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Interobserver Agreement in Assessing Dysplasia in Colorectal Adenomatous Polyps: A Multicentric Iranian Study

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ABSTRACT

Background & Objective: Most colorectal cancers (CRCs) arise from adenomatous polyps, and clinical management of this type of polyp is highly dependent on the reliability and validity of the pathological diagnosis. The aim of this study was to examine the interobserver agreement of five pathologists in assessing dysplasia in adenomatous polyps.

Methods: In this study, a total of 146 adenomatous polyps of patients undergoing colonoscopy were selected from hospitals of Shahid Beheshti University of Medical Sciences, Tehran, Iran between 2017 and 2018. Five pathologists independently classified adenomatous polyps according to histologic type, nuclear pseudostratification, mitotic activity, nuclear polarity, nuclear pleomorphism, nuclear shape, nucleolus, chromatin pattern, cytology grade, architectural features, dysplasia, and final diagnosis. The overall kappa statistic (k) was used to assess agreement among pathologists.

Results: The mean age of the patients was 62.06 ± 13.06 (mean ± SD) with a male-to-female ratio of 2.2:1. The most common site of resection was the sigmoid colon (28.1%). The highest agreement was found for dysplasia grade (k=0.415) and histologic type (k=0.401), whereas the lowest agreement was found for mitotic activity (k=0.185), nuclear shape (k=0.187), and nucleolus (k=0.196).

Conclusion: Our findings indicate that agreement among pathologists in assessing dysplasia in adenomatous polyps is within fair to moderate levels of agreement. Therefore, there is a vital need to better clarify the current diagnostic criteria.

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Introduction

Colorectal cancer (CRC) is the fifth most common cancer and the fourth leading cause of cancer-related death in Iran (1). Most CRCs arise from adenomatous polyps (2), and scientific studies have shown that a considerable reduction of the incidence and mortality of CRC can be achieved by removing adenomatous polyps before their potential progress to adenocarcinomas (3). Currently, in several countries, colonoscopy is the primary modality to detect and remove adenomatous polyps and can be considered as the best method for this purpose (4).

Previous observational studies have shown that several characteristic features of adenomas might be associated with the risk of CRC. Most often cited features include the size, number, grade of dysplasia, and histologic type. Therefore, appropriate clinical management of the adenomatous polyps depends on the reliability and validity of the pathological diagnosis. In addition, as many countries have implemented or are preparing nationwide CRC screening (5,6), reliable and valid histopathological measurement of colorectal polyps is of paramount importance.

Previous studies have indicated moderate degrees of interobserver agreement in the histopathological assessments of colorectal adenomas (7–11), and thus concern has been expressed about the reproducibility of the histopathological interpretation among the pathologists. This study, therefore, aimed to examine

the interobserver agreement of five pathologists in assessing dysplasia in adenomatous polyps.

Materials and Methods

Patients and Study Design

In this study, a series of 146 adenomatous polyps of patients undergoing colonoscopy for the first time were examined. One of the authors prescreened archival hematoxylin and eosin (H&E) slides of colorectal adenomas obtained at Shahid Beheshti Medical Sciences Affiliated Hospitals. These polyps were resected by polypectomy. Specimens were selected from ordinary daily cases of pathology department centers with a high number of gastrointestinal (GI) pathology cases in several hospitals affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran between 2017 and 2018.

Demographic data, including age, sex, and location of polyps, were extracted from the pathology request form and patient's medical files. Five pathologists (named Pathologist 1, 2, 3, 4, and 5 in the study) reviewed the entire set of slides of the 146 adenomatous polyps. These pathologists were the faculty members of the pathology department practicing GI pathology in their daily routine. Two are associate professors, and three of them are assistant professors. The pathologists were blind to the original diagnosis of adenomatous polyps.

The following features were gathered: histologic type, nuclear pseudostratification, mitotic activity, nuclear polarity, nuclear pleomorphism, nuclear shape, nucleolus, chromatin pattern, cytology grade, architectural patterns, degree of dysplasia, and final diagnosis. Dysplasia grading of adenomas was defined as high-grade and low-grade based on the cytological and architectural features. Low-grade dysplasia is defined by the presence of architecturally noncomplex crypts containing nuclei that are pseudostratified or partially stratified, and the nuclei reach only the lower half of the cytoplasm. High-grade dysplasia is interpreted by marked pseudostratification or stratification of neoplastic nuclei that extend up to the luminal half of the cells and usually contain significant pleomorphism, increased mitotic activity, atypical mitoses, and marked loss of polarity.

Architectural changes, including back-to-back gland configuration and cribriforming, may also be seen. With the progression of neoplasia, glands become more irregular and complex. Moreover, neoplastic nuclei become more "open" in appearance and may contain prominent nucleoli (12). Villous architecture is defined as leaflike or fingerlike projections of epithelium overlying a small amount of lamina propria. Tubulovillous adenomas are defined by a mixture of tubular and villous structures, with arbitrary percentages in different studies, typically with between 25% and 75% villous component (13). In our study, the percentage between 20% and 80% was defined for the former purpose. Besides, pathologists were asked to fill out the predefined checklist without discussing their answers with each other.

Ethical Consideration

The Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran approved this study (Registration Number: IR.SBMU.RETECH.REC.1397.316). All patients were informed about the aim of the study, and informed consent was obtained from all patients before participation in this study.

Statistical Analysis

In the present study, continuous variables were presented as mean (standard deviation) and categorical variables as number (percentage). The overall kappa statistic (k) was used to assess agreement among pathologists. The kappa value ranges from -1 to 1. The higher the value of kappa, the stronger the agreement. A kappa value of 0 indicates that the agreement is the same as would be expected by chance. The strength of agreement for the kappa value can be interpreted as follows: < 0.20, poor; 0.21-0.40, fair; 0.41- 0.60, moderate; 0.61-0.80, good; 0.81-1.00, very good. All data analyses were performed by using Minitab release 14.0 (Minitab Inc. State College, PA, USA).

Results

Patients' Characteristics

The mean age of the patients was 62.06 ± 13.06 (mean±SD). One hundred (68.5%) patients were male and 46 (31.5%) were female. As for the location in the colon, the most common site of resection was the sigmoid colon (28.1%), followed by the descending colon (18.5%), as well as transverse colon (17.1%), rectum (13.7%), and ascending colon (11.0%) (Table 1).

Characteristics of the Adenomatous Polyps

Classification of adenomatous polyps based on the histologic type (i.e., tubular, tubulovillous, and villous) was considerably different among the five pathologists. Most of the polyps were tubular adenomas, and the prevalence of this type ranged from 54.8% (for Pathologist 5) to 86.3% (for Pathologist 4). The observed distribution of adenomas, according to dysplasia grade, was also significantly different across the five pathologists. Most of the patients had low-grade dysplasia with a prevalence ranging from 79.5% (for Pathologist 5) to 98.6% (for Pathologist 4). Similar to histologic type and dysplasia grade, considerable variability was observed among pathologists in the histopathological assessments of adenomas according to other characteristics (Tables 2 and 3).

Interobserver Agreement

In our study, the highest agreement was found for dysplasia grade (k=0.415) and histologic type (k=0.401), whereas the lowest agreement was found for mitotic activity (k=0.185), nuclear shape (k=0.187), and nucleolus (k=0.196).

A perfect agreement on histologic type (i.e., all pathologists' assessments agree with each other) among the five pathologists was obtained for 75 polyps (51.4%). More specifically, it was obtained for 68 tubular adenomas, five tubulovillous adenomas, and two villous adenomas. The overall kappa value was 0.401, which is considered to be moderate. After excluding the assessment of Pathologist 4, Pathologist 5, and both, the overall kappa values increased to 0.445, 0.440, and 0.511, respectively.

Table 1. Demographic and clinical characteristics of the patients undergoing colonoscopy for the first time (n = 146).

Variable	n (%) or mean ± SD
Age (years)	62.06 ± 13.06
Sex	
Male	100 (68.5%)
Female	46 (31.5%)
Site of resection (Location of adenomas)	
Rectum	20 (13.7)
Sigmoid colon	41 (28.1)
Ascending colon	16 (11.0)
Descending colon	27 (18.5)
Transverse colon	25 (17.1)
Cecum	6 (4.1)
Rectosigmoid	7 (4.8)
Colon (Unclassified)	4 (2.7)

SD: Standard Deviation

Table 2. Characteristics of the 146 adenomatous polyps according to the five pathologists' assessments.

	Pathologist				
	P1	**P2**	**P3**	**P4**	**P5**
Histologic type					
Tubular	100 (68.5)	111 (76.0)	104 (71.2)	126 (86.3)	80 (54.8)
Tubulovillous	37 (25.3)	31 (21.2)	35 (24.0)	15 (10.3)	60 (41.1)
Villous	9 (6.2)	4 (2.7)	7 (4.8)	5 (3.4)	6 (4.1)
Nuclear Pseudostratification					
Limited to the lower half	131 (89.7)	108 (74.0)	128 (87.7)	115 (78.8)	92 (63.0)
Extended to luminal half	15 (10.3)	38 (26.0)	18 (12.3)	31 (21.2)	54 (37.0)
Mitotic Activity					
Typical (Mild)	129 (88.4)	126 (86.3)	136 (93.2)	124 (84.9)	113 (77.4)
Typical (Moderate)	16 (11.0)	16 (11.0)	10 (6.8)	20 (13.7)	33 (22.6)
Typical (Brisk)	1 (0.7)	2 (1.4)	-	2 (1.4)	-
Atypical	-	2 (1.4)	-	-	-
Nuclear Polarity					
Mildly distorted	127 (87.0)	103 (70.5)	134 (91.8)	137 (93.8)	130 (89.0)
Moderately distorted	18 (12.3)	33 (22.6)	12 (8.2)	9 (6.2)	16 (11.0)
Severally distorted	1 (0.7)	10 (6.8)	-	-	-
Nuclear Pleomorphism					
Mild	112 (76.7)	104 (71.2)	131 (89.7)	113 (77.4)	126 (86.3)
Moderate	33 (22.6)	37 (25.3)	15 (10.3)	32 (21.9)	20 (13.7)
Severe	1 (0.7)	5 (3.4)	-	1 (0.7)	-
Nuclear shape					
Elongated	121 (82.9)	91 (62.3)	126 (86.3)	105 (71.9)	79 (54.1)
Round	11 (7.5)	15 (10.3)	3 (2.1)	1 (0.7)	18 (12.3)
Mixed	14 (9.6)	40 (27.4)	17 (11.6)	40 (27.4)	49 (33.6)
Chromatin Pattern					

	Pathologist				
	P1	P2	P3	P4	P5
Open	9 (6.2)	15 (10.3)	8 (5.5)	-	34 (23.3)
Hyperchrome	115 (78.8)	90 (61.6)	108 (74.0)	94 (64.4)	70 (47.9)
Mixed	22 (15.1)	41 (28.1)	30 (20.5)	52 (35.6)	42 (28.8)
Nucleolus					
Not seen	103 (70.5)	96 (65.8)	117 (80.1)	110 (75.3)	65 (44.5)
Small	33 (22.6)	27 (18.5)	19 (13.0)	34 (23.3)	57 (39.0)
Medium	10 (6.8)	16 (11.0)	9 (6.2)	2 (1.4)	22 (15.1)
Large	-	7 (4.8)	1 (0.7)	-	2 (1.4)
Cytology Grade- Upper Half					
Low-grade	122 (83.6)	113 (77.4)	126 (86.3)	140 (95.9)	102 (69.9)
High-grade	24 (16.4)	33 (22.6)	20 (13.7)	6 (4.1)	44 (30.1)
Cytology Grade- Lower Half					
Low-grade	136 (93.2)	129 (88.4)	131 (89.7)	145 (99.3)	129 (88.4)
High-grade	10 (6.8)	17 (11.6)	15 (10.3)	1 (0.7)	17 (11.6)
Dysplasia Grade					
Low-grade	125 (85.6)	127 (87.0)	125 (85.6)	144 (98.6)	116 (79.5)
High-grade	21 (14.4)	19 (13.0)	21 (14.4)	2 (1.4)	30 (20.5)
Final Diagnosis					
Low grade- Tubular	97 (66.4)	99 (67.8)	96 (65.8)	125 (85.6)	71 (48.6)
High grade- Tubular	3 (2.1)	12 (8.2)	8 (5.5)	1 (0.7)	9 (6.2)
Low grade- Tubulovillous	23 (15.8)	26 (17.8)	24 (16.4)	15 (10.3)	43 (29.5)
High grade- Tubulovillous	14 (9.6)	5 (3.4)	11 (7.5)	-	17 (11.6)
Low grade- Villous	5 (3.4)	2 (1.4)	5 (3.4)	4 (2.7)	2 (1.4)
High grade- Villous	4 (2.7)	2 (1.4)	2 (1.4)	1 (0.7)	4 (2.7)

Values are presented as n (%).

Table 3. Architectural features of the 146 adenomatous polyps according to the five pathologists' assessments.

	Pathologist				
	P1	P2	P3	P4	P5
Grade of Architecture- Upper Half					
Low-grade	123 (84.2)	126 (86.3)	126 (86.3)	145 (99.3)	115 (78.8)
High-grade	23 (15.8)	20 (13.7)	20 (13.7)	1 (0.7)	31 (21.2)
Grade of Architecture- Lower Half					
Low-grade	137 (93.8)	132 (90.4)	132 (90.4)	144 (98.6)	140 (95.9)
High-grade	9 (6.2)	14 (9.6)	14 (9.6)	2 (1.4)	6 (4.1)
Crypts Configuration					
Parallel	119 (81.5)	127 (87.0)	127 (87.0)	133 (00.0)	99 (67.8)
Back-to-back	13 (8.9)	5 (3.4)	8 (5.5)	-	7 (4.8)
Cribriforming	1 (0.7)	2 (1.4)	2 (1.4)	-	1 (0.7)
Complex Budding	2 (1.4)	2 (1.4)	2 (1.4)	-	4 (2.7)
Combined	11 (7.5)	10 (6.8)	7 (4.8)	13 (8.9)	35 (24.0)

Values are presented as n (%).

Table 4. Interobserver agreement in the histopathological assessment of colorectal adenomatous polyps.

Characteristics	All pathologists (P1, P2, P3, P4, and P5)		All pathologist except P4 (P1, P2, P3, and P5)		All pathologist except P5 (P1, P2, P3, and P4)		All pathologist except P4 and P5 (P1, P2, P3)	
	Complete Agreement, n (%)	Overall Kappa	Complete Agreement, n (%)	Overall Kappa	Complete Agreement, n (%)	Overall Kappa	Complete Agreement, n (%)	Overall Kappa
Histologic type	75 (51.4)	0.401	81 (55.5)	0.445	92 (63.0)	0.440	101 (69.2)	0.511
Nuclear Pseudostratification	72 (49.3)	0.250	83 (56.9)	0.311	89 (61.0)	0.256	110 (75.3)	0.395
Mitotic Activity	87 (59.6)	0.185	96 (65.7)	0.220	99 (67.8)	0.145	115 (78.8)	0.258
Nuclear Polarity	91 (62.3)	0.217	93 (63.7)	0.218	94 (64.4)	0.191	97 (64.4)	0.184
Nuclear Pleomorphism	81 (55.5)	0.305	92 (63.0)	0.329	84 (57.5)	0.283	96 (65.5)	0.297
Nuclear shape	48 (32.9)	0.187	58 (39.7)	0.185	68 (46.6)	0.224	87 (59.6)	0.255
Chromatin Pattern	44 (30.1)	0.226	51 (34.9)	0.223	60 (41.1)	0.269	79 (54.1)	0.298
Nucleolus	44 (33.1)	0.196	51 (34.9)	0.224	70 (47.9)	0.242	81 (55.5)	0.279
Cytology Grade- Upper Half	89 (61.0)	0.352	96 (65.7)	0.427	106 (72.6)	0.396	114 (78.1)	0.496
Cytology Grade- Lower Half	117 (80.1)	0.374	122 (83.6)	0.504	121 (82.9)	0.339	127 (87.0)	0.500
Grade of Architecture- Upper Half	101 (69.2)	0.365	109 (74.7)	0.493	110 (75.3)	0.331	119 (81.5)	0.499
Grade of Architecture- Lower Half	123 (84.2)	0.325	124 (84.9)	0.406	126 (86.3)	0.423	132 (90.4)	0.587
Crypts Configuration	83 (56.9)	0.253	88 (60.3)	0.298	104 (71.2)	0.292	113 (77.4)	0.418
Dysplasia Grade	104 (71.2)	0.415	112 (76.7)	0.536	115 (78.8)	0.413	124 (84.9)	0.581
Final Diagnosis	61 (41.8)	0.344	67 (45.9)	0.407	79 (54.1)	0.370	88 (60.27)	0.454

An overall agreement among the five pathologists based on the cytology grade in both the upper and lower halves was obtained for 89 (61.0%) and 117 (80.1%) polyps, respectively. The overall kappa values in the upper and lower halves, respectively, were 0.352 and 0.374, which are considered to be fair. After excluding the assessment of Pathologist 4, the overall kappa values for the upper and lower halves considerably increased to 0.427 and 0.504, respectively.

Regarding the grade of architecture in both the upper and lower halves, an overall agreement among the five pathologists was obtained for 101 (69.2%) and 123 (84.2%) polyps, respectively. The overall kappa values in the upper and lower halves, respectively, were 0.365 and 0.325, which are considered to be fair. After excluding the assessment of Pathologist 4, the overall kappa values for the upper half considerably increased to 0.495. Moreover, after excluding the assessment of both Pathologists 4 and 5, the overall kappa values for the lower half significantly increased to 0.587. Among the 146 adenomas, the overall agreement for crypts' configuration was obtained in 83 polyps (56.9%). Interobserver agreement was fair, with a kappa value of 0.253.

Regarding the dysplasia grade, a perfect agreement among the five pathologists was obtained for 104 polyps (71.2%). The overall kappa value was 0.415, which is considered to be moderate. Despite the overall favorable kappa value for grading of dysplasia, a number of discrepancies were identified, so after excluding the assessment of Pathologist 4 and both Pathologists 4 and 5, the overall kappa values increased to 0.536 and 0.581, respectively. A case of tubulovillous adenoma's illustration with disagreement in grade of dysplasia is presented in Figures 1, 2, and 3.

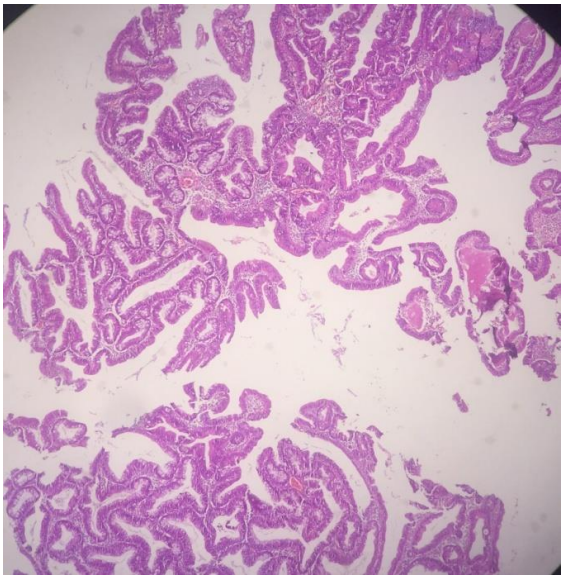

Fig. 1. H&E stain (x40): All pathologist's diagnosis was tubulovillus adenoma for above figure, but there was disagreement for grade of dysplasia. Two high grade and three low grade diagnosis were made.

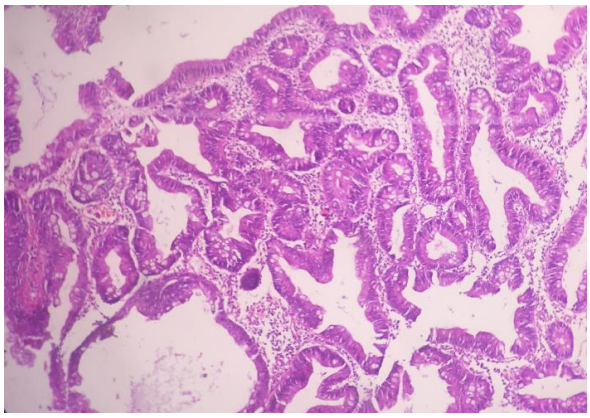

Fig. 2. H&E stain (x40): Architecture of crypts diagnosed parallel by two pathologists so as low-grade dysplasia, while diagnosed as back to back and complex by other three pathologists who considered same case as tubulovillous adenoma with high grade dysplasia.

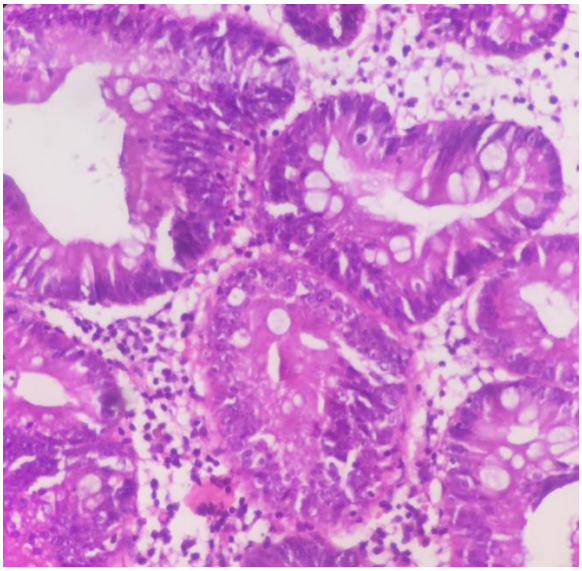

Fig. 3. H&E stain (x100): Cytology grade considered high by two pathologists, while diagnosed as low grade by three pathologists

The overall agreement for the final diagnosis (i.e., both the histologic type and dysplasia grade) of adenomas was obtained in 61 polyps (41.8%). The overall kappa value was 0.344, which is considered to be fair. Interobserver agreement for other features of adenomatous polyps is presented in Table 4.

Discussion

The aim of this study was to assess interobserver variability in the classification of dysplasia in colorectal adenomas among Iranian pathologists. In this study, a total of 146 adenomatous polyps were histopathologically assessed by five pathologists independently. Observational studies have shown that adenomatous polyps occur more frequently in males than in females (14–18). In our series, there was also a male preponderance, with a male to female ratio of 2.2:1. Overall, this study showed that left-sided adenomatous polyps were more prevalent than right-sided ones, which is in line with previous studies (18–21). Furthermore, consistent with previous studies, the sigmoid colon was the most common site of adenomatous polyps in the present study (18, 20).

Our results indicated that the interobserver agreement regarding histologic type is moderate (k=0.412). This level of agreement was lower than what was reported by Jensen *et al.* (k=0.54) (7) and van Putten *et al.* (k=0.55) (8), but approximately consistent with other studies performed by Yoon *et al.* (k=0.46), Foss *et al.* (k=0.0.18, 0.38, and 0.61), and Terry *et al.* (k=0.48) (9–11). Furthermore, a better agreement was obtained after excluding Pathologists 4 and 5 from the assessments. Consistent with previous studies (k ranging from 0.3 to 0.4) (7, 9, 22), the moderate agreement in assessing dysplasia was obtained among Iranian pathologists in this study (k=0.415).

However, several studies have shown a good degree of agreement (k ranging from 0.5 to 0.7) (8, 10, 23, 24). For this feature, a better agreement was also obtained after excluding Pathologist 4 from the assessments. Moreover, agreement on the final diagnosis in colorectal adenomas (i.e., both histologic type and dysplasia grade) was fair in this study, with a kappa value of 0.314. On the other hand, agreement among all five pathologists was seen in 41.8% for the final diagnosis, 51.4% for histologic type, and 71.2% for dysplasia grade. In a study conducted by Jensen *et al.* (7), the agreements among three pathologists for the final diagnosis, histologic type, and dysplasia grade were 35.2%, 61.0%, 47.8%, respectively.

The lowest agreement was found for the mitotic activity, nuclear shape, and nucleolus. For these features, all Kappa values were less than 0.2, indicating a poor level of agreement among pathologists. In this study, fair interobserver agreement was found for the grade of architecture in both the upper and lower halves, as well as for crypts' configuration.

Resection of adenomas eliminates their risk of potential malignant transformation—but not potential for the development of a new metachromatic adenoma or carcinoma. This risk is correlated with the number, localization, size, architecture, and degree of dysplasia of the initially resected adenoma (9). Patients with a resected adenoma, demonstrating the following features: size > 1 cm, villous component, and high-grade dysplasia, have a high risk of recurrence, and should follow up colonoscopy more frequently.

Obviously, histomorphology has a significant role in determining high-risk adenoma, which requires intense surveillance to avoid progression to carcinoma, but no study is available regarding the identification of markers for the distinction between low- and high-grade dysplasia.

Many molecular markers have been identified in the adenoma-carcinoma transition, starting from APC and TP53 to the more recent BRAF, SKA3, and DSN1, but

no investigations have been conducted considering different grades of dysplasia (25).

In order to improve the diagnostic accuracy of dysplasia in adenomas, our study suggests that preparing and incorporating a common national guideline, emphasizing two important criteria with more interobserver variabilities (including cytology grade and architectural features with adding images, such as in atlas), could be beneficial. Other works based on molecular study focus on comparing morphological criteria with outcomes, and molecular abnormalities in adenomas also are required.

Our study has several strengths that should be mentioned, including (a) evaluating the interobserver agreement via a relatively large number of experienced pathologists in the field of GI pathology in Iran and (b) simultaneously evaluating interobserver agreement for most features of adenomatous polyps. There are also a few limitations that should be considered in evaluating the present findings. First, the sample size was relatively small, and a larger multicenter study would be required to confirm the results. Second, because of the practical reasons, intraobserver agreement was not evaluated in this study. Third, we did not have data on the other types of colorectal polyps.

Conclusion

In sum, the assessment of dysplasia in colorectal adenomas requires careful histopathological evaluation, which, in most cases, appears to be sufficient for proper classification, but interobserver variabilities cannot be ignored. Our findings indicate that agreement among pathologists in assessing dysplasia in colorectal adenomatous polyps is within fair to moderate levels of agreement. It seems as if the diagnostic criteria being limited or divided into a major and minor category could be effective in reducing the variability of intra and inter observers. Improving diagnostic criteria requires to design new standardized protocols and examine them in separate studies. Our findings emphasize improving the existing diagnostic criteria, as well as developing new standardized criteria, besides new histochemical, immunohistochemical, or molecular markers, which could allow to categorize the dysplasia in a more accurate way because the surveillance implications and clinical approach are relevant.

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Conflict of Interest

The authors declared that there is no conflict of interest regarding the publication of this article.

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