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Diagnosis of Columnar Metaplasia of the Esophageal Mucosa in Patients with Complicated Gastroesophageal Reflux Disease

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Aim: to improve methods of diagnostics of esophageal mucosal forms of metaplasia and dysplasia in patients with complicated forms of gastroesophageal reflux disease (GERD) using multidisciplinary approach.
Material and methods. Overall, 131 patients aged 18 to 84 years (mean age — 55.8 ± 16.7 years) with confirmed diagnosis of GERD complicated by development of metaplasia of mucosa of distal esophagus were included in retro- and prospective study. At the prehospital stage the patients' complaints were estimated, anamnesis was taken. At the first stage of the diagnostic program all patients underwent detailed esophagogastroduodenoscopy in high resolution with white light. The region of esophageal mucosa with signs of metaplasia and determination of its prevalence was examined and evaluated with special attention. Ultrashort segment was revealed in 26 patients, short segment — in 47 patients, long segment of mucosal metaplasia was revealed in 58 patients. Then to reveal the signs of dysplasia we used specifying endoscopic methods: the structure of pitted and microvascular pattern was estimated in narrow spectral mode using BING classification system. If an irregular type of metaplasized epithelium structure was detected in the process of BING assessment, the areas suspicious for dysplasia were marked, followed by aim forceps biopsy from them. The next stage was staining of the metaplasized segment with 1.5 % ethanic acid solution — acetowhitening. PREDICT classification system was used to evaluate the stained mucosal sections with metaplasia. Targeted forceps biopsy was performed from the altered areas that most quickly lost their coloring. The final stage of the diagnostic program in all patients was a forceps biopsy of the mucosa of the metaplasic segment according to the Seattle protocol, which requires increasing the number of fragments as the metaplasic segment lengthens in a "blind" biopsy. The biopsy material was stained with hematoxylin and eosin, and periodic acid Schiff reaction was performed in combination with alcyanine blue according to the standard technique.
Results. Endoscopic examination in white light and evaluation of metaplasia extent revealed ultrashort segment (<1 cm) in 26/131 (19.9 %) patients; short segment (1–3 cm) — in 47/131 (35.9 %); long segment (> 3 cm) — in 58/131 (44.3 %) patients. Among the diagnostic techniques used, the BING and PREDICT classifications had the highest accuracy, sensitivity, and specificity (accuracy — 88.9 and 95.3 %, sensitivity — 90.5 and 91.3 %, and specificity — 86.7 and 100 %, respectively), which significantly exceeded the Seattle protocol also used in this work. The results showed a low level of specificity (31.2 %), accuracy (54.5 %), and sensitivity (76.8 %) of the Seattle protocol. The use of BING and PREDICT classifications provided marking of compromised zones, allowing targeted histological sampling.
Conclusions. The original study demonstrated the greatest sensitivity, specificity, and accuracy of PREDICT and BING methods in the diagnosis of metaplasia with signs of dysplasia in patients with complicated GERD. It is also important that the use of BING and PREDICT classification systems allows to reduce the number of biopsy samples in comparison with their unreasonably large number according to the Seattle protocol, thereby reducing mucosal and submucosal trauma of the esophagus and the risk of complications.
Keywords: gastroesophageal reflux disease, GERD, esophageal metaplasia, dysplasia, PREDICT, BING, Barrett's esophagus, ultrashort segment, short segment, long segment
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Диагностика цилиндроклеточной метаплазии слизистой оболочки пищевода у пациентов с осложненным течением гастроэзофагеальной рефлюксной болезни

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Цель исследования: усовершенствовать диагностику разновидностей цилиндроклеточной метаплазии и дисплазии слизистой оболочки пищевода с применением мультидисциплинарного подхода и оптимизировать алгоритм лечения пациентов с осложненным течением гастроэзофагеальной рефлюксной болезни (ГЭРБ).

Материал и методы. В ретро- и проспективное исследование включен 131 пациент в возрасте от 18 до 84 лет (средний возраст — 55,8 ± 16,7 года) с подтвержденным диагнозом ГЭРБ и развитием цилиндроклеточной метаплазии слизистой оболочки дистального отдела пищевода. На догоспитальном этапе оценены жалобы пациентов, произведен сбор анамнеза. На первом этапе диагностической программы всем пациентам выполнен детальный осмотр пищевода при эзофагогастродуоденоскопии в белом свете с высоким разрешением с оценкой участков слизистой оболочки пищевода с признаками метаплазии, определением ее распространенности. С целью выявления признаков дисплазии использованы уточняющие эндоскопические методики: в узкоспектральном режиме оценена структура ямочного и микрососудистого рисунка с применением классификационной системы BING. При обнаружении нерегулярного типа структуры метаплазированного эпителия в процессе оценки по системе BING намечены участки, настораживающие в отношении наличия дисплазии, с последующей прицельной щипцовой биопсией из них. Следующим этапом произведено окрашивание метаплазированного сегмента 1,5 %-ным раствором уксусной кислоты — ацетобеление. Для оценки окрашенных участков слизистой оболочки с метаплазией применена классификационная система PREDICT. Из измененных участков, наиболее быстро утративших окраску, выполнена прицельная щипцовая биопсия. Завершающим этапом диагностической программы у всех пациентов стала щипцовая биопсия слизистой оболочки метаплазированного сегмента по Сиэтлскому протоколу, требующему увеличения числа фрагментов по мере удлинения сегмента метаплазии при выполнении биопсии «вслепую». Полученный при биопсии материал окрашен гематоксилином и эозином, проведена ШИК-реакция в сочетании с альциановым синим по стандартной методике.

Результаты. При эндоскопическом осмотре в белом свете и оценке протяженности цилиндроклеточной метаплазии ультракороткий сегмент (менее 1 см) выявлен у 26/131 (19,9 %) пациентов; короткий сегмент (от 1 до 3 см) — у 47/131 (35,9 %); длинный сегмент (более 3 см) — у 58/131 (44,3 %) пациентов. Среди применяемых диагностических методик наибольшей точностью, чувствительностью и специфичностью обладали классификации BING и PREDICT (точность — 88,9 и 95,3 %, чувствительность — 90,5 и 91,3 %, специфичность — 86,7 и 100 % соответственно), что существенно превосходит аналогичные показатели Сиэтлского протокола. Использование классификаций BING и PREDICT обеспечило маркировку компрометированных участков, позволяя прицельно выполнять забор материала для гистологического исследования.

Выводы. Настоящее исследование продемонстрировало наибольшую чувствительность, специфичность и точность классификации PREDICT и BING в диагностике цилиндроклеточной метаплазии с признаками дисплазии у пациентов с осложненным течением ГЭРБ, возможность ограничить количество биоптатов, тем самым снижая травматизацию слизистой оболочки пищевода и риск развития артифициальных нежелательных последствий.

Ключевые слова: гастроэзофагеальная рефлюксная болезнь, цилиндроклеточная метаплазия, дисплазия, PREDICT, BING, пищевод Баррета, ультракороткий сегмент, короткий сегмент, длинный сегмент

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Introduction

Columnar metaplasia of the esophageal epithelium complicates the course of gastroesophageal reflux disease (GERD) in 10–15 % of patients [1]. Esophagogastroduodenoscopy (EGD) allows the primary detection of columnar metaplasia proximal to the esophageal-gastric junction in patients with clinical manifestations of GERD in the range from 0.5 to 1 % [2]. In the absence of complaints characteristic of GERD, columnar metaplasia is detected in 0.36 % of cases when performing an elective EGD for other indications or during emergency diagnosis of gastrointestinal bleeding (GIB) in particular [3].

The risk of esophageal adenocarcinoma in patients with columnar metaplasia without dysplasia is 0.12–0.33 %, increasing to 1.83–9.1 % in patients with low-grade dysplasia [4]. Several authors range the risk of malignancy in patients with confirmed severe dysplasia from 19 to 60 % [5, 6], and Japanese specialists attribute severe neoplasia to early cancer. A short segment (from 1 to 3 cm) and a long segment (over 3 cm) of intestinal type columnar metaplasia, unconditionally interpreted by all experts as the "true" Barrett's esophagus, antecede the esophageal adenocarcinoma, increasing the risk of its development by 30–125 times [7]. For the Caucasian race, this statement is true. The British Clinical Guidelines suggested not to specify the "ultrashort segment of Barrett's esophagus" as a concept [8]. This approach has found numerous supporters also because of the difficulty to distinguish a normal high-amplitude Z-line from ultrashort tongues of columnar metaplasia in EGD. However, not all experts fully agree with this opinion, since up to 49 % of esophageal adenocarcinomas in Japan develop precisely from the ultrashort segment of the columnar metaplasia [9]. The Global Consensus on Landmarks, Definitions, and Classifications in Barrett's Esophagus, approved at the World Congress in Rio de Janeiro in 2020 and published in 2022 [10] defined Barrett's esophagus as a columnar-lined esophagus confirmed with intestinal metaplasia on biopsy, extending at least 1 cm above the gastro-esophageal junction. Of note, 10 % of the world's leading experts voted against this definition, as the gastric-type columnar esophageal metaplasia, including that less than 10 mm long, can transform into esophageal adenocarcinoma, although much less frequently [11].

Intestinal metaplasia and dysplasia are focal and distribute in the segment of columnar metaplasia heterogeneously, complicating their verification using forceps biopsy. To solve this problem, the Seattle Protocol was developed in 2000 for "screening" biopsies in patients with suspected Barrett's esophagus [12]. However, it can miss areas of intestinal metaplasia and neoplasia, even with strict adherence to the biopsy technique; the protocol itself is quite invasive and time-consuming, both for the material obtaining and the slides pathological studying [13, 14]. Even in countries with a developed healthcare system, the Seattle Protocol is observed only in 26–77 % of patients [15, 16], which forces us to seek more reliable diagnostic methods.

High-resolution EGD in white and narrow light spectrum (NBI) has become a promising area for detecting foci of intestinal metaplasia and dysplasia in recent years. With the developing this high-tech endoscopic equipment and the beginning of its use for predicting histology in columnar-lined esophagus, criteria were developed for interpreting a high-definition endoscopic picture got under intravital blue-green light illumination of tissues, resulting in BING (Barrett International NBI Group) classification in 2016. BING has shown high accuracy of 85 %, 80 % sensitivity, 88 % specificity, 81 % positive predictive power, and 88 % negative predictive power in the hands of the authors [17]. To improve the visualization of the microstructure of the surface of the segment of columnar metaplasia and the detection of neoplasia sites, chromoendoscopy with 1.5 % acetic acid solution was proposed. The data allowed setting the PREDICT classification in 2017 [18], which significantly increased the sensitivity of endoscopic diagnosis of neoplasia in the segment of columnar esophagus. The optical magnification of the endoscopic image (×70–80) in close focus mode provides an even more detailed characterization of the pathological areas identified during esophagoscopy, and accordingly increases the sensitivity, specificity, and accuracy of endoscopic diagnosis.

Endoscopic diagnosis of columnar metaplasia of the esophagus, and especially the detection of intestinal metaplasia and neoplasia, remains challenging even for specialized reference centers [19]. High-resolution EGD with magnification, virtual and real chromoendoscopy, supported by BING and PREDICT classifications, significantly improve the accuracy of diagnosis of columnar metaplasia, intestinal metaplasia, and early neoplasia; reduce the study time, lower the diagnostic errors; improve the management and

treatment algorithm for the patients with columnar metaplasia of the esophagus [17]. But they require careful validation and verification in real clinical practice. Rapidly developing medical decision support systems (artificial intelligence) also need carefully verified endo-morphological big data for the effective training of neural networks and subsequent analysis of video images.

The aim of the study was to improve the diagnosis of varieties of columnar metaplasia and dysplasia of the esophageal epithelium using a multidisciplinary approach and to optimize the treatment algorithm for patients with complicated GERD.

Material and methods

The study included 131 patients, 69 (52.7 %) men and 62 (47.3 %) women aged 18 to 84 years (mean age — 55.8 ± 16.7 years) who were examined and treated from January 2017 to September 2019 with a confirmed GERD complicated by the Barrett's columnar metaplasia of the distal esophagus (Table 1). An ultrashort segment of columnar metaplasia (< 1 cm) was detected in 26/131 (19.9 %) patients, short segment (1–3 cm) — in 47/131 (35.9 %), and long segment (> 3 cm) — in 58/131 (44.3 %) patients. GERD and columnar metaplasia were verified before admission to the clinic in 46/131 (35.1 %) patients. In the remaining 85/131 (64.9 %) patients, columnar metaplasia was first detected during examination in the clinic, including 51/131 (38.9 %) persons with elective EGD. In another 34/131 (26.0 %) patients, columnar metaplasia was suspected/detected during emergency EGD performed in patients admitted to the hospital with a picture of gastrointestinal bleeding. In 31/34 (91.2 %) of them, gastrointestinal bleeding developed from chronic ulcers of the upper digestive tract (1 person — Forrest 1a, 4 — Forrest 1b, 2 — Forrest 2a, 4 — Forrest 2c, and 20 — Forrest 3), including that from peptic ulcers of the esophagus in 5 patients and Mallory — Weiss tears in 3/34 (8.8 %) patients. Combined endoscopic hemostasis was required and was successfully performed in 10 (29.4 %) of 34 patients, the rest were treated conservatively; there was no recurrence of gastrointestinal bleeding.

Table 1. Gender, age and main clinical symptoms in patients with GERD complicated by the development of columnar cell metaplasia of the distal esophagus

Таблица 1. Пол, возраст и основные клинические симптомы у пациентов с ГЭРБ, осложненной развитием цилиндроклеточной метаплазии дистальной части пищевода

Characteristics ***Характеристика***		**All patients** ***Все пациенты***		**Length of segment of glandular metaplasia** ***Длина сегмента железистой метаплазии***		***p***
		***n* = 131**	**ultrashort** ***ультракороткий*** ***n* = 26**	**short** ***короткий*** ***n* = 47**	**long** ***длинный*** ***n* = 58**	
Age / *Возраст*		55.8 ± 16.7	52.1 ± 18.9	53.6 ± 15.7	59.4 ± 16.1	0.07
Gender / *Пол*	Male / *Мужской*	69 (52.7 %)	16 (61.5 %)	19 (40.4 %)	34 (58.6 %)	0.19
	Female / *Женский*	62 (47.3 %)	10 (38.5 %)	28 (59.6 %)	24 (41.4 %)	
Asymptomatic GERD *Бессимптомная ГЭРБ*		47 (35.9 %)	10 (38.5 %)	16 (34.0 %)	21 (36.2 %)	0.59
Esophageal manifestations of GERD *Пищеводные проявления ГЭРБ*		72 (55.0 %)	12 (46.2 %)	26 (55.3 %)	34 (58.6 %)	0.70
Heartburn / *Изжога*		72 (55 %)	12 (46.1 %)	26 (55.3 %)	34 (58.6 %)	0.93
Belching / *Отрыжка*		31 (23.7 %)	8 (30.8 %)	9 (19.1 %)	14 (24.1 %)	0.83
Painful swallowing / *Одинофагия*		10 (7.6 %)	1 (3.8 %)	2 (4.3 %)	7 (12.1 %)	0.03
Pain / *Боль*		48 (36.6 %)	11 (42.3 %)	15 (31.9 %)	22 (37.9 %)	0.67
Extraesophageal manifestations of GERD *Внепищеводные проявления ГЭРБ*		53 (40.5 %)	7 (26.9 %)	17 (36.2 %)	29 (50.0 %)	0.92
Cough at night / *Кашель ночью*		40 (30.5 %)	6 (23.1 %)	13 (27.7 %)	21 (36.2 %)	0.42
Ear pain / *Отралгия*		34 (26.0 %)	2 (7.7 %)	11 (23.4 %)	21 (36.2 %)	0.22
Laryngitis / *Ларингит*		9 (6.9 %)	1 (3.8 %)	4 (8.5 %)	4 (6.9 %)	0.51

Careful analysis of complaints and history of patients showed clinical manifestations of GERD in 84/131 (64.1 %) and their absence in 47/131 (35.9 %) patients (Table 1). Esophageal-derived symptoms characteristics of GERD were present in 72/131 (55.0 %) patients. Extraesophageal manifestations of GERD (cough at night, otalgia, and laryngitis) were found in 53/131 (40.5 %) patients, with increased prevalence of otalgia with the longer columnar metaplasia (7.7 % in the ultrashort segment, 23.4 % in the short segment, and 36.2 % in the long segment) (Table 1). In 41 (48.8 %) of 84 patients with clinical manifestations of GERD, its extraesophageal manifestations were combined with classical ones; in 31/84 (36.9 %) patients, only classical esophageal, and in 12/84 (14.3 %) patients, only extraesophageal symptoms were observed.

Endoscopic examination of the upper digestive tract was the leading method of intraluminal examination in patients with columnar metaplasia of the esophagus. EGD was performed in all patients using the EVIS EXERA III video endoscopic system and GIF-H180, GIF-H190, GIF-HQ190 endoscopes ("Olympus", Japan). The studies were performed under intravenous anesthesia with the preservation of patients' independent breathing. Preparation for the study included oral administration of defoamers (simeticone) and mucolytics (acetylcysteine). The first stage was an endoscopic examination in white light with high resolution, while clarifying the individual features of the topographic location of the esophagus and stomach. Special attention was paid to the detection of columnar metaplasia of the esophagus, and the presence or absence of changes in its structure. The extent of the columnar metaplasia was assessed under the Prague criteria [20]. When inflammatory changes in the esophagus were detected, no additional endoscopic studies were performed, including a biopsy from the segment of columnar metaplasia. All these patients received conservative antisecretory therapy under the supervision by a gastroenterologist for 6–8 weeks and only after complete elimination of reflux esophagitis and epithelialization of erosions and ulcers they underwent repeated in-depth endoscopic examination.

The clarifying endoscopic techniques were based on the from-simple-to-complex principle. Following a thorough examination in white light, the mucous membrane of the metaplastic segment was examined in a narrow light spectrum. The structure of the pit-like and microvascular pattern was evaluated using the BING classification system, dividing the microstructure of the metaplastic mucosa into two principal types: regular (without dysplasia) and irregular (characteristic of dysplasia or adenocarcinoma of the esophagus). When detecting an irregular type of microstructure, we selected the most altered areas of the metaplastic mucosa for subsequent targeted forceps biopsy under the BING system. After examination in the NBI mode, the acetowhitening stage was performed, a staining of the metaplastic segment with 1.5 % acetic acid solution. The PREDICT classification system was used to assess the changes. Acetowhitening emphasizes the structure of the pit-like pattern of the columnar epithelium, accentuating the structure of irregular areas (in particular, with dysplastic epithelium). It is also important that the areas of neoplasia are freed from acetowhitening much earlier than the surrounding metaplastic epithelium. They look pink or red on a white background, and it was from these pathological areas that a targeted forceps biopsy was performed. At the end of the diagnostic program, after a targeted biopsy under the PREDICT and BING classification systems, a forceps biopsy was performed under the Seattle protocol from four points evenly spaced at each level of the segment of the columnar metaplasia in increments of one (with previously identified dysplasia) or two centimeters. We did not adjust the biopsy points, depending on the results of virtual and real chromoendoscopy.

Intravital pathologic and anatomical examination. The biopsy fragments were fixed in a buffered neutral 10 % formalin, processed in a standard histological manner, and embedded in paraffin blocks. Histological 3–4 microns' thick slices were prepared using "Sacura" rotary microtomes and stained with hematoxylin and eosin. Immunohistochemical (IHC) study was performed with antibodies to MUC2, MUC5AC, MUC6, p16, p53, Ki67, cyclin D1, β-catenin, and AMACR (alpha-methylacyl coenzyme A racemase) out using immunostainers "Leica Bond maX" (Germany) and "Ventana Bench Mark Ultra" (USA). The IHC with these antibodies was interpreted considering the location of positive cells (in the surface epithelium or in crypts, within or outside dysplastic areas) by counting both the number of stained epithelial cells per 100 cells in 10 fields of view (×400) and the intensity of staining. The quantitative results were expressed as a percentage. The expression was assessed semi-quantitatively in points, where 0 is expression in 0–4 %, +1 — in 5–50 %, +2 —

in 51–75 %, and +3 — in >75 % of the cells. For Ki67, the expression was estimated as 0 in 0–20 %, +1 — in 21–50 %, +2 — in 51–75 %, and +3 — in > 75 % of the cells. The intensity of marker expression was estimated in points, where 0 is lack of expression, 1 is weak cell staining, 2 is moderate staining, and 3 is intense (bright) cell staining.

In cases of intestinal metaplasia, the density of goblet cells in the glands was calculated by morphometry, with less than 5 % of goblet cells from all epithelial cells in the glands, patients were assigned to a subgroup with single goblet cells; from 5 to 50 % — to a low-density subgroup; and over 50 % — to a high-density subgroup.

Statistical data processing. The data analysis was performed using the R 3.6.3 environment for statistical computing ("R Foundation for Statistical Computing", Austria) with additional packages epiR 1.0-14, irr 0.84.1, and emmeans 1.4.8. Descriptive statistics for categorical variables are presented in absolute and relative frequencies (percentages, %), and that for quantitative ones is as mean (standard deviation) and median (1st and 3rd quartiles). To study the relationship of categorical variables, the χ^2 and the exact Fisher tests were used, the association was significant at $p < 0.05$.

Results and discussion

The results of the "primary" endoscopic examination of the esophagus and the cardia zone in high-resolution white light and the benign changes found are presented in Table 2. Of note, 57.3 % (75/131) of the patients were diagnosed with a hiatal hernia, and 80.9 % (106/131) had endoscopic signs of cardia insufficiency confirmed by X-ray, high-resolution manometry, or pH impedancemetry. H. Inoue et al. and our comparative studies have proved that an endoscopic assessment of the topographic, anatomical, and functional state of the cardia zone is appropriate and reliable under adequate anesthesia and technically competent EGD [21, 22]. These anatomical and functional disorders were more common in patients with a long segment of columnar metaplasia. No signs of erosive reflux esophagitis at the time of primary EGD were found in 59/131 (45.0 %) patients. In the remaining 72/131 (55.0 %) patients, it manifested with varying severity, including esophageal ulcers in 14/131 (10.7 %) patients (Table 2).

Gastrointestinal bleeding from esophageal ulcers was detected in 5/131 (3.8 %) patients. Both severe reflux esophagitis (grades C and D under the Los Angeles classification) and peptic ulcers were more common in patients with a long segment of Barrett's metaplasia. Short strictures in the lower third of the esophagus, requiring balloon dilation, were found in 2/131 (1.5 %) patients.

The presence of columnar cell metaplasia of the esophagus, as well as its extent, were convincingly confirmed by an in-depth study. The ultrashort segment of columnar metaplasia (< 1 cm) was significantly differentiated from the high amplitude Z-line in 26/131 (19.8 %) patients, the short segment of columnar cell metaplasia (1–3 cm) was diagnosed in 47/131 (35.9 %) patients, and the long segment (> 3 cm) in 58/131 (44.3 %) patients (Table 3). The recommendations of the British Society of Gastroenterology states any segment of a columnar metaplasia over 1 cm long as Barrett's esophagus, regardless of the presence or absence of intestinal metaplasia [11]. At this stage, we could diagnose Barrett's esophagus in 105/131 (80.2 %) patients without an intravital pathological study in search of intestinal metaplasia. Of course, we did not do this before confirming intestinal metaplasia in biopsies, in strict accordance with the latest European [23] and national clinical guidelines for the diagnosis and treatment of Barrett's esophagus [24].

The results of an endoscopic examination of patients in virtual (NBI, BING assessment) and real (1.5 % acetic acid, PREDICT assessment) chromoendoscopy are shown in Table 4. The uneven nature of the pit-like and microvascular pattern in the zone of columnar metaplasia under the BING system (Fig. 1A) was significantly more prevalent in patients with a long segment of columnar metaplasia ($p = 0.0118$ and $p = 0.007$). Similar differences in the pit-like pattern were determined by the PREDICT ($p = 0.0116$).

Accelerated local loss of acetowhitening (Fig. 1B, 2) was detected in 23 (39.7 %) patients with a long segment, only in 9 (19.2 %) patients with a short segment and in 4 (15.4 %) of those with ultrashort segment ($p = 0.005$).

Under the Seattle Protocol, 716 fragments of metaplastic mucosa were taken from 131 patients; an average of 6.0 ± 3.0 fragments per patient (Table 5). The number of biopsies selected under the Seattle Protocol was significantly higher ($p = 0.0036$) than the targeted one after the assessment of segments of Barrett's metaplasia under the BING ($p = 0.0063$) and PREDICT ($p = 0.0011$) classifications (Table 5).

Table 2. Benign changes in the esophagus and cardia identified during primary endoscopy, including assessment of the degree of esophagitis according to the Los Angeles classification

Таблица 2. Доброкачественные изменения пищевода и кардии, выявленные при первичной ЭГДС, включая оценку степени эзофагита по Лос-Анджелесской классификации

Identified changes ***Выявленные изменения***	**Length of segment of glandular metaplasia** ***Длина сегмента железистой метаплазии***			**All patients** ***Все пациенты***
	ultrashort (< 1 cm) ***ультракороткий (< 1 см)*** ***n* = 26**	**short (1–3 cm)** ***короткий (1–3 см)*** ***n* = 47**	**long (> 3 cm)** ***длинный (> 3 см)*** ***n* = 58**	***n* = 131**
Hiatal hernia *Грыжа пищеводного отверстия диафрагмы*	13 (50.0 %)	24 (51.1 %)	38 (65.5 %)	75 (57.3 %)
Cardia insufficiency *Недостаточность кардии*	20 (76.9 %)	36 (76.6 %)	50 (86.2 %)	106 (80.9 %)
Columnar cell metaplasia without esophagitis *Цилиндроклеточная метаплазия без эзофагита*	25 (96.1 %)	30 (63.8 %)	4 (6.8 %)	59 (45.0 %)
Columnar cell metaplasia + Esophagitis A *Цилиндроклеточная метаплазия + Эзофагит A*	6 (23.1 %)	6 (12.8 %)	10 (17.2 %)	22 (16.8 %)
Columnar cell metaplasia + Esophagitis B *Цилиндроклеточная метаплазия + Эзофагит B*	4 (15.4 %)	11 (23.4 %)	11 (19.0 %)	26 (19.8 %)
Columnar cell metaplasia + Esophagitis C *Цилиндроклеточная метаплазия + Эзофагит C*	1 (3.8 %)	3 (6.4 %)	7 (12.1 %)	11 (8.4 %)
Columnar cell metaplasia + Esophagitis D *Цилиндроклеточная метаплазия + Эзофагит D*	–	2 (4.3 %)	11 (19.0 %)	13 (9.9 %)
Peptic ulcer of the esophagus *Пептическая язва пищевода*	–	2 (4.3 %)	12 (20.7 %)	14 (10.7 %)
Gastrointestinal bleeding from an esophageal ulcer *Желудочно-кишечное кровотечение из язвы пищевода*	–	2 (4.2 %)	3 (5.1 %)	5 (3.8 %)
Esophageal stricture *Стриктура пищевода*	1 (3.8 %)	–	1 (1.7 %)	2 (1.5 %)

Table 3. Results of diagnosing the extent of columnar cell metaplasia of the esophagus according to endoscopy of the upper digestive tract

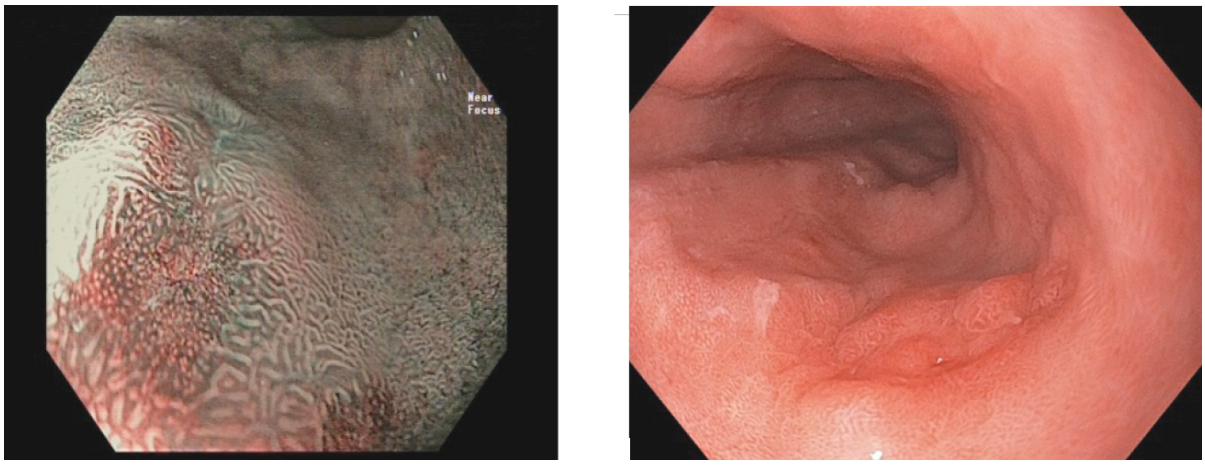
Таблица 3. Результаты диагностики протяженности цилиндроклеточной метаплазии пищевода по данным эндоскопии верхних отделов пищеварительного тракта

Characteristics of metaplasia ***Характеристика метаплазии***	**Length of segment of glandular metaplasia** ***Длина сегмента железистой метаплазии***			**In total** ***Всего***
	ultrashort (< 1 cm) ***ультракороткий (< 1 см)*** ***n* = 26 (19.8 %)**	**short (1–3 cm)** ***короткий (1–3 см)*** ***n* = 47 (35.9 %)**	**long (> 3 cm)** ***длинный (> 3 см)*** ***n* = 58 (44.3 %)**	***n* = 131 (100 %)**
Revealed before the visit to the clinic *Выявлена до обращения в клинику*	11 (42.3 %)	17 (36.2 %)	18 (31.0 %)	46 (35.1 %)
Revealed during elective endoscopy *Выявлена при плановой ЭГДС*	13 (50.0 %)	23 (48.9 %)	15 (25.9 %)	51 (38.9 %)
Revealed during emergency endoscopy *Выявлена при экстренной ЭГДС*	2 (7.7 %)	7 (14.9 %)	25 (43.1 %)	34 (26 %)

Table 4. Results of endoscopic assessment of columnar cell metaplasia of the esophagus according to the BING and PREDICT classifications depending on the length of the segment of metaplasia

Таблица 4. Результаты эндоскопической оценки цилиндроклеточной метаплазии пищевода по классификациям BING и PREDICT в зависимости от длины сегмента цилиндроклеточной метаплазии

Characteristics ***Характеристика***	**Length of the segment** ***Длина сегмента***			**All patients** ***Все пациенты***
	ultrashort (< 1 cm) ***ультракороткий (< 1 см)*** ***n* = 26**	**short (1–3 cm)** ***короткий (1–3 см)*** ***n* = 47**	**long (> 3 cm)** ***длинный (> 3 см)*** ***n* =58**	***n* = 131**
Regular microstructure according to BING *Регулярная микроструктура по BING*	24 (92.3 %)	36 (76.6 %)	38 (65.5 %)	98 (74.8 %)
Irregular microstructure according to BING *Нерегулярная микроструктура по BING*	2 (7.7 %)	11 (23.4 %)	20 (34.5 %)	33 (25.2 %)
Regular pit-like pattern according to PREDICT *Регулярный ямочный рисунок по PREDICT*	21 (80.8 %)	38 (80.8 %)	36 (62 %)	95 (72.5 %)
Irregular pit-like pattern according to PREDICT *Нерегулярный ямочный рисунок по PREDICT*	5 (19.2 %)	9 (19.2 %)	22 (38 %)	36 (27.5 %)
Uniform loss of acetowhitening *Равномерная утрата ацетобеления*	22 (84.6 %)	38 (80.8 %)	35 (60.3 %)	95 (72.5 %)
Accelerated local loss of acetowhitening *Ускоренная локальная утрата ацетобеления*	4 (15.4 %)	9 (19.2 %)	23 (39.7 %)	36 (27.5 %)



A B

Figure 1. Barrett's esophagus (C11M11 according to Prague criteria). Type IIa+IIc esophageal adenoma with severe dysplasia: A — irregular microstructure of the formation in a narrow light spectrum mode according to BING; B — accelerated local loss of acetowhitening by the neoplasm

Рисунок 1. Пищевод Баррета (C11M11 по Пражским критериям). Аденома пищевода IIa+IIc типа с тяжелой дисплазией: A — нерегулярная микроструктура образования в режиме узкого спектра света по BING; B — ускоренная локальная утрата ацетобеления новообразованием

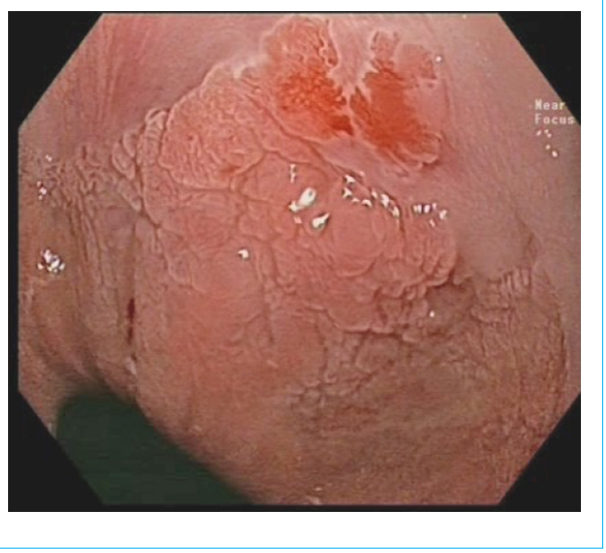


Figure 2. Short (C0M2) segment of glandular metaplasia of the esophagus. Esophageal adenoma type IIa with severe dysplasia: characteristic accelerated local loss of acetowhitening of the neoplasm

Рисунок 2. Короткий (C0M2) сегмент железистой метаплазии пищевода. Аденома пищевода IIa типа с тяжелой дисплазией: характерная ускоренная локальная утрата ацетобеления новообразованием

The morphological type of columnar metaplasia in patients with different segment lengths of metaplasia is shown in Table 6.

The pathomorphological and immunohistochemical studies (positive expression of Muc5AC and Muc6 with a negative expression of Muc2) showed a gastric type of metaplasia significantly more often in patients with ultrashort and short segment ($p = 0.0005$), and the intestinal type of metaplasia (presence of goblet cells in biopsies and positive expression of Muc2) in patients with a long segment ($p = 0.0008$). The prevalence of different types of metaplasia and the distribution of goblet cell density in intestinal metaplasia in patients with different segment lengths of columnar metaplasia were compared. With increasing segment length, the relative number of diagnosed cases of intestinal metaplasia increased: from 61.5 and 51.0 % in the ultrashort and short segments to 67.3 % in the long segment of columnar metaplasia (Fisher's exact criterion, $p < 0.0001$), with 95 % CI: 0.86–3.73 for odds ratio 1.79 (long/short segment; $p > 0.05$).

The type of columnar metaplasia, including depending on the length of the metaplastic segment, was detected with high-resolution

Table 5. Average number of biopsies taken from a segment of columnar cell metaplasia per patient

Таблица 5. Среднее количество биоптатов, взятых из сегмента цилиндроклеточной метаплазии у одного пациента

Biopsy sampling protocol ***Протокол забора биоптатов***	**Length of segment of columnar cell metaplasia** ***Длина сегмента цилиндроклеточной метаплазии***			**All patients** ***Все пациенты*** ***n* = 131**
	ultrashort (< 1 cm) ***ультракороткий (< 1 см)*** ***n* = 26**	**short (1–3 cm)** ***короткий (1–3 см)*** ***n* = 47**	**long (> 3 cm)** ***длинный (> 3 см)*** ***n* = 58**	
Seattle / *Сиэтлский*	4.2 ± 0.8	4.3 ± 1.4	7.0 ± 3.0	6.0 ± 3.0
BING	1.4 ± 0.7	1.5 ± 0.8	2.2 ± 0.9	1.8 ± 1.0
PREDICT	1.5 ± 0.7	1.6 ± 0.7	2.2 ± 0.9	1.9 ± 1.0
Total biopsies *Всего биоптатов*	4.2 ± 2.1	7.1 ± 2.2	9.3 ± 3.8	8.7 ± 3.7

Table 6. The nature of columnar cell metaplasia depending on the length of its segment according to the results of endoscopic and morphological examinations

Таблица 6. Характер цилиндроклеточной метаплазии в зависимости от длины ее сегмента по результатам эндоскопического и морфологического исследований

Biopsy sampling protocol ***Протокол забора биоптатов***	**Length of segment of columnar cell metaplasia** ***Длина сегмента цилиндроклеточной метаплазии***			**Total** ***Всего*** ***n* (%)**
	ultrashort (< 1 cm) ***ультракороткий (< 1 см)*** ***n* = 26**	**short (1–3 cm)** ***короткий (1–3 см)*** ***n* = 47**	**long (> 3 cm)** ***длинный (> 3 см)*** ***n* = 58**	
Gastric type *Желудочный тип*	10 (38.5 %)	23 (49.0 %)	19 (32.7 %)	52 (39.7 %)
Intestinal type *Кишечный тип*	16 (61.5 %)	24 (51.0 %)	39 (67.3 %)	79 (60.3 %)
Total patients *Всего больных*	26 (19.8 %)	47 (35.9 %)	58 (44.3 %)	131 (100 %)

Table 7. Informativeness of endoscopic techniques in determining the type of columnar cell metaplasia of the esophagus depending on the length

Таблица 7. Информативность эндоскопических методик в определении типа цилиндроклеточной метаплазии пищевода в зависимости от длины

Characteristics ***Характеристика***	**Length of the segment / *Длина сегмента***			**All patients** ***Все пациенты***
	ultrashort (< 1 cm) ***ультракороткий (< 1 см)***	**short (1–3 cm)** ***короткий (1–3 см)***	**long (> 3 cm)** ***длинный (> 3 см)***	
Sensitivity *Чувствительность*	87.5 % (70.8; 87.5)	76.9 % (50.7; 93.1)	91.3 % (76.1; 98.2)	86.5 % (77.1; 92.9)
Specificity *Специфичность*	100.0 % (73.3; 100.0)	82.4 % (72.3; 88.5)	91.4 % (81.4; 96.0)	88.6 % (82.4; 92.8)
Accuracy *Точность*	92.3 % (71.7; 92.3)	80.9 % (66.4; 89.8)	91.4 % (79.3; 96.9)	87.8 % (80.3; 92.9)

endoscopic techniques with the 86.5 % sensitivity, 88.6 % specificity, and 87.8 % accuracy (Table 7).

Neoplasia in the segment of columnar metaplasia of the esophagus was found by the biopsy in 36/131 (27.5 %) patients, including esophageal adenocarcinoma in 4/131 (3.1 %) of them (Table 8). Immunohistochemical examination of dysplasia and adenocarcinoma samples showed a significant increase in the expression of markers of neoplastic progression (p16, p53, Ki67, cyclin D1, β-catenin, and AMACR) compared with fragments of columnar metaplasia without dysplasia. Dysplasia, including severe dysplasia, was found less frequently in patients with ultrashort and short segments of columnar metaplasia compared with patients with a long segment ($p = 0.0001$). Our results once again confirm the well-known predominance of oncological potential in the long segment of metaplasia. However, 10 % of the world's leading experts voted in a consensus against the definition of Barrett's esophagus, ratified in 2020, from which the ultrashort segment of metaplasia was excluded [14]. We believe that a more detailed definition can reconcile the differences of the parties, explaining the motivation and consensus nature of the disease evaluation: "It is proposed to consider/call Barrett's esophagus only those varieties of columnar metaplasia of the distal esophagus epithelium with the reliably confirmed intestinal metaplasia and/or dysplasia exceeding 1 cm above the esophageal-gastric junction since it is these segments of metaplasia that are less likely to cause disagreement in the diagnostic process and are most dangerous in relation to transformation into esophageal adenocarcinoma". Of note, one our patient with an ultrashort segment of cardiac metaplasia was diagnosed with a highly differentiated adenocarcinoma, which once again emphasizes the need for a comprehensive examination of patients with an ultrashort segment of metaplasia. We emphasize that this generalizing endomorphological concept is reserved for all

Table 8. Results of morphological diagnosis of the nature of neoplasia (dysplasia) depending on the length of the segment of columnar cell metaplasia

Таблица 8. Результаты морфологической диагностики характера неоплазии (дисплазии) в зависимости от длины сегмента цилиндроклеточной метаплазии

Characteristics ***Характеристика***	**Length of segment of columnar cell metaplasia** ***Длина сегмента цилиндроклеточной метаплазии***			**All patients** ***Все пациенты***
	ultrashort (< 1 cm) ***ультракороткий (< 1 см)*** **$n = 26$**	**короткий (1–3 см)** ***short (1–3 cm)*** **$n = 47$**	**длинный (> 3 см)** ***long (> 3 cm)*** **$n = 58$**	**$n = 131$**
Mild dysplasia *Легкая дисплазия*	4 (15.4 %)	3 (6.4 %)	20 (34.5 %)	27 (20.6 %)
Severe dysplasia *Тяжелая дисплазия*	–	1 (2.1 %)	4 (6.9 %)	5 (3.8 %)
Adenocarcinoma *Аденокарцинома*	1 (3.8 %)	–	2 (3.4 %)	3 (2.3 %)
Poorly differentiated adenocarcinoma *Низкодифференцированная аденокарцинома*	–	–	1 (1.7 %)	1 (0.8 %)
Total / *Всего*	5 (19.2 %)	4 (8.5 %)	27 (46.5 %)	36 (27.5 %)

variants of columnar metaplasia of the esophagus reliably diagnosed with EGD, regardless of their extent and structure. Certainly, Barrett's esophagus is the most threatening variant of columnar metaplasia.

Biopsy using the Seattle Protocol was performed in all examined patients, but only 9/131 (6.9 %) showed dysplastic changes in the distal esophagus as mild dysplasia in 8/9 patients and the severe in only 1/9 patients. Comparative characteristics of the studied classifications and biopsy techniques in the diagnosis of dysplasia are presented in Table 9. PREDICT and BING had the greatest accuracy, sensitivity, and specificity, significantly exceeding the similar indices of the Seattle Protocol. The Seattle Protocol showed a relatively low specificity, accuracy, and sensitivity in our study, compared to 58.8 % sensitivity, 100 % specificity, and 93 % accuracy found by its authors [15]. This discrepancy in the results is caused by the original methodology of the protocol itself. The protocol includes additional targeted biopsy from suspicious areas (!) in all cases except for sampling the mucous fragments from four quadrants of the esophagus along the entire length of glandular metaplasia with an interval of 2 cm (and with previously identified dysplasia with an interval of 1 cm), certainly improving the diagnosis of intestinal metaplasia and dysplasia. Our results once again emphasize the indisputable trend for a gradual abandonment of multiple random biopsies in favor of targeted biopsy, which is determined by high-resolution digital optics with magnification, chromoendoscopy, and the BING and PREDICT classification systems.

BING and PREDICT classifications, labeling of compromised sites, allows for the sampling of biopsy material from areas of the epithelium specific for dysplasia. Using BING and PREDICT in combination provides the maximum specificity (100 %) and increases sensitivity to 92.0 % and accuracy to 96.0 %. This approach significantly limits the number of biopsies compared to their unreasonably large number under the Seattle Protocol, reducing the mucosal and submucosal trauma of the esophagus, the risk of artificial complications and fibrosis of the submucosal layer, hampering the future endoscopic resection of the mucous membrane of the esophagus, if indications arise.

We selected *the therapeutic and diagnostic tactics* for our patients with columnar metaplasia of the esophagus based on the risk stratification of esophageal adenocarcinoma [14] and the results of the examination. Following current clinical recommendations and common sense, we resected adenomas and early non-invasive adenocarcinomas of the esophagus through an endoscope in a single block; removed a segment of Barrett's metaplasia with dysplasia by ablation; and treated patients with columnar metaplasia without neoplastic changes conservatively with endoscopic follow-up and biopsy with frequency depended on the length of the columnar metaplasia and the presence/absence of intestinal metaplasia [15].

Surgical treatment as a radical robot-assisted Lewis surgery with the esophago-gastroanastomosis formation with gastric stem surgery was performed in 1 out of 131 (0.8 %) patients with invasive low-differentiated esophageal adenocarcinoma. When monitoring one year after surgery, no signs were found of the disease recurrence.

Endoscopic resection was performed in 8 out of 131 (6.1 %) patients, including 3 (2.3 %) patients with early esophageal adenocarcinoma and 5 (3.8 %) with esophageal adenoma with severe dysplasia. In 5 patients, tumors were removed by dissection of the submucosal layer (Fig. 3) and in 3 patients — by cap resection of the mucous membrane in a single block within healthy tissues. The pathological criteria considered the endoscopic resection a radical one.

After 6 months, all 8 patients underwent one-stage radiofrequency ablation (RF) (Fig. 4 A–C) of the remaining part of the metaplastic mucosa. In 6 out of 8 patients, complete re-epithelialization of the metaplasia segment with multilayer squamous epithelium was noted during endoscopic control. In 2 out of 8 patients, preserved small islets of Barrett's metaplasia were eliminated by

Table 9. Characteristics of the information content of methods for endoscopic diagnosis of dysplasia
Таблица 9. Характеристика информативности методов эндоскопической диагностики дисплазии

Methods ***Методы***	**Sensitivity** ***Чувствительность***	**Specificity** ***Специфичность***	**Accuracy** ***Точность***
Seattle protocol *Сиэтлский протокол*	76.8 %	31.2 %	54.5 %
BING	90.5 %	86.7 %	88.9 %
PREDICT	91.3 %	100 %	95.3 %

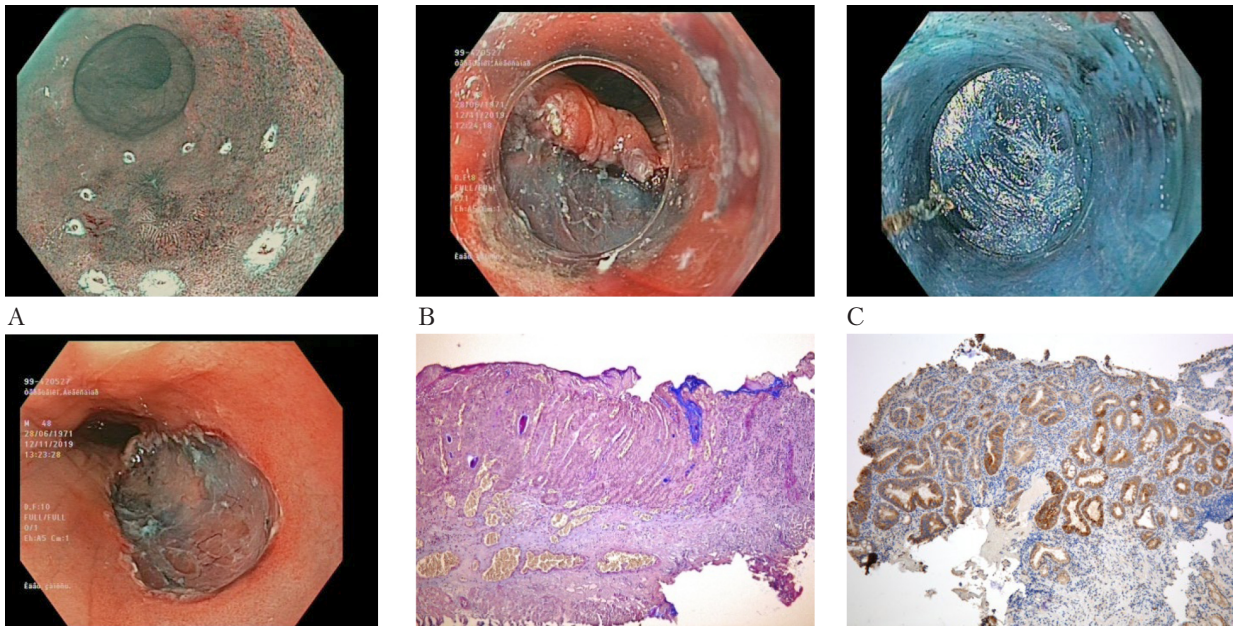


Figure 3. Barrett's esophagus (C11M11 according to the Prague criteria). Endoscopic resection of adenoma in the long segment of Barrett's esophagus using submucosal dissection: A — marking the boundaries of resection; B — primary incision and access to the submucosal layer under the tumor; C —stage of dissection in the submucosal layer; D — post-dissection wound; E — adenoma with severe dysplasia (PAS + Alcian blue, ×100); F — cytoplasmic granular expression of AMACR (immunohistochemical study; ×100)

Рисунок 3. Пищевод Баррета (C11M11 по Пражским критериям). Эндоскопическая резекция аденомы в длинном сегменте пищевода Баррета методом диссекции подслизистого слоя: A — разметка границ резекции; B — первичный разрез и доступ в подслизистый слой под новообразованием; C — этап диссекции в подслизистом слое; D — постдиссекционная рана; E — аденома с тяжелой дисплазией (ШИК-реакция + альциановый синий, ×100); F — цитоплазматическая гранулярная экспрессия AMACR (иммуногистохимическое исследование; ×100)

argon plasma coagulation (Fig. 4 D, E). At follow-up after 6 months, all patients showed complete re-epithelization of the esophageal segment of the Barrett's metaplasia with a multilayer non-keratinizing squamous epithelium (Fig. 4E).

Ablation of the entire segment of the Barrett's metaplasia (as an independent treatment, without preliminary resection of the mucous membrane) was performed in 16 more patients out of 131 (12.2 %) with mild dysplasia twice confirmed in biopsies. Initially, areas of dysplasia without an obvious neoplasm were found in biopsies from 25 out of 131 patients (19.1 %). All of them were prescribed conservative therapy with a double dose of proton pump inhibitors and a follow-up expert EGD after 3–6 months. Mild dysplasia was again confirmed in 14 out of 25 patients (56 %). Mild dysplasia was also detected in 2 out of 131 (1.5 %) patients with a long segment of columnar metaplasia 3 years after the initial diagnosis on the background of conservative therapy. Endoscopic ablation of the metaplasia segment was performed in one-stage RF ablation in 9 out of 16 patients (56.25 %) and in two-stage by the argon plasma coagulation with a 1–1.5-months interval in 7 out of 16 patients (43.75 %). In control EGD performed 6 and 12 months after the intervention, all 16 patients showed epithelialization of the esophageal mucosa in the intervention area with a squamous epithelium. Only 1 out of 16 patients (6.25 %) who underwent argon plasma coagulation developed cicatricial changes in the esophagus without narrowing its lumen.

Conservative therapy was provided to 108 out of 131 (82.4 %) patients with columnar metaplasia without dysplastic changes, who underwent timely endoscopic and morphological control for 2 years. The therapy was effective in 106 out of 108 patients (98.1 %) and the gastroenterologist's follow-up continued. Mild dysplasia was detected in 2 out of 108 (1.8 %) patients with

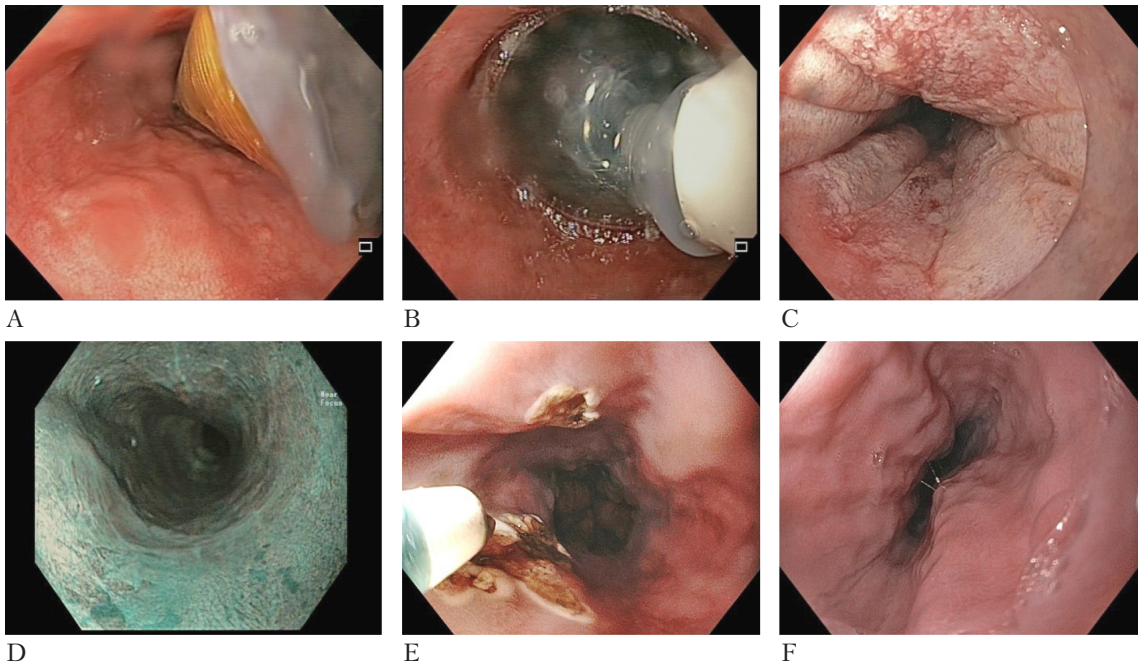


Figure 4. Ablation of a segment of Barrett's esophagus: A — positioning of the catheter for radiofrequency ablation; B — balloon inflation; C — mucous membrane after radiofrequency ablation; D — control examination; E — ablation of remaining islands of metaplasia using argon plasma coagulation method; F — complete replacement of the columnar cell epithelium of the esophagus with stratified squamous epithelium 6 months after ablation

Рисунок 4. Абляция сегмента пищевода Баррета: A — позиционирование катетера для радиочастотной абляции; B — раздувание баллона; C — слизистая оболочка после радиочастотной абляции; D — контрольное обследование; E — абляция сохранившихся островков метаплазии методом аргонно-плазменной коагуляции; F — полное замещение цилиндроклеточного эпителия пищевода многослойным плоским через 6 месяцев после абляции

a long segment of Barrett's metaplasia during the follow-up. As noted above, these patients underwent ablation of the segment of the Barrett's metaplasia by the argon plasma coagulation. We have observed no cases of reverse development of metaplasia sites in the esophagus under the drug treatment.

Conclusion

A complex of high-resolution endoscopy in white and narrow light spectrum with magnification and chromoendoscopy allows not only to diagnose the metaplastic segment and its extent but also the type of columnar metaplasia with 87.8 % accuracy in patients with complicated GERD and to predict the dysplasia in these patients with a 91.3 % sensitivity and a 100 % specificity. Targeted forceps biopsy in combination with morphological and immunohistochemical examination, with a higher reliability, comprising 96 % accuracy, 92 % sensitivity, and 98 % specificity, enables to diagnose varieties of columnar metaplasia and dysplasia of the esophageal mucosa compared with the Seattle protocol. Reliable diagnosis of the extent and type of columnar metaplasia of the esophageal epithelium and early detection of neoplastic changes ensure timely selection of adequate therapeutic tactics in various groups of patients with complicated GERD.

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