifying adenomas as non-advanced or advanced was moderate with kappa 0.58 (95% CI; 0.48 – 0.68) (prevalence-index 0.40, bias-index 0.01).

Among the 322 adenomatous polyps, agreement for low or high grade dysplasia was obtained in 304 polyps (94%). There was consensus for 287 low grade and 17 high-grade dysplastic lesions. Due to the large prevalence-index, inter-observer agreement was only moderate with kappa 0.62 (95% CI; 0.46 – 0.79) (prevalence-index 0.86, bias-index 0.01). Focussing on the high grade dysplastic lesions; pathologists agreed that five lesions had intramucosal carcinoma or carcinoma in situ. On another two lesions there was disagreement in the classification; high grade dysplastic adenoma vs. intramucosal carcinoma/carcinoma in situ. No carcinoma invading the submucosa was observed in any of the samples. Categorizing the 315 adenomas (without intramucosal carcinoma or carcinoma in situ) as tubular adenoma or as adenoma with ≥25% villous

component, obtained consensus in 259 polyps (82%). Pathologists agreed on 203 tubular adenomas and 56 adenomas with ≥25% villous histolology. Inter-observer reproducibility for grading villousness was moderate with a kappa-value of 0.55 (95% CI; 0.44 – 0.66) (prevalence-index 0.47, bias-index 0.01). Overall consensus for the non-adenomatous / adenomatous nature, and histological type and grade of dysplasia of adenomas was obtained in 336/440 polyps (76%).

Influence of polyp size on inter-observer variation

The level of agreement between pathologists was not affected by polyp size (Table 2). Within each size category (1-5mm, 5-9mm and ≥10mm), reproducibility was very good for differentiating between non-adenomas and adenomas (with a kappa-value ranging from 0.84 and 0.89), and reproducibility was moderate for categorizing adenomas as non-advanced and advanced (with a kappa-value ranging from 0.48 and 0.53).

Inter-observer variation between general and expert pathologists, and between expert pathologists

Inter-observer agreement in the classification of colorectal polyps was similar between general and expert pathologists on the one hand, and between two expert pathologists on the other hand (Table 3). Both groups showed very good agreement in categorizing polyps as non-adenomatous and adenomatous. The general and expert pathologists agreed on 310/324 polyps (96%), including 80 non-adenomatous and 230 adenomatous polyps. The two expert pathologists agreed on 111/116 polyps (96%); 19 non-adenomatous and 92 adenomatous polyps. Kappa-values were 0.89 (95% CI; 0.83 - 0.95) and 0.86 (95% CI; 0.73 – 0.98), respectively. Of note, the polyps evaluated by the general and expert pathologist had, as compared to the polyps evaluated by the two expert pathologists, a lower prevalence-index. The bias-index was low for both groups.

Furthermore, both groups showed moderate agreement for categorizing adenomas as non-advanced or advanced. The general and expert pathologist agreed on 184/230 adenomas (80%), including 128 non-advanced and 56 advanced adenomas. The expert pathologists agreed on

82/92 adenomas (89%); 70 non-advanced and 12 advanced adenomas. Kappa-values were 0.56 (95% CI; 0.44 - 0.67) and 0.64 (95% CI; 0.43 – 0.85), respectively. Of note, the adenomas evaluated by the general and expert pathologist had a lower prevalence-index as compared to the adenomas evaluated by the two expert pathologists. The bias-index was low for both groups.

Discussion

This study describes the inter-observer variation in the histological diagnosis of colorectal polyps detected in a CRC screening program. Our data demonstrated very good inter-observer agreement in categorizing polyps as non-adenomatous or adenomatous (kappa-value 0.88). This level of concordance was better than observed by Yoon et al [13], but consistent with other studies [12, 27-30]. Our results showed that inter-observer agreement was only moderate for differentiating between non-advanced and advanced adenomas (kappa-value 0.58). The inconsistency of pathologists in differentiating between non-advanced and advanced adenomas was more frequently based on grading and assessing villousness than on grading of dysplasia. Of note however, kappa-values were moderate for both; grading villous histology (kappa-value 0.55), and due to a large prevalence index also moderate for grading dysplasia (kappa-value 0.62). Our results are in line with other studies also showing a poor to moderate level of agreement for classifying the proportion of villous component and the grade of dysplasia. These studies however did not specifically investigate agreement after stratifying adenomas as non-advanced and advanced [12, 13, 27-32]. Furthermore, we found that the level of agreement between pathologists was not affected by polyp size.

Our results showed that the inter-observer agreement in categorizing of colorectal polyps was similar between general and expert pathologists one the one hand, and between expert pathologists on the other hand. This is in agreement with previous studies on the histopathological interpretation of colorectal polyps [12, 13, 27-32]. In addition, in other fields of pathology it was also found that expert pathologists are just as likely to disagree as general pathologists [33-35].

Our data confirm that the classification of advanced adenoma is subject to inter-observer variation [12, 13, 27-32]. This has major clinical implications for patients with diminutive (1-5mm) and/or small (6-9mm) adenomas, as large adenomas (≥10mm) are already classified as advanced adenomas. A recent systematic review reported that diminutive and/or small adenomas were

found to contain advanced histology in 12.5% of screened subjects in an average risk population [36]. Possible misclassification might therefore occur in a large proportion of patients. This has major implications for the decision on surveillance interval, as current guidelines also base the time interval for a surveillance colonoscopy on the presence of advanced adenoma [8]. Misclassification of low risk patients may therefore lead to inadequate colonoscopic surveillance, whereas misclassification of high risk patients may result in unnecessary invasive and costly colonoscopies with some associated morbidity. Furthermore, postpolypectomy surveillance represents 22% of all colonoscopies [37]. In an era of limited endoscopy resources, it is of paramount importance to have objective criteria for risk stratification of subjects with adenoma for recommendations on surveillance interval [38-43].

Furthermore, it has been suggested that the current postpolypectomy surveillance guidelines have limited predictability for advanced adenoma recurrence [44]. A risk profile based on cumulative findings from multiple previous colonoscopies might better stratify patients in high and low risk than the adenoma findings from the most recent examination [45]. In addition, recent evidence indicates that other factors than histological diagnosis, are stronger associated with the development of metachronous advanced adenomas. A pooled multivariate analysis of postpolypectomy patients showed that after four years of follow-up, the risk of metachronous advanced colorectal neoplasia was strongly associated with the number, size, and location of prior adenomas, as well as patient age. In the multivariate analysis, the presence of villous histology was only modestly associated, and the grade of dysplasia was not associated with metachronous advanced neoplasia [46]. In agreement with our findings, some postpolypectomy surveillance guidelines (e.g. the Dutch revised adenoma surveillance guideline and the United Kingdom NHS Bowel Cancer Screening Program) do not use histological subtyping as indicator for surveillance interval, and only use size and number of adenomas [47, 48]. Guidelines that do use the presence of advanced adenoma for risk stratification may reconsider these criteria given the subjectivity, the poor reproducibility, and the uncertainty on the role as a predictor of future risk.

In addition, the level of inter-observer variability needs to be considered in the context of the outcome of current studies and colorectal cancer screening programs. Colorectal cancer screening programs rely on advanced adenoma as intermediate endpoint.

Our study has some limitations. First, in total twenty-three general and two expert pathologists reviewed the pathology specimens. This was done with the deliberate purpose to resemble a situation as seen in a nation-wide colorectal cancer screening program. In such a setting many general pathologists review the biopsy specimens, whereas only a few expert pathologists will review selected specimens, either for quality assurance or because of uncertain diagnosis. Our results will therefore closely reflect outcomes of a population-based nation-wide screening program.

Second, we should emphasize that the level of agreement between the two expert pathologists might be underestimated. The two expert pathologists had, as compared to the general and expert pathologist, higher prevalence-indexes for the differentiation between non-adenomas and adenomas, and between non-advanced and advanced adenomas (table 3). These higher prevalence-indexes predisposed to diagnose or not to diagnose adenomas and advanced adenomas. This increased the chance of agreement, and subsequently suppressed the kappa-values.

In conclusion, this study demonstrated that pathologists have a very good inter-observer agreement for differentiating between non-adenomatous and adenomatous polyps, while the agreement is only moderate for non-advanced and advanced adenomas. Agreement is comparable between general and expert pathologists on the one hand, and between expert pathologists on the other hand. The considerable variation in the interpretation of advanced histology suggests that more objective criteria are required for risk stratification in screening and surveillance guidelines.

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Table 1. Polyp characteristics as defined by the initial pathologist

	Total (n=440) n (%)	FOBT polyps (n=324) n (%)	FS polyps (n=116) n (%)	p-value
Polyp				
- Non-adenomatous	106 (24%)	84 (26%)	22 (19%)	0.13
- Adenomatous	334 (76%)	240 (74%)	94 (81%)	
Adenoma				
Non-advanced/advanced*				
- non-advanced	239 (54%)	161(50%)	78 (67%)	0.004
- advanced	95 (22%)	79 (24%)	16 (14%)	
Dysplasia				
- Low-grade dysplasia	307 (70%)	219 (68%)	88 (76%)	0.48
- High-grade dysplasia	27 (6%)	21 (6%)	6 (5%)	
Histologic type				
- Tubular	245 (56%)	166 (51%)	79 (68%)	0.002
- Tubulovillous/villous	82 (19%)	70 (21%)	12 (10%)	
- Carcinoma in situ or intramucosal	7 (2%)	4 (1%)	3 (3%)	
Polyp size**				
- Diminutive (1-5mm)	224 (51%)	135 (42%)	89 (77%)	<0.001
- Small (6-9mm)	87 (20%)	68 (21%)	19 (16%)	
- Large (≥10mm)	129 (29%)	121 (37%)	8 (7%)	

*based on histology only.

**The size of each polyp was measured during the endoscopy

Table 2. Inter-observer agreement between pathologists

	n	Agreement, n (%)	K-values (95% CI)
Non-adenomatous / Adenomatous polyps	440	421 (96%)	0.88 (0.83 - 0.94)
- ≤5mm	224	212 (95%)	0.89 (0.82 - 0.95)
- >5mm	216	209 (97%)	0.84 (0.72 - 0.96)
- <10mm	311	295 (95%)	0.88 (0.82 - 0.94)
- ≥10mm	129	126 (98%)	0.85 (0.67 - 1,02)
Non-advanced / Advanced adenoma	322	266 (83%)	0.58 (0.48 – 0.68)
- ≤5mm	134	123 (92%)	0.48 (0.22 - 0.74)
- >5mm	188	143 (76%)	0.52 (0.39 - 0.64)
- <10mm	205	179 (87%)	0.53 (0.37 - 0.69)
- ≥10mm	117	87 (74%)	0.48 (0.33 - 0.64)
Low grade / High grade dysplasia*	322	304 (94%)	0.62 (0.46 – 0.79)
Tubular / Tubulo-villous and villous adenoma	315	259 (82%)	0.55 (0.44 – 0.66)

* including carcinoma in situ and intramucosal carcinoma.

Table 3. Inter-observer agreement between general (GP) and expert pathologists (EP), and between expert pathologists (EP`s).

	Combined	GP and EP	EP and EP
Non-adenomatous / Adenomatous			
- K-value (95% CI)	0.88 (0.83 - 0.94)	0.89 (0.83 - 0.95)	0.86 (0.73 - 0.98)
- Prevalence-index	0.51	0.46	0.62
- Bias-index	0.01	0.02	0.01
Non-advanced / Advanced adenoma			
- K-value (95% CI)	0.58 (0.48 - 0.68)	0.56 (0.44 - 0.67)	0.64 (0.43 - 0.85)
- Prevalence-index	0.40	0.31	0.63
- Bias-index	0.01	0	0.02