

# COMPARATIVE EVALUATION OF MULTIPARAMETRIC ENDORECTAL ULTRASOUND AND ENHANCED IMAGING COLONOSCOPY IN THE DIAGNOSIS OF EARLY COLORECTAL CANCER

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**AIM:** to compare multiparametric endorectal ultrasound (ERUS) and enhanced imaging colonoscopy in the diagnosis of early colorectal cancer. **PATIENTS AND METHODS:** The study included 78 patients with epithelial rectal tumor. All the patients underwent multiparametric ERUS and colonoscopy with examination by narrow beam imaging (NBI) at optical magnification. All the patients were operated on.

**RESULTS:** A morphological examination removed specimens revealed adenomas in 48 cases, in 19 specimens – adenocarcinomas in situ and T1, and in 11 specimens – adenocarcinomas with invasion of the muscle layer or deeper. When calculating the accuracy indicators of diagnostic methods for groups of patients with adenoma, Tis-T1 adenocarcinoma, and T2-T3 adenocarcinoma, the difference in the sensitivity and specificity of the methods in none of the presented groups did not reach the level of statistical significance ( $p > 0.05$ ). ROC analysis showed that ultrasound has a prognostic value comparable to colonoscopy. The area difference was 0.013 ( $p = 0.85$ ).

**CONCLUSION:** Endoscopy and ultrasound have similar value in the diagnosis of malignant transformation of rectal adenomas.

[Key words: early rectal cancer, multiparametric endorectal ultrasound, strain elastography, colonoscopy, pit-pattern, capillary pattern]

**CONFLICTS OF INTERESTS:** The authors declare no conflicts of interest.

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## BACKGROUND

According to the theory of cancerogenesis «adenoma-adenocarcinoma», the transformation of the mucosa with the formation of adenomas of different histological structure and different degrees of epithelial dysplasia is a precancerous condition, its malignant degeneration is a matter of time.

The term «early colorectal cancer», proposed by the Japanese Association for the study of colorectal cancer [1], refers to colorectal epithelial tumors, localized within the mucosal layer or infiltrating the submucosal layer of the intestinal wall without metastatic lesions of regional lymph nodes and distant organs, i.e. in the T1N0M0 stage of the TNM classification [2]. Currently, in the surgery for adenomas and early rectal cancer, it is possible to perform organ-preserving procedures using minimally invasive technologies, such as

transanal endomicrosurgery (TEM) [3].

Methods of local removal, in comparison with abdominal procedures, have a lower level of postoperative complications and shorter recovery, but require careful selection of patients and accurate preoperative determination of the depth of bowel wall invasion.

In case of intraepithelial cancer and invasion of the superficial parts of the submucosal layer corresponding to the levels of T1sm1 and T1sm2 of the Kikuchi R. subclassification, these surgeries can be used as a radical surgical treatment due to the low risk of metastatic lesion of regional lymph nodes [4].

The main methods of instrumental diagnostics used for preoperative staging are magnetic resonance imaging (MRI) and endorectal ultrasound (ERUS).

Both methods have a fairly high level of diagnostic information in determining the depth of colorectal cancer invasion [5-7].

However, ERUS has a higher resolving power in relation to the layers of the bowel wall [8].

At the moment, along with the ERUS, the endoscopic diagnostics of early colorectal cancer is widely used. The possibilities of its application have expanded due to the introduction of enhanced imaging technologies that allow to determine the presence of malignant tumor transformation in real time with high accuracy and to assume the presence of invasion.

This was achieved by examining the microstructure of the mucous membrane and its vascular pattern by narrow beam imaging at optical magnification [9,10]. The combination of these methods, due to the use of special light filters, allows you to get a clearer image of the mucosa surface, and due to the absorption of light by blood hemoglobin, the drawing of the microcapillary net becomes more outlined.

This study makes it possible to assess in detail the epithelium, which normally looks like regularly arranged ring-shaped «mounds» with a microvascular net surrounding the excretory ducts of the glands.

Depending on the nature of these changes, there are 7 types of pit pattern and 3 types of microvascular pattern in accordance with the Kudo-Fujii and Sano Y. classifications, which allow differentiating hyperplastic polyps and adenomas from adenocarcinomas [11,12].

In the literature, there are reports of successful use of both ultrasound and endoscopy for the diagnosis of early colorectal cancer, but a comparison of their diagnostic capabilities has not been done yet.

The aim of this study is the comparative assessment of the informative value of multiparametric endorectal ultrasound (ERUS) and colonoscopy with the use of the refinement technologies in the diagnosis of early colon cancer.

## PATIENTS AND METHODS

The study included 78 patients with histologically confirmed rectal epithelial tumors: 38 (48.7%) females and 40 (51.3%) males.

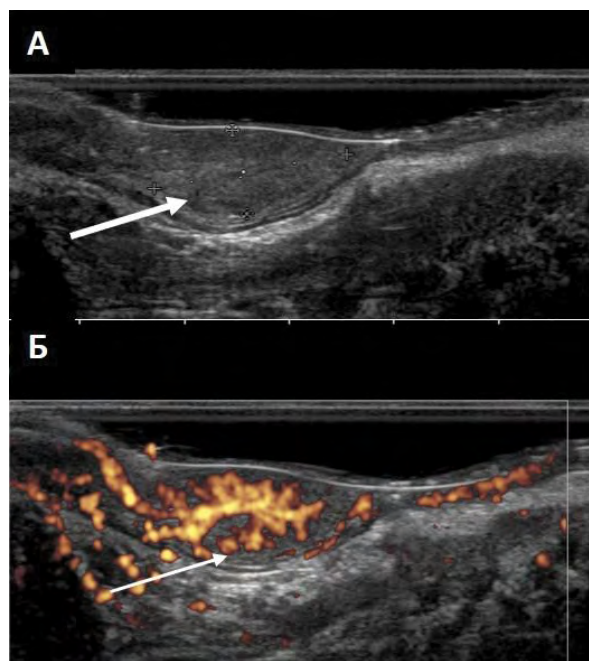
The exclusion criteria were the recurrent nature of the neoplasm and preoperative chemoradiation.

The mean age of patients was  $63 \pm 12$  ( $M \pm \sigma$ ) years. All patients underwent multiparametric ERUS and colonoscopy at the preoperative stage with the assessment of the neoplasm by narrow beam imaging in combination with a close-focus examination.

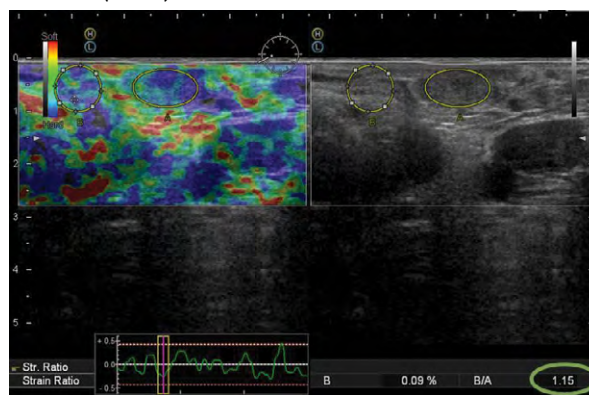
ERUS was performed with Hi Vision Preirus (Hitachi, Japan) using a multi-frequency biplane rectal sensor with a frequency of 5-10 MHz and Profocus (BK Medical, the USA) using a mechanical radial rectal sensor with a frequency of 10-16 MHz.

Multiparametric ERUS included:

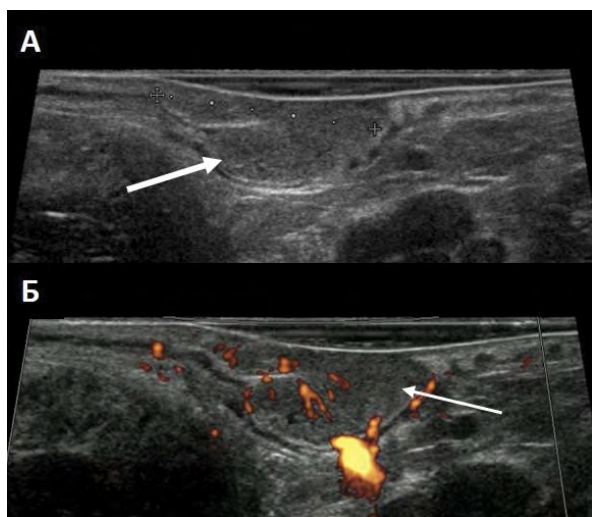
1. Examining the tumor in B-mode followed by three-dimensional reconstruction of the image (3D) with an assessment of its site, structure and shape, depth of invasion; examination of the perirectal tissues for the inflammatory changes, pathological formations, affected regional lymph nodes.
2. Conducting energy dopplerography to determine the type of angioarchitectonics of the neoplasm and



**Figure 1.** Echogram of adenoma (pT0). A – ERUS in B-mode, the arrow marks the adenoma. Б – ERUS with power Doppler – branching vascular pattern are determined in the tissue of adenoma (arrow).



**Figure 2.** Echogram of adenoma (pT0). A – ERUS with strain elastography. A gray-scale image is presented on the right side of the ultrasonogram, on the left side an elastogram with a color chart, compression graph and deformation scale are displayed. The figures highlight the zones of interest (A) and comparisons (B). In the lower right corner is the stiffness coefficient.



**Figure 3.** Echogram of in situ adenocarcinoma. A – ERUS in B-mode, the arrow marks the tumor. B – ERUS with power Doppler – tree-like vascularization with impaired angioarchitectonics is determined in the tumor tissue (arrow).

its preservation, the presence and nature of vascularization of the affected regional lymph nodes.

3. Performing compression elastography with a qualitative assessment of the color chart and calculating the tissue stiffness index in the area of interest (*stiffness coefficient, deformation rate, strain ratio*) (Fig. 1,2,3,4).

Colonoscopy was performed using video endoscopic systems using EC34-i10 M colonoscopes (Pentax, Japan).

The study was performed with a colonoscope with the camera located in the end part of the device and the function of narrow-beam mode i-scan. The survey included:

1. Examination of the tumor in WLE-mode (white light

endoscopy, white light examination) with an assessment of its site, structure and shape.

2. Study in narrow-beam mode with magnification, which allows using special light filters to get a clearer image of the relief and vascular pattern of the mucosa. The Kudo-Fujii and Sano Y. classifications were used to evaluate the character of pit-pattern and capillary pattern of the neoplasm [11,12] (Fig. 5,6).

In 24/78 (30.8%) patients, the tumor was in the low rectum, in 48/78 (61.5%) cases – in the middle part and in 6/78 (7.7%) cases – in the upper rectum.

All the patients were operated depending on the tumor growth: transabdominal (20/78 (25.6%) cases) or organ-preserving (in 58/78 (74.4%) cases) surgeries were performed.

Twelve of 58 (20.7%) patients underwent tumor removal by endoscopic submucosal dissection or polypectomy.

When a pathomorphological study revealed a cancer in removed specimens with invasion of the submucosal layer of the intestinal wall, the tumor was additionally staged according to the classification proposed by Kikuchi R. [4].

Statistical analysis were performed with SPSS v. 23.0 and MedCalc v. 19.2.0 for Windows.

When comparing the results of ultrasound and endoscopy, we assessed the indicators of diagnostic informativity of methods (sensitivity, specificity, prognostic value of positive and negative results) with the calculation of 95% coincidence interval (95% CI) for groups of patients with adenoma, early cancer and adenocarcinoma T2-T3.

A two-way Fisher test was used to assess the significance of differences.

To determine the predictive significance of the models, a ROC analysis was performed with the construc-



**Figure 4.** Echogram of in situ adenocarcinoma. A – ERUS with strain elastography. B-mode image is presented on the right side of the ultrasonogram, on the left side is an elastogram with a color chart, a compression graph and a deformation scale. The yellow figures highlight the zones of interest (A) and comparisons (B). In the lower right corner is the stiffness coefficient. B – 3D reconstruction of the tumor image (arrows).



tion of corresponding curves and the calculation of the area under them.

The Hanley & McNeil test was used to compare the predictive significance of each method. The Youden index was used to determine the cut-off point for continuous data.

The obtained differences were considered statistically significant at  $p < 0.05$ .

## RESULTS

Histological examination of removed specimens in patients with adenomas (48/78 (61.5%) cases), showed the tubular-villous type of structure was more common (27/48 (56.3%) patients), in 15/48 (31.3%) patients, a villous adenoma was detected, in 6/48 (12.5%) cases – a tubular adenoma.

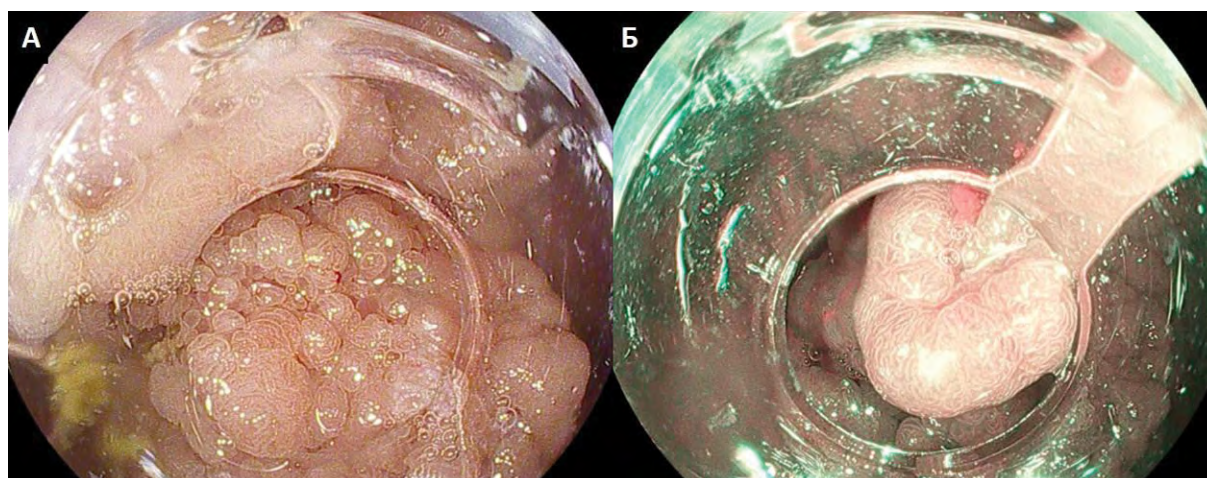
Most resected adenomas had a moderate degree of dysplasia.

In 30/78 (3.5%) cases, adenocarcinoma was detected; and in 14/30 (46.7%) macro-specimens the invasive T1 tumors were diagnosed; and only in 5 cases – intraepithelial cancer (Tis); in 11/30 (36.7%) cases – adenocarcinoma with spread to the muscle layer of the intestinal wall and/or beyond it (T2-3).

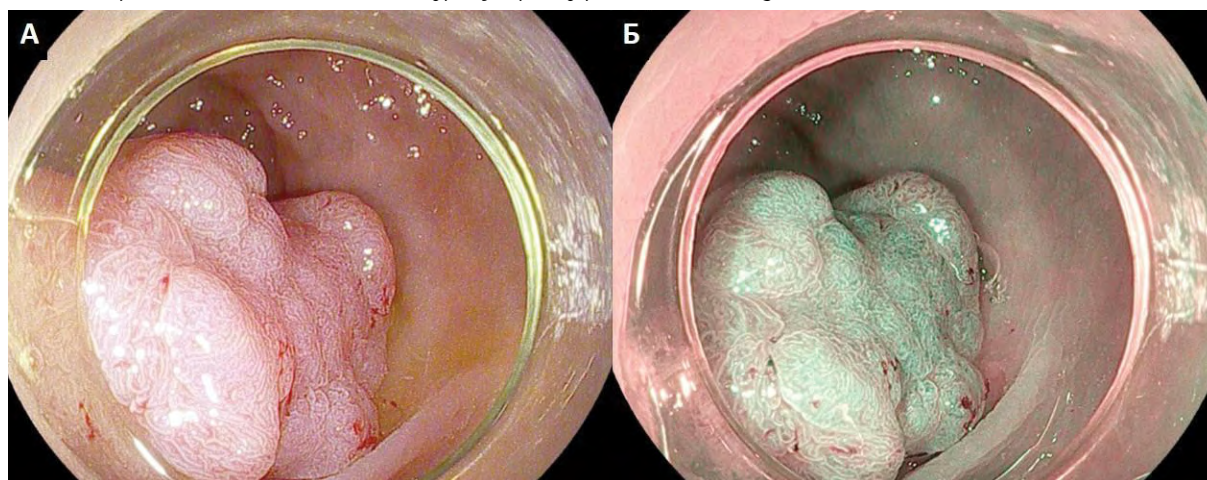
The indicators of diagnostic information content of the methods obtained by comparing the results of ultrasound and endoscopic studies for the study groups are presented in table 1.

There were no significant differences in sensitivity and specificity between ultrasound and colonoscopy. However, it was found that endoscopy has a higher sensitivity for adenomas and the lack of statistical significance may be due to a small sample of patients ( $p = 0.055$ ).

When analyzing incorrect ultrasound results, 13/48 (27.1%) cases of false positive diagnosis of early cancer were found in the group of patients with adeno-



**Figure 5.** Endophoto of adenoma (pT0). A – endoscopic examination in WLE mode, type of pit-pattern IIII according to Kudo-Fujii. B – endoscopic examination in i-Scan mode, type of capillary pattern II according to Sano.



**Figure 6.** Endophoto of adenocarcinoma (pT1). A – study in WLE mode, type of pit-pattern IV-Vn according to Kudo-Fujii. B – i-Scan study, type of vascular pattern II-IIIb according to Sano.

**Table 1.** Indicators of diagnostic information content of ultrasonic and endoscopic methods

		ERUS	95% CI	Colonoscopy	95% CI	p
T0 n=48	sensitivity	0.73	0.58-0.85	0.92	0.80-0.98	0.055
	specificity	0.90	0.074-0.98	0.77	0.58-0.90	0.128
	Positive prognostic value (PPV)*	0.92	0.80-0.97	0.86	0.77-0.92	–
	Negative prognostic value (NPV)*	0.68	0.56-0.77	0.85	0.69-0.94	–
Tis-T1 n=19	sensitivity	0.68	0.44-0.87	0.68	0.44-0.87	1.0
	specificity	0.81	0.69-0.90	0.93	0.84-0.98	0.468
	Positive prognostic value (PPV)*	0.54	0.39-0.69	0.77	0.55-0.90	–
	Negative prognostic value (NPV)*	0.89	0.80-0.94	0.90	0.83-0.95	–
T2-T3 n=11	sensitivity	1.00	0.72-1.00	0.91	0.59-1.00	1.0
	specificity	0.93	0.83-0.98	1.00	0.95-1.00	1.0
	Positive prognostic value (PPV)*	0.69	0.49-0.84	1.00	–	–
	Negative prognostic value (NPV)*	1.00	–	0.99	–	–

PPV – the prognostic value of a positive result, NPV – the prognostic value of a negative result.

mas, and 6/13 (46.2%) of them were concluded to have cancer in situ.

It should be noted that in 9/13 (69.2%) cases, the value of the stiffness coefficient (strain ratio) significantly exceeded the threshold level.

The threshold value of the stiffness coefficient for the diagnosis of adenocarcinoma was used as the value obtained by us as a result of an earlier study, equal to 5.7 [13].

When analyzing false results of endoscopic examination in 7/30 (23.3%) cases in the group of patients with a malignant tumor, there was an under-diagnosis of adenocarcinomas, including 1 patient with a neoplasm that was staged in accordance with the Kudo-Fujii and Sano Y. classifications as an adenoma, while a morphological study of the surgical specimen revealed an adenocarcinoma with a depth of T3 invasion.

In 5/7 (71.4%) cases, the tumors had a significant length (5 cm or more), which in turn made it difficult to detect direct signs of malignancy and subsequent endoscopic staging of neoplasms when using devices with a camera located in the end part of the endoscope. To determine the prognostic model of tests in the verification of malignant degeneration of tumors, we performed a ROC analysis (Fig. 7).

The area under the curve of the deformation ratio was 0.775 (95% CI=0.65-0.85), ultrasound – 0.807 (95% CI=0.7-0.9) and colonoscopy – 0.820 (0.7-0.9), which means that the models have a good prognostic significance. According to the obtained data, ultrasound examination has a prognostic significance comparable to colonoscopy.

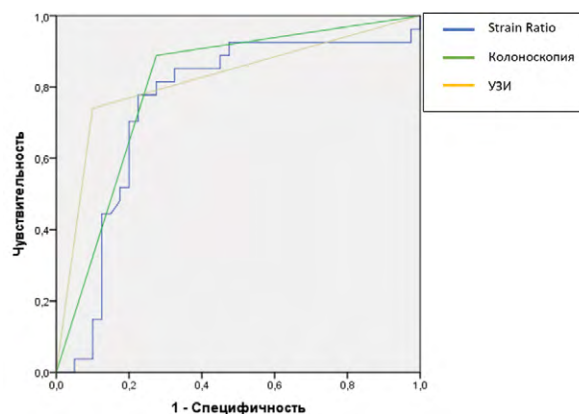
The area difference was 0.013 ( $p=0.85$ ).

To determine which level of the strain ratio had the highest sensitivity and specificity, we calculated the Youden index.

Its maximum value of 0.55 was observed at a threshold value of 5.57 with a sensitivity of 77.8% and specificity of 77.5%.

The difference in areas under the curves of the strainratio with endoscopic examination was 0.04 ( $p=0.56$ ).

Despite the high diagnostic value of the stiffness coefficient, it is important to note that the combination of ultrasound with the measurement of the strain ratio did not significantly increase the predictive value of the test: the area under the curve – 0.81 (95% CI=0.69-0.89,  $p=0.5$ ).



**Figure 7.** ROC analysis. Area under the curve: Strain ratio 0.775 (95% CI=0.65-0.85), ERUS=0.807 (95% CI=0.7-0.9), colonoscopy 0.820 (0.7-0.9).

## DISCUSSION

The importance of detecting hidden malignancy of epithelial rectal tumors is explained by the dependence of the incidence of metastatic lesion of regional lymph nodes on the depth of submucosal invasion and, accordingly, the possibility of local excision as a radical treatment [14].

The use of expert-level video colonoscopes expands the possibilities of early diagnosis of colorectal cancer

due to the availability of such modern refinement technologies as examination by narrow beam imaging with optical magnification. One of the latest achievements in the field of endoscopic technologies aimed at solving this problem today is panoramic or full-spectrum colonoscopy, which increases the rate of adenomas detection and expands the possibilities of their assessment [15, 16].

The diagnostic value of endoscopy increases due to the possibility of conducting a biopsy and obtaining pathomorphological evidence of the malignancy of the studied neoplasm.

However, the information content of the incision biopsy depends on the correctness of the material sampling. According to the results of our previous study, which combined the results of treatment of 347 patients who underwent TEM removal of rectal tumors: in the study of biopsy material, adenomas were identified in 206 patients, however, in the total pathomorphological study, in another 73 (21.0%) cases, adenocarcinomas with different depths of invasion of the intestinal wall were additionally detected.

Thus, this fact indicates a low sensitivity of the biopsy in the diagnosis of malignant neoplasms [17].

In addition, sampling of biopsy material may limit the range of minimally invasive interventions due to the fibrosis in the submucosal layer [18].

Fukunaga S. et al., in a representative sample of 441 patients who underwent endoscopic submucosal dissection, clearly showed that the previous biopsy significantly increases the risk of submucosal fibrosis (11% vs. 20.6%,  $p=0.03$ ).

Fibrosis in the submucosal layer can also be assessed using ultrasound. However, the sensitivity and specificity of the method are only 77.8% and 57.1%, respectively [19].

It is also important to emphasize that the differential diagnosis of fibrosis and latent malignancy at the tumor base using ultrasound is very difficult [20].

In this regard, some methods have been developed to improve the diagnostic value of ultrasound.

The use of compression elastography has a high reproducibility and increases the accuracy of ultrasound in the staging of the tumor process [7,21].

Compression ultrasound elastography is currently included in the European recommendations for endorectal ultrasound for rectal cancer [22].

According to the data obtained, the calculation of the strain ratio allows us to estimate the presence of hidden malignancy in adenomas with sensitivity and specificity of 77.8% and 77.5%, respectively.

When comparing the indicators of diagnostic information content of ERUS and colonoscopy obtained in the study, only in the group of patients with adenomas were differences in the sensitivity of methods whose significance level was close to critical (0.73 vs. 0.92,  $p=0.055$ ).

However, the lack of significant differences can be explained by a small sample of patients, which is the main limitation of the study.

Another limitation of the study is the lack of evaluation of energy dopplerography, which is a promising method for diagnosing latent malignancy in ultrasound [23].

Thus, according to the literature data, there is a dependence of the doppler index of vascularization on the micro vessel density index in the tumor ( $r=0.438$ ,  $p=0.002$ ), which also affects the survival rates of patients ( $p<0.05$ ) [24].

## CONCLUSION

A comparative analysis of ultrasound and endoscopy has shown that the methods under study have a fairly high level of accuracy, sensitivity and specificity in detecting early rectal cancer.

The revealed difference in the prognostic significance of the methods did not reach significant differences ( $p=0.85$ ).

Thus, based on the data obtained, it is possible to recommend the implementation of both research methods to all patients for more accurate preoperative staging of rectal tumors.

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Collection and processing of the material: *Bogdanova E.M., Trubacheva Yu.L., Yugai O.M.*

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