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ENDOSCOPIC DIAGNOSIS OF DYSPLASIA IN PATIENTS WITH LONGSTANDING ULCERATIVE COLITIS

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AIM: to evaluate high-definition colonoscopy (HD-WLE) using chromoendoscopy for dysplasia in the longstanding ulcerative colitis (UC).
PATIENTS AND METHODS: a cohort prospective study included 140 patients (aged 29-79 years old) with a long course of UC (6-44 years) in time of endoscopic remission with good quality of bowel cleansing. A white-light endoscopy was performed using high-definition colonoscopies (HD-WLE). Chromoendoscopy (0.4% solution of indigo carmine), targeted biopsy, and histological analysis were performed.
RESULTS: HD-WLE revealed 34 lesions with endoscopic signs of dysplasia in 27 (19.3%) patients: in 20 patients – 1(74.1%) lesion, in 7 patients – 2(25.9%). In 22(64.7%) patients lesions were more than 1 cm. Chromoendoscopy confirmed the signs of dysplasia in 100.0% of cases (88.2% – low grade dysplasia). Histologically, low-grade dysplasia was detected in 58.8% of cases, undetected dysplasia – in 20.6%, sporadic adenomas – in 20.6%. The effectiveness of endoscopic diagnosis for detecting dysplasia was 74%. A comparative analysis of the endoscopic signs of dysplasia and sporadic adenomas showed the absence of significant differences.
CONCLUSION: the additional chromoendoscopy during HD-WLE colonoscopy with targeted biopsy does not lead to increase of colorectal epithelial dysplasia detection in UC. The experience of endoscopist should be considered when making decision which type of endoscopy for dysplasia detection in UC is needed.

[Key words: ulcerative colitis, colonoscopy, dysplasia, chromoendoscopy]

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INTRODUCTION

Colorectal cancer is one of the most serious consequences of ulcerative colitis (UC) [1-4]. It is believed that cancer in UC occurs against the background of dysplasia, which is a neoplastic transformation of the colorectal epithelium, and one of the main risk factors for cancer is the duration of the disease [1,2,5].
A meta-analysis of studies for risk factors and time intervals of colorectal cancer in patients with UC estimated cumulative risks of colorectal cancer as 1%, 2% and 5% after 10, 20 and more years of UC, and therefore screening colonoscopy was recommended after 10 years from the onset of the disease [6,7].
However, data from a number of studies suggest that some patients may have colorectal cancer earlier, so it is recommended to start screening for neoplasia after 6-8 years of the disease [2,8-11].
Approaches to the diagnosis of dysplasia have evolved with the improvement of endoscopic technologies. When using fiber-optic colonoscopes, it was difficult to visualize dysplasia in UC, so it was recommended to make exploratory segmental biopsies [6,7,12-15].
The implementation of chromoendoscopy, using methylene blue or indigo carmine as a sprayed dye, led to an improvement in the dysplasia detection [2,16].
However, the implementation of endoscopes with high image clarity led to the fact that it became possible to visualize the pit pattern of the colorectal mucosa, and the need for chromoendoscopy in UC was questioned [5,6,11,17,18].
In addition, numerous studies have shown poor results of search biopsies, and a recent prospective randomized study in patients with UC showed that sighting and search biopsies reveal neoplasia with the same incidence, but the study time is significantly shorter in the group of sighting biopsies (41.7 vs. 26.6 minutes, $p<0.001$) [5,6,19].
Therefore, there is need for further studies for improving the endoscopic detection of dysplasia in UC.

AIM

The aim is to evaluate the effectiveness of high-definition colonoscopy (HD-WLE) with chromoendoscopy

for the detection of colorectal epithelial dysplasia in the longstanding UC.

PATIENTS AND METHODS

A prospective study (November, 2017 – June, 2019) included 140 patients who met the following criteria: duration of UC disease – at least 6 years, endoscopic remission of the disease (0 degree according to The Shroeder classification), good quality of bowel cleansing (according to the Boston scale).

Patients were aged 48.7 (29-79) years, 77 (55.0%) of them were females. The duration of UC disease ranged from 6 to 44 years, with an average of 16 years.

All the patients underwent high-definition colonoscopy in white light (HD-WLE). During the endoscopic examination, the incidence of colorectal lesions was assessed (according to the Montreal classification).

The first stage was to assess the condition of the mucosa in all parts of the large intestine in a white light, after which the study was supplemented by a chromoendoscopy using a sprayed dye (0.4% indigocarmine solution) by a standard technique through a spray catheter.

According to the recommendations of the International Consensus (SCENIC) [20], the characteristics of the identified lesions were defined according to the Paris endoscopic classification [21], and the pit pattern was assessed as well according to the pit pattern Kudo classification [22].

Flat and polypoid lesions with pit architectonics differing from the surrounding mucosa and corresponding to type III-V, according to Kudo, S., were identified as suspicious for dysplasia (Fig. 1, Fig. 2).

The next step was a targeted biopsy of the lesions with endoscopic signs of dysplasia.

Histological study of biopsies was performed according to the standard procedure.

Morphological verification of the revealed lesions and their classification by Riddell, R. were performed (Fig. 3, Fig. 4) [23].

Afterwards, the analysis of the results of examination of the colorectal mucosa with a high-definition endoscopy in white light (HD-WLE) and using chromoendoscopy was carried out, the effectiveness of endoscopic

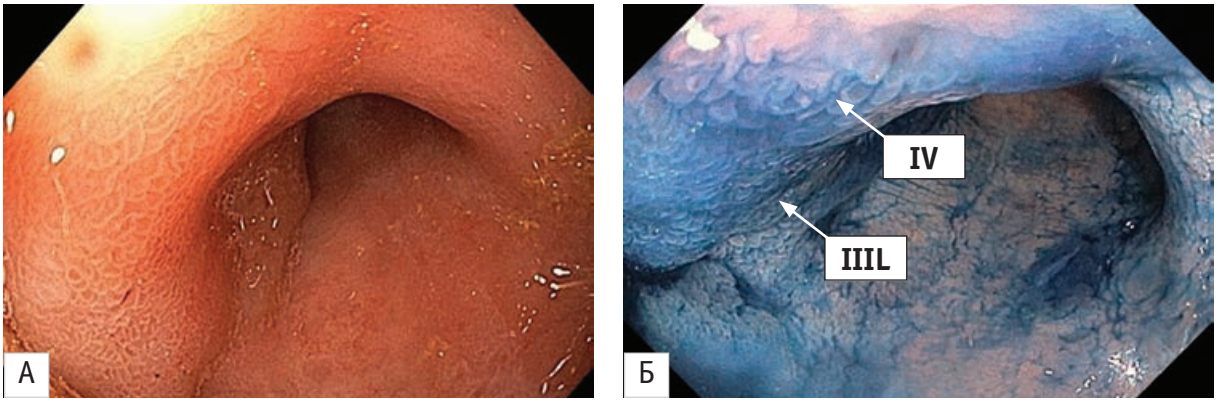

Figure 1. *Endoscopic signs of dysplasia (flat lesion >1 cm).*
A-examination in white light: type LST-G0-IIa, B-chromoendoscopy: type III L-IV by Kudo, S.

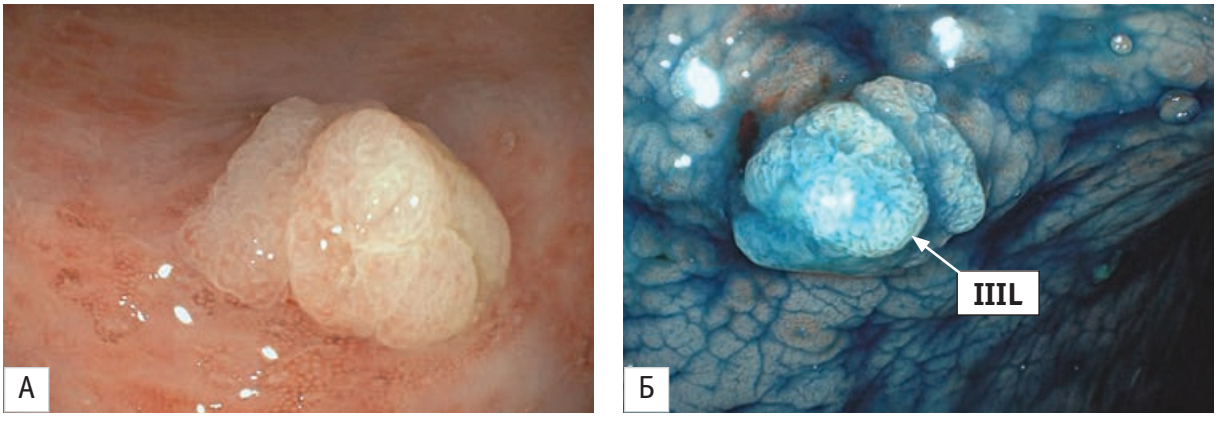

Figure 2. *Endoscopic signs of dysplasia (polypoid lesion <1 cm).*
A-examination in white light: type 0-1s, B-chromoendoscopy: type IIIL by Kudo, S.

diagnosis of dysplasia was assessed.
The comparative analysis was performed using the exact Fisher test.

RESULTS

Of the 140 patients included in the study, endoscopic signs of colorectal epithelial dysplasia were detected in 27 (19.3%) patients. Patients were aged 51 (29-79) years, 15 (55.6%) were females, the average duration of the disease was 16 years (6-44 years).
In 113 (80.7%) patients, when examining the mucosa in white light, as well as with subsequent coloring it with some dye, no signs of dysplastic changes were revealed.
Analysis of the extent of UC large intestine lesions showed that of the 27 patients with the presence of endoscopic signs of dysplastic changes in the mucosa, 24 (88.9%) patients had a total colitis, 2 (7.4%) patients had a left-side colitis. In 1 (3.7%) case, the study was completed at the level of the proximal third of the sigmoid colon due to the steno sing tumor.
In white light endoscopy in this group of the patients (27 patients), a total of 34 lesions with signs of dysplasia were revealed: in 20 (74.1%) patients – 1 lesion, in 7 (25.9%) patients – 2 lesions.
Colon cancer was diagnosed in 2 (7.4%) cases.
Lesions up to 1 cm with endoscopic signs of dysplasia were detected in 12 (35.3%) cases. The average size of these lesions was 6 mm (4-9 mm).
At the same time, in 3,0% a lesion of 0-IIa + IIc type (according to the Paris classification) was detected, and in 11.8% – lesions of 0-Is and 20.6% – 0-IIa types.
Lesions larger than 1 cm, related according to the Paris classification to the lateral lyspreading type (LST), with endoscopic signs of dysplasia were detected in 22 (64.7%) cases.
The average size of the lesions was 20 mm (11-70 mm).
The non-granular type of laterally spreading lesions (LST-NG) was detected in 3 (8.8%) cases, and granular type (LST-G) – in 19 (55.9%), with the majority of them belonging to the LST-G 0-IIa type. In chromoendoscopy, the assessment of pit pattern of lesions with suspected dysplasia in 30 (88.2%) cases revealed changes characteristic of low-grade dysplasia and in 4 (11.8%) cases-high-grade dysplasia.
Endoscopic characteristics of the revealed lesions are presented in table 1.
Chromoendoscopy confirmed white-light signs of dysplasia in all 34 cases, followed by a targeted biopsy.
Histological examination of biopsy revealed low-grade dysplasia in 20 (58.8%) cases, no high-grade dysplasia, in 7 (20.6%) cases – changes undefined as dysplasia, and in 7 (20.6%) cases – sporadic adenomas.
Also, in 2 cases (100.0%), colorectal cancer with adenocarcinoma structure was confirmed.
Given the fact that ambiguous changes in the epithelium (7 cases) cannot be confidently classified as negative or positive for dysplasia, these cases were excluded from the analysis of the effectiveness of endoscopic diagnosis of dysplasia.
Based on this, a comparison of the results of endoscopic verification of dysplasia with the results of histological examination of biopsies showed that the effectiveness of endoscopic diagnosis in the detection of dysplasia was 74%.
Comparative endoscopic characteristics of epithelial dysplasia (20 cases) and sporadic adenomas (7 cases) are presented in table 2.
The analysis of these cases showed no significant differences in the endoscopic characteristics of sporadic adenomas and dysplasia of the colorectal epithelium.

DISCUSSION

In patients with UC, according to meta-analysis, the

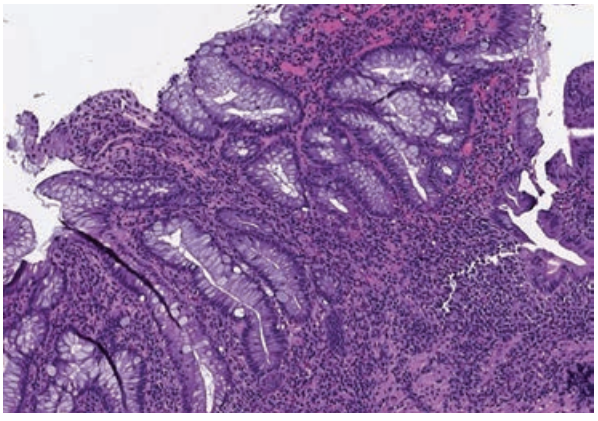

Figure 3. *Histological study (hematoxylin-eosin, ×10). Lesion with changes undefined as dysplasia*

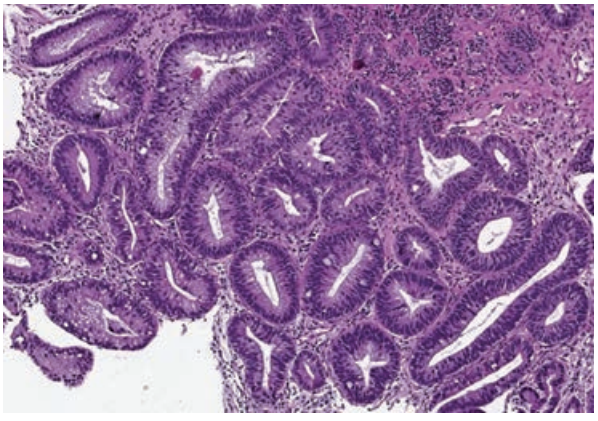

Figure 4. *Histological study (hematoxylin-eosin, ×10). Lesion with low-grade dysplasia.*

Table 1. *Endoscopic characteristics of colorectal epithelial dysplasia in patients with a long UC history*

Indicators		Macroscopic type (according to the Paris classification)						Total	
Type of pit pattern (by S. Kudo)		0-IIa	0-IIa+ IIc	0-Is	LST-G (0-IIa)	LST-G (0-IIa+0-Is)	LST-NG (0-IIa)	*n*	%
IIIS		3	–	–	4	–	1	8	23.6
IIIL		3	–	1	8	–	–	12	35.3
IIIS-IIIL		–	–	–	1	–	–	1	2.9
IV		1	1	1	–	–	–	3	8.8
IIIS-IV		–	–	–	–	–	1	1	2.9
IIIL-IV		–	–	–	3	1	1	5	14.8
IIIL-Vi		–	–	1	1	1	–	3	8.8
Vi		–	–	1	–	–	–	1	2.9
Vn		–	–	–	–	–	–	–	–
Total	n	7	1	4	17	2	3	34	100
	%	20.6	2.9	11.8	50.0	5.9	8.8		

Table 2. *Endoscopic characteristics of epithelial dysplasia and sporadic adenomas in patients with a long UC history*

Indicators		Dysplasia (*n*=20)		Sporadic adenomas (*n*=7)		*p*
Macroscopic type	Type of pit pattern	*n*	%	*n*	%	
0-Is	IIIs-IV	2	10	–	–	*p*>0.05 (=1.00000)
	Vi	1	5	1	14	*p*>0.05 (=0.45869)
0-IIa	IIIs- IV	2	10	–	–	*p*>0.05 (=1.00000)
	Vi	–	–	–	–	–
0-IIa+0IIc	IIIs-IV	1	5	–	–	*p*>0.05 (=1.00000)
	Vi	–	–	–	–	–
LST G 0-IIa	IIIs- IV	11	55	4	58	*p*>0.05 (=1.00000)
	Vi	1	5	–	-	*p*>0.05 (=1.00000)
LST G 0-IIa+0-Is	IIIs- IV	–	–	1	14	*p*>0.05 (=0.25926)
	Vi	–	–	1	14	*p*>0.05 (=0.25926)
LST NG 0-IIa	IIIs- IV	2	10	–	–	*p*>0.05 (=1.00000)
	Vi	–	–	–	–	–

estimated risk of colorectal cancer is 2.4 times higher than in the general population [13]. Dysplasia is currently considered a reliable predictor of colorectal cancer in patients with UC [1,2,13].

The risk of colorectal cancer and precancerous lesions (dysplasia) is determined by the duration, the severity and the extent of the disease [2,10,13,24].

In particular, there is a consensus that patients with poorly controlled disease and signs of chronically active inflammation are most at risk for neoplasia [2,25].

We studied the endoscopic diagnosis of precancerous lesions directly in a group of patients with a duration of the disease from 6 to 44 years.

Previously, it was proved that total colitis carries an extremely high risk of cancer, and with left-sided colitis (before the left bend of the colon), the risk is much lower [2].

The results of the study showed that in the long-term course of UC in patients with endoscopically diagnosed dysplasia total colitis prevailed over the left-sided lesions, and it was noted in 89% of cases, which indicates a high risk of precancerous changes in the large intestine for patients with the total colitis and long story of UC.

The study showed that in detection of dysplasia in long-term UC, the LST types (64.7%) of lesions are more often diagnosed, which is consistent with the data of other studies indicating a high risk of dysplasia in lesions larger than 1 cm [1].

The histology showed that there were no cases of high-grade dysplasia, but the cases of low-grade dysplasia were revealed, characterized by the presence of crypts covered with epithelium with enlarged and hyperchromatic nuclei that are perpendicular to the basal membrane along the long axis, and atypical nuclear features include both the crypt and the surface epithelium.

The interest in this group of dysplasia is that it is the most common type of dysplasia detectable.

It is believed that the low-grade dysplasia is a risk factor for the development of a high-grade dysplasia and colorectal cancer in UC.

However, connection of this type of dysplasia with the development of colorectal cancer is poorly understood, as the reported risk of colorectal cancer associated with low-grade dysplasia differs significantly between studies [1,2,26].

In addition, recent population-based studies have shown that the risk of colorectal cancer in UC patients is lower than previously thought, and the reduction in risk over the past 30 years may be the result of improved therapy in UC patients [2,24,25]. This may also cause more frequent diagnosis of low-grade dysplasia compared to high-grade dysplasia.

A special group consists of dysplasia-undefined lesions that have a higher risk of progression to high-grade dysplasia and cancer compared to lesions without dysplasia [1].

In the study, epithelial changes, uncertain dysplasia were proved in 21%, i.e. ambiguous changes that cannot be confidently classified as negative or positive dysplasia. It is due to cytological atypia, inherent in both regenerative changes and dysplastic changes of the epithelium, as well as due to various cytological signs arising from histological processing (tangential cutting, staining artifacts or fixation), which can lead to this interpretation.

In this situation, it is not possible to unambiguously clarify the presence or absence of dysplasia, which indicates the need for targeted monitoring of this group of patients with a reduction in the intervals between control endoscopic studies according to international giudelines [13].

Multifocal dysplasia is considered one of the most significant risk factors for colorectal cancer [2].

In the study, dysplastic changes in the long-term course of UC often had a unifocal (single) type.

Several randomized studies suggest that chromoendoscopy increases the effectiveness of dysplasia detection and may eliminate the need for exploratory biopsy in UC.

However, a retrospective cohort study revealed a similar number of dysplastic lesions in patients who underwent examination with using white light or dye spraying during chromoendoscopy [11].

A recent prospective randomized study using high-definition colonoscopy with narrow-spectrum imaging and high-definition colonoscopes with dye-spray chromoendoscopy has demonstrated similar dysplasia detection rates [17].

Clinical guidelines (ACG-2019) indicate that when using standard-definition colonoscopes, it is preferable to supplement the white-light examination with chromoendoscopy, while when using high-definition colonoscopes, the white-light examination can be supplemented with both chromoendoscopy and narrow-spectrum endoscopy [13].

Given that the targeted biopsy reduces the time of diagnostic examination almost twice and the same frequency of detection of neoplasia is observed as with random biopsies, the targeted biopsies is preferable [19]. In our study, chromoendoscopy was both a method of clarifying diagnosis and a means of justifying the taking of a targeted biopsy.

The majority of dysplastic changes of the large intestine were visible in white light even with the diameter of the changed area up to 0.4 cm.

Endoscopic signs of dysplasia detected in white light were confirmed by us in all cases and with chromoendoscopy.

Comparison of the results of endoscopic diagnosis with the histology examination showed that the efficacy of endoscopic examination was 74%.

The rate of false positive results was 7 cases, with histologically proved adenomas with signs of epithelial dysplasia.

The comparative analysis of the endoscopic picture of dysplasia and sporadic adenomas shows the absence of fundamental differences in the endoscopic characteristics of these lesions in their assessment by conventional classifications of visual diagnostics. According to the results obtained, it can be concluded that the chromoendoscopy did not lead to an improvement in the diagnosis of dysplasia, all true positive and false positive results were identical for both white light endoscopy and chromoendoscopy.

Thus, when choosing a technique for endoscopic diagnosis of dysplasia in UC, it is necessary to take into account the possibility of high-definition video colonoscopy in white light with targeted biopsy of suspected dysplasia areas of the large intestine, without specifying the diagnosis, which ultimately will lead to a significant reduction in the procedure duration.

In addition, when choosing an endoscopic method of diagnosis, the qualification of an endoscopist should be taken into account [2].

CONCLUSION

Additional use of chromoendoscopy in high-definition colonoscopy with targeted biopsy does not lead to an increase in the incidence of detection of colorectal epithelial dysplasia in UC.

When deciding on the choice of the method of endoscopic diagnosis of dysplasia in UC, it is necessary to take into account the factor of qualification of a specialist.

Issues related to the improvement of endoscopic identification of low-grade dysplasia require further study.

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